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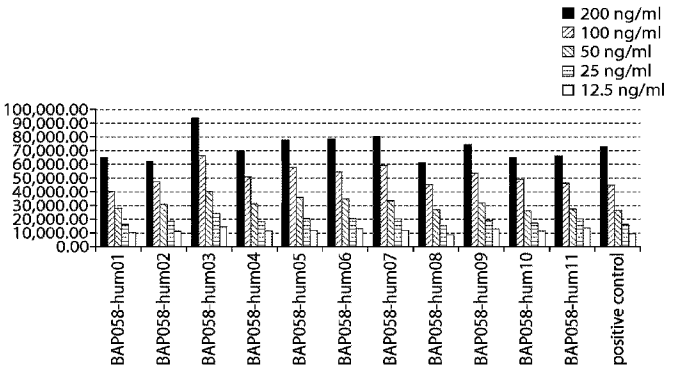
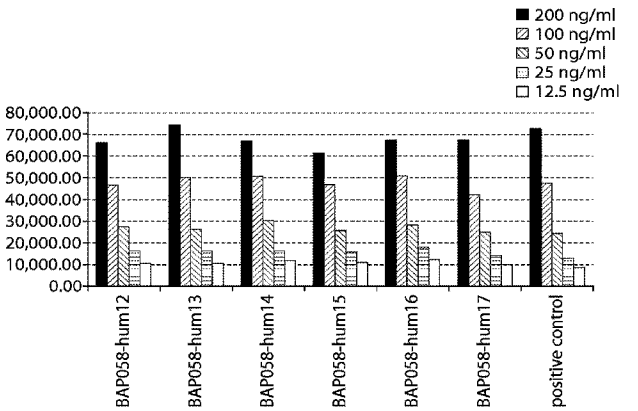
(54) Titre : MOLECULES D'ANTICORPS DE PD-L1 ET LEURS UTILISATIONS
(54) Title: ANTIBODY MOLECULES TO PD-L1 AND USES THEREOF





(57) Abrégé/Abstract:
Antibody molecules that specifically bind to PD-LI are disclosed. Combination therapies comprising the anti-PD-LI antibody molecules are also disclosed. The anti-PD-LI antibody molecules can be used to treat, prevent and/or diagnose cancerous or infectious conditions and disorders.

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[Continued on next page]

(54) Title: ANTIBODY MOLECULES TO PD-L1 AND USES THEREOF

(57) Abstract: Antibody molecules that specifically bind to PD-L1 are disclosed. Combination therapies comprising the anti-PD-L1 antibody molecules are also disclosed. The anti-PD-L1 antibody molecules can be used to treat, prevent and/or diagnose cancerous or infectious conditions and disorders.

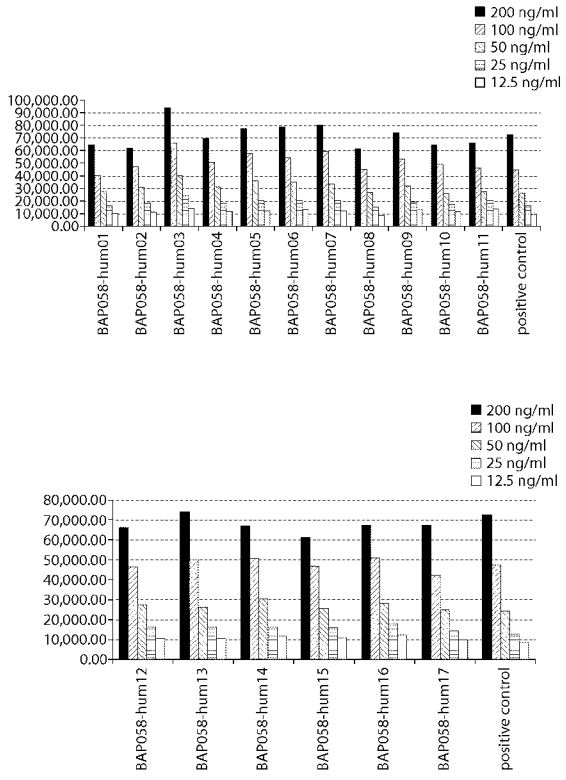

FIGURE 3

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THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 159

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

ANTIBODY MOLECULES TO PD-L1 AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/063,852, filed October 14, 2014, U.S. Provisional Application No. 62/094,847, filed December 19, 2014, U.S. Provisional Application No. 62/198,545, filed July 29, 2015, and U.S. Provisional Application No. 62/213,076, filed September 1, 2015.

BACKGROUND

The ability of T cells to mediate an immune response against an antigen requires two distinct signaling interactions (Viglietta, V. *et al.* (2007) *Neurotherapeutics* 4:666-675; Korman, A. J. *et al.* (2007) *Adv. Immunol.* 90:297-339). First, an antigen that has been arrayed on the surface of antigen-presenting cells (APC) is presented to an antigen-specific naive $CD4^+$ T cell. Such presentation delivers a signal via the T cell receptor (TCR) that directs the T cell to initiate an immune response specific to the presented antigen. Second, various co-stimulatory and inhibitory signals mediated through interactions between the APC and distinct T cell surface molecules trigger the activation and proliferation of the T cells and ultimately their inhibition.

The immune system is tightly controlled by a network of costimulatory and co-inhibitory ligands and receptors. These molecules provide the second signal for T cell activation and provide a balanced network of positive and negative signals to maximize immune responses against infection, while limiting immunity to self (Wang, L. *et al.* (Epub Mar. 7, 2011) *J. Exp. Med.* 208(3):577-92; Lepenies, B. *et al.* (2008) *Endocrine, Metabolic & Immune Disorders--Drug Targets* 8:279-288). Examples of costimulatory signals include the binding between the B7.1 (CD80) and B7.2 (CD86) ligands of the APC and the CD28 and CTLA-4 receptors of the

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$CD4^+$ T-lymphocyte (Sharpe, A. H. *et al.* (2002) *Nature Rev. Immunol.* 2:116-126; Lindley, P. S. *et al.* (2009) *Immunol. Rev.* 229:307-321). Binding of B7.1 or B7.2 to CD28 stimulates T cell activation, whereas binding of B7.1 or B7.2 to CTLA-4 inhibits such activation (Dong, C. *et al.* (2003) *Immunolog. Res.* 28(1):39-48; Greenwald, R. J. *et al.* (2005) *Ann. Rev. Immunol.* 23:515-548). CD28 is constitutively expressed on the surface of T cells (Gross, J., *et al.* (1992) *J. Immunol.* 149:380-388), whereas CTLA-4 expression is rapidly up-regulated following T-cell activation (Linsley, P. *et al.* (1996) *Immunity* 4:535-543).

Other ligands of the CD28 receptor include a group of related B7 molecules, also known as the "B7 Superfamily" (Coyle, A. J. *et al.* (2001) *Nature Immunol.* 2(3):203-209; Sharpe, A. H. *et al.* (2002) *Nature Rev. Immunol.* 2:116-126; Collins, M. *et al.* (2005) *Genome Biol.* 6:223.1-223.7; Korman, A. J. *et al.* (2007) *Adv. Immunol.* 90:297-339). Several members of the B7 Superfamily are known, including B7.1 (CD80), B7.2 (CD86), the inducible co-stimulator ligand (ICOS-L), the programmed death-1 ligand (PD-L1; B7-H1), the programmed death-2 ligand (PD-L2; B7-DC), B7-H3, B7-H4 and B7-H6 (Collins, M. *et al.* (2005) *Genome Biol.* 6:223.1-223.7).

The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA-4 family of T cell regulators (Okazaki *et al.* (2002) *Curr Opin Immunol* 14: 391779-82; Bennett *et al.* (2003) *J. Immunol.* 170:711-8). Other members of the CD28 family include CD28, CTLA-4, ICOS and BTLA. Two cell surface glycoprotein ligands for PD-1 have been identified, Program Death Ligand 1 (PD-L1) and Program Death Ligand 2 (PD-L2). PD-L1 and PD-L2 have been shown to downregulate T cell activation and cytokine secretion upon binding to PD-1 (Freeman *et al.* (2000) *J Exp Med* 192:1027-34; Latchman *et al.* (2001) *Nat Immunol* 2:261-8; Carter *et al.* (2002) *Eur J Immunol* 32:634-43; Ohigashi *et al.* (2005) *Clin Cancer Res* 11:2947-53).

PD-L1 (also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1)) is a 40 kDa type 1 transmembrane protein. PD-L1 binds to its receptor, PD-1, found on activated T cells, B cells, and myeloid cells, to modulate activation or inhibition. Both PD-L1 and PD-L2 are B7 homologs that bind to PD-1, but do not bind to CD28 or CTLA-4 (Blank *et al.* (2005) *Cancer Immunol Immunother.* 54:307-14). Binding of PD-L1 with its receptor PD-1 on T cells delivers a signal that inhibits TCR-mediated activation of IL-2 production and T cell proliferation. The mechanism involves inhibition of ZAP70 phosphorylation and its association

with CD3ζ (Sheppard et al. (2004) *FEBS Lett.* 574:37-41). PD-1 signaling attenuates PKC-θ activation loop phosphorylation resulting from TCR signaling, necessary for the activation of transcription factors NF-κB and AP-1, and for production of IL-2. PD-L1 also binds to the costimulatory molecule CD80 (B7-1), but not CD86 (B7-2) (Butte et al. (2008) *Mol Immunol.* 45:3567-72).

Expression of PD-L1 on the cell surface has been shown to be upregulated through IFN-γ stimulation. PD-L1 expression has been found in many cancers, including human lung, ovarian and colon carcinoma and various myelomas, and is often associated with poor prognosis (Iwai *et al.* (2002) *PNAS* 99:12293-7; Ohigashi *et al.* (2005) *Clin Cancer Res* 11:2947-53; Okazaki *et al.* (2007) *Intern. Immun.* 19:813-24; Thompson *et al.* (2006) *Cancer Res.* 66:3381-5). PD-L1 has been suggested to play a role in tumor immunity by increasing apoptosis of antigen-specific T-cell clones (Dong et al. (2002) *Nat Med* 8:793-800). It has also been suggested that PD-L1 might be involved in intestinal mucosal inflammation and inhibition of PD-L1 suppresses wasting disease associated with colitis (Kanai et al. (2003) *J Immunol* 171:4156-63).

Given the importance of immune checkpoint pathways in regulating an immune response, the need exists for developing novel agents that modulate the activity of immunoinhibitory proteins, such as PD-L1, thus leading to activation of the immune system. Such agents can be used, *e.g.*, for cancer immunotherapy and treatment of other conditions, such as chronic infection.

SUMMARY

Disclosed herein are antibody molecules *(e.g.*, humanized antibody molecules) that bind to Programmed Death-Ligand 1 (PD-L1) with high affinity and specificity. In one embodiment, the anti-PD-L1 antibody molecules comprise a novel combination of framework regions (*e.g.*, FW1, FW2, FW3 and/or FW4), *e.g.*, novel combinations of a heavy chain framework regions and/or light chain framework regions. Nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules are also provided. Immunoconjugates, multi- or bispecific antibody molecules and pharmaceutical compositions comprising the antibody molecules are also provided. The anti-PD-L1 antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose disorders, such as cancerous disorders (*e.g.*, solid

and soft-tissue tumors), as well as infectious diseases (*e.g.*, chronic infectious disorders or sepsis). Additionally disclosed herein are methods and compositions comprising a combination of two, three or more therapeutic agents chosen from one, two, or all of the following categories (i)-(iii): (i) an agent that enhances antigen presentation (*e.g.*, tumor antigen presentation); (ii) an agent that enhances an effector cell response (*e.g.*, B cell and/or T cell activation and/or mobilization); or (iii) an agent that decreases tumor immunosuppression. In some embodiments, the combination includes an inhibitor of PD-L1 (*e.g.*, an anti-PD-L1 antibody molecule as described herein). Thus, compositions and methods for detecting PD-L1, as well as methods for treating various disorders including cancer and/or infectious diseases, using the anti-PD-L1 antibody molecules and combinations thereof are disclosed herein.

Accordingly, in one aspect, the invention features an antibody molecule (*e.g.*, an isolated or recombinant antibody molecule) having one or more of the following properties:

(i) binds to PD-L1, *e.g.*, human PD-L1, with high affinity, *e.g.*, with an affinity constant of at least about 10^7 M^{-1}, typically about 10^8 M^{-1}, and more typically, about 10^9 M^{-1} to 10^{10} M^{-1} or stronger;

(ii) does not substantially bind to CD28, CTLA-4, ICOS or BTLA;

(iii) inhibits or reduces binding of PD-L1 to a receptor, *e.g.*, PD-1 or CD80 (B7-1), or both;

(iv) binds specifically to an epitope on PD-L1, *e.g.*, the same or similar epitope as the epitope recognized by murine monoclonal antibody BAP058 or a chimeric antibody BAP058, *e.g.*, BAP058-chi;

(v) shows the same or similar binding affinity or specificity, or both, as any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(vi) shows the same or similar binding affinity or specificity, or both, as an antibody molecule (*e.g.*, an heavy chain variable region and light chain variable region) described in Table 1;

(vii) shows the same or similar binding affinity or specificity, or both, as an antibody molecule (*e.g.*, an heavy chain variable region and light chain variable region) having an amino acid sequence shown in Table 1;

(viii) shows the same or similar binding affinity or specificity, or both, as an antibody molecule (*e.g.*, an heavy chain variable region and light chain variable region) encoded by the nucleotide sequence shown in Table 1;

(ix) inhibits, *e.g.*, competitively inhibits, the binding of a second antibody molecule to PD-L1, wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(x) binds the same or an overlapping epitope with a second antibody molecule to PD-L1, wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(xi) competes for binding, and/or binds the same epitope, with a second antibody molecule to PD-L1, wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(xii) has one or more biological properties of an antibody molecule described herein, *e.g.*, an antibody molecule chosen from, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08,

BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(xiii) has one or more pharmacokinetic properties of an antibody molecule described herein, *e.g.*, an antibody molecule chosen from, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O;

(xiv) inhibits one or more activities of PD-L1, *e.g.*, results in one or more of: an increase in tumor infiltrating lymphocytes, an increase in T-cell receptor mediated proliferation, or a decrease in immune evasion by cancerous cells; or

(xv) binds human PD-L1 and is cross-reactive with cynomolgus PD-L1.

In some embodiments, the antibody molecule binds to PD-L1 with high affinity, *e.g.*, with a K_D that is about the same, or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% higher or lower than the K_D of a murine or chimeric anti-PD-L1 antibody molecule, *e.g.*, a murine or chimeric anti-PD-L1 antibody molecule described herein. In some embodiments, the K_D of the murine or chimeric anti-PD-L1 antibody molecule is less than about 0.4, 0.3, 0.2, 0.1, or 0.05 nM, *e.g.*, measured by a Biacore method. In some embodiments, the K_D of the murine or chimeric anti-PD-L1 antibody molecule is less than about 0.2 nM, *e.g.*, about 0.171 nM. In other embodiments, the K_D of the murine or chimeric anti PD-L1 antibody molecule is less than about 10, 5, 3, 2, or 1 nM, *e.g.*, measured by binding on cells expressing PD-L1 (*e.g.*, 300.19 cells). In some embodiments, the K_D of the murine or chimeric anti PD-L1 antibody molecule is less than about 1 nM, *e.g.*, about 0.285nM.

In some embodiments, the anti-PD-L1 antibody molecule binds to PD-L1 with a K_d slower than 1×10^{-4}, 5×10^{-5}, or 1×10^{-5} s^{-1}, *e.g.*, about 6.33×10^{-5} s^{-1}. In some embodiments, the the anti-PD-L1 antibody molecule binds to PD-L1 with a K_a faster than 1×10^{4}, 5×10^{4}, 1×10^{5}, or 5×10^{5} $M^{-1}s^{-1}$, *e.g.*, about 3.07×10^{5} $M^{-1}s^{-1}$.

In some embodiments, the expression level of the antibody molecule is higher, *e.g.*, at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10-fold higher, than the expression level of a murine or

chimeric antibody molecule, *e.g.*, a murine or chimeric anti-PD-L1 antibody molecule described herein. In some embodiments, the antibody molecule is expressed in CHO cells.

In some embodiments, the anti-PD-L1 antibody molecule reduces one or more PD-L1-associated activities with an IC_{50} (concentration at 50% inhibition) that is about the same or lower, *e.g.*, at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% lower, than the IC_{50} of a murine or chimeric anti-PD-L1 antibody molecule, *e.g.*, a murine or chimeric anti-PD-L1 antibody molecule described herein. In some embodiments, the IC_{50} of the murine or chimeric anti-PD-L1 antibody molecule is less than about 6, 5, 4, 3, 2, or 1 nM, *e.g.*, measured by binding on cells expressing PD-L1 (*e.g.*, 300.19 cells). In some embodiments, the IC_{50} of the murine or chimeric anti-PD-L1 antibody molecule is less than about 4 nM, *e.g.*, about 3.40 nM (or about 0.51 μg/mL). In some embodiments, the PD-L1-associated activity reduced is the binding of PD-L1 and/or PD-L2 to PD-1. In some embodiments, the anti-PD-L1 antibody molecule binds to peripheral blood mononucleated cells (PBMCs) activated by Staphylococcal enterotoxin B (SEB). In other embodiments, the anti-PD-L1 antibody molecule increases the expression of IL-2 on whole blood activated by SEB. For example, the anti-PD-L1 antibody increases the expression of IL-2 by at least about 2, 3, 4, or 5-fold, compared to the expression of IL-2 when an isotype control (*e.g.*, IgG4) is used.

In some embodiments, the anti-PD-L1 antibody molecule has improved stability, *e.g.*, at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10-fold more stable *in vivo* or *in vitro*, than a murine or chimeric anti-PD-L1 antibody molecule, *e.g.*, a murine or chimeric anti-PD-L1 antibody molecule described herein.

In one embodiment, the anti PD-L1 antibody molecule is a humanized antibody molecule and has a risk score based on T cell epitope analysis of 300 to 700, 400 to 650, 450 to 600, or a risk score as described herein.

In another embodiment, the anti-PD-L1 antibody molecule comprises at least one antigen-binding region, *e.g.*, a variable region or an antigen-binding fragment thereof, from an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-

O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, three or four variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one or two heavy chain variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one or two light chain variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-L1 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4. In one embodiment, the human IgG4 includes a substitution at position 228 (*e.g.*, a Ser to Pro substitution). In still another embodiment, the anti-PD-L1 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1. In one embodiment, the human IgG1 includes a substitution at position 297 (*e.g.*, an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265, a substitution at position 329, or both (*e.g.*, an Asp to Ala substitution at position 265 and/or a Pro to Ala substitution at position 329). In one embodiment, the human IgG1 includes a substitution at position 234, a substitution at position 235, or both (*e.g.*, a Leu to Ala substitution at position 234 and/or a Leu to Ala substitution at position 235). In one embodiment, the heavy chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In yet another embodiment, the anti-PD-L1 antibody molecule includes a kappa light chain constant region, *e.g.*, a human kappa light chain constant region. In one embodiment, the light chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In another embodiment, the anti-PD-L1 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.*, a heavy and light chain constant region comprising an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In yet another embodiment, the anti-PD-L1 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.*, a heavy and light chain constant region comprising an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In one embodiment, the human IgG1 includes a substitution at position 297 (*e.g.*, an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265, a substitution at position 329, or both (*e.g.*, an Asp to Ala substitution at position 265 and/or a Pro to Ala substitution at position 329). In

one embodiment, the human IgG1 includes a substitution at position 234, a substitution at position 235, or both (*e.g.*, a Leu to Ala substitution at position 234 and/or a Leu to Ala substitution at position 235).

In another embodiment, the anti-PD-L1 antibody molecule includes a heavy chain variable domain and a constant region, a light chain variable domain and a constant region, or both, comprising the amino acid sequence of BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences. The anti-PD-1 antibody molecule, optionally, comprises a leader sequence from a heavy chain, a light chain, or both.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a heavy chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three CDRs from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09,

BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequence.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In certain embodiments, the anti-PD-L1 antibody molecule includes a substitution in a light chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain.

In another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In one embodiment, the anti-PD-L1 antibody molecule includes all six CDRs from an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1, or closely related CDRs, *e.g.*, CDRs which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions). In one embodiment, the anti-PD-L1 antibody molecule may include

any CDR described herein. In certain embodiments, the anti-PD-L1 antibody molecule includes a substitution in a light chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain. In another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (*e.g.*, at least one, two, or three CDRs according to the Kabat definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Table 1.

In another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (*e.g.*, at least one, two, or three CDRs according to the Kabat definition as set out in Table 1) from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Kabat *et al.* (*e.g.*, at least one, two, three, four, five, or

six CDRs according to the Kabat definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Kabat *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-L1 antibody molecule includes all six CDRs according to Kabat *et al.* (*e.g.,* all six CDRs according to the Kabat definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to all six CDRs according to Kabat *et al.* shown in Table 1. In one embodiment, the anti-PD-L1 antibody molecule may include any CDR described herein.

In another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three Chothia hypervariable loops (*e.g.,* at least one, two, or three hypervariable loops according to the Chothia definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07,

BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or at least the amino acids from those hypervariable loops that contact PD-L1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia *et al.* shown in Table 1.

In another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three Chothia hypervariable loops (*e.g.,* at least one, two, or three hypervariable loops according to the Chothia definition as set out in Table 1) of a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or at least the amino acids from those hypervariable loops that contact PD-L1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, three, four, five, or six hypervariable loops (*e.g.,* at least one, two, three, four, five, or six hypervariable loops according to the Chothia definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or at least the amino acids from those hypervariable loops that contact PD-

L1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, three, four, five or six hypervariable loops according to Chothia *et al.* shown in Table 1.

In one embodiment, the anti-PD-L1 antibody molecule includes all six hypervariable loops (*e.g.,* all six hypervariable loops according to the Chothia definition as set out in Table 1) of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, or closely related hypervariable loops, *e.g.*, hypervariable loops which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions); or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to all six hypervariable loops according to Chothia *et al.* shown in Table 1. In one embodiment, the anti-PD-L1 antibody molecule may include any hypervariable loop described herein.

In still another embodiment, the anti-PD-L1 antibody molecule includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding hypervariable loop of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, *e.g.*, the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. *See, e.g.*, Chothia *et al.*, (1992) *J. Mol. Biol.* 227:799-817; Tomlinson et *al.*, (1992) *J. Mol. Biol.* 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references.

In certain embodiments, the anti-PD-L1 antibody molecule includes a combination of CDRs or hypervariable loops defined according to the Kabat *et al.* and Chothia *et al.*

In one embodiment, the anti-PD-L1 antibody molecule includes at least one, two or three CDRs or hypervariable loops from a heavy chain variable region of an antibody described herein, *e.g.,* an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, according to the Kabat and Chothia definition (*e.g.,* at least one, two, or three CDRs or hypervariable loops according to the Kabat and Chothia definition as set out in Table 1); or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.,* substitutions, deletions, or insertions, *e.g.,* conservative substitutions) relative to one, two, or three CDRs or hypervariable loops according to Kabat and/or Chothia shown in Table 1.

For example, the anti-PD-L1 antibody molecule can include VH CDR1 according to Kabat *et al.* or VH hypervariable loop 1 according to Chothia *et al.*, or a combination thereof, *e.g.*, as shown in Table 1. In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTSYWMY (SEQ ID NO: 195), or an amino acid sequence substantially identical thereto (*e.g.*, having at least one amino acid alteration, but not more than two, three or four alterations (*e.g.,* substitutions, deletions, or insertions, *e.g.,* conservative substitutions)). The anti-PD-L1 antibody molecule can further include, *e.g.,* VH CDRs 2-3 according to Kabat *et al.* and VL CDRs 1-3 according to Kabat *et al., e.g.*, as shown in Table 1. Accordingly, in some embodiments, framework regions are defined based on a combination of CDRs defined according to Kabat *et al.* and hypervariable loops defined according to Chothia *et al.* For example, the anti-PD-L1 antibody molecule can include VH FR1 defined based on VH hypervariable loop 1 according to Chothia *et al.* and VH FR2 defined based on VH CDRs 1-2 according to Kabat *et al., e.g.*, as shown in Table 1. The anti-PD-L1 antibody molecule can further include, *e.g.,* VH FRs 3-4 defined based on VH CDRs

2-3 according to Kabat *et al.* and VL FRs 1-4 defined based on VL CDRs 1-3 according to Kabat *et al.*

The anti-PD-L1 antibody molecule can contain any combination of CDRs or hypervariable loops according to the Kabat and Chothia definitions. In one embodiment, the anti-PD-L1 antibody molecule includes at least one, two or three CDRs from a light chain variable region of an antibody described herein, *e.g.,* an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, according to the Kabat and Chothia definition (*e.g.,* at least one, two, or three CDRs according to the Kabat and Chothia definition as set out in Table 1).

In an embodiment, *e.g.*, an embodiment comprising a variable region, a CDR (*e.g.*, Chothia CDR or Kabat CDR), or other sequence referred to herein, *e.g.*, in Table 1, the antibody molecule is a monospecific antibody molecule, a bispecific antibody molecule, or is an antibody molecule that comprises an antigen binding fragment of an antibody, *e.g.,* a half antibody or antigen binding fragment of a half antibody. In embodiments the antibody molecule is a bispecific antibody molecule having a first binding specificity for PD-L1 and a second binding specificity for TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), PD-1 or PD-L2. In embodiments, the second binding specificity for TIM-3, LAG-3 and/or PD-1 includes an amino acid sequence, or is encoded by a nucleotide sequence as described herein (*e.g.*, as disclosed in the section entitled "Inhibitors of Immune Checkpoint Molecules" starting on page 218 hereinbelow (including all publications mentioned therein).

In one embodiment, the anti-PD-L1 antibody molecule includes:

(i) a heavy chain variable region (VH) including a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) including a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO: 10, and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In another embodiment, the anti-PD-L1 antibody molecule includes:

(i) a heavy chain variable region (VH) including a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) including a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

In one embodiment, the anti-PD-L1 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 1. In another embodiment, the anti-PD-L1 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 4. In yet another embodiment, the anti-PD-L1 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 195.

In one embodiment, the light or the heavy chain variable framework (*e.g.*, the region encompassing at least FR1, FR2, FR3, and optionally FR4) of the anti-PD-L1 antibody molecule can be chosen from: (a) a light or heavy chain variable framework including at least 80%, 85%, 87% 90%, 92%, 93%, 95%, 97%, 98%, or preferably 100% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (b) a light or heavy chain variable framework including from 20% to 80%, 40% to 60%, 60% to 90%, or 70% to 95% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (c) a non-human framework (*e.g.*, a rodent framework); or (d) a non-human framework that has been modified, *e.g.,* to remove antigenic or cytotoxic determinants, *e.g.*, deimmunized, or partially humanized. In one embodiment, the light or heavy chain variable framework region (particularly FR1, FR2 and/or FR3) includes a light or heavy chain variable framework sequence at least 70, 75, 80, 85, 87, 88, 90, 92, 94, 95, 96, 97, 98, 99% identical or identical to the frameworks of a VL or VH segment of a human germline gene.

In certain embodiments, the anti-PD-L1 antibody molecule comprises a heavy chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more changes, *e.g.*, amino acid substitutions or deletions, from an amino acid sequence of BAP058-chi-HC, *e.g.*, the amino acid sequence of the FR region in the entire variable region, *e.g.*, shown

in FIGs. 8A-8B, or SEQ ID NO: 16. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain variable domain having one or more of: Q at position 1, I at position 2, T at position 3, V or K at position 5, P at position 9, T at position 10, V at position 11, K at position 12, T at position 15, E or Q at position 16, T at position 17, L at position 18, R or T at position 19, I or V at position 20, T at position 21, T at position 23, G, V, or F at position 24, I at position 37, R at position 38, A or P or S at position 40, T or R at position 41, S at position 42, Q or K at position 43, M or L or V at position 48, R at position 67, F or V or L at position 68, I at position 70, S at position 71, A, K, or R at position 72, D or T or N at position 74, T or K at position 76, N at position 77, Q at position 78, F or V or L at position 79, S or V at position 80, L at position 81, E or K or T at position 82, M at position 83, T or N at position 84, N at position 85, V or M at position 86, K or R or D at position 87, T or A or P at position 88, A or V at position 89, T at position 91, or T at position 93, of amino acid sequence of BAP058-chi-HC, *e.g.*, the amino acid sequence of the FR in the entire variable region, *e.g.*, shown in FIGs. 8A-8B, or SEQ ID NO: 16.

Alternatively, or in combination with the heavy chain substitutions of BAP058-chi-HC described herein, the anti-PD-L1 antibody molecule comprises a light chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more amino acid changes, *e.g.*, amino acid substitutions or deletions, from an amino acid sequence of BAP058-chi-LC, *e.g.*, the amino acid sequence shown in FIGs. 9A-9B, or SEQ ID NO: 17. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain variable domain having one or more of: E or A at position 1, V at position 2, V or Q at position 3, L at position 4, T at position 7, P at position 8, D or L or S or A at position 9, S or T at position 10, Q or L at position 11, P at position 12, V or L or A at position 13, T at position 14, P or L at position 15, K at position 16, Q or E at position 17, K or P at position 18, A at position 19, T at position 20, L at position 21, S at position 22, L at position 37, A at position 43, R or Q at position 45, I at position 58, A or S or P at position 60, S at position 63, Y at position 67, E at position 70, F at position 73, K at position 74, N at position 76, S or R at position 77, I or L at position 78, E at position 79, P or A at position 80, D at position 81, F or I or V or A at position 83, G at position 84, T or V or Y at position 85, or Y at position 87 of the amino acid sequence of BAP058-chi-LC, *e.g.*, the amino acid sequence shown in FIGs. 10A-10B, or SEQ ID NO: 24 or 26.

In other embodiments, the anti-PD-L1 antibody molecule includes one, two, three, or four heavy chain framework regions (*e.g.*, a VHFW amino acid sequence shown in Table 2, or encoded by the nucleotide sequence shown in Table 2), or a sequence substantially identical thereto.

In yet other embodiments, the anti-PD-L1 antibody molecule includes one, two, three, or four light chain framework regions (*e.g.*, a VLFW amino acid sequence shown in Table 2, or encoded by the nucleotide sequence shown in Table 2), or a sequence substantially identical thereto.

In other embodiments, the anti-PD-L1 antibody molecule includes one, two, three, or four heavy chain framework regions (*e.g.*, a VHFW amino acid sequence shown in Table 2, or encoded by the nucleotide sequence shown in Table 2), or a sequence substantially identical thereto; and one, two, three, or four light chain framework regions (*e.g.*, a VLFW amino acid equence shown in Table 2, or encoded by the nucleotide sequence shown in Table 2), or a sequence substantially identical thereto.

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP058-hum01, BAP058-hum02, BAP058-hum07, BAP058-hum14, or BAP058-hum16 (*e.g.*, SEQ ID NO: 124). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP058-hum04, BAP058-hum06, BAP058-hum08, BAP058-hum09, BAP058-hum12, BAP058-hum15, BAP058-hum17, BAP058-Clone-L, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 126). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP058-hum03, BAP058-hum05, BAP058-hum11, BAP058-hum13, BAP058-Clone-K, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 128). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP058-hum10 (*e.g.*, SEQ ID NO: 130).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum11, BAP058-hum14, BAP058-Clone-K, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 132). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP058-hum04, BAP058-hum12, or BAP058-Clone-L (*e.g.*, SEQ ID NO: 134). In some embodiments, the antibody molecule comprises the heavy chain framework region 2

(VHFW2) of BAP058-hum06, BAP058-hum09, BAP058-hum15, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 136). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP058-hum05, BAP058-hum07, or BAP058-hum16 (*e.g.*, SEQ ID NO: 138). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP058-hum08, BAP058-hum13, BAP058-hum17, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 140). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 of BAP058-hum10 (*e.g.*, SEQ ID NO: 142).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP058-hum01, BAP058-hum02, BAP058-hum07, BAP058-hum14, or BAP058-hum16, (*e.g.*, SEQ ID NO: 144). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP058-hum03, BAP058-hum06, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum15, BAP058-Clone-K, BAP058-Clone-M, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 146). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP058-hum04, BAP058-hum12, or BAP058-Clone-L (*e.g.*, SEQ ID NO: 148). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP058-hum05, BAP058-hum08, or BAP058-hum17 (*e.g.*, SEQ ID NO: 150). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 152). In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework region 4 (VHFW4) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 154).

In some embodiments, the anti-PD-L1 antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 156). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-BAPhum08, BAP058-hum10, BAP058-hum11, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 158). In

some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-hum01 or BAP058-hum09 (*e.g.*, SEQ ID NO: 160). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-hum02 or BAP058-hum12 (*e.g.*, SEQ ID NO: 162). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-hum07 (*e.g.*, SEQ ID NO: 164). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP058-hum13 or or BAP058-Clone-O (*e.g.*, SEQ ID NO: 166).

In some embodiments, the anti-PD-L1 antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP058-hum08, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 168). In some embodiments, the antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum09, BAP058-hum13, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 170).

In some embodiments, the anti-PD-L1 antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum08, BAP058-hum10, BAP058-hum11, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 172). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum12, BAP058-Clone-L, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 174). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum01 or BAP058-hum09 (*e.g.*, SEQ ID NO: 176). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum02 (*e.g.*, SEQ ID NO: 178). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum03 or BAP058-Clone-K (*e.g.*, SEQ ID NO: 180). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum07 (*e.g.*, SEQ ID NO: 182). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 184).

In some embodiments, the anti-PD-L1 antibody molecule comprises the light chain framework region 4 (VLFW4) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 186).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum01, BAP058-hum02, or BAP058-hum14 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 144 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum07, or BAP058-hum16 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 138 (VHFW2), and SEQ ID NO: 144 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum04, BAP058-hum12, or BAP058-Clone-L (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 134 (VHFW2), and SEQ ID NO: 148 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum06, BAP058-hum09, BAP058-hum15, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 136 (VHFW2), and SEQ ID NO: 146 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum08 or BAP058-hum17 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 140 (VHFW2), and SEQ ID NO: 150 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum03, BAP058-hum11, BAP058-Clone-K, or BAP058-Clone-N (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 146 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 140 (VHFW2), and SEQ ID NO: 152 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum05 (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 138 (VHFW2), and SEQ ID NO: 150 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum10 (*e.g.*, SEQ ID NO: 130 (VHFW1), SEQ ID NO: 142 (VHFW2), and SEQ ID NO: 146 (VHFW3)). In some embodiments, the antibody molecule further comprises the heavy chain framework region 4 (VHFW4) of BAP058-hum01, BAP058-

hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 154).

In some embodiments, the anti-PD-L1 antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum01 or BAP058-hum09 (*e.g.*, SEQ ID NO: 160 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 176 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum14, BAP058-hum15, BAP058-hum16, or BAP058-hum17 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-Clone-L, or BAP058-Clone-M (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 174 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum08, BAP058-hum10, or BAP058-hum11 (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 166 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 184 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum02 (*e.g.*, SEQ ID NO: 162 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 178 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum03 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 180 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum07 (*e.g.*, SEQ ID NO: 164 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 182 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-hum12 (*e.g.*, SEQ ID NO: 162 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 174 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP058-Clone-K (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 180 (VLFW3)). In some embodiments, the antibody molecule

comprises the light chain framework regions 1-3 of BAP058-Clone-N (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 172 (VLFW3)). In some embodiments, the antibody molecule further comprises the light chain framework region 4 (VLFW4) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 186).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum01 (*e.g.*, SEQ ID NO: 124(VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 144 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum01 (*e.g.*, SEQ ID NO: 160 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 176 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum02 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 144 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum02 (*e.g.*, SEQ ID NO: 162 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 178 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum03 (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum03 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 180 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum04 or BAP058-Clone-L (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 134 (VHFW2), and SEQ ID NO: 148(VHFW3)) and the light chain framework regions 1-3 of BAP058-hum04 or BAP058-Clone-L (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 174 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum05 (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 138 (VHFW2), and SEQ ID NO: 150 (VHFW3)) and the light chain framework regions 1-3 of

BAP058-hum05 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 174 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum06 or BAP058-Clone-M (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 136 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum06 or BAP058-Clone-M (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 174 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum07 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 138 (VHFW2), and SEQ ID NO: 144 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum07 (*e.g.*, SEQ ID NO: 164 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 182 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum08 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 140 (VHFW2), and SEQ ID NO: 150 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum08 (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 168(VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum09 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 136 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum09 (*e.g.*, SEQ ID NO: 160 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 176 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum10 (*e.g.*, SEQ ID NO: 130 (VHFW1), SEQ ID NO: 142 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum10 (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum11 (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of

BAP058-hum11 (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum12 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 134 (VHFW2), and SEQ ID NO: 148 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum12 (*e.g.*, SEQ ID NO: 162 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 174 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 140 (VHFW2), and SEQ ID NO: 152 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum13 or BAP058-Clone-O (*e.g.*, SEQ ID NO: 166 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 184 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum14 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 144 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum14 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum15 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 136 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum15 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum16 (*e.g.*, SEQ ID NO: 124 (VHFW1), SEQ ID NO: 138 (VHFW2), and SEQ ID NO: 144 (VHFW3)) and the light chain framework regions 1-3 of BAP058-hum16 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-hum17 (*e.g.*, SEQ ID NO: 126 (VHFW1), SEQ ID NO: 140 (VHFW2), and SEQ ID NO: 150 (VHFW3)) and the light chain framework regions 1-3 of

BAP058-hum17 (*e.g.*, SEQ ID NO: 156 (VLFW1), SEQ ID NO: 168 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule comprises the heavy chain framework regions 1-3 of BAP058-Clone-N (*e.g.*, SEQ ID NO: 128 (VHFW1), SEQ ID NO: 132 (VHFW2), and SEQ ID NO: 146 (VHFW3)) and the light chain framework regions 1-3 of BAP058-Clone-N (*e.g.*, SEQ ID NO: 158 (VLFW1), SEQ ID NO: 170 (VLFW2), and SEQ ID NO: 172 (VLFW3)).

In some embodiments, the anti-PD-L1 antibody molecule further comprises the heavy chain framework region 4 (VHFW4) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 154) and the light chain framework region 4 (VLFW4) of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O (*e.g.*, SEQ ID NO: 186).

In some embodiments, the anti-PD-L1 antibody molecule comprises a heavy chain framework region having a combination of framework regions FW1, FW2 and FW3 as showin in FIGs. 4 or 6. In other embodiment, the antibody molecule comprises a light chain framework region having a combination of framework regions FW1, FW2 and FW3 as showin in FIGs. 4 or 6. In yet other embodiments, the antibody molecule comprises a heavy chain framework region having a combination of framework regions FW1, FW2 and FW3 as showin in FIGs. 4 or 6, and a light chain framework region having a combination of framework regions FW1, FW2 and FW3 as showin in FIGs. 4 or 6.

In one embodiment, the heavy or light chain variable domain, or both, of the anti-PD-L1 antibody molecule includes an amino acid sequence, which is substantially identical to an amino acid disclosed herein, *e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a variable region of an antibody described herein, *e.g.*, an antibody chosen from any

of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or which differs at least 1 or 5 residues, but less than 40, 30, 20, or 10 residues, from a variable region of an antibody described herein.

In one embodiment, the heavy or light chain variable region, or both, of the anti-PD-L1 antibody molecule includes an amino acid sequence encoded by a nucleic acid sequence described herein or a nucleic acid that hybridizes to a nucleic acid sequence described herein (*e.g.*, a nucleic acid sequence as shown in Tables 1 and 2) or its complement, *e.g.*, under low stringency, medium stringency, or high stringency, or other hybridization condition described herein.

In another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, three, or four antigen-binding regions, *e.g.*, variable regions, having an amino acid sequence as set forth in Table 1, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the sequences shown in Table 1. In another embodiment, the anti-PD-L1 antibody molecule includes a VH and/or VL domain encoded by a nucleic acid having a nucleotide sequence as set forth in Table 1, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Table 1.

In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, or three CDRs from a heavy chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, or three CDRs from a light chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*,

conserved substitutions). In yet another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, three, four, five or six CDRs from heavy and light chain variable regions having an amino acid sequence as set forth in Table 1), or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In one embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, or three CDRs and/or hypervariable loops from a heavy chain variable region having an amino acid sequence of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, as summarized in Table 1, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In another embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, or three CDRs and/or hypervariable loops from a light chain variable region having an amino acid sequence of of an antibody described herein, *e.g.*, an antibody chosen from any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, as summarized in Table 1, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In one embodiment, the anti-PD-L1antibody molecule comprises all six CDRs and/or hypervariable loops described herein, *e.g.*, described in Table 1.

In one embodiment, the anti-PD-L1 antibody molecule has a variable region that is identical in sequence, or which differs by 1, 2, 3, or 4 amino acids from a variable region described herein (*e.g.*, an FR region disclosed herein).

In one embodiment, the anti-PD-L1 antibody molecule is a full antibody or fragment thereof (*e.g.*, a Fab, $F(ab')_2$, Fv, or a single chain Fv fragment (scFv)). In certain embodiments, the anti-PD-L1 antibody molecule is a monoclonal antibody or an antibody with single specificity. The anti-PD-L1 antibody molecule can also be a humanized, chimeric, camelid, shark, or an *in vitro*-generated antibody molecule. In one embodiment, the anti-PD-L1 antibody molecule thereof is a humanized antibody molecule. The heavy and light chains of the anti-PD-L1 antibody molecule can be full-length (*e.g.*, an antibody can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains) or can include an antigen-binding fragment (*e.g.*, a Fab, $F(ab')_2$, Fv, a single chain Fv fragment, a single domain antibody, a diabody (dAb), a bivalent antibody, or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In certain embodiments, the anti-PD-L1 antibody molecule is in the form of a bispecific or a multispecific antibody molecule. In one embodiment, the bispecific antibody molecule has a first binding specificity for PD-L1 and a second binding specifity for TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), PD-1 or PD-L2. In one embodiment, the bispecific antibody molecule binds to PD-L1 and TIM-3. In another embodiment, the bispecific antibody molecule binds to PD-L1 and LAG-3. In another embodiment, the bispecific antibody molecule binds to PD-L1 and CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5). In another embodiment, the bispecific antibody molecule binds to PD-L1 and CEACAM-1. In yet another embodiment, the bispecific antibody molecule binds to PD-L1 and CEACAM-5. In another embodiment, the bispecific antibody molecule binds to PD-L1 and PD-1. In yet another embodiment, the bispecific antibody molecule binds to PD-L1 and PD-L2. Any combination of the aforesaid molecules can be made in a multispecific antibody molecule, *e.g.*, a trispecific antibody that includes a first binding specificity to PD-L1, and a second and third binding specificity to one or more of: TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), PD-1 or PD-L2. In embodiments, the second and/or third binding specifity for TIM-3, LAG-3 and/or PD-1 includes an amino acid sequence, or is encoded by a nucleotide sequence as disclosed herein (*e.g.*, as disclosed in the section entitled "Inhibitors of Immune Checkpoint Molecules" starting on page 218 herein below (including all publications mentioned therein).

In other embodiments, the anti-PD-L1 antibody molecule is used in combination with a bispecific molecule comprising one or more of: TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), PD-1 or PD-L2. In one embodiment, the bispecific antibody molecule used in combination binds to CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5) and LAG-3. In another embodiment, the bispecific antibody molecule used in combination binds to CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5) and TIM-3. In another embodiment, the bispecific antibody molecule used in combination binds to LAG-3 and TIM-3.

In yet other embodiments, the anti-PD-L1 antibody molecule has a heavy chain constant region (Fc) chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4, more particularly, the heavy chain constant region of IgG1 or IgG2 (*e.g.*, human IgG1, IgG2 or IgG4). In one embodiment, the heavy chain constant region is human IgG1. In another embodiment, the anti-PD-L1 antibody molecule has a light chain constant region chosen from, *e.g.*, the light chain constant regions of kappa or lambda, preferably kappa (*e.g.*, human kappa). In one embodiment, the constant region is altered, *e.g.*, mutated, to modify the properties of the anti-PD-L1 antibody molecule (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function). For example, the constant region is mutated at positions 296 (M to Y), 298 (S to T), 300 (T to E), 477 (H to K) and 478 (N to F) to alter Fc receptor binding (*e.g.*, the mutated positions correspond to positions 132 (M to Y), 134 (S to T), 136 (T to E), 313 (H to K) and 314 (N to F) of SEQ ID NOs: 212 or 214; or positions 135 (M to Y), 137 (S to T), 139 (T to E), 316 (H to K) and 317 (N to F) of SEQ ID NOs: 215, 216, 217 or 218). In another embodiment, the heavy chain constant region of an IgG4, *e.g.*, a human IgG4, is mutated at position 228 (*e.g.*, S to P), *e.g.*, as shown in Table 3. In certain embodiments, the anti-PD-L1 antibody molecules comprises a human IgG4 mutated at position 228 (*e.g.*, S to P), *e.g.*, as shown in Table 3; and a kappa light chain constant region, *e.g.*, as shown in Table 3. In still another embodiment, the heavy chain constant region of an IgG1, *e.g.*, a human IgG1, is mutated at one or more of position 297 (*e.g.*, N to A), position 265 (*e.g.*, D to A), position 329 (*e.g.*, P to A), position 234 (*e.g.*, L to A), or position 235 (*e.g.*, L to A), *e.g.*, as shown in Table 3. In certain embodiments, the anti-PD-L1 antibody molecules comprises a human IgG1 mutated at

one or more of the aforesaid positions, *e.g.*, as shown in Table 3; and a kappa light chain constant region, *e.g.*, as shown in Table 3.

In one embodiment, the anti-PD-L1 antibody molecule is isolated or recombinant.

In one embodiment, the anti-PD-L1 antibody molecule is a humanized antibody molecule.

The invention also features a nucleic acid molecule that comprise one or both nucleotide sequences that encode heavy and light chain variable regions, CDRs, hypervariable loops, framework regions of the anti-PD-L1 antibody molecules, as described herein. In certain embodiments, the nucleotide sequence that encodes the anti-PD-L1 antibody molecule is codon optimized. For example, the invention features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-PD-L1 antibody molecule chosen from one or more of, *e.g.*, any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, as summarized in Table 1, or a sequence substantially identical thereto. For example, the nucleic acid can comprise a nucleotide sequence as set forth in Tables 1 and 2, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Tables 1 and 2).

In other embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes a heavy chain variable domain and/or a heavy chain constant region comprising the amino acid sequence of BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1; or the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences.

In other embodiments, the nucleic acid molecule comprises a nucleotide sequence that encodes a light chain variable domain and/or a light chain constant region comprising the amino acid sequence of BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O; or as described in Table 1; or the nucleotide sequence in Table 1; or a

sequence substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences.

The aforesaid nucleotide sequences encoding the anti-PD-L1 heavy and light chain variable domain and constant regions can be present in a separate nucleic acid molecule, or in the same nucleic acid molecule. In certain embodiments, the nucleic acid molecules comprise a nucleotide sequence encoding a leader sequence.

In certain embodiments, the nucleic acid molecule comprises a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a heavy chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In another embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a light chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In yet another embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs, or hypervariable loops, from heavy and light chain variable regions having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In another embodiment, the nucleic acid molecule includes one or more heavy chain framework region (*e.g.*, any of VHFW1 (type a), VHFW1 (type b), VHFW1 (type c), VHFW1 (type d), VHFW2 (type a), VHFW2 (type a'), VHFW2 (type b), VHFW2 (type c), VHFW2 (type d), VHFW2 (type e),VHFW3 (type a), VHFW3 (type b), VHFW3 (type c), VHFW3 (type d), VHFW3 (type e),or VHFW4, or any combination thereof, *e.g.*, a framework combination as described herein) for any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09,

BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, as summarized in Table 1 and 2, or a sequence substantially identical thereto. For example, the nucleic acid molecule can comprise a nucleotide sequence as set forth in Tables 1 and 2, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Tables 1 and 2).

In another embodiment, the nucleic acid molecule includes one or more light chain framework region (*e.g.*, any of VLFW1 (type a), VLFW1 (type b), VLFW1 (type c), VLFW1 (type d), VLFW1 (type e), VLFW1 (type f), VLFW2 (type a), VLFW2 (type c), VLFW3 (type a), VLFW3 (type b), VLFW3 (type c), VLFW3 (type d), VLFW3 (type e), VLFW3 (type f), VLFW3 (type g), or VLFW4, or any combination thereof, *e.g.*, a framework combination as described herein) for any of BAP058-hum01, BAP058-hum02, BAP058-hum03, BAP058-hum04, BAP058-hum05, BAP058-hum06, BAP058-hum07, BAP058-hum08, BAP058-hum09, BAP058-hum10, BAP058-hum11, BAP058-hum12, BAP058-hum13, BAP058-hum14, BAP058-hum15, BAP058-hum16, BAP058-hum17, BAP058-Clone-K, BAP058-Clone-L, BAP058-Clone-M, BAP058-Clone-N, or BAP058-Clone-O, as summarized in Table 1 and 2, or a sequence substantially identical thereto. For example, the nucleic acid molecule can comprise a nucleotide sequence as set forth in Tables 1 and 2, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Tables 1 and 2).

In another embodiment, the nucleic acid molecule includes one or more heavy chain framework region and one or more light chain framework region as described herein. The heavy and light chain framework regions may be present in the same vector or separate vectors.

In another aspect, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell. The host cell can be a eukaryotic cell, *e.g.*, a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, *e.g.*, *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include lymphocytic cell lines (*e.g.*, NSO), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal, *e.g.*, mammary epithelial cell.

In one aspect, the invention features a method of providing an antibody molecule described herein. The method includes: providing a PD-L1 antigen (*e.g.*, an antigen comprising at least a portion of a PD-L1 epitope); obtaining an antibody molecule that specifically binds to the PD-L1 polypeptide; and evaluating if the antibody molecule specifically binds to the PD-L1 polypeptide, or evaluating efficacy of the antibody molecule in modulating, *e.g.*, inhibiting, the activity of the PD-L1. The method can further include administering the antibody molecule to a subject, *e.g.*, a human or non-human animal.

In another aspect, the invention provides, compositions, *e.g.*, pharmaceutical compositions, which include a pharmaceutically acceptable carrier, excipient or stabilizer, and at least one of the anti-PD-L1 antibody molecules described herein. In one embodiment, the composition, *e.g.*, the pharmaceutical composition, includes a combination of the antibody molecule and one or more agents, *e.g.*, a therapeutic agent or other antibody molecule, as described herein. In one embodiment, the antibody molecule is conjugated to a label or a therapeutic agent.

The anti-PD-L1 antibody molecules disclosed herein can inhibit, reduce or neutralize one or more activities of PD-L1, resulting in blockade or reduction of an immune checkpoint. In one embodiment, the antibody molecule results in one or more of: an increase in tumor infiltrating lymphocytes, an increase in T-cell receptor mediated proliferation, a decrease in immune evasion by cancerous cells, restoration of effector cell function (*e.g.*, one or more of T cell proliferation, IFN-γ secretion or cytolytic function), inhibition of regulatory T cell function, or an effect on the activity of multiple cell types, such as regulatory T cell, effector T cells and NK cells). Thus, such antibody molecules can be used to treat or prevent disorders where enhancing an immune response in a subject is desired.

Uses of the Anti-PD-L1 Antibody Molecules

Accordingly, in another aspect, a method of modulating an immune response in a subject is provided. The method comprises administering to the subject an anti-PD-L1 antibody molecule disclosed herein (*e.g.*, a therapeutically effective amount of an anti-PD-L1 antibody

molecule), alone or in combination with one or more agents or procedures, such that the immune response in the subject is modulated. In one embodiment, the antibody molecule enhances, stimulates or increases the immune response in the subject. The subject can be a mammal, *e.g.*, a primate, preferably a higher primate, *e.g.*, a human (*e.g.*, a patient having, or at risk of having, a disorder described herein). In one embodiment, the subject is in need of enhancing an immune response. In one embodiment, the subject has, or is at risk of, having a disorder described herein, *e.g.*, a cancer or an infectious disorder as described herein. In certain embodiments, the subject is, or is at risk of being, immunocompromised. For example, the subject is undergoing or has undergone a chemotherapeutic treatment and/or radiation therapy. Alternatively, or in combination, the subject is, or is at risk of being, immunocompromised as a result of an infection.

In one aspect, a method of treating (*e.g.*, one or more of reducing, inhibiting, or delaying progression) a cancer or a tumor in a subject is provided. The method comprises administering to the subject an anti-PD-L1 antibody molecule described herein, *e.g.*, a therapeutically effective amount of an anti-PD-L1 antibody molecule, alone or in combination with one or more agents or procedures. In certain embodiments, the anti-PD-L1 antibody molecule is administered in combination with a modulator of a costimulatory molecule (*e.g.*, an agonist of a costimulatory molecule) or a modulator of an inhibitory molecule (*e.g.*, an inhibitor of an immune checkpoint inhibitor), *e.g.*, as described herein.

In certain embodiments, the cancer treated with the anti-PD-L1 antibody molecule, includes but is not limited to, a solid tumor, a hematological cancer (*e.g.*, leukemia, lymphoma, myeloma, *e.g.*, multiple myeloma), and a metastatic lesion. In one embodiment, the cancer is a solid tumor. Examples of solid tumors include malignancies, *e.g.*, sarcomas and carcinomas, *e.g.*, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting the lung, breast, ovarian, lymphoid, gastrointestinal (*e.g.*, colon), anal, genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells, prostate), pharynx, CNS (*e.g.*, brain, neural or glial cells), head and neck, skin (*e.g.*, melanoma), a nasopharyngeal cancer, *e.g.*, differentiated or undifferentiated metastatic or locally recurrent nasopharyngeal carcinoma), and pancreas, as well as adenocarcinomas which include malignancies such as colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell lung cancer, cancer of the small intestine and cancer of the esophagus. The cancer may be at an early, intermediate, late stage or metastatic cancer.

In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, or a NSCLC adenocarcinoma)), a melanoma (*e.g.*, an advanced melanoma), a renal cancer (*e.g.*, a renal cell carcinoma), a liver cancer, a myeloma (*e.g.*, a multiple myeloma), a prostate cancer, a breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer), a colorectal cancer, a pancreatic cancer, a head and neck cancer (*e.g.*, head and neck squamous cell carcinoma (HNSCC), anal cancer, gastro-esophageal cancer, thyroid cancer, cervical cancer, a lymphoproliferative disease (*e.g.*, a post-transplant lymphoproliferative disease) or a hematological cancer, T-cell lymphoma, B-cell lymphoma, a non-Hogdkin lymphoma, or a leukemia (*e.g.*, a myeloid leukemia or a lymphoid leukemia).

In another embodiment, the cancer is chosen form a carcinoma (*e.g.*, advanced or metastatic carcinoma), melanoma or a lung carcinoma, *e.g.*, a non-small cell lung carcinoma.

In one embodiment, the cancer is a lymphoma, *e.g.*, diffuse large B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin's lymphoma.

In one embodiment, the cancer is a breast cancer, *e.g.*, metastic breast cancer.

In one embodiment, the cancer is leukemia, *e.g.*, chronic myelogenous leukemia.

In one embodiment, the cancer is a head and neck cancer, *e.g.*, head and neck squamous cell carcinoma (HNSCC).

In one embodiment, the cancer is myelodysplastic syndrome.

In one embodiment, the cancer is a bladder cancer (*e.g.*, transitional cell carcinoma).

In one embodiment, the cancer is a colon cancer.

In one embodiment, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC), *e.g.*, stage IV or recurrent NSCLC, a NSCLC adenocarcinoma, or a NSCLC squamous cell carcinoma or small cell lung cancer.

In one embodiment, the cancer is skin cancer, *e.g.*, melanoma (*e.g.*, stage III or IV melanoma) or Merkel cell carcinoma. In one embodiment, the cancer is a melanoma, *e.g.*, an advanced melanoma. In one embodiment, the cancer is an advanced or unresectable melanoma that does not respond to other therapies. In other embodiments, the cancer is a melanoma with a BRAF mutation (*e.g.*, a BRAF V600 mutation). In yet other embodiments, the anti-PD-L1

antibody molecule is administered after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

In another embodiment, the cancer is a hepatocarcinoma, *e.g.*, an advanced hepatocarcinoma, with or without a viral infection, *e.g.*, a chronic viral hepatitis.

In another embodiment, the cancer is a prostate cancer, *e.g.*, an advanced prostate cancer.

In yet another embodiment, the cancer is a myeloma, *e.g.*, multiple myeloma.

In yet another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic RCC or clear cell renal cell carcinoma (CCRCC), *e.g.,* advanced or metastatic clear-cell renal cell carcinoma).

In one embodiment, the cancer microenvironment has an elevated level of PD-L1 expression. Alternatively, or in combination, the cancer microenvironment can have increased IFNγ and/or CD8 expression. In one embodiment, alternatively or in combination, the subjet has elevated level of Bim expression (*e.g.,* in PD-1+CD8+ T cells compared to PD-1-CD8+ T cells).

In some embodiments, the subject has, or is identified as having, a tumor that has one or more of high PD-L1 level or expression, or as being Tumor Infiltrating Lymphocyte (TIL)+ (*e.g.*, as having an increased number of TILs), or both. In certain embodiments, the subject has, or is identified as having, a tumor that has high PD-L1 level or expression and that is TIL+. In some embodiments, the methods described herein further include identifying a subject based on having a tumor that has one or more of high PD-L1 level or expression, or as being TIL+, or both. In certain embodiments, the methods described herein further include identifying a subject based on having a tumor that has high PD-L1 level or expression and as being TIL+. In some embodiments, tumors that are TIL+ are positive for CD8 and IFNγ. In some embodiments, the subject has, or is identified as having, a high percentage of cells that are positive for one, two or more of PD-L1, CD8, and/or IFNγ. In certain embodiments, the subject has or is identified as having a high percentage of cells that are positive for all of PD-L1, CD8, and IFNγ. The subject can be identified prior to, during, or after receiving a therapy, *e.g.*, an anti-PD-L1 antibody molecule therapy and/or another therapy as described herein. In one embodiment, the subject is identified prior to receiving a therapy, *e.g.*, a therapy as described herein (*e.g.*, prior to the onset of a therapy or between treatment intervals).

In some embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for one, two or more of PD-L1, CD8,

and/or IFNγ. In certain embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for all of PD-L1, CD8, and IFNγ. In some embodiments, the subject has, or is identified as having, one, two or more of PD-L1, CD8, and/or IFNγ, and one or more of a lung cancer, *e.g.,* squamous cell lung cancer or lung adenocarcinoma; a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; an esophageal cancer; a thyroid cancer; a melanoma, and/or a nasopharyngeal cancer (NPC). In certain embodiments, the methods described herein further describe identifying a subject based on having one, two or more of PD-L1, CD8, and/or IFNγ, and one or more of a lung cancer, *e.g.,* squamous cell lung cancer or lung adenocarcinoma; a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; a thyroid cancer; a melanoma, and or a nasopharyngeal cancer. The subject can be identified prior to, during, or after receiving a therapy, *e.g.*, an anti-PD-L1 antibody molecule therapy and/or another therapy as described herein. In one embodiment, the subject is identified prior to receiving a therapy, *e.g.*, a therapy as described herein (*e.g.*, prior to the onset of a therapy or between treatment intervals).

Methods and compositions disclosed herein are useful for treating metastatic lesions associated with the aforementioned cancers.

In a further aspect, the invention provides a method of treating an infectious disease in a subject, comprising administering to a subject a therapeutically effective amount of an anti-PD-L1 antibody molecule described herein, alone or in combination with one or more agents or procedures. In one embodiment, the infection disease is chosen from hepatitis (*e.g.*, hepatis C infection), or sepsis.

Still further, the invention provides a method of enhancing an immune response to an antigen in a subject, comprising administering to the subject: (i) the antigen; and (ii) an anti-PD-L1 antibody molecule, such that an immune response to the antigen in the subject is enhanced. The antigen can be, for example, a tumor antigen, a viral antigen, a bacterial antigen or an antigen from a pathogen.

The anti-PD-L1 antibody molecule can be administered to the subject systemically (*e.g.*, orally, parenterally, subcutaneously, intravenously, rectally, intramuscularly, intraperitoneally,

intranasally, transdermally, or by inhalation or intracavitary installation), topically, or by application to mucous membranes, such as the nose, throat and bronchial tubes.

Dosages and therapeutic regimens of the anti-PD-L1 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-PD-L1 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. The dosing schedule can vary from *e.g.*, once a week to once every 2, 3, or 4 weeks. In one embodiment, the anti-PD-L1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week. In one embodiment, the anti-PD-L1 antibody molecule is administered, alone or in combination (*e.g.*, in combination with an anti-LAG-3 antibody molecule), at a dose of less than, or about, 5 mg/kg; less than, or about, 4 mg/kg; less than, or about, 3 mg/kg; less than, or about, 2 mg/kg; less than, or about, 1 mg/kg, every other week. In one embodiment, the anti-PD-L1 antibody molecule is administered at a dose of 1 to 5 mg/kg every other week; 1 to 4 mg/kg every other week, 1 to 3 mg/kg every other week, or 1 to 2 mg/kg every other week. In one embodiment, the anti-LAG-3 antibody molecule is administered, alone or in combination (*e.g.*, in combination with an anti-PD-L1 antibody molecule) at a dose of 1 to 5 mg/kg every other week; 1 to 4 mg/kg every other week, 1 to 3 mg/kg every other week, or 1 to 2 mg/kg every other week.

The antibody molecules described herein can be used in the methods described herein, although other anti-PD-L1 antibodies can be used instead, or in combination with an anti-PD-L1 antibody molecule of the invention.

Combination therapies

The methods and compositions described herein can be used in combination with other agents or therapeutic modalities. In one embodiment, the methods described herein include administering to the subject an anti-PD-L1 antibody molecule as described herein, in combination with an agent or therapeutic procedure or modality, in an amount effective to treat or prevent a disorder. The anti-PD-L1 antibody molecule and the agent or therapeutic procedure or modality can be administered simultaneously or sequentially in any order. Any combination and sequence of the anti-PD-L1 antibody molecules and other therapeutic agents, procedures or modalities (*e.g.*, as described herein) can be used. The antibody molecule and/or other

therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The antibody molecule can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

In certain embodiments, the methods and compositions described herein are administered in combination with one or more of other antibody molecules, chemotherapy, other anti-cancer therapy (*e.g.*, targeted anti-cancer therapies, gene therapy, viral therapy, RNA therapy bone marrow transplantation, nanotherapy, or oncolytic drugs), cytotoxic agents, immune-based therapies (*e.g.*, cytokines or cell-based immune therapies), surgical procedures (*e.g.*, lumpectomy or mastectomy) or radiation procedures, or a combination of any of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy. In some embodiments, the additional therapy is an enzymatic inhibitor (*e.g.*, a small molecule enzymatic inhibitor) or a metastatic inhibitor. Exemplary cytotoxic agents that can be administered in combination with include antimicrotubule agents, topoisomerase inhibitors, anti-metabolites, mitotic inhibitors, alkylating agents, anthracyclines, vinca alkaloids, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis, proteosome inhibitors, and radiation (*e.g.*, local or whole body irradiation (*e.g.*, gamma irradiation). In other embodiments, the additional therapy is surgery or radiation, or a combination thereof. In other embodiments, the additional therapy is a therapy targeting one or more of PI3K/AKT/mTOR pathway, an HSP90 inhibitor, or a tubulin inhibitor.

Alternatively, or in combination with the aforesaid combinations, the methods and compositions described herein can be administered in combination with one or more of: an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule, *e.g.,* an immune checkpoint molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy.

Exemplary non-limiting combinations and uses of the anti-PD-L1 antibody molecules include the following.

In certain embodiments, the anti-PD-L1 antibody molecule is administered in combination with a modulator of a costimulatory molecule or an inhibitory molecule, *e.g.*, a co-inhibitory ligand or receptor.

In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with a modulator, *e.g.*, agonist, of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with an inhibitor of an inhibitory (or immune checkpoint) molecule chosen from PD-1, PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. Inhibition of an inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule. In one embodiment, the inhibitor is a soluble ligand (*e.g.*, a CTLA-4-Ig), or an antibody or antibody fragment that binds to PD-1, PD-L2 or CTLA-4. For example, the anti-PD-L1 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, *e.g.*, ipilimumab, for example, to treat a cancer (*e.g.*, a cancer chosen from: a melanoma, *e.g.*, a metastatic melanoma; a lung cancer, *e.g.*, a non-small cell lung carcinoma; or a prostate cancer). In one embodiment, the anti-PD-1 antibody molecule is administered after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody or antigen-binding fragment thereof.

In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof.

In yet other embodiments, the anti-PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody and an anti-TIM-3 antibody (or antigen-binding fragments thereof).

In another embodiment, the anti-PD-L1 antibody is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), *e.g.*, an anti-

CEACAM antibody molecule. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti-CEACAM-1 antibody molecule. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a CEACAM-5 inhibitor, *e.g.*, an anti-CEACAM-5 antibody molecule.

The combination of antibodies recited herein can be administered separately, *e.g.*, as separate antibodies or antigen-binding fragments thereof, or linked, *e.g.*, as a bispecific or trispecific antibody molecule. In one embodiment, a bispecific antibody that includes an anti-PD-L1 antibody molecule and an anti-TIM-3, anti-CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), or anti-LAG-3 antibody, or an antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor or a hematologic malignancy).

In some embodiments, the antibody molecule (*e.g.*, mono-, bi- or trispecific antibody) for TIM-3, LAG-3 and/or PD-1 used in any of the methods and compositions disclosed herein includes an amino acid sequence, or is encoded by a nucleotide sequence as described herein (*e.g.*, as disclosed in the section entitled "Inhibitors of Immune Checkpoint Molecules" starting on page 218 hereinbelow (including all publications mentioned therein).

In other embodiments, the anti-PD-L1 antibody molecule is administered in combination with a cytokine. The cytokine can be administered as a fusion to the anti-PD-L1 antibody molecule, or as separate compositions. In one embodiment, the anti-PD-L1 antibody is administered in combination with one, two, three or more cytokines, *e.g.*, as a fusion molecule or as separate compositions. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-15 or IL-21. In certain embodiments, the combination of anti-PD-L1 antibody molecule and the cytokine described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor).

In certain embodiments, the anti-PD-L1 antibody molecule is administered in combination with an antibody specific against an HLA C, *e.g.*, an antibody specific to Killer-cell Immunoglobulin-like Receptors (also referred to herein as an "anti-KIR antibody"). In certain embodiments, the combination of anti-PD-L1 antibody molecule and anti-KIR antibody is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor, *e.g.*, an advanced solid tumor).

In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with a cellular immunotherapy (*e.g.*, Provenge® (*e.g.*, Sipuleucel-T)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination of anti-PD-L1 antibody molecule, Provenge® and/or cyclophosphamide is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a prostate cancer, *e.g.*, an advanced prostate cancer).

In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a vaccine, *e.g.*, a cancer vaccine, (*e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine). In one embodiment, the vaccine is peptide-based, DNA-based, RNA-based, or antigen-based, or a combination thereof. In embodiments, the vaccine comprises one or more peptides, nucleic acids (*e.g.,* DNA or RNA), antigens, or a combination thereof. In certain embodiments, the combination of anti-PD-L1 antibody molecule and the DC-RCC vaccine is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a renal carcinoma, *e.g.*, metastatic renal cell carcinoma (RCC) or clear cell renal cell carcinoma (CCRCC)).

In another embodiment, the anti-PD-1 antibody molecule is administered in combination with an adjuvant.

In yet another embodiment, the anti-PD-L1 antibody molecule is administered in combination with chemotherapy, and/or immunotherapy. For example, the anti-PD-L1 antibody molecule can be used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), an anti-TIM-3 antibody, tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells. In one embodiment, the anti-PD-L1 antibody molecule is used in combination with an anti-TIM-3 antibody to treat a myeloma, *e.g.*, a multiple myeloma.

In one embodiment, the anti-PD-L1 antibody molecule is used in combination with chemotherapy to treat a lung cancer, *e.g.*, non-small cell lung cancer. In one embodiment, the anti-PD-L1 antibody molecule is used with standard lung, *e.g.*, NSCLC, chemotherapy, *e.g.*, platinum doublet therapy, to treat lung cancer. In yet other embodiments, the anti-PD-L1 antibody molecule is used in combination with an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor (*e.g.*, (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine (also known as INCB24360), indoximod (1-methyl-D-tryptophan), α -cyclohexyl-5H-

Imidazo[5,1-a]isoindole-5-ethanol (also known as NLG919), etc.)) in a subject with advanced or metastatic cancer (*e.g.,* a patient with metastic and recurrent NSCL cancer).

In yet other embodiments, the anti-PD-L1 antibody molecule is used in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeting agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib; an RNAi inhibitor; or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus. Any of such combinations can be used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) (*e.g.,* clear cell renal cell carcinoma (CCRCC)) or metastatic RCC.

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used in combination with a MEK inhibitor (*e.g.*, a MEK inhibitor as described herein). In some embodiments, the combination of the anti-PD-L1 antibody and the MEK inhibitor is used to treat a cancer (*e.g.,* a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. In certain embodiments, the cancer includes a BRAF mutation (*e.g.*, a BRAF V600E mutation), a BRAF wildtype, a KRAS wildtype or an activating KRAS mutation. The cancer may be at an early, intermediate or late stage.

In another embodiment, the anti-PD-L1 antibody molecule is used in combination with one, two or all of oxaliplatin, leucovorin or 5-FU (*e.g.*, a FOLFOX co-treatment). Alternatively or in combination, combination further includes a VEGF inhibitor (*e.g.*, a VEGF inhibitor as disclosed herein). In some embodiments, the combination of the anti-PD-L1 antibody, the FOLFOX co-treatment, and the VEGF inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. The cancer may be at an early, intermediate or late stage.

In other embodiments, the anti-PD-L1 antibody molecule is administered with a tyrosine kinase inhibitor (*e.g.*, axitinib) to treat renal cell carcinoma and other solid tumors.

In other embodiments, the anti-PD-L1 antibody molecule is administered with a 4-1BB receptor targeting agent (*e.g.*, an antibody that stimulates signaling through 4-1BB (CD-137), *e.g.*, PF-2566). In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with a tyrosine kinase inhibitor (*e.g.*, axitinib) and a 4-1BB receptor targeting agent.

The anti-PD-L1 antibody molecule can be bound to a substance, *e.g.*, a cytotoxic agent or moiety (*e.g.*, a therapeutic drug; a compound emitting radiation; molecules of plant, fungal, or bacterial origin; or a biological protein (*e.g.*, a protein toxin) or particle (*e.g.*, a recombinant viral particle, *e.g.*, via a viral coat protein). For example, the antibody can be coupled to a radioactive isotope such as an α-, β-, or γ-emitter, or a β-and γ-emitter.

Any combination and sequence of the anti-PD-L1 antibody molecules and other therapeutic agents, procedures or modalities (*e.g.*, as described herein) can be used. The antibody molecule and/or other therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The antibody molecule can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

Additional Combination Therapies

The methods and compositions described herein (*e.g.*, PD-L1 antibodies and methods of using them) can be used in combination with other agents or therapeutic modalities, *e.g.*, a second therapeutic agent chosen from one or more of the agents listed in Table 6. In one embodiment, the methods described herein include administering to the subject an anti-PD-L1 antibody molecule as described herein (optionally in combination with one or more inhibitors of PD-1, LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5), or CTLA-4)), further include administration of a second therapeutic agent chosen from one or more of the agents listed in Table 6, in an amount effective to treat or prevent a disorder, *e.g.*, a disorder as described herein, *e.g.*, a cancer. When administered in combination, the anti-PD-L1 antibody molecule, the additional agent (*e.g.*, second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, *e.g.*, as a monotherapy. In certain embodiments, the administered amount or dosage of the anti-PD-L1 antibody, the additional agent (*e.g.*, second or third agent), or all, is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage

of each agent used individually, *e.g.*, as a monotherapy. In other embodiments, the amount or dosage of the anti-PD-L1 antibody, the additional agent (*e.g.*, second or third agent), or all, that results in a desired effect (*e.g.*, treatment of cancer) is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50% lower).

In other embodiments, the second therapeutic agent is chosen from one or more of the agents listed in Table 6 In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, or a NSCLC adenocarcinoma), or disclosed in a publication listed in Table 6. In some embodiments, the second therapeutic agent is chosen from one or more of: 1) a protein kinase C (PKC) inhibitor; 2) a heat shock protein 90 (HSP90) inhibitor; 3) an inhibitor of a phosphoinositide 3-kinase (PI3K) and/or target of rapamycin (mTOR); 4) an inhibitor of cytochrome P450 (*e.g.*, a CYP17 inhibitor or a 17alpha-Hydroxylase/C17-20 Lyase inhibitor); 5) an iron chelating agent; 6) an aromatase inhibitor; 7) an inhibitor of p53, *e.g.*, an inhibitor of a p53/Mdm2 interaction; 8) an apoptosis inducer; 9) an angiogenesis inhibitor; 10) an aldosterone synthase inhibitor; 11) a smoothened (SMO) receptor inhibitor; 12) a prolactin receptor (PRLR) inhibitor; 13) a Wnt signaling inhibitor; 14) a CDK4/6 inhibitor; 15) a fibroblast growth factor receptor 2 (FGFR2)/fibroblast growth factor receptor 4 (FGFR4) inhibitor; 16) an inhibitor of macrophage colony-stimulating factor (M-CSF); 17) an inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC; 18) an inhibitor of one or more of VEGFR-2 (*e.g.*, FLK-1/KDR), PDGFRbeta, c-KIT or Raf kinase C; 19) a somatostatin agonist and/or a growth hormone release inhibitor; 20) an anaplastic lymphoma kinase (ALK) inhibitor; 21) an insulin-like growth factor 1 receptor (IGF-1R) inhibitor; 22) a P-Glycoprotein 1 inhibitor; 23) a vascular endothelial growth factor receptor (VEGFR) inhibitor; 24) a BCR-ABL kinase inhibitor; 25) an FGFR inhibitor; 26) an inhibitor of CYP11B2; 27) a HDM2 inhibitor, *e.g.*, an inhibitor of the HDM2-p53 interaction; 28) an inhibitor of a tyrosine kinase; 29) an inhibitor of c-MET; 30) an inhibitor of JAK; 31) an inhibitor of DAC; 32) an inhibitor of 11β-hydroxylase; 33) an inhibitor of IAP; 34) an inhibitor of PIM kinase; 35) an inhibitor of Porcupine; 36) an inhibitor of BRAF, *e.g.*, BRAF V600E or wild-type BRAF; 37) an inhibitor of HER3; 38) an inhibitor of MEK; or 39) an inhibitor of a lipid kinase, *e.g.*, as described herein and in Table 6.

In one embodiment, the second therapeutic agent is chosen from one or more of: Compound A8, Compound A17, Compound A23, Compound A24, Compound A27, Compound A29, Compound A33, and Compound A13.

In other embodiments, the second therapeutic agent is chosen from one or more of: Compound A5, Compound A8, Compound A17, Compound A23, Compound A24, Compound A29, and Compound A40.

In other embodiments, the second therapeutic agent is chosen from one or more of: Compound A9, Compound A16, Compound A17, Compound A21, Compound A22, Compound A25, Compound A28, Compound A48, and Compound 49.

In some embodiments, the second therapeutic agent is administered at a therapeutic or lower-than therapeutic dose. In certain embodiments, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the second therapeutic agent is administered in combination with the anti-PD-L1 antibody molecule than when the second therapeutic agent is administered individually. In certain embodiments, the concentration of the anti-PD-L1 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the anti-PD-L1 antibody molecule is administered in combination with the second therapeutic agent than when the anti-PD-L1 antibody molecule is administered individually. In certain embodiments, in a combination therapy, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the second therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower. In certain embodiments, in a combination therapy, the concentration of the anti-PD-L1 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the anti-PD-L1 antibody molecule as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower.

Additional features and embodiments

Alternatively, or in combination with, the methods disclosed herein, the invention features a method of treating (*e.g.*, inhibiting, reducing, ameliorating, or preventing) a disorder, *e.g.*, a hyperproliferative condition or disorder (*e.g.*, a cancer) in a subject. The method includes administering to the subject a combination of two, three or more therapeutic agents chosen from

one, two or all of the following categories (i)-(iii): (i) an agent that enhances antigen (*e.g.*, tumor antigen) presentation; (ii) an agent that enhances an effector cell response (*e.g.*, B cell and/or T cell activation and/or mobilization); or (iii) an agent that decreases tumor immunosuppression, thereby treating the disorder, *e.g.*, the hyperproliferative condition or disorder (*e.g.*, the cancer). In some embodiments, the combination includes a PD-L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein). The cancer treated can be, *e.g.*, a cancer described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, nasopharyngeal cancer, or breast cancer.

In another aspect, the invention features a method of reducing an activity (*e.*g., growth, survival, or viability, or all), of a hyperproliferative (*e.g.*, a cancer) cell. The method includes contacting the cell with a combination of two, three or more therapeutic agents chosen from one, two or all of the following categories (i)-(iii): (i) an agent that enhances antigen (*e.g.*, tumor antigen) presentation; (ii) an agent that enhances an effector cell response (*e.g.*, B cell and/or T cell activation and/or mobilization); or (iii) an agent that decreases tumor immunosuppression, thereby reducing an activity in the hyperproliferative cell. In some embodiments, the combination includes a PD- L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein). The method can be performed in a subject, *e.g.*, as part of a therapeutic protocol. The cancer cell can be, *e.g.*, a cell from a cancer described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, nasopharyngeal cancer, or breast cancer.

In certain embodiments of the methods disclosed herein, the method further includes determining the level and/or distribution of an immune cell (*e.g.*, a T cell) infiltrate (*e.g.*, the level and/or distribution of tumor infiltrating lymphocytes (TIL)) in the subject. In one embodiment, the level and/or distribution of the immune cell infiltrate is determined *in vivo*, *e.g.*, non-invasively (*e.*g., by detecting an antibody to a T cell marker detectably labeled using a suitable imaging technique, *e.g.*, positron emission tomography (PET) scan). In other embodiments, the level of the immune cell infiltrate is determined in a sample (*e.g.*, a tumor biopsy) acquired from the subject (*e.g.*, using immunohistochemical techniques). In some embodiments, an elevated level and/or more widespread distribution of the TIL in a cancer, *e.g.*, a tumor, (*e.g.*, relative to a reference or a control) is indicative of a better prognosis for the subject, *e.g.*, more positive therapeutic outcome. In some embodiments, a decreased level and/or

less widespread distribution of the TIL in a cancer, *e.g.*, a tumor, (*e.g.*, relative to a reference or a control) is indicative of a worse prognosis for the subject, *e.g.*, more negative therapeutic outcome. In some embodiments, the reference is a subject at a different time interval, *e.g.*, prior to, or an earlier stage in therapy). In embodiments, responsive to a low level of, or no detectable, tumor infiltrate in the subject, one or more agents of categories (i) or (ii), or both (i) and (ii), is/are administered. In other embodiments, responsive to a detectable level, or an elevated level, of tumor infiltrate in the subject, one or more agents of category (iii) is/are administered. The detection steps can also be used, *e.g.*, to monitor the effectiveness of a therapeutic agent described herein. For example, the detection step can be used to monitor the effectiveness of therapeutic agents of categories (i), (ii) and/or (iii).

In another aspect, the invention features a composition (*e.g.*, one or more compositions or dosage forms), that includes a combination of two, three or more therapeutic agents chosen from one, two or all of the following categories (i)-(iii): (i) an agent that enhances antigen (*e.g.*, tumor antigen) presentation; (ii) an agent that enhances an effector cell response (*e.g.*, activation and/or mobilization of B cell and/or T cell); or (iii) an agent that decreases tumor immunosuppression. In some embodiments, the combination includes a PD-L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein).

In yet another aspect, the invention features a composition (*e.g.*, one or more compositions or dosage forms as described hereom), for use in treating a disorder, *e.g.*, a cancer. In embodiments, the composition for use includes a combination of two, three or more therapeutic agents chosen from one, two or all of the following categories (i)-(iii): (i) an agent that enhances antigen (*e.g.,* tumor antigen) presentation; (ii) an agent that enhances an effector cell response (*e.g.,* activation and/or mobilization of B cell and/or T cell); or (iii) an agent that decreases tumor immunosuppression. In some embodiments, the combination used includes a PD-L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein). The cancer can be, *e.g.*, a cancer described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, nasopharyngeal cancer, or breast cancer.

Formulations, *e.g.*, dosage formulations, and kits, *e.g.*, therapeutic kits, that include a combination of two, three or more therapeutic agents chosen from one, two or all of the following categories (i)-(iii): (i) an agent that enhances antigen (*e.g.,* tumor antigen)

presentation; (ii) an agent that enhances an effector cell response (*e.g.,* activation and/or mobilization of B cell and/or T cell); or (iii) an agent that decreases tumor immunosuppression, thereby reducing an activity in the cell, and (optionally) instructions for use, are also disclosed. In some embodiments, the combination includes a PD-L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein).

The combinations of therapeutic agents disclosed herein include two or more therapeutic agents described herein. The therapeutic agents in the combination can belong to the same category, *e.g.*, two or more therapeutic agents of category (i), or can include at least one agent of two or more categories (*e.g.*, a therapeutic agent of category (i) combined with a therapeutic agent of category (ii)), as described below. Certain therapeutic agents can belong to two or more categories of categories (i)-(iii). For example, a therapeutic agent (*e.g.*, a GITR agonist, an IDO antagonist, a TGF-b inhibitor, among others) can act as a therapeutic agent in multiple categories.

In certain embodiments, the combination disclosed herein includes one, two, three, four or more therapeutic agents that enhance antigen (*e.g.*, tumor antigen) presentation (referred to herein as an "antigen-presentation combination"). In certain embodiments, the antigen presentation combination includes one or more of: an agent that enhances antigen presentation (*e.g.*, a vaccine, *e.g.*, a cell- or antigen-based vaccine); an agent that enhances lysis of tumor cells (*e.g.*, an oncolytic virus); an agent that stimulates (*e.g.*, disinhibits) a phagocyte, *e.g.*, a Type I interferon (IFN) activator (*e.g.*, a TLR agonist, a RIG-I-like receptor agonist (RLRs)), and/or an agent that activates and/or recruits a dendritic cell or a macrophage (*e.g.*, a macrophage I), *e.g.*, a bi- or tri-specific cell engager.

In some embodiments, the antigen-presentation combination includes one, two, three, four, five or more therapeutic agents chosen from: (i) an agonist of Stimulator of Interferon Genes (a STING agonist), (ii) an agonist of a Toll-like receptor (TLR) (*e.g.*, an agonist of TLR-3, -4, -5, -7, -8, or -9), (iii) a TIM-3 modulator (*e.g.*, an anti-TIM-3 antibody molecule), (iv) a vascular endothelial growth factor receptor (VEGFR) inhibitor, (v) a c-Met inhibitor, (vi) a TGFb inhibitor (*e.g.*, an anti-TGFb antibody), (vii) an IDO/TDO inhibitor, (viii) an A2AR antagonist, (ix) an oncolytic virus, (x) a vaccine (*e.g.*, a scaffold vaccine), or (xi) a bi- or tri-specific cell engager. Any combination of the aforesaid agents (i)-(xi) can be used in the antigen-presentation combination. In one exemplary embodiment, the antigen-presentation

combination includes a STING agonist. In another exemplary embodiment, the antigen-presentation combination includes a TLR agonist (*e.g.*, a TLR7 agonist). In another exemplary embodiment, the antigen-presentation combination includes a STING agonist and a TLR agonist (*e.g.*, a TLR7 agonist). In some embodiments, the antigen presentation combination is chosen from a STING agonist, a TLR agonist, an A2AR antagonist, or an oncolytic virus or a combination thereof, and optionally, one or more of (iii)-(vii) or (x)-(xi). In some embodiments, the antigen presentation combination is chosen from a STING agonist or a TLR agonist, or a combination of both, and optionally, one or more of (iii)-(xi). In another embodiment, the antigen-presentation combination includes a STING agonist, a TLR agonist (*e.g.*, a TLR7 agonist) and a TIM-3 modulator (*e.g.*, an anti-TIM-3 inhibitor). In another embodiment, the antigen-presentation combination includes a STING agonist, a TLR agonist (*e.g.*, a TLR7 agonist) and a VEGFR inhibitor. In another embodiment, the antigen-presentation combination includes a STING agonist, a TLR agonist (*e.g.*, a TLR7 agonist) and a c-MET inhibitor. In yet other embodiments, the antigen-presenting combination includes an oncolytic virus. In other embodiments, the antigen-presenting combination includes an oncolytic virus and a cytokine, *e.g.,* an oncolytic virus expressing one or more of GM-CSF, or a CSF (*e.g.,* CSF1, or CSF2). In some embodiments, the antigen-presenting combination includes a bi- or tri-specific cell engager, *e.g.*, a bi- or tri-specific antibody molecule to CD47 and CD19, with or without an Fc domain. In some embodiments, the antigen-presenting combination includes a TGFb inhibitor (*e.g.*, an anti-TGFb antibody). In other embodiments, the antigen-presenting combination includes an IDO/TDO inhibitor. In yet other embodiments, the antigen-presenting combination includes an A2AR antagonist. In yet other embodiments, the antigen-presenting combination includes a vaccine (*e.g.*, IL-2 in combination with MUC1, or a dendritic cell based vaccine (*e.g.*, Provenge®)). In yet other embodiments, the antigen-presenting combination includes a vaccine and a TLR agonist (*e.g.*, a TLR agonist as described herein). In certain embodiment, the antigen-presentation combination includes a vaccine and a STING agonist. In certain embodiment, the antigen-presentation combination includes a vaccine, a STING agonist and a TLR agonist.

In certain embodiments, the combination includes one, two, three, four, five or more therapeutic agents that enhance an effector cell response (referred to herein as an "effector cell combination"). In some embodiments, the effector cell combination includes a lymphocyte activator, *e.g.*, an NK cell activator and/or a T cell activator. In some embodiments, the effector

cell combination activates (*e.g.*, disinhibits) a tumor infiltrating lymphocyte (TIL), *e.g.*, an NK cell or a T cell. In some embodiments, the effector cell combination includes an NK cell modulator chosen from a modulator (*e.g.*, an antibody molecule) of an NK receptor (*e.g.*, a modulator of one or more of NKG2A, KIR3DL, NKp46, MICA or CEACAM1); an interleukin or an interleukin variant (*e.g.*, IL-2, IL-15, IL-21, IL-13R or IL-12 cytokine or variant thereof, or a combination thereof); a bi- or tri-specific cell engager (*e.g.*, a bispecific antibody molecule of NKG2A and CD138, or a bispecific antibody molecule of CD3 and TCR); an NK cell therapy; or a vaccine that includes NK cells and an antigen/immune stimulant. In some embodiments, the effector cell combination includes an immunomodulator (*e.g.*, one or more of: an activator of a costimulatory molecule or an inhibitor of an immune checkpoint molecule as described herein). In some embodiments, the effector cell combination includes a T cell modulator chosen from an inhibitor of a checkpoint inhibitor (*e.g.*, an inhibitor of one or more of: PD-1, PD-L1, TIM-3, LAG-3, VISTA, DKG-α, B7-H3, B7-H4, TIGIT, CTLA-4, BTLA, CD160, TIM1, IDO, LAIR1, IL-12, or a combination thereof, *e.g.*, an inhibitor of PD-1 and TIM-3, or an inhibitor of PD-1 and LAG-3). In one embodiment, the inhibitor of the checkpoint inhibitor is an antibody molecule (*e.g.*, a mono- or bispecific antibody or fragment thereof as described herein). For example, the inhibitor of the checkpoint inhibitor is an antibody molecule against PD-1, PD-L1, TIM-3, LAG-3, VISTA, B7-H4, CTLA-4 or TIGIT, or any combination thereof (*e.g.* a combination as described herein). In some embodiments, the effector cell combination includes a T cell modulator chosen from an agonist or an activator of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of GITR, OX40, ICOS, SLAM (*e.g.*, SLAMF7), HVEM, LIGHT, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), CD30, CD40, BAFFR, CD7, NKG2C, NKp80, CD160, B7-H3, or CD83 ligand. In other embodiments, the effector cell combination includes a bispecific T cell engager (*e.g.*, a bispecific antibody molecule that binds to CD3 and a tumor antigen (*e.g.*, EGFR, PSCA, PSMA, EpCAM, HER2 among others).

In some embodiments, the effector cell combination includes one, two, three, four, five or more therapeutic agents chosen from: (i) a GITR modulator (*e.g.*, a GITR agonist), (ii) a PD-L1 inhibitor *(e.g.*, an anti-PD-L1 antibody molecule as described herein), (iii) a PD-1 inhibitor, (iv)

an inhibitor of IAP (Inhibitor of Apoptosis Protein), (v) an inhibitor of EGFR (Epidermal Growth Factor Receptor), (vi) an inhibitor of target of rapamycin (mTOR), (vii) IL-15 or a variant thereof, (viii) a CTLA-4 inhibitor, (ix) a bispecific T cell engager (*e.g.*, a bispecific antibody molecule that binds to CD3 and a tumor antigen (*e.g.*, EGFR, PSCA, PSMA, EpCAM, HER2 among others), (x) a CD40 agonist (*e.g.*, an anti-CD40 antibody molecule), (xi) an OX40 agonist (*e.g.*, an anti-OX40 antibody molecule), or (xii) a CD27 agonist (*e.g.*, an anti-CD27 antibody molecule). Any combination of the aforesaid agents can be used in the effector cell combination. In one exemplary embodiment, the effector cell combination includes a GITR agonist. In another embodiment, the effector cell combination includes a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein). In another embodiment, the effector cell combination includes a PD-1 inhibitor. In other embodiments, the effector cell combination includes a GITR agonist and a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein). In other embodiments, the effector cell combination includes a GITR agonist and a PD-1 inhibitor. In other embodiments, the effector cell combination includes a GITR agonist, a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein), and a PD-1 inhibitor. In other embodiments, the effector cell combination includes a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein), and a PD-1 inhibitor. In one embodiment, the effector cell combination includes a GITR agonist and an inhibitor of IAP. In another embodiment, the effector cell combination includes a GITR agonist and an inhibitor of an EGFR inhibitor. In yet another embodiment, the effector cell combination includes a GITR agonist and an inhibitor of an mTOR inhibitor. In one embodiment, the effector cell combination includes IL-15 or a variant thereof. In one embodiment, the effector cell combination includes a CTLA-4 inhibitor. In one embodiment, the effector cell combination includes a bispecific T cell engager (*e.g.*, a bispecific antibody molecule that binds to CD3 and a tumor antigen (*e.g.*, EGFR, PSCA, PSMA, EpCAM, HER2 among others). In one embodiment, the effector cell combination includes a CD40 agonist (*e.g.*, an anti-CD40 antibody molecule). In one embodiment, the effector cell combination includes an OX40 agonist (*e.g.*, an anti-OX40 antibody molecule). In one embodiment, the effector cell combination includes a CD27 agonist (*e.g.*, an anti-CD27 antibody molecule).

In certain embodiments, the combination includes one, two, three, four, five or more therapeutic agents that decrease tumor immunosuppression (referred to herein as an "anti-tumor

immunosuppression combination"). In some embodiments, the combination modulates the activity or level of one or more of T_{reg}, macrophage 2 or MDSCs. In some embodiments, the combination increases one or more of M2 polarization, T_{reg} depletion, or T cell recruitment. In some embodiments, the anti-tumor immunosuppression combination includes one, two, three, four, five or more therapeutic agents chosen from: (i) an immunomodulator (*e.g.*, one or more of: an activator of a costimulatory molecule (*e.g.*, a GITR agonist), or an inhibitor of an immune checkpoint molecule (*e.g.*, one or more of PD-L1, PD-1, LAG-3, TIM-3 or CTLA-4), as described herein), (ii) a CSF-1/1R inhibitor (*e.g.*, an inhibitor of macrophage colony-stimulating factor (M-CSF)), (iii) an IL-17 inhibitor, (iv) an IL-1beta inhibitor, (v) a CXCR2 inhibitor, (vi) an inhibitor of a phosphoinositide 3-kinase (PI3K, *e.g.*, PI3Kdelta or PI3Kgamma), (vii) a BAFF-R inhibitor, (viii) a MALT-1/BTK inhibitor, (ix) a JAK inhibitor, (x) a CRTH2 inhibitor, (xi) a VEGFR inhibitor, (xiii) an IL-15 or a variant thereof, (xiv) a CTLA-4 inhibitor, (xv) an IDO/TDO inhibitor, (xvi) an A2AR antagonist, (xvii) a TGFb inhibitor, or (xviii) a PFKFB3 inhibitor. In certain embodiments, the immunomodulator is an inhibitor of an immune checkpoint molecule (*e.g.*, an inhibitor of PD-L1, PD-1, LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or CTLA-4, or any combination thereof). Any combination of the aforesaid agents can be used in the tumor immunosuppression combination. In one exemplary embodiment, the anti-tumor immunosuppression combination includes one, two, three, four, five or more therapeutic agents chosen from a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein), a PD-1 inhibitor, a LAG-3 inhibitor, a TIM-3 modulator (*e.g.*, an anti-TIM-3 inhibitor), a GITR agonist, a CSF-1/1R inhibitor (*e.g.,* an M-CSF inhibitor), an IL-17 inhibitor, an IL-1beta inhibitor, or a CXCR2 inhibitor. In one embodiment, the anti-tumor immunosuppression combination includes one, two, or all of a CSF-1/1R inhibitor (*e.g.*, an M-CSF inhibitor), an IL-17 inhibitor, an IL-1beta inhibitor. In one embodiment, the anti-tumor immunosuppression combination includes an IL-17 inhibitor, a CXCR2 inhibitor, a CRTH2 inhibitor, an A2AR antagonist, or a PFKFB3 inhibitor, or a combination thereof.

In some embodiments, the combination includes one or more therapeutic agents of the antigen-presentation combination. In other embodiments, the combination includes one or more therapeutic agents of the effector cell combination. In yet other embodiments, the combination includes one or more therapeutic agents of the anti-tumor immunosuppression combination. In other embodiments, the combination includes one or more therapeutic agents of the antigen-

presentation combination and one or more therapeutic agents of the effector cell combination. In other embodiments, the one or more therapeutic agents of the antigen-presentation combination and one or more therapeutic agents of the anti-tumor immunosuppression combination. In other embodiments, the combination includes one or more therapeutic agents of the antigen-presentation combination, one or more therapeutic agents of the effector cell combination and one or more therapeutic agents of the anti-tumor immunosuppression combination. In other embodiments, the combination includes one or more therapeutic agents of the antigen-presentation combination, one or more therapeutic agents of the effector cell combination and one or more therapeutic agents of the anti-tumor immunosuppression combination.

In certain embodiments, the combination includes:

(i) one or more therapeutic agents of the antigen-presentation combination chosen from one, two or all of a STING agonist, a TLR agonist (*e.g.*, a TLR7 agonist), or a TIM-3 modulator (*e.g.*, a TIM-3 inhibitor);

(ii) one or more therapeutic agents of the effector cell combination chosen from one, two or all of a GITR modulator (*e.g.*, a GITR agonist), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein), or a PD-1 inhibitor;

(iii) one or more therapeutic agents of the anti-tumor immunosuppression combination chosen from one, two or all of a CSF-1/1R inhibitor (*e.g.*, an M-CSF inhibitor), an IL-17 inhibitor, or an IL-1beta inhibitor:

(iv) a combination of (i) and (ii);

(v) a combination of (i) and (iii);

(vi) a combination of (ii) and (iii); or

(vii) a combination of (i), (ii) and (iii).

The combination can be used to treat a cancer as described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma (*e.g.,* advanced melanoma), nasopharyngeal cancer, or breast cancer.

In other embodiments, the combination includes a therapeutic agent from the antigen-presentation combination (*e.g.*, one or more of a STING agonist, a TLR agonist, a vaccine or an oncolytic virus) in combination with a therapeutic agent from the effector cell and/or anti-tumor immunosuppression combination (*e.g.,* an inhibitor of a checkpoint inhibitor, *e.g.*, an inhibitor of

PD-L1, PD-1, LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or CTLA-4, or any combination thereof. In one embodiment, one or more of a STING agonist, a TLR agonist, a vaccine or an oncolytic virus is administered in combination with an anti-PD-L1 antibody molecule as described herein. In one embodiment, a STING agonist and/or a vaccine is administered in combination with an anti-PD-L1 antibody molecule as described herein. In one embodiment, an oncolytic virus is administered in combination with an anti-PD-L1 antibody molecule as described herein. The combination can be used to treat a cancer as described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma (*e.g.*, advanced melanoma), nasopharyngeal cancer, or breast cancer.

In certain embodiments, the combination includes a combination of therapeutic agents as provided in the section entitled "Exemplary Combinations of Antigen-Presentation Combinations, Effector Cell Combinations and Anti-tumor Immunosuppression Combinations" provided in the Detailed Description.

The combinations disclosed herein can be administered together in a single composition or administered separately in two or more different compositions, *e.g.*, compositions or dosage forms as described herein. The administration of the therapeutic agents can be in any order. The first agent and the additional agents (*e.g.*, second, third agents) can be administered via the same administration route or via different administration routes. For example, a first therapeutic agent can be administered concurrently with, prior to, or subsequent to, the additional agent. In certain embodiments, a first agent is administered locally, *e.g.*, a therapeutic agent of any of categories (i)-(iii) can be coupled to a tumor targeting agent, *e.g.*, a tumor-targeting antibody (*e.g.*, to form an antibody-drug conjugate), or any other delivery agent (*e.g.*, a formulation such as a targeted formulation) such that administration of the first agent is localized to a desired site, *e.g.*, a tumor site (*e.g.*, a dendritic cell-enriched site). In one embodiment, the therapeutic agent is an antigen (*e.g.*, a vaccine, *e.g.*, an *in situ* cancer vaccine), which is targeted to the tumor environment, thus resulting in activation of dendritic cells. The therapeutic agent also can be locally administered, *e.g.*, injected, at a tumor site (*e.g.*, intratumoral or peritumoral administration). Localized delivery or administration of the therapeutic agent can reduce one or more side effects or toxicities that would otherwise be associated with systemic administration of the therapeutic agent. In one exemplary embodiment, a therapeutic agent (*e.g.*, STING or a TLR) can be

conjugated to a tumor-binding antibody (*e.g.,* an antibody that binds to HER2), thereby delivering the therapeutic agent to a HER-2-expressing cell.

Detection/Theranostics

In another aspect, the invention features methods for detecting the presence of PD-L1 in a sample, *e.g.*, *in vitro* or *in vivo* (*e.g.*, a biological sample, *e.g.*, serum, semen or urine, or a tissue biopsy, *e.g.*, from a hyperproliferative or cancerous lesion). The subject method can be used to evaluate (*e.g.*, monitor treatment or progression of, diagnose and/or stage a disorder described herein, *e.g.*, a hyperproliferative or cancerous disorder, in a subject). The method includes: (i) contacting the sample with (and optionally, a reference, *e.g.*, a control sample), or administering to the subject, an antibody molecule as described herein, under conditions that allow interaction to occur, and (ii) detecting formation of a complex between the antibody molecule, and the sample (and optionally, the reference, *e.g.*, control, sample). Formation of the complex is indicative of the presence of PD-L1, and can indicate the suitability or need for a treatment described herein. In some embodiments, PD-L1 is detected prior to treatment, *e.g.*, prior to an initial treatment, or prior to a treatment after a treatment interval. Detection can involve an immunohistochemistry, immunocytochemistry, FACS, antibody molecule complexed magnetic beads, ELISA assays, PCR-techniques (*e.g.*, RT-PCR), or an *in vivo* imaging technique. Typically, the antibody molecule used in the *in vivo* and *in vitro* detection methods is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound binding agent. Suitable detectable substances include various biologically active enzymes, prosthetic groups, fluorescent materials, luminescent materials, paramagnetic (*e.g.*, nuclear magnetic resonance active) materials, and radioactive materials. In other embodiments, the antibody molecule is detected *in vivo*, *e.g.*, using an *in vivo* imaging technique as described herein (*e.g.*, PET imaging).

Additional embodiments provide a method of treating a cancer, comprising: identifying in a subject, *e.g.,* a sample (*e.g.*, a subject's sample comprising cancer cells and optionally immune cells such as TILs) the presence of one, two or all of PD-L1, CD8, or IFN-γ, thereby providing a value for one, two or all of PD-L1, CD8, and IFN-γ. The method can further include comparing the PD-L1, CD8, and/or IFN-γ values to a reference value, *e.g.*, a control value. If the

PD-L1, CD8, and/or IFN-γ values are greater than the reference value, *e.g.*, the control values, administering a therapeutically effective amount of an anti-PD-L1 antibody (*e.g.*, an anti-PD-L1 antibody described herein) to the subject, optionally in combination with one or more other agents, thereby treating the cancer. In some embodiments, the subject is identified prior to treatment, *e.g.*, prior to an initial treatment, or prior to a treatment after a treatment interval. The cancer may be, *e.g.*, a cancer described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, nasopharyngeal cancer, or breast cancer, *e.g.*, TN breast cancer, *e.g.*, IM-TN breast cancer. In some embodiments, the cancer is ER+ breast cancer or pancreatic cancer.

Also provided is a method of treating a cancer, comprising: testing a subject, *e.g.*, a sample (*e.g.*, a subject's sample comprising cancer cells) for the presence of PD-L1, thereby identifying a PD-L1 value, comparing the PD-L1 value to a control value, and if the PD-L1 value is greater than the control value, administering a therapeutically effective amount of an anti-PD-L1 antibody (*e.g.*, an anti-PD-L1 antibody described herein) to the subject, optionally in combination with one or more other agents, thereby treating the cancer. The cancer may be, *e.g.*, a cancer as described herein, such as cancer is non-small cell lung (NSCLC) adenocarcinoma (ACA), NSCLC squamous cell carcinoma (SCC), or hepatocellular carcinoma (HCC).

Without being bound by theory, it is believed that a subject that shows a pre-existing immune response to a cancer, for example, an immune reaction prior to an immunomodulator therapy (*e.g.*, a checkpoint molecule inhibitor therapy) can have a prolonged and/or more robust response to the therapy, compared to a subject that does not have the same immune response. Thus, in some embodiments, evaluation of a subject's status of immune cell (*e.g.*, T cell) activation prior to an immunomodulator therapy can serve as a means for evaluating and/or monitoring a subject's responsiveness to the immunomodulator therapy. In embodiments, such evaluation can be used to identify, select and/or stratify a subject (*e.g.*, a patient or a patient population) as being more or less likely to respond to the immunomodulator therapy.

Accordingly, alternatively, or in combination with the methods described herein, a method for evaluating a subject's status of immune cell (*e.g.*, T cell) activation (*e.g.*, evaluating a subject's likely responsiveness to an immunomodulator therapy) is disclosed. The method includes determining the level and/or distribution of T cell activation in the subject. In one embodiment, the level and/or distribution of T activation includes a measure of the level and/or

distribution of one or more of: CD8, PD-L1, or other checkpoint inhibitor (*e.g.*, one or more of PD-1, LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or CTLA-4), or any combination thereof. For example, the level and/or distribution of CD8-expressing cells can be evaluated as a marker for activated T cells. In other embodiments, the level and/or distribution of cells expressing PD-L1, or other checkpoint inhibitor can be evaluated. The subject can be evaluated prior to, during, or after, administration of the immunomodulator therapy. In one embodiment, the subject is evaluated prior to the immunomodulator therapy (*e.g.*, the checkpoint molecule inhibitor therapy), *e.g.*, prior to an initial treatment, or prior to a treatment after a treatment interval. In one embodiment, an elevated level of one or more of CD8, PD-L1, or other checkpoint inhibitor in the subject (*e.g.*, relative to a reference, *e.g.*, control) is indicative of increased responsiveness of the subject to the therapy (also referred to herein as "a positive immune activation status"). In another embodiment, a decreased level of one or more of CD8, PD-L1, or other checkpoint inhibitor in the subject (*e.g.*, relative to a reference, *e.g.*, control) is indicative of decreased responsiveness of the subject to the therapy (also referred to herein as "a negative immune activation status"). The method can, optionally, include administration of the immunomodulator therapy as described herein (*e.g.*, a checkpoint molecule inhibitor therapy as described herein), if the subject is determined to have a positive immune activation status.

In one embodiment, the immunomodulator therapy includes an activator of a costimulatory molecule, *e.g.*, one or more activators as described herein (*e.g.*, an agonist of a GITR molecule as described herein). In other embodiments, the immunomodulator therapy includes an inhibitor of an immune checkpoint molecule, *e.g.*, one or more inhibitors of checkpoint inhibitor as described herein (*e.g.*, an inhibitor of one or more of PD-L1, PD-1, TIM-3, or CTLA-4, as described herein). In one embodiment, the immunomodulator therapy includes an anti-PD-L1 antibody molecule as described herein. In other embodiments, the immunomodulator therapy includes a combination of an activator of a costimulatory molecule and an inhibitor of a checkpoint inhibitor.

In some embodiments, the level and/or distribution of the CD8, PD-L1, or other checkpoint inhibitor is determined *in vivo*, *e.g.*, non-invasively (*e.*g., by detecting an antibody to a T cell marker detectably labeled using a suitable imaging technique, *e.g.*, positron emission tomography (PET) scan. For example, target antibody-PET or immune-PET (*e.g.*, an anti-CD8 PET or an anti- PD-L1 PET) can be used to detect the level and/or distribution (*e.g.*, tumor

localization) of the target CD8- or PD-L1-expressing cells *in vivo*. Techniques for antibody imaging (*e.g.*, antibody-PET imaging) are known in the art, *e.g.*, as described by Lamberts, L. E. *et al.* (2015) *J. Clin. Oncol.* 33 (DOI: 10.1200/JCO.2014.57.8278); Tavare, R. et al. (2014) PNAS 111(3):1108-1113; and Boerman and Oyen (2011) *The Journal of Nuclear Medicine* 52 (8):1171-72, incorporated herein by reference. In other embodiments, the level of the CD8, PD-L1, or other checkpoint inhibitor is determined in a sample (*e.g.*, a tumor biopsy) acquired from the subject (*e.g.*, using immunohistochemical techniques).

As an illustrative embodiment, an increased number of, or a change in location of, CD8-expressing cells from a tumor margin to the interior of the tumor may be indicative of an improved outcome, *e.g.*, increased responsiveness, of the subject to the immunomodulator therapy. In certain embodiments, the positive immune activation status (*e.g.*, an increase in activated T cells) occurs in response to a previous treatment of the cancer, for example, in response to one or more of radiotherapy, a chemotherapy, an oncolytic virus, a bispecific T cell engager, a biologic or a targeted therapy (*e.g.*, an anti-cancer therapy as described herein). In some embodiments, a subject that shows a positive immune activation status in response to the previous treatment becomes a better candidate for the immunomodulator therapy. In one embodiment, the subject that has a B-Raf mutation (*e.g.*, a B-Raf mutation as described herein) is treated with a B-Raf inhibitor (*e.g.*, a B-Raf inhibitor as described herein). The subject may have an increase in CD8-expressing T cells after treatment with the B-Raf inhibitor, and thus may become a better candidate for the immunomodulator therapy.

In another illustrative embodiment, an expression of PD-L1 or other checkpoint inhibitors (*e.g.*, relative to a reference) can be used to determine or analyze a subject's responsiveness to a cancer therapy. In one embodiment, a PET imaging agent can show that a subject has pre-existing expression of PD-L1 or other checkpoint molecules. Expression of these molecules on a tumor could help stratify patients for a companion diagnostic purpose. If a subject had no detectable immune response pre-existing to the immunomodulator therapy and no detectable checkpoint molecule expression, such subject is likely to be a poor candidate for the therapy. PET imaging can also show heterogeneity of expression, and show those tumors (positive for PET) that are the actual tumors best/lesions suited for response. This would be beneficial because sampling of a small number of target lesions could be misleading; for example, for determining if the subject was responding or not by sampling error of the biopsy technique and

low number of samples. Using PET imaging, it is possible to detect most of the tumors and thereby obtain a more accurate determination of tumor burden efficacy and better understand how the therapies are working.

In another aspect, the invention features diagnostic or therapeutic kits that include the antibody molecules described herein and instructions for use.

In an embodiment, there is provided a method of producing an antibody molecule or fragment thereof, comprising culturing one or more host cells of claim 123 under conditions suitable for gene expression, wherein the host cell(s) produce heavy and light chains, wherein the heavy chain comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and the light chain comprises a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO: 10, and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In an embodiment, there is provided the isolated antibody molecule as described herein for use in stimulating the immune response.

In an embodiment, there is provided the isolated antibody molecule as described herein for use in treating a cancer.

In an embodiment, there is provided a method of detecting PD-L1 in a biological sample, comprising (i) contacting the sample with the isolated antibody molecule as described herein under conditions that allow interaction of the antibody molecule and the polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample.

In an embodiment, there is provided use of the antibody molecule as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating a cancer in a subject.

In an embodiment, there is provided use of a combination of the antibody molecule as described herein, or a pharmaceutical composition as described herein, and a second therapeutic agent or procedure, in the manufacture of a medicament for treating a cancer in a subject.

In an embodiment, there is provided use of the anti-PD-L1 antibody molecule as described herein in combination with two, three or more therapeutic agents in the manufacture of a medicament for treating a cancer in a subject, wherein the therapeutic agents are chosen from at least two of the following categories (i)-(iii): (i) an agent that

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enhances tumor antigen presentation chosen from one or more of: a STING agonist, a TLR agonist, an A2AR antagonist, an oncolytic virus, a TIM-3 modulator, a vascular endothelial growth factor receptor (VEGFR) inhibitor, a c-Met inhibitor, a TGFb inhibitor, an IDO/TDO inhibitor, a vaccine, and a bi- or tri-specific cell engager; (ii) an agent that enhances an effector cell response chosen from one or more of: a GITR agonist, a PD-1 inhibitor, a PD-L1 inhibitor, an inhibitor of IAP (Inhibitor of Apoptosis Protein), an inhibitor of EGFR (Epidermal Growth Factor Receptor), an inhibitor of target of rapamycin (mTOR), IL-15 or a variant thereof, a CTLA-4 inhibitor, a bispecific antibody molecule that binds to CD3 and a tumor antigen, a CD40 agonist, an OX40 agonist, and a CD27 agonist; or (iii) an agent that decreases tumor immunosuppression chosen from one or more of: a GITR agonist, an inhibitor of an immune checkpoint molecule chosen from one or more of PD-1, LAG-3, TIM-3 or CTLA-4, a CSF-1/1R inhibitor, an IL-17 inhibitor, an IL-Iβ inhibitor, a CXCR2 inhibitor, an inhibitor of PBKγ or PBKδ), (vii) a BAFF-R inhibitor, a MALT-l/BTK inhibitor, a JAK inhibitor, a CRTH2 inhibitor, a VEGFR inhibitor, an IL-15 or a variant thereof, a CTLA-4 inhibitor, an IDO/TDO inhibitor, an A2AR antagonist, a TGFb inhibitor, and a PFKFB3 inhibitor.

In an embodiment, there is provided use of the anti-PD-L1 antibody molecule as described herein in combination with an AKT inhibitor in the manufacture of a medicament for treating a cancer in a subject.

Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the amino acid sequences of the light (SEQ ID NO: 8) and heavy chain (SEQ ID NO: 6) variable regions of murine anti-PD-Ll mAb BAP058. The light and heavy chain CDR sequences based on Kabat numbering are underlined. The light heavy chain CDR sequences based on Chothia numbering are shown in bold italics.

Figure 2 depicts the amino acid sequences of the light (SEQ ID NOS 8 and 249, respectively, in order of appearance) and heavy chain (SEQ ID NOS 6 and 248, respectively, in order of appearance) variable regions of murine anti-PD-Ll mAb BAP058 aligned with the germline sequences. The upper and lower sequences are the germline (GL) and BAP058 (Mu mAb) sequences, respectively. The light and heavy chain CDR sequences based on Kabat

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numbering are underlined. The light heavy chain CDR sequences based on Chothia numbering are shown in bold italics. "-" means identical amino acid residue.

Figure 3 is a bar graph showing the results of FACS binding analysis for the seventeen humanized BAP058 clones (BAP058-hum01 to BAP058-hum17). The antibody concentrations are 200, 100, 50, 25 and 12.5 ng/ml from the leftmost bar to the rightmost bar for each tested mAb.

Figure 4 depicts the structural analysis of the humanized BAP0058 clones (a, b, c, d, e, f, and g represent various types of framework region sequences). The concentrations of the mAbs in the samples are also shown.

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Figure 5 depicts the binding affinity and specificity of humanized BAP058 mAb measured in a competition binding assay using a constant concentration of Alexa 488-labeled murine mAb BAP058, serial dilutions of the test antibodies, and PD-L1-expressing 300.19 cells.

Figure 6 depicts the ranking of humanized BAP058 clones based on FACS data, competition binding and structural analysis. The concentrations of the mAbs in the samples are also shown.

Figure 7 depicts blocking of ligand binding to PD-1 by selected humanized BAP058 clones. Blocking of PD-1-Ig to PD-L1 expressing cells is shown BAP058-hum01, BAP058-hum03, BAP058-hum04, BAP058-hum06, BAP058-hum07, BAP058-hum11, and BAP058-hum13 were evaluated. Murine mAb BAP058 and chimeric mAb were also included in the analyses.

Figures 8A-8B depict the alignment of heavy chain variable domain sequences for the seventeen humanized BAP058 clones and BAP058-chi In Figure 8A, all of the sequences are shown. Figure 8A discloses SEQ ID NOS 250, 251, 251, 251, 252, 252, 252, 253, 253, 254, 254, 255, 255, 256, 256, 257, 258, 259, respectively, in order of appearance. In Figure 8B, only amino acid sequences that are different from mouse sequence are shown. Figure 8B discloses SEQ ID NOS 250, 251, 251, 251, 252, 252, 252, 253, 253, 254, 254, 255, 255, 256, 256, 257, 258, 259, respectively, in order of appearance.

Figures 9A-9B depict the alignment of light chain variable domain sequences for the seventeen humanized BAP058 clones and BAP058-chi In Figure 9A, all of the sequences are shown. Figure 9A discloses SEQ ID NOS 17, 86, 86, 86, 86, 42, 42, 42, 66, 66, 66, 22, 22, 26, 34, 58, 82, 74, respectively, in order of appearance. In Figure 9B, only amino acid sequences that are different from mouse sequence are shown. Figure 9B discloses SEQ ID NOS 17, 86, 86, 86, 86, 42, 42, 42, 66, 66, 66, 22, 22, 26, 34, 58, 82, 74, respectively, in order of appearance.

Figure 10 shows exemplary cancers having relatively high proportions of patients that are triple-positive for PD-L1/CD8/IFN-γ.

Figure 11 shows exemplary ER+ breast cancer and pancreatic cancer having relatively low proportions for patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 12 shows the proportion of exemplary breast cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 13 shows the proportion of exemplary colon cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 14 shows a graphical representation of flow cytometry of PD-L1 surface expression in EBC-1 cells *in vitro* with or without Compound A17 treatment. EBC-1 cells are non-small cell lung cancer cells with a cMET amplification.

Figure 15 shows a graphical representation of PD-L1 mRNA expression in Hs.746.T cells in a tumor xenograft model with or without Compound A17 treatment. Hs.746.T cells are gastric cancer cells with a c-MET amplification and a c-MET mutation.

Figure 16 shows a graphical representation of PD-L1 mRNA expression in H3122 cells *in vitro* with or without Compound A23. H3122 cells are non-small cell lung cancer (NSCLC) cells with an ALK translocation.

Figure 17 shows a graphical representation of PD-L1 mRNA expression in LOXIMV1 cells (BRAF mutant melanoma cells) in a tumor xenograft model with or without Compound A29 treatment.

Figure 18 shows a graphical representation of PD-L1 mRNA expression in HEYA8 cells (KRAS mutant ovarian cancer cells) in a tumor xenograft model with or without Compound A34 treatment.

Figure 19 shows a graphical representation of PD-L1 mRNA expression in UKE-1 cells (JAK2 V617F mutant myeloproliferative neoplasm cells) in a tumor xenograft model with or without Compound A18 treatment.

Figure 20 is a schematic diagram that outlines the antigen processing and presentation, effector cell responses and immunosuppression pathways targeted by the combination therapies disclosed herein.

Figure 21 depicts the effect of exemplary anti-PD-L1 antibodies on stimulation of IFN-γ release from co-cultures of dendritic cells and CD4+ T cells.

Figure 22 depicts the effect of exemplary anti-PD-L1 antibodies on SEB-induced IL-2 secretion by T cells.

BRIEF DESCRIPTION OF THE TABLES

Table 1 is a summary of the amino acid and nucleotide sequences for the murine, chimeric and humanized anti-PD-L1 antibody molecules. The antibody molecules include

murine mAb BAP058, chimeric mAb BAP058-chi, and humanized mAbs BAP058-hum01 to BAP058-hum17 and BAP058-Clone-K to BAP058-Clone-O. The amino acid and nucleotide sequences of the heavy and light chain CDRs, the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the amino acid and nucleotide sequences of the heavy and light chains are shown in this Table.

Table 2 depicts the amino acid and nucleotide sequences of the heavy and light chain framework regions for humanized mAbs BAP058-hum01 to BAP058-hum17 and BAP058-Clone-K to BAP058-Clone-O.

Table 3 depicts constant region amino acid sequences of human IgG heavy chains and human kappa light chain.

Table 4 is a summary of yield, titre, monomer content and endotoxin levels for selected humanized BAP058 mAbs expressed in CHO cells.

Table 5 shows the charge isoforms as detected by Novex IEF analysis for selected humanized BAP058 mAbs expressed in CHO cells.

Table 6 is a summary of selected therapeutic agents that can be administered in combination with the anti-PD-1 antibody molecules and other immunomodulators (*e.g.*, one or more of: an activator of a costimulatory molecule and/or an inhibitor of an immune checkpoint molecule) described herein. **Table 6** provides from left to right the following: the Compound Designation of the second therapeutic agent, the Compound structure, and Patent publication(s) disclosing the Compound.

Table 7 provides an exemplary listing of the therapeutic agents from Antigen-Presentation Combinations (Category A), Effector Cell Combinations (Category B) and Anti-tumor Immunosuppression Combinations (Category C).

Table 8 shows cross species binding of exemplary anti-PD-L1 antibodies as assessed by Biacore.

DETAILED DESCRIPTION

The immune system has the capability of recognizing and eliminating tumor cells; however, tumors can use multiple strategies to evade immunity. Blockade of immune checkpoints is one of the approaches to activating or reactivating therapeutic antitumor immunity. Programmed Death Ligand 1 (PD-L1) has been described as a ligand for the

immunoinhibiotry receptor Programmed Death 1 (PD-1). Binding of PD-L1 to PD-1 leads to the inhibition of T cell receptor-mediated lymphocyte proliferation and cytokine secretion (Freeman *et al.* (2000) *J Exp Med* 192:1027-34). Thus, blocking of PD-L1 can lead to enhancement of antitumor immunity.

Several cell types express PD-L1. For example, PD-L1 is expressed on activated T cells, dendritic cells (DCs), natural killer (NK) cells, macrophages, B cells, monocytes, and vascular endothelium cells. PD-L1 is expressed in many cancers, including human lung, ovarian and colon carcinoma and various myelomas, (Iwai *et al.* (2002) *PNAS* 99:12293-7; Ohigashi *et al.* (2005) *Clin Cancer Res* 11:2947-53; Okazaki *et al.* (2007) *Intern. Immun.* 19:813-24; Thompson *et al.* (2006) *Cancer Res.* 66:3381-5). PD-L1 expression strongly correlates with unfavorable prognosis in various types of cancer including kidney, ovarian, bladder, breast, gastric and pancreatic cancer.

Many tumor infiltrating T lymphocytes predominantly express PD-1 compared to T lymphocytes in normal tissues and peripheral blood T lymphocytes. This indicates that up-regulation of PD-1 on tumor-reactive T cells can contribute to impaired antitumor immune responses (Ahmadzadeh *et al.* (2009) *Blood* 114:1537-44). Thus, PD-L1 signaling mediated by PD-L1 expressing tumor cells interacting with PD-1 expressing T cells may lead to attenuation of T cell activation and evasion of immune surveillance (Sharpe *et al.* (2002) *Nat Rev Immunol.* 2:116-26; Keir *et al.* (2008) *Annu Rev Immunol.* 26:677-704). PD-1 blockade can inhibit hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells (Iwai *et al.* (2005) *Int. Immunol.* 17:133-144).

Anti-PD-L1 can enhance T-cell immunity, *e.g.,* through blocking both its inhibitory interactions with PD-1 and B7-1. Anti-PD-1 can also allow for immune regulation via PD-L2/PD-1. Both PD-1 and B7-1 are expressed on T cells, B cells, DCs, and macrophages, which provides potential for bidirectional interactions between B7-1 and PD-L1 on these cell types. PD-L1 on non-hematopoietic cells may interact with B7-1 as well as PD-1 on T cells.

Accordingly, the present invention provides, at least in part, antibody molecules *(e.g.,* humanized antibody molecules) that bind to Programmed Death Ligand 1 (PD-L1) with high affinity and specificity. In one embodiment, humanized antibodies against PD-L1 are disclosed, which show a surprisingly low immunogenicity. For example, humanized anti-PD-L1 antibodies can have a risk score of less than 650, 600, 550, or less than 500, according to a T cell epitope

assay. In other embodiments, selected combination of framework regions, *e.g.*, as shown in FIGs. 5 and 7, were shown to have distinct production efficiencies and binding properties.

Additional aspects of the invention include nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules. Immunoconjugates, multi- or bispecific molecules and pharmaceutical compositions comprising the antibody molecules are also provided. The anti-PD-L1 antibody molecules disclosed herein can be used to treat, prevent and/or diagnose cancerous or malignant disorders (*e.g.*, solid and soft-tissue tumors; melanoma, *e.g.*, advanced melanoma; hepatocellular carcinoma; pancreatic cancer; renal cell carcinoma (RCC), *e.g.*, metastatic RCC or clear cell RCC; gliomas or glioblastomas; multiple myeloma; colorectal cancer; and lung cancer, *e.g.*, non-small cell carcinoma), as well as infectious diseases (*e.g.*, infectious disorders such as hepatitis, *e.g.*, hepatitis C (*e.g.*, chronic viral hepatitis); sepsis). Thus, methods for detecting PD-L1, as well as methods for treating various disorders, including cancer and infectious diseases using the anti-PD-L1 antibody molecules are disclosed herein.

Additionally disclosed herein are methods and compositions comprising a combination of two, three or more therapeutic agents chosen from one, two, or all of the following categories (i)-(iii): (i) an agent that enhances antigen presentation (*e.g.*, tumor antigen presentation) (*e.g.*, by enhancing one or more of dendritic cell activity or maturation, antigen uptake, or antigen processing); (ii) an agent that enhances an effector cell response (*e.g.*, an immune effector cell response, *e.g.*, B cell and/or T cell activation and/or mobilization, *e.g.*, in the lymph node); or (iii) an agent that decreases tumor immunosuppression (*e.g.*, increasing T cell infiltration and tumor cell killing). In some embodiments, the combination includes a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule as described herein). Without wishing to be bound by theory, it is believed that therapeutic approaches that enhance anti-tumor immunity work more effectively when the immune response is optimized via multiple targets at different stages of the immune response. Each of these stages in depicted in schematic form in Figure 20. For example, approaches that result in activation of dendritic cells combined with approaches that enhance cellular and humoral immune can result in a more effective and/or prolonged therapeutic response.

The term "Programmed Death Ligand 1" or "PD-L1" include isoforms, mammalian, *e.g.*, human PD-L1, species homologs of human PD-1, and analogs comprising at least one common

epitope with PD-L1. The amino acid sequence of PD-L1, *e.g.*, human PD-1, is known in the art, *e.g.*, Dong *et al.* (1999) *Nat Med.* 5(12):1365-9; Freeman *et al.* (2000) *J Exp Med.* 192(7):1027-34).

Additional terms are defined below and throughout the application.

As used herein, the articles "a" and "an" refer to one or to more than one (*e.g.*, to at least one) of the grammatical object of the article.

The term "or" is used herein to mean, and is used interchangeably with, the term "and/or", unless context clearly indicates otherwise.

"About" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

By "a combination" or "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The therapeutic agents in the combination can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The therapeutic agents or therapeutic protocol can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutic agent utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In embodiments, the additional therapeutic agent is administered at a therapeutic or lower-than therapeutic dose. In certain embodiments, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the second therapeutic agent is administered in combination with the first therapeutic agent, *e.g.*, the anti-PD-L1 antibody molecule, than when the second therapeutic agent is administered individually. In certain embodiments, the concentration of the first therapeutic agent that is required to achieve

inhibition, *e.g.*, growth inhibition, is lower when the first therapeutic agent is administered in combination with the second therapeutic agent than when the first therapeutic agent is administered individually. In certain embodiments, in a combination therapy, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the second therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower. In certain embodiments, in a combination therapy, the concentration of the first therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the first therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower.

The term "inhibition," "inhibitor," or "antagonist" includes a reduction in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, an immune checkpoint inhibitor. For example, inhibition of an activity, *e.g.*, a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40% or more is included by this term. Thus, inhibition need not be 100%.

The term "activation," "activator," or "agonist" includes an increase in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, a costimulatory molecule. For example, increase of an activity, *e.g.*, a costimulatory activity, of at least 5%, 10%, 25%, 50%, 75% or more is included by this term.

The term "anti-cancer effect" refers to a biological effect which can be manifested by various means, including but not limited to, *e.g.,* a decrease in tumor volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place.

The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, *e.g.,* a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, or a decrease in tumor cell survival.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described

herein and include but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. The terms "tumor" and "cancer" are used interchangeably herein, *e.g.,* both terms encompass solid and liquid, *e.g.,* diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (*e.g.,* a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

The term "costimulatory molecule" refers to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory molecules include, but are not limited to, an MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

"Immune effector cell," or "effector cell" as that term is used herein, refers to a cell that is involved in an immune response, *e.g.*, in the promotion of an immune effector response.

Examples of immune effector cells include T cells, *e.g.,* alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloid-derived phagocytes.

"Immune effector" or "effector" "function" or "response," as that term is used herein, refers to function or response, *e.g.,* of an immune effector cell, that enhances or promotes an immune attack of a target cell. *E.g.,* an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of a target cell. In the case of a T cell, primary stimulation and co-stimulation are examples of immune effector function or response.

The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

The term "immune activation status" refers to the likelihood that a subject has for responding to a therapy, *e.g.,* an immunomodulator therapy. In embodiments, the immune activation status can be a positive status or a negative status. In embodiments, a positive immune activation status means that there is more than a 50% probability (*e.g.,* more than 50%, 60%, 70%, 80%, 90%, or greater probability) that the subject will respond to the therapy, *e.g.,* the immunomodulator therapy. In embodiments, a negative immune activation status means that there is more than a 50% probability (*e.g.,* more than 50%, 60%, 70%, 80%, 90%, or greater probability) that the subject will not respond to the therapy *e.g.,* the immunomodulator therapy.

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, *e.g.,* a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of the disorder resulting from the administration of one or more therapies. In specific embodiments, the terms "treat," "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" -refer to the inhibition of the progression of a proliferative disorder, either physically by, *e.g.,* stabilization of a discernible symptom, physiologically by, *e.g.,* stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count.

The compositions and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, *e.g.*, sequences at least 85%, 90%, 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term "substantially identical" is used herein to refer to a first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a common structural domain having at least about 85%, 90%. 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

In the context of nucleotide sequence, the term "substantially identical" is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

The term "functional variant" refers to polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared.

When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology").

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) *CABIOS*, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain

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gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used.

As used herein, the term "hybridizes under low stringency, medium stringency, high stringency, or very high stringency conditions" describes conditions for hybridization and washing. Guidance for performing hybridization reactions can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. Specific hybridization conditions referred to herein are as follows: 1) low stringency hybridization conditions in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by two washes in 0.2X SSC, 0.1% SDS at least at 50°C (the temperature of the washes can be increased to 55°C for low stringency conditions); 2) medium stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C; 3) high stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C; and preferably 4) very high stringency hybridization conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C. Very high stringency conditions (4) are the preferred conditions and the ones that should be used unless otherwise specified.

It is understood that the molecules of the present invention may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing. As used herein the term "amino acid" includes both the D- or L- optical isomers and peptidomimetics.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with

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basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

The terms "polypeptide", "peptide" and "protein" (if single chain) are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. The polypeptide can be isolated from natural sources, can be a produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

The terms "nucleic acid," "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence," and "polynucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a nonnatural arrangement.

The term "isolated," as used herein, refers to material that is removed from its original or native environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be

isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the invention are described in further detail below. Additional definitions are set out throughout the specification.

Antibody Molecules

In one embodiment, the antibody molecule binds to a mammalian, *e.g.*, human, PD-L1. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, (*e.g.*, an epitope as described herein) on PD-L1.

As used herein, the term "antibody molecule" refers to a protein, *e.g.*, an immunoglobin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term "antibody molecule" includes, for example, a monoclonal antibody (including a full length antibody which has an immunoglobulin Fc region). In an embodiment, an antibody molecule comprises a full length antibody, or a full length immunoglobin chain. In an embodiment, an antibody molecule comprises an antigen binding or functional fragment of a full length antibody, or a full length immunoglobin chain.

In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope. *E.g.*, a monospecific antibody molecule having a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope.

In an embodiment an antibody molecule is a multispecific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or tetraspecific antibody molecule,

In an embodiment a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, *e.g.,* the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, *e.g.,* the different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope. In an embodiment the first epitope is located on PD-L1 and the second epitope is located on a TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5), PD-1, or PD-L2.

In an embodiment, an antibody molecule comprises a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (*e.g.,* Fab, F(ab')$_2$, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In an embodiment an antibody molecule comprises or consists of a heavy chain and a light chain (referred to herein as a half antibody. In another example, an antibody molecule includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')$_2$, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab)

(bivalent and bispecific), and chimeric (*e.g.*, humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments retain the ability to selectively bind with their respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (*e.g.*, IgG1, IgG2, IgG3, and IgG4) of antibodies. The preparation of antibody molecules can be monoclonal or polyclonal. An antibodymolecule can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. The antibody can have a heavy chain constant region chosen from, *e.g.*, IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, *e.g.*, kappa or lambda. The term "immunoglobulin" (Ig) is used interchangeably with the term "antibody" herein.

Examples of antigen-binding fragments of an antibody molecule include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), *see e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883); (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

The term "antibody" includes intact molecules as well as functional fragments thereof. Constant regions of the antibodies can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

Antibody molecules can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain

antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to another aspect of the invention, a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 9404678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides *Camelidae* may produce heavy chain antibodies naturally devoid of light chain; such VHHs are within the scope of the invention.

The VH and VL regions can be subdivided into regions of hypervariability, termed "complementarity determining regions" (CDR), interspersed with regions that are more conserved, termed "framework regions" (FR or FW).

The extent of the framework region and CDRs has been precisely defined by a number of methods (*see*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular's AbM antibody modeling software. *See*, generally, *e.g.*, *Protein Sequence and Structure Analysis of Antibody Variable Domains.* In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg).

The terms "complementarity determining region," and "CDR," as used herein refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, LCDR3).

The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat *et al.* (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani *et al.*, (1997) *JMB* 273,927-948 ("Chothia" numbering scheme). As used herein, the CDRs defined according the "Chothia" number scheme are also sometimes referred to as "hypervariable loops."

For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-66 (HCDR2), and 99-109 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-57 (HCDR2), and 99-109 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-66 (HCDR2), and 99-109 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL.

Generally, unless specifically indicated, the anti-PD-L1 antibody molecules can include any combination of one or more Kabat CDRs and/or Chothia hypervariable loops, *e.g.*, described in Table 1. In one embodiment, the following definitions are used for the anti-PD-L1 antibody molecules described in Table 1: HCDR1 according to the combined CDR definitions of both Kabat and Chothia, and HCCDRs 2-3 and LCCDRs 1-3 according the CDR definition of Kabat. Under all definitions, each VH and VL typically includes three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

As used herein, an "immunoglobulin variable domain sequence" refers to an amino acid sequence which can form the structure of an immunoglobulin variable domain. For example, the sequence may include all or part of the amino acid sequence of a naturally-occurring variable domain. For example, the sequence may or may not include one, two, or more N- or C-terminal amino acids, or may include other alterations that are compatible with formation of the protein structure.

The term "antigen-binding site" refers to the part of an antibody molecule that comprises determinants that form an interface that binds to the PD-L1 polypeptide, or an epitope thereof. With respect to proteins (or protein mimetics), the antigen-binding site typically includes one or more loops (of at least four amino acids or amino acid mimics) that form an interface that binds to the PD-L1 polypeptide. Typically, the antigen-binding site of an antibody molecule includes at least one or two CDRs and/or hypervariable loops, or more typically at least three, four, five or six CDRs and/or hypervariable loops.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. A monoclonal antibody can be made by hybridoma technology or by methods that do not use hybridoma technology (*e.g.*, recombinant methods).

An "effectively human" protein is a protein that does not evoke a neutralizing antibody response, *e.g.*, the human anti-murine antibody (HAMA) response. HAMA can be problematic in a number of circumstances, *e.g.*, if the antibody molecule is administered repeatedly, *e.g.*, in treatment of a chronic or recurrent disease condition. A HAMA response can make repeated antibody administration potentially ineffective because of an increased antibody clearance from the serum (*see, e.g.,* Saleh *et al.*, *Cancer Immunol. Immunother.*, 32:180-190 (1990)) and also because of potential allergic reactions (*see, e.g.,* LoBuglio *et al., Hybridoma*, 5:5117-5123 (1986)).

The antibody molecule can be a polyclonal or a monoclonal antibody. In other embodiments, the antibody can be recombinantly produced, *e.g.*, produced by phage display or by combinatorial methods.

Phage display and combinatorial methods for generating antibodies are known in the art (as described in, *e.g.,* Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* International Publication No. WO 92/18619; Dower *et al.* International Publication No. WO 91/17271; Winter *et al.* International Publication WO 92/20791; Markland *et al.* International Publication No. WO 92/15679; Breitling *et al.* International Publication WO 93/01288; McCafferty *et al.* International Publication No. WO 92/01047; Garrard *et al.* International Publication No. WO 92/09690; Ladner *et al.* International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982).

In one embodiment, the antibody is a fully human antibody (*e.g.*, an antibody made in a mouse which has been genetically engineered to produce an antibody from a human

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immunoglobulin sequence), or a non-human antibody, *e.g.*, a rodent (mouse or rat), goat, primate (*e.g.*, monkey), camel antibody. Preferably, the non-human antibody is a rodent (mouse or rat antibody). Methods of producing rodent antibodies are known in the art.

Human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest are used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (see, *e.g.*, Wood *et al.* International Application WO 91/00906, Kucherlapati *et al.* PCT publication WO 91/10741; Lonberg *et al.* International Application WO 92/03918; Kay *et al.* International Application 92/03917; Lonberg, N. *et al.* 1994 *Nature* 368:856-859; Green, L.L. *et al.* 1994 *Nature Genet.* 7:13-21; Morrison, S.L. *et al.* 1994 *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Bruggeman *et al.* 1993 *Year Immunol* 7:33-40; Tuaillon *et al.* 1993 *PNAS* 90:3720-3724; Bruggeman *et al.* 1991 *Eur J Immunol* 21:1323-1326).

An antibody can be one in which the variable region, or a portion thereof, *e.g.*, the CDRs, are generated in a non-human organism, *e.g.*, a rat or mouse. Chimeric, CDR-grafted, and humanized antibodies are within the invention. Antibodies generated in a non-human organism, *e.g.*, a rat or mouse, and then modified, *e.g.*, in the variable framework or constant region, to decrease antigenicity in a human are within the invention.

Chimeric antibodies can be produced by recombinant DNA techniques known in the art (see Robinson *et al.*, International Patent Publication PCT/US86/02269; Akira, *et al.*, European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.*, European Patent Application 173,494; Neuberger *et al.*, International Application WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent Application 125,023; Better *et al.* (1988 *Science* 240:1041-1043); Liu *et al.* (1987) *PNAS* 84:3439-3443; Liu *et al.*, 1987, *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *PNAS* 84:214-218; Nishimura *et al.*, 1987, *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.*, 1988, *J. Natl Cancer Inst.* 80:1553-1559).

A humanized or CDR-grafted antibody will have at least one or two but generally all three recipient CDRs (of heavy and or light immuoglobulin chains) replaced with a donor CDR. The antibody may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of

CDRs required for binding of the humanized antibody to PD-L1. Preferably, the donor will be a rodent antibody, *e.g.*, a rat or mouse antibody, and the recipient will be a human framework or a human consensus framework. Typically, the immunoglobulin providing the CDRs is called the "donor" and the immunoglobulin providing the framework is called the "acceptor." In one embodiment, the donor immunoglobulin is a non-human (*e.g.*, rodent). The acceptor framework is a naturally-occurring (*e.g.*, a human) framework or a consensus framework, or a sequence about 85% or higher, preferably 90%, 95%, 99% or higher identical thereto.

As used herein, the term "consensus sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences (See *e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence. A "consensus framework" refers to the framework region in the consensus immunoglobulin sequence.

An antibody can be humanized by methods known in the art (*see e.g.*, Morrison, S. L., 1985, *Science* 229:1202-1207, by Oi *et al.*, 1986, *BioTechniques* 4:214, and by Queen *et al.* US 5,585,089, US 5,693,761 and US 5,693,762).

Humanized or CDR-grafted antibodies can be produced by CDR-grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. *See e.g.*, U.S. Patent 5,225,539; Jones *et al.* 1986 *Nature* 321:552-525; Verhoeyan *et al.* 1988 *Science* 239:1534; Beidler *et al.* 1988 *J. Immunol.* 141:4053-4060; Winter US 5,225,539. Winter describes a CDR-grafting method which may be used to prepare the humanized antibodies of the present invention (UK Patent Application GB 2188638A, filed on March 26, 1987; Winter US 5,225,539).

Also within the scope of the invention are humanized antibodies in which specific amino acids have been substituted, deleted or added. Criteria for selecting amino acids from the donor are described in US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089. Other techniques for

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humanizing antibodies are described in Padlan *et al.* EP 519596 A1, published on December 23, 1992.

The antibody molecule can be a single chain antibody. A single-chain antibody (scFV) may be engineered (see, for example, Colcher, D. *et al.* (1999) *Ann N Y Acad Sci* 880:263-80; and Reiter, Y. (1996) *Clin Cancer Res* 2:245-52). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein.

In yet other embodiments, the antibody molecule has a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the (*e.g.*, human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, *e.g.*, the (*e.g.*, human) light chain constant regions of kappa or lambda. The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In one embodiment the antibody has: effector function; and can fix complement. In other embodiments the antibody does not; recruit effector cells; or fix complement. In another embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it is a isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

Methods for altering an antibody constant region are known in the art. Antibodies with altered function, *e.g.* altered affinity for an effector ligand, such as FcR on a cell, or the C1 component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (*see e.g.,* EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648,260). Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

An antibody molecule can be derivatized or linked to another functional molecule (*e.g.*, another peptide or protein). As used herein, a "derivatized" antibody molecule is one that has been modified. Methods of derivatization include but are not limited to the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin.

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Accordingly, the antibody molecules of the invention are intended to include derivatized and otherwise modified forms of the antibodies described herein, including immunoadhesion molecules. For example, an antibody molecule can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody molecule is produced by crosslinking two or more antibodies (of the same type or of different types, *e.g.,* to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Useful detectable agents with which an antibody molecule of the invention may be derivatized (or labeled) to include fluorescent compounds, various enzymes, prosthetic groups, luminescent materials, bioluminescent materials, fluorescent emitting metal atoms, *e.g.*, europium (Eu), and other anthanides, and radioactive materials (described below). Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, β-galactosidase, acetylcholinesterase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody molecule may also be derivatized with a prosthetic group (*e.g.*, streptavidin/biotin and avidin/biotin). For example, an antibody may be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl

chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of bioluminescent materials include luciferase, luciferin, and aequorin.

Labeled antibody molecule can be used, for example, diagnostically and/or experimentally in a number of contexts, including (i) to isolate a predetermined antigen by standard techniques, such as affinity chromatography or immunoprecipitation; (ii) to detect a predetermined antigen (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the protein; (iii) to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen.

An antibody molecules may be conjugated to another molecular entity, typically a label or a therapeutic (*e.g.*, a cytotoxic or cytostatic) agent or moiety. Radioactive isotopes can be used in diagnostic or therapeutic applications. Radioactive isotopes that can be coupled to the anti-PSMA antibodies include, but are not limited to α-, β-, or γ-emitters, or β-and γ-emitters. Such radioactive isotopes include, but are not limited to iodine (^{131}I or ^{125}I), yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), indium (^{111}In), technetium (^{99} mTc), phosphorus (^{32}P), rhodium (^{188}Rh), sulfur (^{35}S), carbon (^{14}C), tritium (^{3}H), chromium (^{51}Cr), chlorine (^{36}Cl), cobalt (^{57}Co or ^{58}Co), iron (^{59}Fe), selenium (^{75}Se), or gallium (^{67}Ga). Radioisotopes useful as therapeutic agents include yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212} Bi or ^{213}Bi), and rhodium (^{188}Rh). Radioisotopes useful as labels, *e.g.*, for use in diagnostics, include iodine (^{131}I or ^{125}I), indium (^{111}In), technetium (^{99}mTc), phosphorus (^{32}P), carbon (^{14}C), and tritium (^{3} H), or one or more of the therapeutic isotopes listed above.

The invention provides radiolabeled antibody molecules and methods of labeling the same. In one embodiment, a method of labeling an antibody molecule is disclosed. The method includes contacting an antibody molecule, with a chelating agent, to thereby produce a conjugated antibody. The conjugated antibody is radiolabeled with a radioisotope, *e.g.*, ^{111}Indium, ^{90}Yttrium and ^{177}Lutetium, to thereby produce a labeled antibody molecule.

As is discussed above, the antibody molecule can be conjugated to a therapeutic agent. Therapeutically active radioisotopes have already been mentioned. Examples of other therapeutic agents include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-

dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, maytansinoids, *e.g.,* maytansinol (*see* U.S. Pat. No. 5,208,020), CC-1065 (see U.S. Pat. Nos. 5,475,092, 5,585,499, 5,846, 545) and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.,* mechlorethamine, thioepa chlorambucil, CC-1065, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclinies (*e.g.,* daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.,* dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine, vinblastine, taxol and maytansinoids).

In one aspect, the invention features a method of providing a target binding molecule that specifically binds to a PD-L1 receptor. For example, the target binding molecule is an antibody molecule. The method includes: providing a target protein that comprises at least a portion of non-human protein, the portion being homologous to (at least 70, 75, 80, 85, 87, 90, 92, 94, 95, 96, 97, 98% identical to) a corresponding portion of a human target protein, but differing by at least one amino acid (*e.g.,* at least one, two, three, four, five, six, seven, eight, or nine amino acids); obtaining an antibody molecule that specifically binds to the antigen; and evaluating efficacy of the binding agent in modulating activity of the target protein. The method can further include administering the binding agent (*e.g.*, antibody molecule) or a derivative (*e.g.*, a humanized antibody molecule) to a human subject.

In certain embodiments, the antibody molecule is a multi-specific (*e.g.*, a bispecific or a trispecific) antibody molecule. Protocols for generating bispecific or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the "knob in a hole" approach described in, *e.g.*, US 5731168; the electrostatic steering Fc pairing as described in, *e.g.*, WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US 4433059; bispecific antibody determinants generated by recombining half

antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab' fragments cross-linked through sulfhdryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono-and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also encompassed creating for bispecifc, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*, US5844094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus futher associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, *e.g.*, US5869620. Additional exemplary multispecific and bispecific

molecules and methods of making the same are found, for example, in US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1, US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1.

In other embodiments, the anti-PD-L1 antibody molecule (*e.g.,* a monospecific, bispecific, or multispecific antibody molecule) is covalently linked, *e.g.,* fused, to another partner *e.g.,* a protein *e.g.,* one, two or more cytokines, *e.g.,* as a fusion molecule for example a fusion protein. In other embodiments, the fusion molecule comprises one or more proteins, *e.g.,* one, two or more cytokines. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-12, IL-15 or IL-21. In one embodiment, a bispecific antibody molecule has a first binding specificity to a first target (*e.g.,* to PD-L1), a second binding specificity to a second target (*e.g.,* LAG-3 or TIM-3), and is optionally linked to an interleukin (*e.g.,* IL-12) domain *e.g.,* full length IL-12 or a portion thereof.

A "fusion protein" and a "fusion polypeptide" refer to a polypeptide having at least two portions covalently linked together, where each of the portions is a polypeptide having a

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different property. The property may be a biological property, such as activity *in vitro* or *in vivo*. The property can also be simple chemical or physical property, such as binding to a target molecule, catalysis of a reaction, etc. The two portions can be linked directly by a single peptide bond or through a peptide linker, but are in reading frame with each other.

This invention provides an isolated nucleic acid molecule encoding the above antibody molecule, vectors and host cells thereof. The nucleic acid molecule includes but is not limited to RNA, genomic DNA and cDNA.

Exemplary Anti-PD-L1 Antibody Molecules

In certain embodiments, the anti-PD-L1 antibody molecule comprises:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO: 10, and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In other embodiments, the anti-PD-L1 antibody molecule comprises:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

In embodiments of the aforesaid antibody molecules, the VHCDR1 comprises the amino acid sequence of SEQ ID NO: 1. In other embodiments, the VHCDR1 comprises the amino acid sequence of SEQ ID NO: 4. In yet other embodiments, the VHCDR1 amino acid sequence of SEQ ID NO: 195.

In embodiments, the aforesaid antibody molecules have a heavy chain variable region comprising at least one framework (FW) region comprising the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154, or an amino acid sequence at least 90% identical thereto, or having no more than two amino acid

substitutions, insertions or deletions compared to the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

In other embodiments, the aforesaid antibody molecules have a heavy chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

In yet other embodiments, the aforesaid antibody molecules have a heavy chain variable region comprising at least two, three, or four framework regions comprising the amino acid sequences of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

In other embodiments, the aforesaid antibody molecules comprise a VHFW1 amino acid sequence of SEQ ID NO: 124, 126, 128, or 130, a VHFW2 amino acid sequence of SEQ ID NO: 132, 134, 136, 138, 140, or 142, and a VHFW3 amino acid sequence of SEQ ID NO: 144, 146, 148, 150, or 152, and, optionally, further comprising a VHFW4 amino acid sequence of SEQ ID NO: 154.

In other embodiments, the aforesaid antibody molecules have a light chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186, or an amino acid sequence at least 90% identical thereto, or having no more than two amino acid substitutions, insertions or deletions compared to the amino acid sequence of any of 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

In other embodiments, the aforesaid antibody molecules have a light chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

In other embodiments, the aforesaid antibody molecules have a light chain variable region comprising at least two, three, or four framework regions comprising the amino acid sequences of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

In other embodiments, the aforesaid antibody molecules comprise a VLFW1 amino acid sequence of SEQ ID NO: 156, 158, 160, 162, 164, or 166, a VLFW2 amino acid sequence of SEQ ID NO: 168 or 170, and a VLFW3 amino acid sequence of SEQ ID NO: 172, 174, 176,

178, 180, 182, or 184, and, optionally, further comprising a VLFW4 amino acid sequence of SEQ ID NO: 186.

In other embodiments, the aforesaid antibodies comprise a heavy chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 18. 30. 38, 46, 50, 54, 62, 70, or 78.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18, 30, 38, 46, 50, 54, 62, 70, or 78.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 22, 26, 34, 42, 58, 66, 74, 82, or 86.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22, 26, 34, 42, 58, 66, 74, 82, or 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 32.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 96.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 197.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 91.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 46.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 48.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 70.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 72.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 78.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 80.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 247.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 260.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22. In other embodiments, the

aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 24.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 26.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 28.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 34.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibodies comprise a light chain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 74.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 76

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 82.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 84.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 26.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 34.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 74.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 46 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 82.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 24.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 40 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 40 and a light chain comprising the amino acid sequence of SEQ ID NO: 76.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 24.

In other embodiments, the aforesaid antibodies comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 260 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 and a light chain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 72 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain comprising the amino acid sequence of SEQ ID NO: 84.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 247 and a light chain comprising the amino acid sequence of SEQ ID NO: 84.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 197 and a light chain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibodies comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 96 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules are chosen from a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv).

In other embodiments, the aforesaid antibody molecules comprise a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4.

In other embodiments, the aforesaid antibody molecules comprise a light chain constant region chosen from the light chain constant regions of kappa or lambda.

In other embodiments, the aforesaid antibody molecules comprise a human IgG4 heavy chain constant region with a mutation at position 228 of SEQ ID NO: 188 or 190 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules comprise a human IgG4 heavy chain constant region with a Serine to Proline mutation at position 228 of SEQ ID NO: 188 or 190 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules comprise a human IgG1 heavy chain constant region with an Asparagine to Alanine mutation at position 297 of SEQ ID NO: 192 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules comprise a human IgG1 heavy chain constant region with an Aspartate to Alanine mutation at position 265, and Proline to Alanine mutation at position 329 of SEQ ID NO: 193 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules comprise a human IgG1 heavy chain constant region with a Leucine to Alanine mutation at position 234 and Leucine to Alanine mutation at position 235 of SEQ ID NO: 194 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules are capable of binding to human PD-L1 with a dissociation constant (K_D) of less than about 0.2 nM.

In some embodiments, the aforesaid antibody molecules bind to human PD-L1 with a K_D of less than about 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.5nM, 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.,* about 0.2 nM to 0.1 nM, *e.g.,* about 0.166 nM to 0.176 nM, *e.g.,* about 0.171 nM, or *e.g.,* about 0.1 nM to 1.5 nM, *e.g.,* about 0.25 to 0.46 nM, *e.g.,* about 0.137 nM, 0.931 nM, or 2.14 nM, *e.g.,* as measured by a Biacore method.

In other embodiments, the aforesaid antibody molecules bind to cynomolgus PD-L1 with a K_D of less than about 1 nM, 0.8 nM, 0.6 nM, 0.4 nM, 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.,* about 0.1 nM to 1 nM, *e.g.,* about 0.2 nM to 0.8 nM, *e.g.,* about 0.13 nM to 0.11

nM, *e.g.*, about 0.124 nM, 0.369 nM, 0.431 nM, 0.735 nM, *e.g.*, as measured by a Biacore method.

In other embodiments, the aforesaid antibody molecules bind to murine PD-L1 with a K_D of less than about 100 nM, 60 nM, 10 nM, 1 nM, 0.5 nM, 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.*, about 0.13 nM to 0.11 nM, *e.g.*, about 0.124 nM, 0.04nM, 0.075nM, or 77.4nM, *e.g.*, as measured by a Biacore method.

In other embodiments, the aforesaid antibody molecules bind to rat PD-L1 with a K_D of less than about 15 nM, 10 nM, 5 nM, 1 nM, 0.5 nM, 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.*, about 0.1 nM to 3.5 nM, *e.g.*, about 0.13 nM to 0.11 nM, *e.g.*, about 0.124 nM, 0.04nM, 0.075nM, 0.431 nM, 1.36 nM, 6.14 nM, or 77.4nM, *e.g.*, as measured by a Biacore method.In certain embodiments, the aforesaid antibody molecules bind to both human PD-L1 and cynomolgus PD-L1 with similar K_D, *e.g.*, in the nM range, *e.g.*, as measured by a Biacore method.

In some embodiments, the aforesaid antibody molecules bind to 300.19 cells that express human PD-L1 (*e.g.*, human PD-L1-transfected 300.19cells) with a K_D of less than about 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, 0.075 nM, 0.05 nM, 0.025 nM, or 0.01 nM, *e.g.*, about 0.285 nM, *e.g.*, as measured by FACS analysis.

In some embodiments, the aforesaid antibody molecules bind to cells that express cynomolgus PD-L1 (*e.g.*, cells transfected with cynomolgus PD-L1) with a K_D of less than about 1nM, 0.75 nM, 0.5 nM, 0.25 nM, or 0.01 nM, *e.g.*, about 0..129 nM, *e.g.*, as measured by FACS analysis.

In certain embodiments, the aforesaid antibody molecules are not cross-reactive with mouse or rat PD-L1. In other embodiments, the aforesaid antibodies are cross-reactive with rhesus PD-L1. For example, the cross-reactivity can be measured by a Biacore method or a binding assay using cells that expresses PD-L1 (*e.g.*, human PD-L1-expressing 300.19 cells). In other embodiments, the aforesaid antibody molecules bind an extracellular Ig-like domain of PD-L1.

In other embodiments, the aforesaid antibody molecules are capable of reducing binding of PD-1 or B7-1 to PD-L1 or a cell that expresses PD-L1. In some embodiments, the aforesaid antibody molecules reduce (*e.g.*, block) PD-L1 binding to a cell that expresses PD-L1 (*e.g.*, human PD-L1-expressing 300.19 cells) with an IC50 of less than about 1.5 nM, 1 nM, 0.8 nM,

0.6 nM, 0.4 nM, 0.2 nM, or 0.1 nM, *e.g.*, between about 0.2 nM and about 0.1 nM, *e.g.*, about 0.15 nM or less, *e.g.*, about 0.145 nM. In some embodiments, the aforesaid antibodies reduce (*e.g.*, block) B7-1 binding to a cell that expresses PD-L1 (*e.g.*, human PD-L1-expressing 300.19 cells) with an IC50 of less than about 2 nM, 1.5 nM, 1 nM, 0.5 nM, or 0.2 nM, *e.g.*, between about 0.5 nM and about 0.01 nM, or about 0.2 nM or less, *e.g.*, about 0.1 nM.

In other embodiments, the aforesaid antibody molecules are capable of enhancing an antigen-specific T cell response.

In some embodiments, the aforesaid antibody molecules increase the expression of IL-2 from cells activated by Staphylococcal enterotoxin B (SEB) (*e.g.*, at 25 μg/mL) by at least about 2, 3, 4, 5, 6, 7, or 8-fold, *e.g.*, about 2 to 3-fold, *e.g.*, about 2 to 2.6-fold, *e.g.*, about 2.39-fold, or *e.g.*, about 2.4 to 6.4-fold, compared to the expression of IL-2 when an isotype control (*e.g.*, IgG4) is used, *e.g.*, as measured in a SEB T cell activation assay, *e.g.*, using peripheral blood mononuclear cells (PMBCs), or a human whole blood *ex vivo* assay.

In some embodiments, the aforesaid antibody molecules increase the expression of IFN-γ from T cells activated by SEB (*e.g.*, at 3 pg/mL) by at least about 2, 3, 4, 5, 6, 7, or 8-fold, *e.g.*, about 0.5 to 4.5-fold, *e.g.*, about 2.72-fold, or *e.g.*, about 4 to 7-fold compared to the expression of IFN-γ when an isotype control (*e.g.*, IgG4) is used, *e.g.*, as measured in an IFN-γ activity assay.

In some embodiments, the aforesaid antibody molecules bind to PD-L1 with a Kd slower than 5×10^{-4}, 1×10^{-4}, 5×10^{-5}, or 1×10^{-5} s^{-1}, *e.g.*, about 6.33×10^{-5} s^{-1}, *e.g.*, as measured by a Biacore method. In some embodiments, the aforesaid antibody molecules bind to PD-L1 with a Ka faster than 1×10^{4}, 5×10^{4}, 1×10^{5}, or 5×10^{5} $M^{-1}s^{-1}$, *e.g.*, about 3.07×10^{4} $M^{-1}s^{-1}$, *e.g.*, as measured by a Biacore method.

In embodiments, the anti-PD-L1 antibody molecule is a monospecific antibody molecule or a bispecific antibody molecule. In embodiments, the anti-PD-L1 antibody molecule has a first binding specificity for PD-L1 and a second binding specifity for TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5), PD-1 or PD-L2. In embodiments, the antibody molecule comprises an antigen binding fragment of an antibody, *e.g.*, a half antibody or antigen binding fragment of a half antibody.

In another aspect, the invention provides an isolated nucleic acid molecule encoding any of the aforesaid antibody molecules, vectors and host cells thereof.

An isolated nucleic acid encoding the antibody heavy chain variable region or light chain variable region, or both, of any the aforesaid antibody molecules.

In one embodiment, the isolated nucleic acid encoding heavy chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 104-108, 113-117, or 205-208.

In another embodiment, the isolated nucleic acid encoding light chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 109-112, 118-123, 209-214, and 245-246.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a heavy chain variable domain, wherein said nucleotide sequence is at least 85% identical to any of SEQ ID NO: 19, 31, 39, 47, 51, 55, 63, 71, 79, 90, 95, 100, 196, or 201.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a heavy chain variable domain, wherein said nucleotide sequence comprises any of SEQ ID NO: 19, 31, 39, 47, 51, 55, 63, 71, 79, 90, 95, 100, 196, or 201.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a heavy chain, wherein said nucleotide sequence is at least 85% identical to any of SEQ ID NO: 21, 33, 41, 49, 53, 57, 65, 73, 81, 92, 97, 101, 198, or 202.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a heavy chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 21, 33, 41, 49, 53, 57, 65, 73, 81, 92, 97, 101, 198, or 202.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a light chain variable domain, wherein said nucleotide sequence is at least 85% identical to any of SEQ ID NO: 23, 27, 35, 43, 59, 67, 75, 83, 87, 93, 98, 102, 199, or 203.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a light chain variable domain, wherein said nucleotide sequence comprises any of SEQ ID NO: 23, 27, 35, 43, 59, 67, 75, 83, 87, 93, 98, 102, 199, or 203.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a light chain, wherein said nucleotide sequence is at least 85% identical to any of SEQ ID NO: 25, 29, 37, 45, 61, 69, 77, 85, 89, 94, 99, 103, 200, or 204.

In other embodiments, the aforesaid nucleic acid further comprises a nucleotide sequence encoding a light chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 25, 29, 37, 45, 61, 69, 77, 85, 89, 94, 99, 103, 200, or 204.

In certain embodiments, one or more expression vectors and host cells comprising the aforesaid nucleic acids are provided.

A method of producing an antibody molecule or fragment thereof, comprising culturing the host cell as described herein under conditions suitable for gene expression is also provided.

Pharmaceutical Compositions and Kits

In another aspect, the present invention provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an antibody molecule described herein, formulated together with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.* by injection or infusion).

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Therapeutic compositions typically should be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high antibody concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.*, antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

The antibody molecules can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. For example, the antibody molecules can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and typically, greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m ^{2}, typically, about 70 to 310 mg/m^2, and more typically, about 110 to 130 mg/m^2. For example, the antibody molecules can be administered by intravenous infusion at a rate of less than 10 mg/min; typically less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m^2, typically about 5 to 50 mg/m^2, about 7 to 25 mg/m^2 and more typically, about 10 mg/m^2. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such

formulations are patented or generally known to those skilled in the art. *See, e.g., Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, an antibody molecule can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. Therapeutic compositions can also be administered with medical devices known in the art.

Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody molecule is 0.1-30 mg/kg, more preferably 1-25 mg/kg. Dosages and therapeutic regimens of the anti-PD-L1 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-PD-L1 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 40 mg/kg, *e.g.,* 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, 1 to 10 mg/kg, 5 to 15 mg/kg, 10 to 20 mg/kg, 15 to 25 mg/kg, or about 3 mg/kg. The dosing schedule can vary from *e.g.*, once a

week to once every 2, 3, or 4 weeks. In one embodiment, the anti-PD-L1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week. The antibody molecule can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.,* 20-40 mg/min, and typically greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m ^{2}, typically about 70 to 310 mg/m^2, and more typically, about 110 to 130 mg/m^2. In embodiments, the infusion rate of about 110 to 130 mg/m^2 achieves a level of about 3 mg/kg. In other embodiments, the antibody molecule can be administered by intravenous infusion at a rate of less than 10 mg/min, *e.g.*, less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m^2, *e.g.,* about 5 to 50 mg/m^2, about 7 to 25 mg/m^2, or, about 10 mg/m^2. In some embodiments, the antibody is infused over a period of about 30 min. The antibody molecule can be administered by intravenous infusion at a rate of less than 10 mg/min, preferably less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m ^{2}, preferably about 5 to 50 mg/m^2, about 7 to 25 mg/m^2, and more preferably, about 10 mg/m^2. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the modified antibody or antibody fragment may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the modified antibody or antibody fragment is outweighed by the therapeutically beneficial effects. A "therapeutically effective dosage" preferably inhibits a measurable parameter, *e.g.,* tumor growth rate by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. The ability of a compound to inhibit a measurable parameter, *e.g.,* cancer, can be evaluated in an animal model

system predictive of efficacy in human tumors. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner.

A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Also within the scope of the invention is a kit comprising an antibody molecule described herein. The kit can include one or more other elements including: instructions for use; other reagents, *e.g.,* a label, a therapeutic agent, or an agent useful for chelating, or otherwise coupling, an antibody to a label or therapeutic agent, or a radioprotective composition; devices or other materials for preparing the antibody for administration; pharmaceutically acceptable carriers; and devices or other materials for administration to a subject.

Uses of Anti-PD-L1 Antibody Molecules

The anti-PD-L1 antibody molecules disclosed herein have *in vitro and in vivo* diagnostic, as well as therapeutic and prophylactic utilities. For example, these molecules can be administered to cells in culture, *in vitro* or *ex vivo*, or to a subject, *e.g.*, a human subject, to treat, prevent, and/or diagnose a variety of disorders, such as cancers and infectious disorders.

Accordingly, in one aspect, the invention provides a method of modifying an immune response in a subject comprising administering to the subject the antibody molecule described herein, such that the immune response in the subject is modified. In one embodiment, the immune response is enhanced, stimulated or up-regulated. In one embodiment, the antibody molecules enhance an immune response in a subject by blockade of PD-L1.

As used herein, the term "subject" is intended to include human and non-human animals. In one embodiment, the subject is a human subject, *e.g.*, a human patient having a disorder or condition characterized by abnormal PD-L1 functioning. The term "non-human animals" includes mammals and non-mammals, such as non-human primates. In one embodiment, the subject is a human. In one embodiment, the subject is a human patient in need of enhancement of an immune response. In one embodiment, the subject is immunocompromised, *e.g.*, the subject is undergoing, or has undergone a chemotherapeutic or radiation therapy. Alternatively,

or in combination, the subject is, or is at risk of being, immunocompromised as a result of an infection. The methods and compositions described herein are suitable for treating human patients having a disorder that can be treated by augmenting the T-cell mediated immune response. For example, the methods and compositions described herein can enhance a number of immune activities. In one embodiment, the subject has increased number or activity of tumour-infiltrating T lymphocytes (TILs). In another embodiment, the subject has increased expression or activity of interferon-gamma (IFN-γ). In yet another embodiment, the subject has decreased PD-L1 expression or activity.

Therapeutic Uses

Blockade of PD-L1 by antibodies can enhance the immune response to cancerous cells in the patient. PD-L1 is typically not expressed in normal human cells, but is abundant in a variety of human cancers (Dong *et al.* (2002) *Nat Med* 8:787-9). The interaction between PD-1 and PD-L1 results in a decrease in tumor infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and immune evasion by the cancerous cells (Dong *et al.* (2003) *J Mol Med* 81:281-7; Blank *et al.* (2005) *Cancer Immunol Immunother.* 54:307-14); Konishi *et al.* (2004) *Clin. Cancer Res.* 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-L1 to PD-1 and the effect is additive when the interaction of PD-L2 to PD-1 is blocked as well (Iwai et al. (2002) *PNAS* 99:12293-7; Brown et al. (2003) *J. Immunol.* 170:1257-66). An anti-PD-L1 antibody may be used alone to inhibit the growth of cancerous tumors. Alternatively, an anti-PD-L1 antibody may be used in conjunction with other immunogenic agents, standard cancer treatments, or other antibodies, as described herein. Thus, inhibition of PD-L1 can augment an immune response.

In one aspect, the invention relates to treatment of a subject *in vivo* using an anti-PD-L1 antibody molecule such that growth of cancerous tumors is inhibited or reduced. An anti-PD-L1 antibody may be used alone to inhibit the growth of cancerous tumors. Alternatively, an anti-PD-L1 antibody may be used in combination with one or more of: a standard of care treatment (*e.g.*, for cancers or infectious disorders), another antibody or antigen-binding fragment thereof, an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy, as described below.

Accordingly, in one embodiment, the invention provides a method of inhibiting growth of tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of an anti-PD-L1 antibody molecule described herein.

In one embodiment, the methods are suitable for the treatment of cancer *in vivo*. To achieve antigen-specific enhancement of immunity, the anti-PD-L1 antibody molecule can be administered together with an antigen of interest. When antibodies to PD-L1 are administered in combination with one or more agents, the combination can be administered in either order or simultaneously.

Types of cancer; theranostic methods

In another aspect, a method of treating a subject, *e.g.*, reducing or ameliorating, a hyperproliferative condition or disorder (*e.g.*, a cancer), *e.g.*, solid tumor, a soft tissue tumor, or a metastatic lesion, in a subject is provided. The method includes administering to the subject one or more anti-PD-L1 antibody molecules described herein, alone or in combination with other agents or therapeutic modalities.

As used herein, the term "cancer" is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Examples of cancerous disorders include, but are not limited to, solid tumors, hematological cancers, soft tissue tumors, and metastatic lesions.

Examples of solid tumors include malignancies, *e.g.*, sarcomas, and carcinomas (including adenocarcinomas, and squamous cell carcinomas), of the various organ systems, such as those affecting liver, lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), genitourinary tract (*e.g.*, renal, urothelial cells), prostate and pharynx. Adenocarcinomas include malignancies such as most colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. Squamous cell carcinomas include malignancies, *e.g.*, in the lung, esophagus, skin, head and neck region, oral cavity, anus, and cervix. In one embodiment, the cancer is a melanoma, *e.g.*, an advanced stage melanoma. Metastatic lesions of the aforementioned cancers can also be treated or prevented using the methods and compositions of the invention.

Exemplary cancers whose growth can be inhibited using the antibodies molecules disclosed herein include cancers typically responsive to immunotherapy. Non-limiting examples of preferred cancers for treatment include lymphoma (*e.g.,* diffuse large B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin's lymphoma), breast cancer (*e.g.,* metastic breast cancer), lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* stage IV or recurrent non-small cell lung cancer, a NSCLC adenocarcinoma, or a NSCLC squamous cell carcinoma), myeloma (*e.g.,* multiple myeloma), leukemia (*e.g.,* chronic myelogenous leukemia), skin cancer (*e.g.,* melanoma (*e.g.,* stage III or IV melanoma) or Merkel cell carcinoma), head and neck cancer (*e.g.,* head and neck squamous cell carcinoma (HNSCC)), myelodysplastic syndrome, bladder cancer (*e.g.,* transitional cell carcinoma), kidney cancer (*e.g.,* renal cell cancer, *e.g.,* clear-cell renal cell carcinoma, *e.g.,* advanced or metastatic clear-cell renal cell carcinoma), and colon cancer. Additionally, refractory or recurrent malignancies can be treated using the antibody molecules described herein.

Examples of other cancers that can be treated include bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, anal cancer, gastro-esophageal, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Merkel cell cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, multiple myeloma, myelodisplastic syndromes, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos (*e.g.,* mesothelioma), and combinations of said cancers.

Treatment of metastatic cancers, *e.g.*, metastatic cancers that express PD-L1 (Iwai *et al.* (2005) *Int. Immunol.* 17:133-144) can be effected using the antibody molecules described herein. In one embodiment, the cancer expresses an elevated level of PD-L1, IFNγ and /or CD8.

PD-L1 signaling can contribute to elevated Bim expression in CD8+ T cells. Treatment of cancers, *e.g.*, advanced melanomas, in patients that express high level of Bim (*e.g.*, elevated Bim levels in PD-1+CD8+ T cells compared to PD-1-CD8+ T cells) can be effected using the antibody molecules described herein.

Animal models that can be used to test the efficacy of an anti-PD-L1 antibody in a monotherapy or combination therapy for cancer include, *e.g.*, CT26 colon carcinoma model (Sakuishi *et al.* (2010) *J Exp Med.* 207(10): 2187–2194) and 5T33 myeloma model (Manning *et al.* (1992) *Br J Cancer.* 66(6): 1088–1093).

In one embodiment, the cancer expresses an elevated level of PD-L1, IFNγ and /or CD8.

While not wishing to be bound by theory, in some embodiments, a patient is more likely to respond to treatment with an immunomodulator (optionally in combination with one or more agents as described herein) if the patient has a cancer that highly expresses PD-L1, and/or the cancer is infiltrated by anti-tumor immune cells, *e.g.*, TILs. The anti-tumor immunce cells may be positive for CD8, PD-L1, and/or IFN-γ; thus levels of CD8, PD-L1, and/or IFN-γ can serve as a readout for levels of TILs in the microenvironment. In certain embodiments, the cancer microenvironment is referred to as triple-positive for PD-L1/CD8/IFN-γ.

Accordingly, in certain aspects, this application provides methods of determining whether a tumor sample is positive for one or more of PD-L1, CD8, and IFN-γ, and if the tumor sample is positive for one or more, *e.g.*, two, or all three, of the markers, then administering to the patient a therapeutically effective amount of an anti-PD-L1 antibody molecule, optionally in combination with one or more other immunnomodulators or anti-cancer agents.

In the following indications, a large fraction of patients are triple-positive for PD-L1/CD8/IFN-γ: Lung cancer (squamous); lung cancer (adenocarcinoma); head and neck cancer; stomach cancer; NSCLC; HNSCC; gastric cancers (*e.g.*, MSIhi and/or EBV+); CRC (*e.g.*, MSIhi); nasopharyngeal cancer (NPC); cervical cancer (*e.g.*, squamous); thyroid cancer *e.g.*, papillary thyroid; melanoma; TN breast cancer; and DLBCL (Diffuse Large B-Cell Lymphoma). In breast cancer generally and in colon cancer generally, a moderate fraction of patients is triple-positive for PD-L1/CD8/IFN-γ. In the following indications, a small fraction of patients are

triple-positive for PD-L1/CD8/IFN-γ: ER+ breast cancer, and pancreatic cancer. These findings are discussed further in Example 4. Regardless of whether a large or small fraction of patients is triple-positive for these markers, screening the patients for these markers allows one to identify a fraction of patients that has an especially high likelihood of responding favorably to therapy with a PD-L1 antibody (*e.g.*, a blocking PD-L1 antibody), optionally in combination with one or more other immunomodulators (*e.g.*, an anti-TIM-3 antibody molecule, an anti-LAG-3 antibody molecule, or an anti-PD-L1 antibody molecule) and/or anti-cancer agents, *e.g.*, those listed in Table 6 and disclosed in the publications listed in Table 6.

In some embodiments, the cancer sample is classified as triple-positive for PD-L1/CD8/IFN-γ. This measurement can roughly be broken down into two thresholds: whether an individual cell is classified as positive, and whether the sample as a whole is classified as positive. First, one can measure, within an individual cell, the level of PD-L1, CD8, and/or IFN-γ. In some embodiments, a cell that is positive for one or more of these markers is a cell that has a higher level of the marker compared to a control cell or a reference value. For example, in some embodiments, a high level of PD-L1 in a given cell is a level higher than the level of PD-L1 in a corresponding non-cancerous tissue in the patient. As another example, in some embodiments, a high level of CD8 or IFN-γ in a given cell is a level of that protein typically seen in a TIL. Second, one can also measure the percentage of cells in the sample that are positive for PD-L1, CD8, and/or IFN-γ. (It is not necessary for a single cell to express all three markers.) In some embodiments, a triple positive sample is one that has a high percentage of cells, *e.g.*, higher than a reference value or higher than a control sample, that are positive for these markers.

In other embodiments, one can measure the levels of PD-L1, CD8, and/or IFN-γ overall in the sample. In this case, a high level of CD8 or IFN-γ in the sample can be the level of that protein typically seen in a tumor infiltrated with TIL. Similarly, a high level of PD-L1 can be the level of that protein typically seen in a tumor sample, *e.g.*, a tumor microenvironment.

The identification of subsets of patients that are triple-positive for PD-L1/CD8/IFN-γ, as shown in Example 4 herein, reveals certain sub-populations of patients that are likely to be especially responsive to PD-L1 antibody therapy. For instance, many IM-TN (immunomodulatory, triple negative) breast cancer patients are triple-positive for PD-L1/CD8/IFN-γ. IM-TN breast cancer is described in, *e.g.*, Brian D. Lehmann *et al.*, "Identification of human triple-negative breast cancer subtypes and preclinical models for

selection of targeted therapies", *J Clin Invest.* Jul 1, 2011; 121(7): 2750–2767. Triple-negative breast cancers are those that do not express estrogen receptor (ER), progesterone receptor (PR) and Her2/neu. These cancers are difficult to treat because they are typically not responsive to agents that target ER, PR, and Her2/neu. Triple-negative breast cancers can be further subdivided into different classes, one of which is immunomodulatory. As described in Lehmann *et al.*, IM-TN breast cancer is enriched for factors involved in immune cell processes, for example, one or more of immune cell signaling (*e.g.,* TH1/TH2 pathway, NK cell pathway, B cell receptor signaling pathway, DC pathway, and T cell receptor signaling), cytokine signaling (*e.g.,* cytokine pathway, IL-12 pathway, and IL-7 pathway), antigen processing and presentation, signaling through core immune signal transduction pathways (*e.g.,* NFKB, TNF, and JAK/STAT signaling), genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing. Accordingly, in some embodiments, the cancer treated is a cancer that is, or is determined to be, positive for one or more marker of IM-TN breast cancer, *e.g.,* a factor that promotes one or more of immune cell signaling (*e.g.,* TH1/TH2 pathway, NK cell pathway, B cell receptor signaling pathway, DC pathway, and T cell receptor signaling), cytokine signaling (*e.g.*, cytokine pathway, IL-12 pathway, and IL-7 pathway), antigen processing and presentation, signaling through core immune signal transduction pathways (*e.g.*, NFKB, TNF, and JAK/STAT signaling), genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing.

As another example, it is shown herein that a subset of colon cancer patients having high MSI (microsatellite instability) is also triple-positive for PD-L1/CD8/IFN-γ. Accordingly, in some embodiments, a PD-L1 antibody, *e.g.*, a PD-L1 antibody as described herein, (optionally in combination with one or more immunomodulators such as a LAG-3 antibody, TIM-3 antibody, or PD-1 antibody, and one or more anti-cancer agents, *e.g.,* an anti-cancer agent described in Table 6 or in a publication in Table 6) is administered to a patient who has, or who is identified as having, colon cancer with high MSI, thereby treating the cancer. In some embodiments, a cell with high MSI is a cell having MSI at a level higher than a reference value or a control cell, *e.g.*, a non-cancerous cell of the same tissue type as the cancer.

As another example, it is shown herein that a subset of gastric cancer patients having high MSI, and/or which is EBV+, is also triple-positive for PD-L1/CD8/IFN-γ. Accordingly, in some embodiments, a PD-L1 antibody, *e.g.*, a PD-L1 antibody as described herein, (optionally in

combination with one or more immunomodulators such as a LAG-3 antibody, TIM-3 antibody, or PD-1 antibody, and one or more anti-cancer agents, *e.g.,* an anti-cancer agent described in Table 6 or in a publication in Table 6) is administered to a patient who has, or who is identified as having, gastric cancer with high MSI and/or EBV+, thereby treating the cancer. In some embodiments, a cell with high MSI is a cell having MSI at a level higher than a reference value or a control cell, *e.g.,* a non-cancerous cell of the same tissue type as the cancer.

Additionally disclosed herein are methods of assaying a cancer for PD-L1, and then treating the cancer with a PD-L1 antibody. As described in Example 5 herein, a cancer sample can be assayed for PD-L1 protein levels or mRNA levels. A sample having levels of PD-L1 (protein or mRNA) higher than a reference value or a control cell (*e.g.,* a non-cancerous cell) can be classified as PD-L1 positive. Accordingly, in some embodiments, a PD-L1 antibody, *e.g.,* a PD-L1 antibody as described herein, (optionally in combination with one or more anti-cancer agents) is administered to a patient who has, or who is identified as having, a cancer that is PD-L1 positive. The cancer may be, *e.g.,* non-small cell lung (NSCLC) adenocarcinoma (ACA), NSCLC squamous cell carcinoma (SCC), or hepatocellular carcinoma (HCC).

In some embodiments, the methods herein involve using a PD-L1 antibody, *e.g.,* a PD-L1 antibody as described herein, *e.g.,* as a monotherapy, for treating a cancer that is (or is identified as being) positive for PD-L1. In some embodiments, the cancer is colorectal cancer (*e.g.,* MSI-high), gastric cancer (*e.g.,* MSI-high and/or EBV+), NPC, cervical cancer, breast cancer (*e.g.,* TN breast cancer), and ovarian cancer. In some embodiments, the cancer is NSCLC, melanoma, or HNSCC. In some embodiments, the PD-L1 antibody is administered at a dose of, *e.g.,* 1, 3, 10, or 20 mg/kg.

Based on, *e.g,* Example 4 herein, it was found that certain gastric cancers that are triple-positive for PD-L1/CD8/IFN-γ are also positive for PIK3CA. Accordingly, in some embodiments, a cancer can be treated with an anti-PD-1 antibody molecule (optionally in combination with one or more immunomodulators, *e.g.,* an anti-LAG-3 antibody molecule, an anti-TIM-3 antibody molecule, or an anti-PD-1 antibody molecule) and an agent that inhibits PIK3CA. Exemplary agents in this category are described in Stein RC (September 2001). "Prospects for phosphoinositide 3-kinase inhibition as a cancer treatment". Endocrine-related Cancer 8 (3): 237–48 and Marone R, Cmiljanovic V, Giese B, Wymann MP (January 2008).

"Targeting phosphoinositide 3-kinase: moving towards therapy". Biochimica et Biophysica Acta 1784 (1): 159–85.

Based on, *e.g*, Example 4 herein, CRC, *e.g.,* a patient that has (or is identified as having) MSI-high CRC may be treated with a PD-L1 antibody, optionally in combination with a therapeutic that targets one or more of LAG-3, RNF43, and BRAF. For instance, these cancers may be treated with a PD-L1 antibody, optionally in combination with one or more therapeutics that target one or more of LAG-3, PD-1, RNF43, and BRAF. In embodiments, the one or more therapeutics include an immunomodulators such as an anti-LAG-3 antibody molecule, and an anti-cancer agent described in Table 6 or a publication listed in Table 6. LAG-3 inhibitors, *e.g.,* antibodies, are described herein. RNF43 can be inhibited, *e.g.,* with an antibody, small molecule (*e.g.,* 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28)), siRNA, or a Rspo ligand or derivative thereof. BRAF inhibitors (*e.g.*, vemurafenib or dabrafenib) are described herein.

Based on, *e.g*, Example 4 herein, a patient that has (or is identified as having) a squamous cell lung cancer may be treated with a PD-L1 antibody molecule in combination with a therapeutic that targets LAG-3, *e.g.,* a LAG-3 antibody molecule, and optionally with one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 6 or in a publication in Table 6.

In some embodiments, a subject that has (or is identified as having) a squamous cell lung cancer may be treated with a PD-1 antibody, optionally in combination with a therapeutic that targets TIM-3, *e.g.*, a TIM-3 antibody. TIM-3 inhibitors, *e.g.*, antibodies, are described herein.

Based on, *e.g*, Example 4 herein, a patient that has (or is identified as having) a thyroid cancer may be treated with a PD-1 antibody molecule, optionally in combination with a therapeutic that targets BRAF, and optionally in combination with one or more immunomodulators, *e.g.,* an anti-LAG-3 antibody molecule, an anti-TIM-3 antibody molecule, and an anti-PD-L1 antibody molecule. BRAF inhibitors (*e.g.*, vemurafenib or dabrafenib) are described herein, *e.g.,* in Table 6 and the publications listed in Table 6.

In some embodiments, the therapies here can be used to treat a patient that has (or is identified as having) a cancer associated with an infection, *e.g.,* a viral or bacterial infection. Exemplary cancers include cervical cancer, anal cancer, HPV-associated head and neck squamous cell cancer, HPV-associated esophageal papillomas, HHV6-associated lymphomas,

EBV-associated lymphomas (including Burkitt lymphoma), Gastric MALT lymphoma, other infection-associated MALT lymphomas, HCC, Kaposi's sarcoma.

In other embodiments, the cancer is a hematological malignancy or cancer including but is not limited to a leukemia or a lymphoma. For example, the anti-PD-L1 antibody molecule can be used to treat cancers and malignancies including, but not limited to, *e.g.*, acute leukemias including but not limited to, *e.g.,* B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, *e.g.*, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, *e.g.*, B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like.

In one embodiment, the cancer is a breast cancer, *e.g.,* a metastatic breast cancer, *e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer.

In another embodiment, the cancer is a lung cancer, *e.g.,* a non-small cell lung cancer (*e.g.,* squamous non-small cell lung cancer), *e.g.,* locally advanced or metastic non-small cell lung cancer, *e.g.,* stage IV or recurrent non-small cell lung cancer.

In yet another embodiment, the cancer is a skin cancer, *e.g.,* Merkel cell carcinoma (MCC), *e.g.,* metastatic Merkel cell carcinoma.

In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, a NSCLC adenocarcinoma, or a NSCLC squamous cell carcinoma)), a melanoma (*e.g.*, an advanced melanoma), a renal cancer (*e.g.*, a renal cell carcinoma, *e.g.,* clear cell renal cell carcinoma), a liver cancer, a myeloma (*e.g.*, a multiple myeloma), a prostate cancer, a breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or

Her2/neu, *e.g.*, a triple negative breast cancer), a colorectal cancer, a pancreatic cancer, a head and neck cancer (*e.g.*, head and neck squamous cell carcinoma (HNSCC), anal cancer, gastro-esophageal cancer, thyroid cancer, cervical cancer, a lymphoproliferative disease (*e.g.*, a post-transplant lymphoproliferative disease) or a hematological cancer, T-cell lymphoma, a non-Hogdkin's lymphoma, or a leukemia (*e.g.*, a myeloid leukemia).

In another embodiment, the cancer is chosen form a carcinoma (*e.g.*, advanced or metastatic carcinoma), melanoma or a lung carcinoma, *e.g.*, a non-small cell lung carcinoma.

In one embodiment, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer.

In another embodiment, the cancer is a hepatocarcinoma, *e.g.*, an advanced hepatocarcinoma, with or without a viral infection, *e.g.*, a chronic viral hepatitis.

In another embodiment, the cancer is a prostate cancer, *e.g.*, an advanced prostate cancer.

In yet another embodiment, the cancer is a myeloma, *e.g.*, multiple myeloma.

In yet another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic RCC or clear cell renal cell carcinoma).

In one embodiment, the cancer is a melanoma, *e.g.*, an advanced melanoma. In one embodiment, the cancer is an advanced or unresectable melanoma that does not respond to other therapies. In other embodiments, the cancer is a melanoma with a BRAF mutation (*e.g.*, a BRAF V600 mutation). In yet other embodiments, the anti-PD-L1 antibody molecule is administered after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

Methods and compositions disclosed herein are useful for treating metastatic lesions associated with the aforementioned cancers.

Combination of Anti-PD-L1 antibodies with cancer vaccines

Antibody molecules to PD-L1 can be combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines (He *et al.* (2004) *J. Immunol.* 173:4919-28). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine

GM-CSF. DNA-based vaccines, RNA-based vaccines, and viral transduction-based vaccines. The cancer vaccine may be prophylactic or therapeutic.

PD-L1 blockade can be combined with a vaccination protocol. Many experimental strategies for vaccination against tumors have been devised (*see* Rosenberg, S., 2000, Development of Cancer Vaccines, ASCO Educational Book Spring: 60-62; Logothetis, C., 2000, ASCO Educational Book Spring: 300-302; Khayat, D. 2000, ASCO Educational Book Spring: 414-428; Foon, K. 2000, ASCO Educational Book Spring: 730-738; *see* also Restifo, N. and Sznol, M., *Cancer Vaccines*, Ch. 61, pp. 3023-3043 in DeVita, V. *et al.* (eds.), 1997, *Cancer*: Principles and Practice of Oncology. Fifth Edition). In one of these strategies, a vaccine is prepared using autologous or allogeneic tumor cells. These cellular vaccines have been shown to be most effective when the tumor cells are transduced to express GM-CSF. GM-CSF has been shown to be a potent activator of antigen presentation for tumor vaccination (Dranoff *et al.* (1993) *Proc. Natl. Acad. Sci.* U.S.A. 90: 3539-43).

PD-L1 blockade can be used in conjunction with a collection of recombinant proteins and/or peptides expressed in a tumor in order to generate an immune response to these proteins. These proteins are normally viewed by the immune system as self antigens and are therefore tolerant to them. The tumor antigen may also include the protein telomerase, which is required for the synthesis of telomeres of chromosomes and which is expressed in more than 85% of human cancers and in only a limited number of somatic tissues (Kim, N *et al.* (1994) *Science* 266: 2011-2013). (These somatic tissues may be protected from immune attack by various means). Tumor antigen may also be "neo-antigens" expressed in cancer cells because of somatic mutations that alter protein sequence or create fusion proteins between two unrelated sequences (ie. bcr-abl in the Philadelphia chromosome), or idiotype from B cell tumors.

Other tumor vaccines may include the proteins from viruses implicated in human cancers such a Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV), Kaposi's Herpes Sarcoma Virus (KHSV), and Epstein–Barr virus (EBV). Another form of tumor specific antigen which may be used in conjunction with PD-1 blockade is purified heat shock proteins (HSP) isolated from the tumor tissue itself. These heat shock proteins contain fragments of proteins from the tumor cells and these HSPs are highly efficient at delivery to antigen presenting cells for eliciting tumor immunity (Suot, R & Srivastava, P (1995) *Science* 269:1585-1588; Tamura, Y. *et al.* (1997) *Science* 278:117-120).

Dendritic cells (DC) are potent antigen presenting cells that can be used to prime antigen-specific responses. DC's can be produced *ex vivo* and loaded with various protein and peptide antigens as well as tumor cell extracts (Nestle, F. *et al.* (1998) *Nature Medicine* 4: 328-332). DCs may also be transduced by genetic means to express these tumor antigens as well. DCs have also been fused directly to tumor cells for the purposes of immunization (Kugler, A. *et al.* (2000) *Nature Medicine* 6:332-336). As a method of vaccination, DC immunization may be effectively combined with PD-1 blockade to activate more potent anti-tumor responses.

In another embodiment, the combination further includes an inhibitor or activator of an immune checkpoint modulator (*e.g.*, a LAG-3 inhibitor (*e.g.*, an anti-LAG-3 antibody molecule), a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a TIM-3 modulator (*e.g.*, a TIM-3 activator or inhibitor, *e.g.*, an anti-TIM-3 antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA-4 antibody), or any combination thereof.

PD-L1 blockade may also be combined with a standard cancer treatment. PD-L1 blockade may be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of chemotherapeutic reagent administered (Mokyr, M. *et al.* (1998) *Cancer Research* 58: 5301-5304). In certain embodiments, the methods and compositions described herein are administered in combination with one or more of other antibody molecules, chemotherapy, other anti-cancer therapy (*e.g.*, targeted anti-cancer therapies, or oncolytic drugs), cytotoxic agents, immune-based therapies (*e.g.*, cytokines), surgical and/or radiation procedures. Exemplary cytotoxic agents that can be administered in combination with include antimicrotubule agents, topoisomerase inhibitors, anti-metabolites, mitotic inhibitors, alkylating agents, anthracyclines, vinca alkaloids, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis, proteosome inhibitors, and radiation (*e.g.*, local or whole body irradiation).

Alternatively, or in combination with the aforesaid combinations, the methods and compositions described herein can be administered in combination with one or more of: an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy.

Exemplary non-limiting combinations and uses of the anti-PD-L1 antibody molecules include the following.

In certain embodiments, the anti-PD-L1 antibody molecule is administered in combination with a modulator of a costimulatory molecule or an inhibitory molecule, *e.g.*, a co-inhibitory ligand or receptor.

In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with a modulator, *e.g.*, agonist, of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

In another embodiment, the anti-PD-L1 antibody molecule is used in combination with a costimulatory molecule, *e.g.*, an agonist associated with a positive signal that includes a costimulatory domain of CD28, CD27, ICOS and GITR.

Exemplary GITR agonists include, *e.g.*, GITR fusion proteins and anti-GITR antibodies (*e.g.*, bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B1, U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, *e.g.*, in U.S. Patent No.: 7,025,962, European Patent No.: 1947183B1, U.S. Patent No.: 7,812,135, U.S. Patent No.: 8,388,967, U.S. Patent No.: 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.:WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Patent No.: 7,618,632, and PCT Publication No.: WO 2011/051726.

In one embodiment, the anti-PD-L1 antibody molecule is administered in combination with an inhibitor of an inhibitory molecule of an immune checkpoint molecule. It will be understood by those of ordinary skill in the art, that the term "immune checkpoints" means a group of molecules on the cell surface of CD4 and CD8 T cells. These molecules can effectively serve as "brakes" to down-modulate or inhibit an anti-tumor immune response. Immune checkpoint molecules include, but are not limited to, Programmed Death 1 (PD-1), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), B7H1, B7H4, OX-40, CD137, CD40, and LAG-3, which directly inhibit immune cells. Immunotherapeutic agents which can act as immune checkpoint

inhibitors useful in the methods of the present invention, include, but are not limited to, inhibitors of PD-1, PD-L2, CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), and/or TGFR beta. Inhibition of an inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule.

In one embodiment, the inhibitor is a soluble ligand (*e.g.*, a CTLA-4-Ig or a TIM-3-Ig), or an antibody or antibody fragment that binds to PD-1, PD-L2 or CTLA-4. For example, the anti-PD-L1 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, *e.g.*, ipilimumab, for example, to treat a cancer (*e.g.*, a cancer chosen from: a melanoma, *e.g.*, a metastatic melanoma; a lung cancer, *e.g.*, a non-small cell lung carcinoma; or a prostate cancer). Exemplary anti-CTLA-4 antibodies include Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9). In one embodiment, the anti-PD-L1 antibody molecule is administered after treatment, *e.g.*, after treatment of a melanoma, with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib). Exemplary doses that can be use include a dose of anti-PD-L1 antibody molecule of about 1 to 10 mg/kg, *e.g.*, 3 mg/kg, and a dose of an anti-CTLA-4 antibody, *e.g.*, ipilimumab, of about 3 mg/kg.

Immune inhibitory molecules, *e.g.*, PD-L1 and LAG-3, can regulate, *e.g.*, synergistically regulate, T-cell function to promote tumoral immune escape. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody or an antigen-binding fragment thereof. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof. In yet other embodiments, the anti-PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody and an anti-TIM-3 antibody, or antigen-binding fragments thereof. The combination of antibodies recited herein can be administered separately, *e.g.*, as separate antibodies, or linked, *e.g.*, as a bispecific or trispecific antibody molecule.

In some embodiments, the antibody molecule (*e.g.*, mono-, bi- or trispecific antibody) for TIM-3, LAG-3 and/or PD-1 used in any of the methods disclosed herein includes an amino acid sequence, or is encoded by a nucleotide sequence as described herein (*e.g.*, as disclosed in the section entitled "Inhibitors of Immune Checkpoint Molecules" starting on page 218 hereinbelow (including all publications mentioned therein).

In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5 inhibitor), *e.g.*, an anti-CEACAM antibody molecule. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti-CEACAM-1 antibody molecule. In another embodiment, the anti-PD-L1 antibody molecule is administered in combination with a CEACAM-5 inhibitor, *e.g.*, an anti- CEACAM-5 antibody molecule. In one embodiment, a bispecific antibody that includes an anti-PD-L1 antibody molecule and an anti-TIM-3 or anti-LAG-3 antibody, or antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor). The efficacy of the aforesaid combinations can be tested in animal models known in the art.

In one embodiment, the inhibitor of CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5) is an anti-CEACAM antibody molecule. Without wishing to be bound by theory, CEACAM-1 has been described as a ligand and partner of TIM-3 (see *e.g.*, WO 2014/022332). Synergistic *in vivo* effect of the combination of anti-TIM-3 and anti-CEACAM-1 antibodies have been detected in xenograft cancer models (*see e.g.*, WO 2014/022332). Tumors are believed to use CEACAM-1 or CEACAM-5 to inhibit the immune system, as described in, *e.g.*, Markel *et al. J Immunol.* 2002 Mar 15;168(6):2803-10; Markel et al. *J Immunol.* 2006 Nov 1;177(9):6062-71; Markel et al. *Immunology.* 2009 Feb;126(2):186-200; Markel et al. *Cancer Immunol Immunother.* 2010 Feb;59(2):215-30; Ortenberg et al. *Mol Cancer Ther.* 2012 Jun;11(6):1300-10; Stern et al. *J Immunol.* 2005 Jun 1;174(11):6692-701; Zheng et al. *PLoS One.* 2010 Sep 2;5(9). pii: e12529. Thus, CEACAM inhibitors can be used with the other immunomodulators described herein (*e.g.*, anti-PD-1 or anti-TIM-3 inhibitors) to enhance an immune response against a cancer, *e.g.*, melanoma, lung cancer (*e.g.*, NSCLC), bladder, colon or ovarian cancer, or other cancers as described herein. In one embodiment, the inhibitor of CEACAM is an anti-CEACAM-1 antibody as described in WO 2010/125571, WO 2013/82366 and WO 2014/022332, *e.g.*, a

monoclonal antibody 34B1, 26H7, and 5F4 or a recombinant form thereof, as described in, *e.g.*, US 2004/0047858, US 7,132,255 and WO 99/52552. In other embodiments, the anti-CEACAM antibody is an anti-CEACAM-1 and/or anti-CEACAM-5 antibody molecule as described in, *e.g.*, WO 2010/125571, WO 2013/054331 and US 2014/0271618.

In some embodiments, the PD-L1 and LAG-3 immune inhibitory molecules (*e.g.*, antibody molecules) are administered in combination with each other, *e.g.*, to treat cancer. In some embodiments, the patient is a patient who progressed (*e.g.*, experienced tumor growth) during therapy with a PD-1 inhibitor (*e.g.*, an antibody molecule as described herein) and/or a PD-L1 inhibitor (*e.g.*, antibody molecule). In some embodiments, therapy with the PD-L1 antibody molecule and/or PD-L1 antibody molecule is continued, and a LAG-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.

In some embodiments, the PD-L1 and TIM-3 immune inhibitory molecules (*e.g.*, antibody molecules) are administered in combination with each other, *e.g.*, to treat cancer. In some embodiments, the patient is a patient who progressed (*e.g.*, experienced tumor growth) during therapy with a PD-L1 inhibitor (*e.g.*, an antibody molecule as described herein) and/or a PD-L1 inhibitor (*e.g.*, antibody molecule). In some embodiments, therapy with the PD-1 antibody molecule and/or PD-L1 antibody molecule is continued, and a TIM-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.

In other embodiments, the anti-PD-L1 antibody molecule is administered in combination with a cytokine, *e.g.*, interleukin-2, -15, -12, or -21. In certain embodiments, the combination of anti-PD-L1 antibody molecule and cytokine described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor or melanoma).

Exemplary immunomodulators that can be used in combination with anti-PD-L1 antibody molecules include, but are not limited to, *e.g.*, afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®), actimid (CC4047); and cytokines, *e.g.*, IL-21 or IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

In yet other embodiments, the anti-PD-L1 antibody molecule is used in combination with an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor (*e.g.*, INCB24360) in a subject with advanced or metastatic cancer (*e.g.*, a patient with metastic and recurrent NSCL cancer).

In other embodiments, the anti-PD-L1 antibody molecules are administered to a subject in conjunction with (*e.g.,* before, simultaneously or following) one or more of: bone marrow transplantation, T cell ablative therapy using chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, and/or antibodies such as OKT3 or CAMPATH. In one embodiment, the anti-PD-L1 antibody molecules are administered following B-cell ablative therapy such as agents that react with CD20, *e.g.*, Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive the anti-PD-L1 antibody molecules. In an additional embodiment, the anti-PD-L1 antibody molecules are administered before or following surgery.

Another example of a combination is an anti-PD-L1 antibody in combination with decarbazine for the treatment of melanoma. Without being bound by theory, the combined use of PD-L1 blockade and chemotherapy is believed to be facilitated by cell death, that is a consequence of the cytotoxic action of most chemotherapeutic compounds, which can result in increased levels of tumor antigen in the antigen presentation pathway. Other combination therapies that may result in synergy with PD-L1 blockade through cell death are radiation, surgery, and hormone deprivation. Each of these protocols creates a source of tumor antigen in the host. Angiogenesis inhibitors may also be combined with PD-L1 blockade. Inhibition of angiogenesis leads to tumor cell death which may feed tumor antigen into host antigen presentation pathways.

PD-L1 blocking antibodies can also be used in combination with bispecific antibodies. Bispecific antibodies can be used to target two separate antigens. For example anti-Fc receptor/anti tumor antigen (*e.g.*, Her-2/neu) bispecific antibodies have been used to target macrophages to sites of tumor. This targeting may more effectively activate tumor specific responses. The T cell arm of these responses would by augmented by the use of PD-L1 blockade. Alternatively, antigen may be delivered directly to DCs by the use of bispecific antibodies which bind to tumor antigen and a dendritic cell specific cell surface marker.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of proteins which are expressed by the tumors and which are immunosuppressive. These include among others TGF-beta (Kehrl, J. *et al.* (1986) *J. Exp. Med.* 163: 1037-1050), IL-10 (Howard, M. & O'Garra, A. (1992) *Immunology*

Today 13: 198-200), and Fas ligand (Hahne, M. *et al.* (1996) *Science* 274: 1363-1365). Antibodies or antigen-binding fragments thereof to each of these entities may be used in combination with anti-PD-L1 to counteract the effects of the immunosuppressive agent and favor tumor immune responses by the host.

Other antibodies which may be used to activate host immune responsiveness can be used in combination with anti-PD-L1. These include molecules on the surface of dendritic cells which activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity (Ridge, J. *et al.* (1998) *Nature* 393: 474-478) and can be used in conjunction with PD-L1 antibodies (Ito, N. *et al.* (2000) I*mmunobiology* 201 (5) 527-40). Antibodies to T cell costimulatory molecules such as CTLA-4 (*e.g.,* U.S. Pat. No. 5,811,097), OX-40 (Weinberg, A. *et al.* (2000) *Immunol* 164: 2160-2169), 4-1BB (Melero, I. *et al.* (1997) *Nature Medicine* 3: 682-685 (1997), and ICOS (Hutloff, A. *et al.* (1999) *Nature* 397: 262-266) may also provide for increased levels of T cell activation.

Additional exemplary standard of care treatments are described in the section entitled "Combination Therapies" below.

In all of the methods described herein, PD-L1 blockade can be combined with other forms of immunotherapy such as cytokine treatment (*e.g.,* interferons, GM-CSF, G-CSF, IL-2, IL-21), or bispecific antibody therapy, which provides for enhanced presentation of tumor antigens (*see e.g.*, Holliger (1993) *Proc. Natl. Acad. Sci.* USA 90:6444-6448; Poljak (1994) *Structure* 2:1121-1123).

Methods of administering the antibody molecules are known in the art and are described below. Suitable dosages of the molecules used will depend on the age and weight of the subject and the particular drug used. Dosages and therapeutic regimens of the anti-PD-L1 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-PD-L1 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. In some embodiments, the anti-PD-L1 antibody molecule is administered at a dose of about 1 mg/kg, about 3 mg/kg, or 10 mg/kg, about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg. In some embodiments, the anti-PD-L1 antibody molecule is administered at a dose of about 1-3 mg/kg, or about 3-10 mg/kg. In some embodiments, the anti-PD-L1 antibody molecule is administered at a dose of about 0.5-2, 2-4, 2-5, 5-15, or 5-20 mg/kg. The dosing

schedule can vary from *e.g.*, once a week to once every 2, 3, or 4 weeks. In one embodiment, the anti-PD-L1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

The antibody molecules can be used unconjugated or conjugated to a second agent, *e.g.*, a cytotoxic drug, radioisotope, or a protein, *e.g.*, a protein toxin or a viral protein. This method includes: administering the antibody molecule, alone or conjugated to a cytotoxic drug, to a subject requiring such treatment. The antibody molecules can be used to deliver a variety of therapeutic agents, *e.g.*, a cytotoxic moiety, *e.g.*, a therapeutic drug, a radioisotope, molecules of plant, fungal, or bacterial origin, or biological proteins (*e.g.*, protein toxins) or particles (*e.g.*, a recombinant viral particles, *e.g.*; via a viral coat protein), or mixtures thereof.

Immunosuppression

Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions.

Deliberately induced immunosuppression (*e.g.,* by an immunosuppressant (*e.g.,* an immunosuppressive drug or an environmental toxin), surgery (splenectomy), plasmapharesis, or radiation) can be performed to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease.

Non-deliberate immunosuppression can occur in, *e.g.,* malnutrition, aging, many types of cancer (*e.g.,* leukemia, lymphoma, multiple myeloma), and certain chronic infections *e.g.,* Human Immunodeficiency virus (HIV). The unwanted effect in non-deliberate immunosuppression is immunodeficiency that results in increased susceptibility to pathogens *e.g.,* bacteria and virus. Immunodeficiency can be a potential adverse effect of certain immunosuppressant drugs. As used herein, in some embodiments, the terms "immunosuppressed," "immunodificient" or "immunocompromised" may be used interchangeably.

Immunosuppression is one of the leading causes of death in septic patients. Neutrophils are classical components of innate immunology, but neutrophils might display antigen presenting function and inhibit lymphocyte proliferation by expressing PD-L1.

Accordingly, in one embodiment, the invention provides a method of inhibiting immunosuppression in a subject, comprising administering to the subject a therapeutically effective amount of an anti-PD-L1 antibody molecule described herein. In one embodiment, the methods are suitable for the treatment of sepsis.

In one aspect, a method of treating a subject, *e.g.*, reducing or ameliorating, immunosuppression, in a subject is provided. In an embodiment, the subject is suffering from sepsis or is at risk of developing sepsis. In another embodiment, the subject has or is at risk of developing chronic infection (*e.g.,* HIV) or cancer. In yet another embodiment, the subject is receiving or has received an anti-cancer therapy, *e.g.,* chemotherapy or radiation therapy. The method includes administering to the subject one or more anti-PD-L1 antibody molecules described herein, alone or in combination with other agents or therapeutic modalities.

Additional Combination Therapies

The anti-PD-L1 antibody molecule can be used in combination with other therapies. For example, the combination therapy can include a composition of the present invention co-formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the antibody molecules are administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

By "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The anti-PD-L1 antibody molecules can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The anti-PD-L1 antibody molecule and the other agent or therapeutic protocol can be administered in any order. In general, each agent will be

administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutic agent utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Immunomodulators

In certain embodiments, the immunomodulator used in combination with an anti-PD-L1 antibody molecule, or in the combinations disclosed herein (*e.g.*, in combination with a therapeutic agent chosen from an antigen-presentation combination) is an inhibitor of an immune checkpoint molecule. In one embodiment, the immunomodulator is an inhibitor of PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. In one embodiment, the inhibitor of an immune checkpoint molecule inhibits PD-1, PD-L1, LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), CTLA-4, or any combination thereof.

Inhibition of an inhibitory molecule can be performed at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand (*e.g.*, PD-1-Ig or CTLA-4 Ig), or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule; *e.g.*, an antibody or fragment thereof (also referred to herein as "an antibody molecule") that binds to PD-1, PD-L1, PD-L2, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta, or a combination thereof.

In certain embodiments, the antibody molecule is in the form of a bispecific or multispecific antibody molecule. In one embodiment, the bispecific antibody molecule has a first binding specificity to PD-1 or PD-L1 and a second binding specifity, *e.g.*, a second binding specificity to TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), LAG-3, or PD-L2. In one embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and TIM-3. In another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and LAG-3. In another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and CEACAM (*e.g.*,

CEACAM-1, -3 and/or -5). In another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and CEACAM-1. In still another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and CEACAM-3. In yet another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and CEACAM-5. In another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1. In yet another embodiment, the bispecific antibody molecule binds to PD-1 and PD-L2. In another embodiment, the bispecific antibody molecule binds to TIM-3 and LAG-3. In another embodiment, the bispecific antibody molecule binds to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) and LAG-3. In another embodiment, the bispecific antibody molecule binds to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) and TIM-3. Any combination of the aforesaid molecules can be made in a multispecific antibody molecule, *e.g.*, a trispecific antibody that includes a first binding specificity to PD-1 or PD-1, and a second and third binding specifities to two or more of: TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), LAG-3, or PD-L2.

In certain embodiments, the immunomodulator is an inhibitor of PD-1, *e.g.*, human PD-1 (*e.g.*, an antibody molecule as described herein). In another embodiment, the immunomodulator is an inhibitor of PD-L1, *e.g.*, human PD-L1. In one embodiment, the inhibitor of PD-1 or PD-L1 is an antibody molecule to PD-1 or PD-L1. The PD-1 or PD-L1 inhibitor can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of LAG-3, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) or CTLA-4. In an exemplary embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a LAG-3 inhibitor, *e.g.*, an anti-LAG-3 antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a TIM-3 inhibitor, *e.g.*, an anti-TIM-3 antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, -3 and/or -5 inhibitor), *e.g.*, an anti- CEACAM antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti- CEACAM-1 antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a CEACAM-5 inhibitor, *e.g.*, an anti- CEACAM-5 antibody molecule. In yet other embodiments, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-

PD-1 antibody molecule, is administered in combination with a LAG-3 inhibitor, *e.g.*, an anti-LAG-3 antibody molecule, and a TIM-3 inhibitor, *e.g.*, an anti-TIM-3 antibody molecule. Other combinations of immunomodulators with a PD-1 inhibitor (*e.g.,* one or more of PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR) are also within the present invention. Any of the antibody molecules known in the art or disclosed herein can be used in the aforesaid combinations of inhibitors of checkpoint molecule.

In other embodiments, the immunomodulator is an inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), *e.g.*, human CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). In one embodiment, the immunomodulator is an inhibitor of CEACAM-1, *e.g.*, human CEACAM-1. In another embodiment, the immunomodulator is an inhibitor of CEACAM-3, *e.g.*, human CEACAM-3. In another embodiment, the immunomodulator is an inhibitor of CEACAM-5, *e.g.*, human CEACAM-5. In one embodiment, the inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) is an antibody molecule to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). The CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) inhibitor can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of LAG-3, TIM-3, PD-1, PD-L1 or CTLA-4.

In other embodiments, the immunomodulator is an inhibitor of LAG-3, *e.g.*, human LAG-3. In one embodiment, the inhibitor of LAG-3 is an antibody molecule to LAG-3. The LAG-3 inhibitor can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3, PD-1, PD-L1 or CTLA-4.

In other embodiments, the immunomodulator is an inhibitor of TIM-3, *e.g.*, human TIM-3. In one embodiment, the inhibitor of TIM-3 is an antibody molecule to TIM-3. The TIM-3 inhibitor can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), LAG-3, PD-1, PD-L1 or CTLA-4.

In certain embodiments, the immunomodulator used in the combinations disclosed herein (*e.g.*, in combination with a therapeutic agent chosen from an antigen-presentation combination) is an activator or agonist of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding

fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, or CD83 ligand.

In other embodiments, the immunomodulator is a GITR agonist. In one embodiment, the GITR agonist is an antibody molecule to GITR. The GITR agonist can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3 or LAG-3. In some embodiments, the anti-GITR antibody molecule is a bispecific antibody that binds to GITR and PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3 or LAG-3. In one exemplary embodiment, the anti-GITR antibody molecule is administered in combination with an anti-PD-1 antibody molecule (*e.g.*, an anti-PD-1 molecule as described herein). The GITR antibody molecule and the anti-PD-1 antibody molecule may be in the form of separate antibody composition, or as a bispecific antibody molecule. In other embodiments, a GITR agonist can be administered in combination with other costimulatory molecule, *e.g.*, an agonist of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, or CD83 ligand.

In other embodiments, the immunomodulator is an activator of a costimulatory molecule (*e.g.*, an OX40 agonist). In one embodiment, the OX40 agonist is an antibody molecule to OX40. The OX40 agonist can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3 or LAG-3. In some embodiments, the anti- OX40 antibody molecule is a bispecific antibody that binds to GITR and PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3 or LAG-3. In one exemplary embodiment, an OX40 antibody molecule is administered in combination with an anti-PD-1 antibody molecule (*e.g.*, an anti-PD-1 molecule as described herein). The OX40 antibody molecule and the anti-PD-1 antibody molecule may be in the form of separate antibody composition, or as a bispecific antibody molecule. In other embodiments, the OX40 agonist can be administered in combination with other costimulatory molecule, *e.g.*, an agonist of GITR, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, or CD83 ligand.

It is noted that only exemplary combinations of inhibitors of checkpoint inhibitors or agonists of costimulatory molecules are provided herein. Additional combinations of these agents are within the scope of the present invention.

In certain embodiments, the anti-PD-L1 molecules described herein are administered in combination with one or more other inhibitors of PD-1, PD-L1 and/or PD-L2 known in the art. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. In some embodiments, the other anti-PD-1 antibody is chosen from MDX-1106, Merck 3475 or CT-011. In some embodiments, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-Ll or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 inhibitor is AMP-224. In some embodiments, the PD-Ll inhibitor is anti-PD-Ll antibody. In some embodiments, the anti-PD-Ll binding antagonist is chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105. MDX-1105, also known as BMS-936559, is an anti-PD-Ll antibody described in WO2007/005874. Antibody YW243.55.S70 (heavy and light chain variable region sequences shown in SEQ ID Nos. 20 and 21, respectively) is an anti-PD-Ll described in WO 2010/077634.

MDX-1106, also known as MDX-1106-04, ONO-4538 or BMS-936558, is an anti-PD-1 antibody described in WO2006/121168. Merck 3745, also known as MK-3475 or SCH-900475, is an anti-PD-1 antibody described in WO2009/114335. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD-1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. In other embodiments, the anti-PD-1 antibody is pembrolizumab. Pembrolizumab (Trade name Keytruda formerly lambrolizumab also known as MK-3475) disclosed, *e.g.*, in Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44. AMP-224 (B7-DCIg; Amplimmune; *e.g.*, disclosed in WO2010/027827 and WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1. Other anti-PD-1 antibodies include AMP 514 (Amplimmune), among others, *e.g.*, anti-PD-1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

In some embodiments, the other anti-PD-1 antibody is MDX-1106. Alternative names for MDX- 1106 include MDX-1106-04, ONO-4538, BMS-936558 or Nivolumab. In some embodiments, the anti-PD- 1 antibody is Nivolumab (CAS Registry Number: 946414-94-4).

Nivolumab (also referred to as BMS-936558 or MDX1106; Bristol-Myers Squibb) is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO2006/121168. Pembrolizumab or Lambrolizumab (also referred to as MK-3475; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in US 8,354,509 and WO09/114335. MDPL3280A (Genentech / Roche) is a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906. Other anti-PD-L1 binding agents include YW243.55.S70 (heavy and light chain variable regions are shown in SEQ ID NOs 20 and 21 in WO2010/077634) and MDX-1105 (also referred to as BMS-936559, and, *e.g.*, anti-PD-L1 binding agents disclosed in WO2007/005874).

In some embodiments, the antibody molecule (*e.g.*, mono-, bi- or trispecific antibody) for TIM-3, LAG-3 and/or PD-1 used in any of the methods and combinations disclosed herein includes an amino acid sequence, or is encoded by a nucleotide sequence as described herein (*e.g.*, as disclosed in the section entitled "Inhibitors of Immune Checkpoint Molecules" starting on page 218 hereinbelow (including all publications mentioned therein).

Cancer Therapies

Exemplary combinations of anti-PD-L1 antibody molecules (alone or in combination with other stimulatory agents) and standard of care for cancer, include at least the following. In certain embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used in combination with a standard of cancer care chemotherapeutic agent including, but not limited to, anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride

(Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), vinorelbine (Navelbine®), Ibrutinib, idelalisib, and brentuximab vedotin.

Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as

hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

Exemplary anthracyclines include, *e.g.*, doxorubicin (Adriamycin® and Rubex®); bleomycin (lenoxane®); daunorubicin (dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, Cerubidine®); daunorubicin liposomal (daunorubicin citrate liposome, DaunoXome®); mitoxantrone (DHAD, Novantrone®); epirubicin (Ellence™); idarubicin (Idamycin®, Idamycin PFS®); mitomycin C (Mutamycin®); geldanamycin; herbimycin; ravidomycin; and desacetylravidomycin.

Exemplary vinca alkaloids that can be used in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), include, but ate not limited to, vinorelbine tartrate (Navelbine®), Vincristine (Oncovin®), and Vindesine (Eldisine®)); vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, Alkaban-AQ® and Velban®); and vinorelbine (Navelbine®).

Exemplary proteosome inhibitors that can be used in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), include, but ate not limited to, bortezomib (Velcade®); carfilzomib (PX-171-007, (*S*)-4-Methyl-*N*-((*S*)-1-(((*S*)-4-methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-pentanamide); marizomib (NPI-0052); ixazomib citrate (MLN-9708); delanzomib (CEP-18770); and *O*-Methyl-*N*-[(2-methyl-5-thiazolyl)carbonyl]-L-seryl-*O*-methyl-*N*-[(1*S*)-2-[(2*R*)-2-methyl-2-oxiranyl]-2-oxo-1-(phenylmethyl)ethyl]- L-serinamide (ONX-0912).

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a tyrosine kinase inhibitor (*e.g.*, a receptor tyrosine kinase (RTK) inhibitor). Exemplary tyrosine kinase inhibitor include, but are not limited to, an epidermal growth factor (EGF) pathway

inhibitor (*e.g.*, an epidermal growth factor receptor (EGFR) inhibitor), a vascular endothelial growth factor (VEGF) pathway inhibitor (*e.g.*, a vascular endothelial growth factor receptor (VEGFR) inhibitor (*e.g.*, a VEGFR-1 inhibitor, a VEGFR-2 inhibitor, a VEGFR-3 inhibitor)), a platelet derived growth factor (PDGF) pathway inhibitor (*e.g.*, a platelet derived growth factor receptor (PDGFR) inhibitor (*e.g.*, a PDGFR-ß inhibitor)), a RAF-1 inhibitor, a KIT inhibitor and a RET inhibitor. In some embodiments, the anti-cancer agent used in combination with the hedgehog inhibitor is selected from the group consisting of: axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, AEE788, AG-490, AST-6, BMS-599626, CUDC-101, PD153035, pelitinib (EKB-569), vandetanib (zactima), WZ3146, WZ4002, WZ8040, ABT-869 (linifanib), AEE788, AP24534 (ponatinib), AV-951(tivozanib), axitinib, BAY 73-4506 (regorafenib), brivanib alaninate (BMS-582664), brivanib (BMS-540215), cediranib (AZD2171), CHIR-258 (dovitinib), CP 673451, CYC116, E7080, Ki8751, masitinib (AB1010), MGCD-265, motesanib diphosphate (AMG-706), MP-470, OSI-930, Pazopanib Hydrochloride, PD173074, Sorafenib Tosylate(Bay 43-9006), SU 5402, TSU-68(SU6668), vatalanib, XL880 (GSK1363089, EXEL-2880). Selected tyrosine kinase inhibitors are chosen from sunitinib, erlotinib, gefitinib, or sorafenib.

In certain embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a

Vascular Endothelial Growth Factor (VEGF) receptor inhibitors. Exemplary inhibitors of the VEGF/VEGFR are disclosed herein below, *e.g.*, in the section entitled "Exemplary Agents used in the Combinations."

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a PI3K inhibitor. In one embodiment, the PI3K inhibitor is an inhibitor of delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described herein below, *e.g.*, in the section entitled "Exemplary Agents used in the Combinations."

In some embodiments, the anti-PD-L1 antibody molecules described herein is used, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a mTOR inhibitor, *e.g.*, one or more mTOR inhibitors disclosed herein below, *e.g.*, in the section entitled "Exemplary Agents used in the Combinations."

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a BRAF inhibitor, *e.g.*, GSK2118436, RG7204, PLX4032, GDC-0879, PLX4720, and sorafenib tosylate (Bay 43-9006). In some embodiments, the combination includes a RAF inhibitor, *e.g.*, debrafinib or N-{3-[5-(2-aminopyrimidin-4-yl)-2-tert-butyl-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide.

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a MEK inhibitor. In some embodiments, the combination of the anti-PD-L1 antibody and the MEK inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. In certain embodiments, the cancer includes a BRAF mutation (*e.g.*, a BRAF V600E mutation), a BRAF wildtype, a KRAS wildtype or an activating KRAS mutation. The cancer may be at an early, intermediate or late stage.

Any MEK inhibitor can be used in combination including, but not limited to, ARRY-142886, G02442104 (also known as GSK1120212), RDEA436, RDEA119/BAY 869766, AS703026, G00039805 (also known as AZD-6244 or selumetinib), BIX 02188, BIX 02189, CI-1040 (PD-184352), PD0325901, PD98059, U0126, GDC-0973 (Methanone, [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3- hydroxy-3-(25)-2-piperidinyl- 1 -azetidinyl]-), G-38963, G02443714 (also known as AS703206), or a pharmaceutically acceptable salt or solvate thereof..Additional examples of MEK inhibitors are disclosed in WO 2013/019906, WO 03/077914, WO 2005/121142, WO 2007/04415, WO 2008/024725 and WO 2009/085983. In some embodiments, the MEK inhibitor is trametinib or N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide.

In some embodiments, the anti-PD-L1 antibody molecule, *e.g.*, the anti-PD-L1 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), in combination with a JAK2 inhibitor, *e.g.,* CEP-701, INCB18424, CP-690550 (tasocitinib).

In some embodiments, the pharmaceutical composition described herein is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-TIM-3 antibody molecule), in combination with paclitaxel or a paclitaxel agent, *e.g.,* TAXOL®, protein-bound paclitaxel (*e.g.*, ABRAXANE®). Exemplary paclitaxel agents include, but are not limited to, nanoparticle albumin-bound paclitaxel (ABRAXANE, marketed by Abraxis Bioscience), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin, marketed by Protarga), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, marketed by Cell Therapeutic), the tumor-activated prodrug (TAP), ANG105 (Angiopep-2 bound to three molecules of paclitaxel, marketed by ImmunoGen), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1; *see* Li *et al., Biopolymers* (2007) 87:225-230), and glucose-conjugated paclitaxel (*e.g.,* 2'-paclitaxel methyl 2-glucopyranosyl succinate, *see* Liu *et al., Bioorganic & Medicinal Chemistry Letters* (2007) 17:617-620).

Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," refers to radiation

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therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.* At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present invention include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.*, a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

Anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), can be administered in combination with one or more of the existing modalities for treating cancers, including, but not limited to: surgery; radiation therapy (*e.g.*, external-beam therapy which involves three dimensional, conformal radiation therapy where the field of radiation is designed, local radiation (*e.g.*, radition directed to a preselected target or organ), or focused radiation). Focused radiation can be selected from the group consisting of stereotactic radiosurgery, fractionated stereotactic radiosurgery, and intensity-modulated radiation therapy. The focused radiation can have a radiation source selected from the group consisting of a particle beam (proton), cobalt-60 (photon), and a linear accelerator (x-ray), *e.g.*, as decribed in WO 2012/177624.

In certain embodiments, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is administered in combination with an antibody against a Killer-cell Immunoglobulin-like Receptors (also referred to herein as an "anti-KIR antibody"), a pan-KIR antibody, or an anti-NKG2D antibody, and/or an anti-MICA antibody. In certain embodiments, the combination of anti-PD-L1 antibody molecule and anti-KIR antibody, pan-KIR antibody, or an anti-NKG2D antibody described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor, *e.g.*, an advanced solid tumor).

In one embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is administered in combination with a cellular immunotherapy (*e.g.*, Provenge (*e.g.*, Sipuleucel)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination of anti-PD-L1 antibody molecule, Provenge and/or cyclophosphamide is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a prostate cancer, *e.g.*, an advanced prostate cancer).

In another embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is administered in combination with a vaccine, *e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine. In certain embodiments, the combination of anti-PD-L1 antibody molecule and the DC-RCC vaccine is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a renal carcinoma, *e.g.*, metastatic renal cell carcinoma (RCC) or clear cell renal cell carcinoma (CCRCC)).

In yet another embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is administered in combination with chemotherapy, and/or immunotherapy. For example, the anti-PD-L1 antibody molecule can be used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), an anti-TIM-3 antibody, tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells. In one embodiment, the anti-PD-L1 antibody molecule is used in combination with an anti-TIM-3 antibody to treat a myeloma, *e.g.*, a multiple myeloma.

In one embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is used in combination with chemotherapy to treat a lung cancer, *e.g.*, non-small cell lung cancer. In one embodiment, the anti-PD-L1 antibody molecule is used with platinum doublet therapy to treat lung cancer.

In yet another embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) (*e.g.*, clear cell renal cell carcinoma (CCRCC) or metastatic RCC. The anti-PD-L1 antibody molecule can be

administered in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeted agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib; an RNAi inhibitor), or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of pancreatic cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, paclitaxel or a paclitaxel agent (*e.g.*, a paclitaxel formulation such as TAXOL, an albumin-stabilized nanoparticle paclitaxel formulation (*e.g.*, ABRAXANE) or a liposomal paclitaxel formulation); gemcitabine (*e.g.*, gemcitabine alone or in combination with AXP107-11); other chemotherapeutic agents such as oxaliplatin, 5-fluorouracil, capecitabine, rubitecan, epirubicin hydrochloride, NC-6004, cisplatin, docetaxel (*e.g.*, TAXOTERE), mitomycin C, ifosfamide; interferon; tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, panitumumab, cetuximab, nimotuzumab); HER2/neu receptor inhibitor (*e.g.*, trastuzumab); dual kinase inhibitor (*e.g.*, bosutinib, saracatinib, lapatinib, vandetanib); multikinase inhibitor (*e.g.*, sorafenib, sunitinib, XL184, pazopanib); VEGF inhibitor (*e.g.*, bevacizumab, AV-951, brivanib); radioimmunotherapy (*e.g.*, XR303); cancer vaccine (*e.g.*, GVAX, survivin peptide); COX-2 inhibitor (*e.g.*, celecoxib); IGF-1 receptor inhibitor (*e.g.*, AMG 479, MK-0646); mTOR inhibitor (*e.g.*, everolimus, temsirolimus); IL-6 inhibitor (*e.g.*, CNTO 328); cyclin-dependent kinase inhibitor (*e.g.*, P276-00, UCN-01); Altered Energy Metabolism-Directed (AEMD) compound (*e.g.*, CPI-613); HDAC inhibitor (*e.g.*, vorinostat); TRAIL receptor 2 (TR-2) agonist (*e.g.*, conatumumab); MEK inhibitor (*e.g.*, AS703026, selumetinib, GSK1120212); Raf/MEK dual kinase inhibitor (*e.g.*, RO5126766); Notch signaling inhibitor (*e.g.*, MK0752); monoclonal antibody-antibody fusion protein (*e.g.*, L19IL2); curcumin; HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090); rIL-2;, denileukin diftitox; topoisomerase 1 inhibitor (*e.g.*, irinotecan, PEP02); statin (*e.g.*, simvastatin); Factor VIIa inhibitor (*e.g.*, PCI-27483); AKT inhibitor (*e.g.*, RX-0201); hypoxia-activated prodrug (*e.g.*, TH-302); metformin hydrochloride, gamma-secretase inhibitor (*e.g.*, RO4929097); ribonucleotide reductase inhibitor (*e.g.*, 3-AP); immunotoxin (*e.g.*, HuC242-DM4); PARP inhibitor (*e.g.*, KU-0059436, veliparib); CTLA-4 inhbitor (*e.g.*, CP-675,206, ipilimumab); AdV-tk therapy;

proteasome inhibitor (*e.g.*, bortezomib (Velcade), NPI-0052); thiazolidinedione (*e.g.*, pioglitazone); NPC-1C; Aurora kinase inhibitor (*e.g.*, R763/AS703569), CTGF inhibitor (*e.g.*, FG-3019); siG12D LODER; and radiation therapy (*e.g.*, tomotherapy, stereotactic radiation, proton therapy), surgery, and a combination thereof. In certain embodiments, a combination of paclitaxel or a paclitaxel agent, and gemcitabine can be used with the anti-PD-L1 antibody molecules described herein.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of small cell lung cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, etoposide, carboplatin, cisplatin, oxaliplatin, irinotecan, topotecan, gemcitabine, liposomal SN-38, bendamustine, temozolomide, belotecan, NK012, FR901228, flavopiridol); tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, gefitinib, cetuximab, panitumumab); multikinase inhibitor (*e.g.*, sorafenib, sunitinib); VEGF inhibitor (*e.g.*, bevacizumab, vandetanib); cancer vaccine (*e.g.*, GVAX); Bcl-2 inhibitor (*e.g.*, oblimersen sodium, ABT-263); proteasome inhibitor (*e.g.*, bortezomib (Velcade), NPI-0052), paclitaxel or a paclitaxel agent; docetaxel; IGF-1 receptor inhibitor (*e.g.*, AMG 479); HGF/SF inhibitor (*e.g.*, AMG 102, MK-0646); chloroquine; Aurora kinase inhibitor (*e.g.*, MLN8237); radioimmunotherapy (*e.g.*, TF2); HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090); mTOR inhibitor (*e.g.*, everolimus); Ep-CAM-/CD3-bispecific antibody (*e.g.*, MT110); CK-2 inhibitor (*e.g.*, CX-4945); HDAC inhibitor (*e.g.*, belinostat); SMO antagonist (*e.g.*, BMS 833923); peptide cancer vaccine, and radiation therapy (*e.g.*, intensity-modulated radiation therapy (IMRT), hypofractionated radiotherapy, hypoxia-guided radiotherapy), surgery, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of non-small cell lung cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, vinorelbine, cisplatin, docetaxel, pemetrexed disodium, etoposide, gemcitabine, carboplatin, liposomal SN-38, TLK286, temozolomide, topotecan, pemetrexed disodium, azacitidine, irinotecan, tegafur-gimeracil-oteracil potassium, sapacitabine); tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, gefitinib, cetuximab, panitumumab, necitumumab, PF-00299804, nimotuzumab, RO5083945), MET inhibitor (*e.g.*, PF-02341066, ARQ 197), PI3K kinase inhibitor (*e.g.*, XL147, GDC-0941),

Raf/MEK dual kinase inhibitor (*e.g.*, RO5126766), PI3K/mTOR dual kinase inhibitor (*e.g.*, XL765), SRC inhibitor (*e.g.*, dasatinib), dual inhibitor (*e.g.*, BIBW 2992, GSK1363089, ZD6474, AZD0530, AG-013736, lapatinib, MEHD7945A, linifanib), multikinase inhibitor (*e.g.*, sorafenib, sunitinib, pazopanib, AMG 706, XL184, MGCD265, BMS-690514, R935788), VEGF inhibitor (*e.g.*, endostar, endostatin, bevacizumab, cediranib, BIBF 1120, axitinib, tivozanib, AZD2171), cancer vaccine (*e.g.*, BLP25 liposome vaccine , GVAX, recombinant DNA and adenovirus expressing L523S protein), Bcl-2 inhibitor (*e.g.*, oblimersen sodium), proteasome inhibitor (*e.g.*, bortezomib, carfilzomib, NPI-0052, MLN9708), paclitaxel or a paclitaxel agent, docetaxel, IGF-1 receptor inhibitor (*e.g.*, cixutumumab, MK-0646, OSI 906, CP-751,871, BIIB022), hydroxychloroquine, HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090, AUY922, XL888), mTOR inhibitor (*e.g.*, everolimus, temsirolimus, ridaforolimus), Ep-CAM-/CD3-bispecific antibody (*e.g.*, MT110), CK-2 inhibitor (*e.g.*, CX-4945), HDAC inhibitor (*e.g.*, MS 275, LBH589, vorinostat, valproic acid, FR901228), DHFR inhibitor (*e.g.*, pralatrexate), retinoid (*e.g.*, bexarotene, tretinoin), antibody-drug conjugate (*e.g.*, SGN-15), bisphosphonate (*e.g.*, zoledronic acid), cancer vaccine (*e.g.*, belagenpumatucel-L), low molecular weight heparin (LMWH) (*e.g.*, tinzaparin, enoxaparin), GSK1572932A, melatonin, talactoferrin, dimesna, topoisomerase inhibitor (*e.g.*, amrubicin, etoposide, karenitecin), nelfinavir, cilengitide, ErbB3 inhibitor (*e.g.*, MM-121, U3-1287), survivin inhibitor (*e.g.*, YM155, LY2181308), eribulin mesylate, COX-2 inhibitor (*e.g.*, celecoxib), pegfilgrastim, Polo-like kinase 1 inhibitor (*e.g.*, BI 6727), TRAIL receptor 2 (TR-2) agonist (*e.g.*, CS-1008), CNGRC peptide (SEQ ID NO: 225)-TNF alpha conjugate, dichloroacetate (DCA), HGF inhibitor (*e.g.*, SCH 900105), SAR240550, PPAR-gamma agonist (*e.g.*, CS-7017), gamma-secretase inhibitor (*e.g.*, RO4929097), epigenetic therapy (*e.g.*, 5-azacitidine), nitroglycerin, MEK inhibitor (*e.g.*, AZD6244), cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), cholesterol-Fus1, antitubulin agent (*e.g.*, E7389), farnesyl-OH-transferase inhibitor (*e.g.*, lonafarnib), immunotoxin (*e.g.*, BB-10901, SS1 (dsFv) PE38), fondaparinux, vascular-disrupting agent (*e.g.*, AVE8062), PD-L1 inhibitor (*e.g.*, MDX-1105, MDX-1106), beta-glucan, NGR-hTNF, EMD 521873, MEK inhibitor (*e.g.*, GSK1120212), epothilone analog (*e.g.*, ixabepilone), kinesin-spindle inhibitor (*e.g.*, 4SC-205), telomere targeting agent (*e.g.*, KML-001), P70 pathway inhibitor (*e.g.*, LY2584702), AKT inhibitor (*e.g.*, MK-2206), angiogenesis inhibitor (*e.g.*, lenalidomide), Notch signaling inhibitor (*e.g.*, OMP-21M18), radiation therapy, surgery, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of ovarian cancer includes, but is not limited to, a chemotherapeutic agent (*e.g.*, paclitaxel or a paclitaxel agent; docetaxel; carboplatin; gemcitabine; doxorubicin; topotecan; cisplatin; irinotecan, TLK286, ifosfamide, olaparib, oxaliplatin, melphalan, pemetrexed disodium, SJG-136, cyclophosphamide, etoposide, decitabine); ghrelin antagonist (*e.g.*, AEZS-130), immunotherapy (*e.g.*, APC8024, oregovomab, OPT-821), tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib), dual inhibitor (*e.g.*, E7080), multikinase inhibitor (*e.g.*, AZD0530, JI-101, sorafenib, sunitinib, pazopanib), ON 01910.Na), VEGF inhibitor (*e.g.*, bevacizumab, BIBF 1120, cediranib, AZD2171), PDGFR inhibitor (*e.g.*, IMC-3G3), paclitaxel, topoisomerase inhibitor (*e.g.*, karenitecin, Irinotecan), HDAC inhibitor (*e.g.*, valproate, vorinostat), folate receptor inhibitor (*e.g.*, farletuzumab), angiopoietin inhibitor (*e.g.*, AMG 386), epothilone analog (*e.g.*, ixabepilone), proteasome inhibitor (*e.g.*, carfilzomib), IGF-1 receptor inhibitor (*e.g.*, OSI 906, AMG 479), PARP inhibitor (*e.g.*, veliparib, AG014699, iniparib, MK-4827), Aurora kinase inhibitor (*e.g.*, MLN8237, ENMD-2076), angiogenesis inhibitor (*e.g.*, lenalidomide), DHFR inhibitor (*e.g.*, pralatrexate), radioimmunotherapeutic agnet (*e.g.*, Hu3S193), statin (*e.g.*, lovastatin), topoisomerase 1 inhibitor (*e.g.*, NKTR-102), cancer vaccine (*e.g.*, p53 synthetic long peptides vaccine, autologous OC-DC vaccine), mTOR inhibitor (*e.g.*, temsirolimus, everolimus), BCR/ABL inhibitor (*e.g.*, imatinib), ET-A receptor antagonist (*e.g.*, ZD4054), TRAIL receptor 2 (TR-2) agonist (*e.g.*, CS-1008), HGF/SF inhibitor (*e.g.*, AMG 102), EGEN-001, Polo-like kinase 1 inhibitor (*e.g.*, BI 6727), gamma-secretase inhibitor (*e.g.*, RO4929097), Wee-1 inhibitor (*e.g.*, MK-1775), antitubulin agent (*e.g.*, vinorelbine, E7389), immunotoxin (*e.g.*, denileukin diftitox), SB-485232, vascular-disrupting agent (*e.g.*, AVE8062), integrin inhibitor (*e.g.*, EMD 525797), kinesin-spindle inhibitor (*e.g.*, 4SC-205), revlimid, HER2 inhibitor (*e.g.*, MGAH22), ErrB3 inhibitor (*e.g.*, MM-121), radiation therapy; and combinations thereof.

In one exemplary embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), HSCT (Cook, R. (2008) *J Manag Care Pharm.* 14(7 Suppl):19-25), an anti-TIM-3 antibody (Hallett,

WHD *et al.* (2011) *J of American Society for Blood and Marrow Transplantation* 17(8):1133-145), tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells (reviewed in Yi, Q. (2009) *Cancer J.* 15(6):502-10).

In yet another embodiment, the anti-PD-L1 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), is used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) or metastatic RCC. The anti-PD-L1 antibody molecule can be administered in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeted agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF, *e.g.*, bevacizumab (Rini, B.I. *et al.* (2010) *J. Clin. Oncol.* 28(13):2137-2143)); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib (reviewed in Pal. S.K. *et al.* (2014) *Clin. Advances in Hematology & Oncology* 12(2):90-99)); an RNAi inhibitor), or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus (Hudes, G. *et al.* (2007) *N. Engl. J. Med.* 356(22):2271-2281, Motzer, R.J. *et al.* (2008) *Lancet* 372: 449-456).

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of chronic myelogenous leukemia (AML) according to the invention includes, but is not limited to, a chemotherapeutic (*e.g.*, cytarabine, hydroxyurea, clofarabine, melphalan, thiotepa, fludarabine, busulfan, etoposide, cordycepin, pentostatin, capecitabine, azacitidine, cyclophosphamide, cladribine, topotecan), tyrosine kinase inhibitor (*e.g.*, BCR/ABL inhibitor (*e.g.*, imatinib, nilotinib), ON 01910.Na, dual inhibitor (*e.g.*, dasatinib, bosutinib), multikinase inhibitor (*e.g.*, DCC-2036, ponatinib, sorafenib, sunitinib, RGB-286638)), interferon alfa, steroids, apoptotic agent (*e.g.*, omacetaxine mepesuccinat), immunotherapy (*e.g.*, allogeneic CD4+ memory Th1-like T cells/microparticle-bound anti-CD3/anti-CD28, autologous cytokine induced killer cells (CIK), AHN-12), CD52 targeting agent (*e.g.*, alemtuzumab), HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090, AUY922, XL888), mTOR inhibitor (*e.g.*, everolimus), SMO antagonist (*e.g.*, BMS 833923), ribonucleotide reductase inhibitor (*e.g.*, 3-AP), JAK-2 inhibitor (*e.g.*, INCB018424), Hydroxychloroquine, retinoid (*e.g.*, fenretinide), cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), HDAC inhibitor

(*e.g.*, belinostat, vorinostat, JNJ-26481585), PARP inhibitor (*e.g.*, veliparib), MDM2 antagonist (*e.g.*, RO5045337), Aurora B kinase inhibitor (*e.g.*, TAK-901), radioimmunotherapy (*e.g.*, actinium-225-labeled anti-CD33 antibody HuM195), Hedgehog inhibitor (*e.g.*, PF-04449913), STAT3 inhibitor (*e.g.*, OPB-31121), KB004, cancer vaccine (*e.g.*, AG858), bone marrow transplantation, stem cell transplantation, radiation therapy, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of chronic lymphocytic leukemia (CLL) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, fludarabine, cyclophosphamide, doxorubicin, vincristine, chlorambucil, bendamustine, chlorambucil, busulfan, gemcitabine, melphalan, pentostatin, mitoxantrone, 5-azacytidine, pemetrexed disodium), tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib), BTK inhibitor (*e.g.*, PCI-32765), multikinase inhibitor (*e.g.*, MGCD265, RGB-286638), CD-20 targeting agent (*e.g.*, rituximab, ofatumumab, RO5072759, LFB-R603), CD52 targeting agent (*e.g.*, alemtuzumab), prednisolone, darbepoetin alfa, lenalidomide, Bcl-2 inhibitor (*e.g.*, ABT-263), immunotherapy (*e.g.*, allogeneic CD4+ memory Th1-like T cells/microparticle-bound anti-CD3/anti-CD28, autologous cytokine induced killer cells (CIK)), HDAC inhibitor (*e.g.*, vorinostat, valproic acid, LBH589, JNJ-26481585, AR-42), XIAP inhibitor (*e.g.*, AEG35156), CD-74 targeting agent (*e.g.*, milatuzumab), mTOR inhibitor (*e.g.*, everolimus), AT-101, immunotoxin (*e.g.*, CAT-8015, anti-Tac(Fv)-PE38 (LMB-2)), CD37 targeting agent (*e.g.*, TRU-016), radioimmunotherapy (*e.g.*, 131-tositumomab), hydroxychloroquine, perifosine, SRC inhibitor (*e.g.*, dasatinib), thalidomide, PI3K delta inhibitor (*e.g.*, CAL-101), retinoid (*e.g.*, fenretinide), MDM2 antagonist (*e.g.*, RO5045337), plerixafor, Aurora kinase inhibitor (*e.g.*, MLN8237, TAK-901), proteasome inhibitor (*e.g.*, bortezomib), CD-19 targeting agent (*e.g.*, MEDI-551, MOR208), MEK inhibitor (*e.g.*, ABT-348), JAK-2 inhibitor (*e.g.*, INCB018424), hypoxia-activated prodrug (*e.g.*, TH-302), paclitaxel or a paclitaxel agent, HSP90 inhibitor, AKT inhibitor (*e.g.*, MK2206), HMG-CoA inhibitor (*e.g.*, simvastatin), GNKG186, radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of acute lymphocytic

leukemia (ALL) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, prednisolone, dexamethasone, vincristine, asparaginase, daunorubicin, cyclophosphamide, cytarabine, etoposide, thioguanine, mercaptopurine, clofarabine, liposomal annamycin, busulfan, etoposide, capecitabine, decitabine, azacitidine, topotecan, temozolomide), tyrosine kinase inhibitor (*e.g.*, BCR/ABL inhibitor (*e.g.*, imatinib, nilotinib), ON 01910.Na, multikinase inhibitor (*e.g.*, sorafenib)), CD-20 targeting agent (*e.g.*, rituximab), CD52 targeting agent (*e.g.*, alemtuzumab), HSP90 inhibitor (*e.g.*, STA-9090), mTOR inhibitor (*e.g.*, everolimus, rapamycin), JAK-2 inhibitor (*e.g.*, INCB018424), HER2/neu receptor inhibitor (*e.g.*, trastuzumab), proteasome inhibitor (*e.g.*, bortezomib), methotrexate, asparaginase, CD-22 targeting agent (*e.g.*, epratuzumab, inotuzumab), immunotherapy (*e.g.*, autologous cytokine induced killer cells (CIK), AHN-12), blinatumomab, cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), CD45 targeting agent (*e.g.*, BC8), MDM2 antagonist (*e.g.*, RO5045337), immunotoxin (*e.g.*, CAT-8015, DT2219ARL), HDAC inhibitor (*e.g.*, JNJ-26481585), JVRS-100, paclitaxel or a paclitaxel agent, STAT3 inhibitor (*e.g.*, OPB-31121), PARP inhibitor (*e.g.*, veliparib), EZN-2285, radiation therapy, steroid, bone marrow transplantation, stem cell transplantation, or a combination thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of acute myeloid leukemia (AML) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, cytarabine, daunorubicin, idarubicin, clofarabine, decitabine, vosaroxin, azacitidine, clofarabine, ribavirin, CPX-351, treosulfan, elacytarabine, azacitidine), tyrosine kinase inhibitor (*e.g.*, BCR/ABL inhibitor (*e.g.*, imatinib, nilotinib), ON 01910.Na, multikinase inhibitor (*e.g.*, midostaurin, SU 11248, quizartinib, sorafinib)), immunotoxin (*e.g.*, gemtuzumab ozogamicin), DT388IL3 fusion protein, HDAC inhibitor (*e.g.*, vorinostat, LBH589), plerixafor, mTOR inhibitor (*e.g.*, everolimus), SRC inhibitor (*e.g.*, dasatinib), HSP90 inhbitor (*e.g.*, STA-9090), retinoid (*e.g.*, bexarotene, Aurora kinase inhibitor (*e.g.*, BI 811283), JAK-2 inhibitor (*e.g.*, INCB018424), Polo-like kinase inhibitor (*e.g.*, BI 6727), cenersen, CD45 targeting agent (*e.g.*, BC8), cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), MDM2 antagonist (*e.g.*, RO5045337), mTOR inhibitor (*e.g.*, everolimus), LY573636-sodium, ZRx-101, MLN4924, lenalidomide,

immunotherapy (*e.g.*, AHN-12), histamine dihydrochloride, radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of multiple myeloma (MM) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, melphalan, amifostine, cyclophosphamide, doxorubicin, clofarabine, bendamustine, fludarabine, adriamycin, SyB L-0501), thalidomide, lenalidomide, dexamethasone, prednisone, pomalidomide, proteasome inhibitor (*e.g.*, bortezomib, carfilzomib, MLN9708), cancer vaccine (*e.g.*, GVAX), CD-40 targeting agent (*e.g.*, SGN-40, CHIR-12.12), perifosine, zoledronic acid, Immunotherapy (*e.g.*, MAGE-A3, NY-ESO-1 , HuMax-CD38), HDAC inhibitor (*e.g.*, vorinostat, LBH589, AR-42), aplidin, cycline-dependent kinase inhibitor (*e.g.*, PD-0332991, dinaciclib), arsenic trioxide, CB3304, HSP90 inhibitor (*e.g.*, KW-2478), tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, cetuximab), multikinase inhibitor (*e.g.*, AT9283)), VEGF inhibitor (*e.g.*, bevacizumab), plerixafor, MEK inhibitor (*e.g.*, AZD6244), IPH2101, atorvastatin, immunotoxin (*e.g.*, BB-10901), NPI-0052, radioimmunotherapeutic (*e.g.*, yttrium Y 90 ibritumomab tiuxetan), STAT3 inhibitor (*e.g.*, OPB-31121), MLN4924, Aurora kinase inhibitor (*e.g.*, ENMD-2076), IMGN901, ACE-041, CK-2 inhibitor (*e.g.*, CX-4945), radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of prostate cancer includes, but is not limited to, a chemotherapeutic agent (*e.g.*, docetaxel, carboplatin, fludarabine), abiraterone, hormonal therapy (*e.g.*, flutamide, bicalutamide, nilutamide, cyproterone acetate, ketoconazole, aminoglutethimide, abarelix, degarelix, leuprolide, goserelin, triptorelin, buserelin), tyrosine kinase inhibitor (*e.g.*, dual kinase inhibitor (*e.g.*, lapatanib), multikinase inhibitor (*e.g.*, sorafenib, sunitinib)), VEGF inhibitor (*e.g.*, bevacizumab), TAK-700, cancer vaccine (*e.g.*, BPX-101, PEP223), lenalidomide, TOK-001, IGF-1 receptor inhibitor (*e.g.*, cixutumumab), TRC105, Aurora A kinase inhibitor (*e.g.*, MLN8237), proteasome inhibitor (*e.g.*, bortezomib), OGX-011, radioimmunotherapy (*e.g.*, HuJ591-GS), HDAC inhibitor (*e.g.*, valproic acid, SB939, LBH589), hydroxychloroquine, mTOR inhibitor (*e.g.*, everolimus), dovitinib lactate, diindolylmethane,

efavirenz, OGX-427, genistein, IMC-3G3, bafetinib, CP-675,206, radiation therapy, surgery, or a combination thereof.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of HNSCC includes, but is not limited to, one or both of Compound A8 as described herein (or a compound described in PCT Publication No. WO2010/029082) and cetuximab (*e.g.,* Erbitux, marketed by BMS). In some embodiments, the therapeutic (*e.g.,* the Compound A8 or compound related to A8) is a PI3K modulator, *e.g.,* a PI3K inhibitor. In some embodiments, the therapeutic (*e.g.,* cetuximab) modulates, *e.g.,* inhibits, EGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of PI3K or EGFR compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of gastric cancer, *e.g.,* MSI-high and/or EBV+ gastric cancer, includes, but is not limited to, Compound A8 as described herein (or a compound described in PCT Publication No. WO2010/029082). In some embodiments, the therapeutic (*e.g.,* the Compound A8 or compound related to A8) is a PI3K modulator, *e.g.,* a PI3K inhibitor. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of PI3K compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of gastric cancer, *e.g.,* MSI-high and/or RNF43-inactivated gastric cancer, includes, but is not limited to, Compound A28 as described herein (or a compound described in PCT Publication No. WO2010/101849). In some embodiments, the therapeutic (*e.g.,* the Compound A28 or compound related to A28) is a modulator, *e.g.,* inhibitor, of porcupine. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of porcupine compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of GI stromal tumor (GIST), includes, but is not limited to, Compound A16 as described herein (or a compound described in PCT

Publication No. WO1999/003854). In some embodiments, the therapeutic (*e.g.*, the Compound A16 or compound related to A16) is a modulator, *e.g.*, inhibitor, of a tyrosine kinase. In some embodiments, the cancer has, or is determined to have, elevated levels or activity of a tyrosine kinase compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of NSCLC, *e.g.*, squamous or adenocarcinoma, includes, but is not limited to, one or both of Compound A17 as described herein (or a compound described in US Patent No. 7,767,675 and 8,420,645) and Compound A23 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the compound (*e.g.*, the Compound A17 or compound related to A17) modulates, *e.g.*, inhibits, c-MET. In some embodiments, the compound (*e.g.*, the Compound A23 or compound related to A23) modulates, *e.g.*, inhibits, Alk. In some embodiments, the cancer has, or is determined to have, elevated levels or activity of one or both of c-MET or Alk compared to a control cell or reference value. In some embodiments, the cancer has, or is identified as having, a mutation in EGFR.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of melanoma (*e.g.*, NRAS melanoma) includes, but is not limited to, one or both of Compound A24 as described herein (or a compound described in US Patent Nos. 8,415,355 and 8,685,980) and Compound A34 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the compound (*e.g.*, the Compound A24 or compound related to A24) modulates, *e.g.*, inhibits, one or more of JAK and CDK4/6. In some embodiments, the compound (*e.g.*, the Compound A34 or compound related to A34) modulates, *e.g.*, inhibits, MEK. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of one or more of JAK, CDK4/6, and MEK compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of melanoma (*e.g.*, NRAS melanoma) includes, but is not limited to, one or both of Compound A29 as described herein (or a compound

described in PCT Publication No. WO2011/025927) and Compound A34 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the compound (*e.g.*, the Compound A29 or compound related to A29) modulates, *e.g.*, inhibits, BRAF. In some embodiments, the compound (*e.g.*, the Compound A34 or compound related to A34) modulates, *e.g.*, inhibits, MEK. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of one or both of BRAF and MEK compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of squamous NSCLC includes, but is not limited to, Compound A5 as described herein (or a compound described in US Patent No. 8,552,002). In some embodiments, the compound (*e.g.*, the Compound A5 or compound related to A5) modulates, *e.g.*, inhibits, FGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of FGFR compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), for treatment of colorectal cancer includes, but is not limited to, one or both of Compound A29 as described herein (or a compound PCT Publication No. WO2011/025927) and cetuximab (*e.g.*, Erbitux, marketed by BMS). In some embodiments, the therapeutic (*e.g.*, the Compound A29 or compound related to A29) modulates, *e.g.*, inhibits, BRAF. In some embodiments, the therapeutic (*e.g.*, cetuximab) modulates, *e.g.*, inhibits EGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of BRAF or EGFR compared to a control cell or reference value.

This disclosure also provides a method of treating cancer with Compound A8, cetuximab, and a PD-L1 antibody molecule (optionally in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule). In some embodiments, the patient is first treated with Compound A8 and cetuximab. This treatment continues for an amount of time, *e.g.*, a predetermined amount of time, *e.g.*, about 1, 2, 4, 6, 8, 10, or 12 months. Next, the PD-L1 antibody molecule (optionally in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule) is administered. The PD-L1 antibody can optionally be administered in combination with cetuximab.

In some embodiments, the patient is first treated with all three of Compound A8, cetuximab, and a PD-L1 antibody molecule (optionally in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule). This treatment continues for an amount of time, *e.g.,* a predetermined amount of time, *e.g.,* about 6, 8, 10, or 12 months. Next, the Compound A8 and/or cetuximab can be tapered off, so that the maintenance phase involves treatment with the PD-L1 antibody molecule (*e.g.,* as a monotherapy, or in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule) but not Compound A8 or cetuximab.

In other embodiments, the three compounds (Compound A8, cetuximab, and a PD-L1 antibody molecule, optionally in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule) are given sequentially at the outset of the treatment. For instance, Compound A8 and cetuximab can be given first, as described above. Next, the PD-L1 antibody molecule (optionally in combination with a TIM-3 antibody molecule or LAG-3 antibody molecule) is added to the regimen. Next, the Compound A8 and/or cetuximab can be tapered off as described above.

Exemplary doses for the three (or more) agent regimens are as follows. The PD-L1 antibody molecule can be administered, *e.g.,* at a dose of about 1 to 40 mg/kg, *e.g.,* 1 to 30 mg/kg, *e.g.,* about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. In some embodiments, the Compound A8 is administered at a dose of approximately 200-300, 300-400, or 200-400 mg. In some embodiments, the cetuximab is administered at a 400 mg/m2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m2 weekly infused over 60 minutes. In embodiments, one or more of the Compound A8, cetuximab, and PD-L1 antibody molecule is administered at a dose that is lower than the dose at which that agent is typically administered as a monotherapy, *e.g.,* about 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower than the dose at which that agent is typically administered as a monotherapy. In embodiments, the one or more of the Compound A8, cetuximab, and PD-L1 antibody molecule is administered at a dose that is lower than the dose of that agent recited in this paragraph, *e.g.,* about 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower than the dose of that agent recited in this paragraph. In certain embodiments, the concentration of the Compound A8 that is required to achieve inhibition, *e.g.,* growth inhibition, is lower when the Compound A8 is administered in combination with one or both of the cetuximab and PD-L1 antibody molecule than when the Compound A8 is

administered individually. In certain embodiments, the concentration of the cetuximab that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the cetuximab is administered in combination with one or both of the Compound A8 and PD-L1 antibody molecule than when the cetuximab is administered individually. In certain embodiments, the concentration of the PD-L1 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the PD-L1 antibody molecule is administered in combination with one or both of the cetuximab and Compound A8 than when the PD-L1 antibody molecule is administered individually.

Additionally disclosed herein is a method of treating cancer with the anti-PD-L1 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-LAG-3, anti-PD-1 or anti-TIM-3 antibody molecule), and a targeted anti-cancer agent, *e.g.*, an agent that targets one or more proteins. In some embodiments, the anti-PD-L1 antibody molecule (and optionally other immunomodulator(s)) are administered first, and the targeted anti-cancer agent is administered second. The length of time between administration of the anti-PD-L1 antibody molecule and the targeted anti-cancer agent can be, *e.g.*, 10, 20, or 30 minutes, 1, 2, 4, 6, or 12 hours, or 1, 2, 3, 4, 5, 6, or 7 days, or any span of time within this range. In certain embodiments, the anti-PD-L1 antibody molecule is administered repeatedly over a period of time (*e.g.*, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 4, 8, 12, 16, or 20 weeks, or any span of time within this range) before the targeted anti-cancer agent is administered. In other embodiments, the anti-PD-L1 antibody molecule and the targeted anti-cancer agent are administered at substantially the same time.

Infectious Diseases

Other methods of the invention are used to treat patients that have been exposed to particular toxins or pathogens. Accordingly, another aspect of the invention provides a method of treating an infectious disease in a subject comprising administering to the subject an anti-PD-L1 antibody molecule, such that the subject is treated for the infectious disease.

In the treatment of infection (*e.g.*, acute and/or chronic), administration of the anti-PD-L1 antibody molecules can be combined with conventional treatments in addition to or in lieu of stimulating natural host immune defenses to infection. Natural host immune defenses to infection include, but are not limited to inflammation, fever, antibody-mediated host defense, T-

lymphocyte-mediated host defenses, including lymphokine secretion and cytotoxic T-cells (especially during viral infection), complement mediated lysis and opsonization (facilitated phagocytosis), and phagocytosis. The ability of the anti-PD-L1 antibody molecules to reactivate dysfunctional T-cells would be useful to treat chronic infections, in particular those in which cell-mediated immunity is important for complete recovery.

Similar to its application to tumors as discussed above, antibody mediated PD-L1 blockade can be used alone, or as an adjuvant, in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, *Staphylococcus aureus*, *Pseudomonas Aeruginosa*. PD-L1 blockade is particularly useful against established infections by agents such as HIV that present altered antigens over the course of the infections. These novel epitopes are recognized as foreign at the time of anti-human PD-L1 administration, thus provoking a strong T cell response that is not dampened by negative signals through PD-L1.

Viruses

For infections resulting from viral causes, the anti-PD-L1 antibody molecules can be combined by application simultaneous with, prior to or subsequent to application of standard therapies for treating viral infections. Such standard therapies vary depending upon type of virus, although in almost all cases, administration of human serum containing antibodies (*e.g.*, IgA, IgG) specific to the virus can be effective.

Some examples of pathogenic viruses causing infections treatable by methods include HIV, hepatitis (A, B, or C), herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

In one embodiment, the infection is an influenza infection. Influenza infection can result in fever, cough, myalgia, headache and malaise, which often occur in seasonal epidemics.

Influenza is also associated with a number of postinfectious disorders, such as encephalitis, myopericarditis, Goodpasture's syndrome, and Reye's syndrome. Influenza infection also suppresses normal pulmonary antibacterial defenses, such that patient's recovering from influenza have an increased risk of developing bacterial pneumonia. Influenza viral surface proteins show marked antigenic variation, resulting from mutation and recombination. Thus, cytolytic T lymphocytes are the host's primary vehicle for the elimination of virus after infection. Influenza is classified into three primary types: A, B and C. Influenza A is unique in that it infects both humans and many other animals (*e.g.,* pigs, horses, birds and seals) and is the principal cause of pandemic influenza. Also, when a cell is infected by two different influenza A strains, the segmented RNA genomes of two parental virus types mix during replication to create a hybrid replicant, resulting in new epidemic strains. Influenza B does not replicate in animals and thus has less genetic variation and influenza C has only a single serotype.

Most conventional therapies are palliatives of the symptoms resulting from infection, while the host's immune response actually clears the disease. However, certain strains (*e.g.*, influenza A) can cause more serious illness and death. Influenza A may be treated both clinically and prophylactically by the administration of the cyclic amines inhibitors amantadine and rimantadine, which inhibit viral replication. However, the clinical utility of these drugs is limited due to the relatively high incidence of adverse reactions, their narrow anti-viral spectrum (influenza A only), and the propensity of the virus to become resistant. The administration of serum IgG antibody to the major influenza surface proteins, hemagglutinin and neuraminidase can prevent pulmonary infection, whereas mucosal IgA is required to prevent infection of the upper respiratory tract and trachea. The most effective current treatment for influenza is vaccination with the administration of virus inactivated with formalin or β-propiolactone.

In another embodiment, the infection is a hepatitis infection, *e.g.*, a Hepatitis B or C infection.

Hepatitis B virus (HB-V) is the most infectious known bloodborne pathogen. It is a major cause of acute and chronic heptatis and hepatic carcinoma, as well as life-long, chronic infection. Following infection, the virus replicates in hepatocytes, which also then shed the surface antigen HBsAg. The detection of excessive levels of HBsAg in serum is used a standard method for diagnosing a hepatitis B infection. An acute infection may resolve or it can develop into a chronic persistent infection. Current treatments for chronic HBV include α-interferon, which

increases the expression of class I human leukocyte antigen (HLA) on the surface of hepatocytes, thereby facilitating their recognition by cytotoxic T lymphocytes. Additionally, the nucleoside analogs ganciclovir, famciclovir and lamivudine have also shown some efficacy in the treatment of HBV infection in clinical trials. Additional treatments for HBV include pegylated a-interferon, adenfovir, entecavir and telbivudine. While passive immunity can be conferred through parental administration of anti-HBsAg serum antibodies, vaccination with inactivated or recombinant HBsAg also confers resistance to infection. The anti-PD-L1 antibody molecules may be combined with conventional treatments for hepatitis B infections for therapeutic advantage.

Hepatitis C virus (HC-V) infection may lead to a chronic form of hepatitis, resulting in cirrosis. While symptoms are similar to infections resulting from Hepatitis B, in distinct contrast to HB-V, infected hosts can be asymptomatic for 10-20 years. The anti-PD-L1 antibody molecule can be administered as a monotherapy, or combined with the standard of care for hepatitis C infection. For example, the anti-PD-L1 antibody molecule can be administered with one or more of Sovaldi (sofosbuvir) Olysio (simeprevir), plus ribavirin or pegylated interferon. Although regimens that include Incivek (telaprevir) or Victrelis (boceprevir) plus ribavirin and pegylated interferon are also approved, they are associated with increased side effects and longer duration of treatment and are therefore not considered preferred regimens.

Conventional treatment for HC-V infection includes the administration of a combination of α-interferon and ribavirin. A promising potential therapy for HC-V infection is the protease inhibitor telaprevir (VX-960). Additional treatments include: anti-PD-1 antibody (MDX-1106, Medarex), bavituximab (an antibody that binds anionic phospholipid phosphatidylserine in a B2-glycoprotein I dependent manner, Peregrine Pharmaceuticals), anti-HPV viral coat protein E2 antibod(y)(ies) (*e.g.*, ATL 6865−Ab68+Ab65, XTL Pharmaceuticals) and Civacir® (polyclonal anti-HCV human immune globulin). The anti-PD-L1 antibodies of the invention may be combined with one or more of these treatments for hepatitis C infections for therapeutic advantage. Protease, polymerase and NS5A inhibitors which may be used in combination with the anti-PD-L1 antibody molecules to specifically treat Hepatitis C infection include those described in US 2013/0045202.

In another embodiment, the infection is a measles virus. After an incubation of 9-11 days, hosts infected with the measles virus develop fever, cough, coryza and conjunctivitis. Within 1-2 days, an erythematous, maculopapular rash develop, which quickly spreads over the

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DEMANDE OU BREVET VOLUMINEUX

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JUMBO APPLICATIONS/PATENTS

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS:

1. An isolated antibody molecule capable of binding to human Programmed Death-Ligand 1 (PD-L1), comprising:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO: 10, and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

2. The antibody molecule of claim 1, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 1.

3. The antibody molecule of claim 1, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 4.

4. The antibody molecule of claim 1, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 195.

5. An isolated antibody molecule capable of binding to human Programmed Death-Ligand 1 (PD-L1), comprising:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 4, SEQ ID NO: 1, or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

6. The antibody molecule of claim 5, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 1.

7. The antibody molecule of claim 5, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 4.

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8. The antibody molecule of claim 5, which comprises the VHCDR1 amino acid sequence of SEQ ID NO: 195.

9. The antibody molecule of any of claims 1-8, which has a heavy chain variable region comprising at least one framework (FW) region comprising the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154, or an amino acid sequence at least 90% identical thereto, or having no more than two amino acid substitutions, insertions or deletions compared to the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

10. The antibody molecule of any of claims 1-9, which has a heavy chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

11. The antibody molecule of any of claims 1-10, which has a heavy chain variable region comprising at least two, three, or four framework regions comprising the amino acid sequences of any of SEQ ID NOs: 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, or 154.

12. The antibody molecule of any of claims 1-10, which comprises a VHFW1 amino acid sequence of SEQ ID NO: 124, 126, 128, or 130, a VHFW2 amino acid sequence of SEQ ID NO: 132, 134, 136, 138, 140, or 142, and a VHFW3 amino acid sequence of SEQ ID NO: 144, 146, 148, 150, or 152, and, optionally, further comprising a VHFW4 amino acid sequence of SEQ ID NO: 154.

13. The antibody molecule of any of claims 1-12, which has a light chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186, or an amino acid sequence at least 90% identical thereto, or having no more than two amino acid substitutions, insertions or deletions compared to the amino acid sequence of any of 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

14. The antibody molecule of any of claims 1-13, which has a light chain variable region comprising at least one framework region comprising the amino acid sequence of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

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15. The antibody molecule of any of claims 1-14, which has a light chain variable region comprising at least two, three, or four framework regions comprising the amino acid sequences of any of SEQ ID NOs: 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, or 186.

16. The antibody molecule of any of claims 1-15, which comprises a VLFW1 amino acid sequence of SEQ ID NO: 156, 158, 160, 162, 164, or 166, a VLFW2 amino acid sequence of SEQ ID NO: 168 or 170, and a VLFW3 amino acid sequence of SEQ ID NO: 172, 174, 176, 178, 180, 182, or 184, and, optionally, further comprising a VLFW4 amino acid sequence of SEQ ID NO: 186.

17. The antibody molecule of any of claims 1-16, which comprises a heavy chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 18, 30, 38, 46, 50, 54, 62, 70, or 78.

18. The antibody molecule of any of claims 1-17, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18, 30, 38, 46, 50, 54, 62, 70, or 78.

19. The antibody molecule of any of claims 1-18, which comprises a light chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 22, 26, 34, 42, 58, 66, 74, 82, or 86.

20. The antibody molecule of any of claims 1-19, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22, 26, 34, 42, 58, 66, 74, 82, or 86.

21. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18.

22. The antibody molecule of any of claims 1-21, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20.

23. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30.

24. The antibody molecule of any of claims 1-20 and 23, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 96, or SEQ ID NO: 197.

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25. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38.

26. The antibody molecule of any of claims 1-20 and 25, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 91.

27. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 46.

28. The antibody molecule of any of claims 1-20 and 27, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 48.

29. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50.

30. The antibody molecule of any of claims 1-20 and 29, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

31. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54.

32. The antibody molecule of any of claims 1 -20 and 31 , which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 56.

33. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62.

34. The antibody molecule of any of claims 1-20 and 33, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 64.

35. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 70.

36. The antibody molecule of any of claims 1-20 and 35, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 72.

37. The antibody molecule of any one of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 78.

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38. The antibody molecule of any of claims 1-20 and 37, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 80.

39. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22.

40. The antibody molecule of any of claims 1-39, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 24.

41. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 26.

42. The antibody molecule of any of claims 1-28 and 41, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 28.

43. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 34.

44. The antibody molecule of any of claims 1-28 and 43, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 36.

45. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

46. The antibody molecule of any of claims 1-28 and 45, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 44.

47. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 58.

48. The antibody molecule of any of claims 1-28 and 47, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 60.

49. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

50. The antibody molecule of any of claims 1-28 and 49, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 68.

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51. The antibody molecule of any of claims 1 -28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 74.

52. The antibody molecule of any of claims 1-28 and 51, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 76.

53. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 82.

54. The antibody molecule of any of claims 1-28 and 53, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 84.

55. The antibody molecule of any of claims 1-28, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

56. The antibody molecule of any of claims 1-28 and 55, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 88.

57. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22.

58. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 26.

59. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

60. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 34.

61. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 30 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

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62. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

63. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 74.

64. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 46 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

65. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

66. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22.

67. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

68. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 58.

69. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

70. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

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71. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 86.

72. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 66.

73. The antibody molecule of any of claims 1-20, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 82.

74. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 24.

75. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

76. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

77. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 36.

78. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

79. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 40 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

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80. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 40 and a light chain comprising the amino acid sequence of SEQ ID NO: 76.

81. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

82. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

83. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 24.

84. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

85. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 and a light chain comprising the amino acid sequence of SEQ ID NO: 60.

86. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

87. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

88. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 and a light chain comprising the amino acid sequence of SEQ ID NO: 88.

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89. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 72 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

90. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain comprising the amino acid sequence of SEQ ID NO: 84.

91. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 197 and a light chain comprising the amino acid sequence of SEQ ID NO: 36.

92. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 44.

93. The antibody molecule of any of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 96 and a light chain comprising the amino acid sequence of SEQ ID NO: 68.

94. The antibody molecule of any of claims 1-93, which is a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv).

95. The antibody molecule of any of claims 1-93, which comprises a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4.

96. The antibody molecule of claim 95, which comprises a light chain constant chosen from the light chain constant regions of kappa or lambda.

97. The antibody of claim 95 or 96, which comprises a human IgG4 heavy chain constant region with a mutation at position 228 of SEQ ID NO: 188 or 190 and a kappa light chain constant region.

98. The antibody of claim 95 or 96, which comprises a human IgG4 heavy chain constant region with a Serine to Proline mutation at position 228 of SEQ ID NO: 188 or 190 and a kappa light chain constant region.

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99. The antibody of claim 95 or 96, which comprises a human IgG1 heavy chain constant region with an Asparagine to Alanine mutation at position 297 of SEQ ID NO: 192 and a kappa light chain constant region.

100. The antibody of claim 95 or 96, which comprises a human IgG1 heavy chain constant region with an Aspartate to Alanine mutation at position 265, and Proline to Alanine mutation at position 329 of SEQ ID NO: 193 and a kappa light chain constant region.

101. The antibody of claim 95 or 96, which comprises a human IgG1 heavy chain constant region with a Leucine to Alanine mutation at position 234 and Leucine to Alanine mutation at position 235 of SEQ ID NO: 194 and a kappa light chain constant region.

102. The antibody molecule of any of claims 1-101, which is capable of binding to human PD-L1 with a dissociation constant (KD) of less than 0.2 nM or about 0.2 nM.

103. The antibody molecule of any of claims 1-102, which binds an extracellular domain of PD-L1.

104. The antibody molecule of any of claims 1-103, which is capable of reducing binding of PD-1 to PD-L1.

105. The antibody molecule of any of claims 1-104, which is capable of enhancing an antigen-specific T cell response.

106. The antibody molecule of any of claims 1-105, wherein said antibody molecule is a monospecific antibody molecule.

107. The antibody molecule of any of claims 1-105, wherein said antibody molecule is a bispecific antibody molecule.

108. The antibody molecule of claim 107, wherein said antibody molecule has a first binding specificity for PD-L1 and a second binding specificity for TIM-3, LAG-3, CEACAM, PD-1 or PD-L2.

109. The antibody molecule of any of claims 1-105, wherein said antibody molecule comprises an antigen binding fragment of an antibody.

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110. A pharmaceutical composition comprising the isolated antibody molecule of any of claims 1-109 and a pharmaceutically acceptable carrier, excipient or stabilizer.

111. An isolated nucleic acid encoding the antibody heavy or light chain variable region of the antibody molecule of any of claims 1-110.

112. An isolated nucleic acid encoding heavy chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 104-108, 113-117, or 205-208.

113. An isolated nucleic acid encoding light chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 109-112, 118-123, 209-214, and 245-246.

114. The nucleic acid of claim 112, further comprising a nucleotide sequence encoding a heavy chain variable domain, wherein said nucleotide sequence comprises any of SEQ ID NO: 19, 31, 39, 47, 51, 55, 63, 71, 79, 90, 95, 100, 196, or 201.

115. The nucleic acid of claim 114, further comprising a nucleotide sequence encoding a heavy chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 21, 33, 41, 49, 53, 57, 65, 73, 81, 92, 97, 101, 198, or 202.

116. The nucleic acid of claim 113, which further comprises a nucleotide sequence encoding a light chain variable domain, wherein said nucleotide sequence comprises any of SEQ ID NO: 23, 27, 35, 43, 59, 67, 75, 83, 87, 93, 98, 102, 199, or 203.

117. The nucleic acid of claim 116, further comprising a nucleotide sequence encoding a light chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 25, 29, 37, 45, 61, 69, 77, 85, 89, 94, 99, 103, 200, or 204.

118. An expression vector comprising the nucleic acid of any of claims 111-117.

119. A host cell comprising the nucleic acid of any of claims 111-117.

120. A method of producing an antibody molecule or fragment thereof, comprising culturing one or more host cells of claim 119 under conditions suitable for gene expression, wherein the host cell(s) produce heavy and light chains, wherein the heavy chain comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4 or SEQ ID NO: 195; a VHCDR2 amino acid sequence of SEQ ID

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NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and the light chain comprises a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO: 10, and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

121. The isolated antibody molecule of any of claims 1-109 for use in stimulating the immune response.

122. The isolated antibody molecule of any of claims 1-109 for use in treating a cancer.

123. The isolated antibody molecule of claim 122, wherein the cancer is chosen from a lung cancer, a squamous cell lung cancer, a melanoma, a renal cancer, a liver cancer, a myeloma, a prostate cancer, a breast cancer, an ER+ breast cancer, an IM-TN breast cancer, a colorectal cancer, a colorectal cancer with high microsatellite instability, an EBV+ gastric cancer, a pancreatic cancer, a thyroid cancer, a nasopharyngeal cancer, a hematological cancer, a non-Hodgkin lymphoma, a leukemia, and a metastatic lesion of the cancer.

124. The isolated antibody molecule of claim 122, wherein the cancer is chosen from a non-small cell lung cancer (NSCLC), a NSCLC adenocarcinoma, a NSCLC squamous cell carcinoma, a hepatocellular carcinoma, an advanced melanoma, a metastatic renal cell carcinoma, and a multiple myeloma.

125. The isolated antibody molecule of any of claims 121-124, wherein the antibody molecule is for use in combination with a second therapeutic agent or procedure.

126. The isolated antibody molecule of claim 125, wherein the second therapeutic agent or procedure is chosen from one or more of chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, and a cellular immunotherapy.

127. The isolated antibody molecule of claim 125, wherein the antibody molecule is for use in combination with an agonist of a costimulatory molecule chosen from one or more of GITR, OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD1 la/CD18), ICOS (CD278), 4- IBB (CD137), CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 and CD83 ligand.

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128. The isolated antibody molecule of claim 125, wherein the antibody molecule is for use in combination with an inhibitor of an immune checkpoint chosen from one or more of PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR-beta.

129. A method of detecting PD-L1 in a biological sample, comprising (i) contacting the sample with the isolated antibody molecule of any of claims 1-109 under conditions that allow interaction of the antibody molecule and the polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample.

130. The anti-PD-L1 antibody molecule of any of claims 1-109 for use in treating a cancer in a subject, in combination of two, three or more therapeutic agents chosen from at least two of the following categories (i)-(iii):

(i) an agent that enhances tumor antigen presentation chosen from one or more of: a STING agonist, a TLR agonist, an A2AR antagonist, an oncolytic virus, a TIM-3 modulator, a vascular endothelial growth factor receptor (VEGFR) inhibitor, a c-Met inhibitor, a TGFb inhibitor, an IDO/TDO inhibitor, a vaccine, and a bi- or tri-specific cell engager;

(ii) an agent that enhances an effector cell response chosen from one or more of: a GITR agonist, a PD-1 inhibitor, a PD-L1 inhibitor, an inhibitor of IAP (Inhibitor of Apoptosis Protein), an inhibitor of EGFR (Epidermal Growth Factor Receptor), an inhibitor of target of rapamycin (mTOR), IL-15 or a variant thereof, a CTLA-4 inhibitor, a bispecific antibody molecule that binds to CD3 and a tumor antigen, a CD40 agonist, an OX40 agonist, and a CD27 agonist, or a combination thereof; or

(iii) an agent that decreases tumor immunosuppression chosen from one or more of: a GITR agonist, an inhibitor of an immune checkpoint molecule chosen from one or more of PD-1, LAG-3, TIM-3 or CTLA-4, a CSF-1/1R inhibitor, an IL-17 inhibitor, an IL-Iβ inhibitor, a CXCR2 inhibitor, an inhibitor of PI3Kγ or PI3K5), (vii) a BAFF-R inhibitor, a MALT-1/BTK inhibitor, a JAK inhibitor, a CRTH2 inhibitor, a VEGFR inhibitor, an IL-15 or a variant thereof, a CTLA-4 inhibitor, an IDO/TDO inhibitor, an A2AR antagonist, a TGFb inhibitor, and a PFKFB3 inhibitor.

131. Use of the antibody molecule of any of claims 1-109, or a pharmaceutical composition of claim 110, in the manufacture of a medicament for treating a cancer in a subject.

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132. Use of a combination of the antibody molecule of any of claims 1-109, or a pharmaceutical composition of claim 110, and a second therapeutic agent or procedure, in the manufacture of a medicament for treating a cancer in a subject.

133. The use of claim 132, wherein the second therapeutic agent or procedure is chosen from one or more of chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, and a cellular immunotherapy.

134. The use of any of claims 131-133, wherein the cancer is chosen from a lung cancer, a squamous cell lung cancer, a melanoma, a renal cancer, a liver cancer, a myeloma, a prostate cancer, a breast cancer, an ER+ breast cancer, an IM-TN breast cancer, a colorectal cancer, a colorectal cancer with high microsatellite instability, an EBV+ gastric cancer, a pancreatic cancer, a thyroid cancer, a nasopharyngeal cancer, a hematological cancer, a non-Hodgkin lymphoma, a leukemia, and a metastatic lesion of the cancer.

135. The use of any of claims 131-133, wherein the cancer is chosen from a non-small cell lung cancer (NSCLC), a NSCLC adenocarcinoma, a NSCLC squamous cell carcinoma, a hepatocellular carcinoma, an advanced melanoma, a metastatic renal cell carcinoma, and a multiple myeloma.

136. Use of the anti-PD-L1 antibody molecule of any of claims 1-109 in combination with two, three or more therapeutic agents in the manufacture of a medicament for treating a cancer in a subject, wherein the therapeutic agents are chosen from at least two of the following categories (i)-(iii):

(i) an agent that enhances tumor antigen presentation chosen from one or more of: a STING agonist, a TLR agonist, an A2AR antagonist, an oncolytic virus, a TIM-3 modulator, a vascular endothelial growth factor receptor (VEGFR) inhibitor, a c-Met inhibitor, a TGFb inhibitor, an IDO/TDO inhibitor, a vaccine, and a bi- or tri-specific cell engager;

(ii) an agent that enhances an effector cell response chosen from one or more of: a GITR agonist, a PD-1 inhibitor, a PD-L1 inhibitor, an inhibitor of IAP (Inhibitor of Apoptosis Protein), an inhibitor of EGFR (Epidermal Growth Factor Receptor), an inhibitor of target of rapamycin

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(mTOR), IL-15 or a variant thereof, a CTLA-4 inhibitor, a bispecific antibody molecule that binds to CD3 and a tumor antigen, a CD40 agonist, an OX40 agonist, and a CD27 agonist; or

(iii) an agent that decreases tumor immunosuppression chosen from one or more of: a GITR agonist, an inhibitor of an immune checkpoint molecule chosen from one or more of PD-1, LAG-3, TIM-3 or CTLA-4, a CSF-1/1R inhibitor, an IL-17 inhibitor, an IL-Iβ inhibitor, a CXCR2 inhibitor, an inhibitor of PBKγ or PBKδ), (vii) a BAFF-R inhibitor, a MALT-l/BTK inhibitor, a JAK inhibitor, a CRTH2 inhibitor, a VEGFR inhibitor, an IL-15 or a variant thereof, a CTLA-4 inhibitor, an IDO/TDO inhibitor, an A2AR antagonist, a TGFb inhibitor, and a PFKFB3 inhibitor.

137. Use of the anti-PD-L1 antibody molecule of any of claims 1-109 in combination with an AKT inhibitor in the manufacture of a medicament for treating a cancer in a subject.

138. The use of claim 137, further in combination with one or more therapeutic agents or procedures.

139. The use of claim 137, wherein the AKT inhibitor is RX-0201 or MK-2206.

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Heavy Chain (murine IgG1)

FWH1 CDRH1 FWH2 CDRH2
QVHLQQPGAE LVKPGASVKL SCKAS***GYTFT*** ***SY***WMY WVKQG PGRGLEWIGR I***DPNSGS***TKY
FWH3 CDRH3 FWH4
NEKFKNKATL TVDKSSSTAY MQLSSLTSED SAVYYCAR***DY RKGLYAMDY***W GQGTSVTVSS

Light Chain(murine κ)

FWL1 CDRL1 FWL2 CDRL2
DIVMTQSHKF MSTSVGDRVS ITCKA***SQDVG*** ***TA***VAWYQQKP GQSPKLLIY***W AS***TRHTGVPD
FWL3 CDRL3 FWL4
RFTGSGSGTD FTLTISNVQS EDLADYFCQQ ***YNSYPL***TFGA GSKLELK

FIGURE 1

Heavy Chain

GL QVQLQQPGAE LVKPGASVKL SCKAS***GYTFT*** ***SY***WMHWVKQR PGRGLEWIGR I***DPNSGG***TKY
Mu mAb --H------- ---------- ---------- ----***Y***----G ----------- ------***S***---

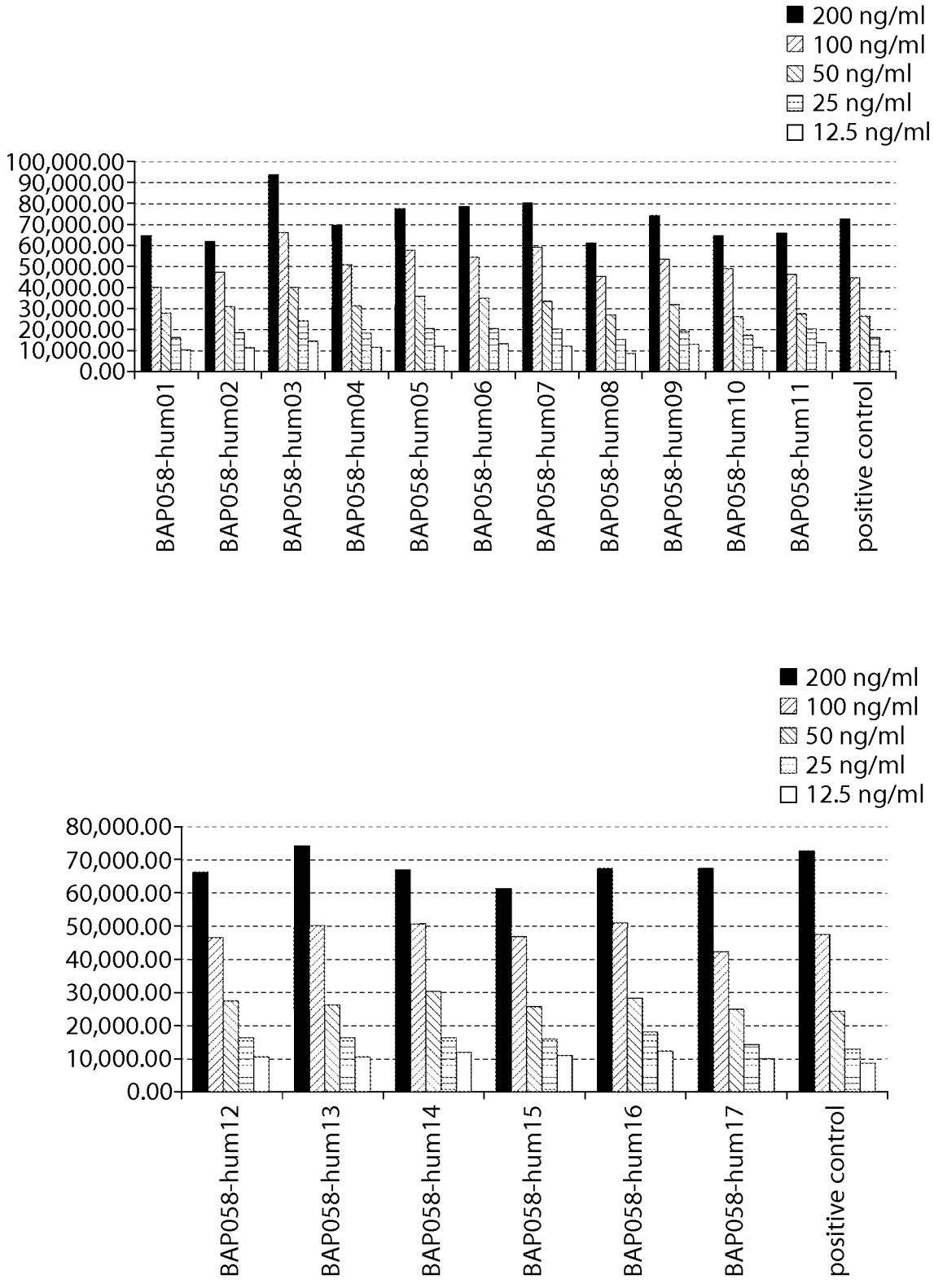
GL NEKFKSKATL TVDKPSSTAY MQLSSLTSED SAVYYCAR
Mu mAb -----N---- ----S----- ---------- --------***DY RKGLYAMDY***W GQGTSVTVSS

Light Chain

GL DIVMTQSHKF MSTSVGDRVS ITCKA***SQDVG TA***VAWYQQKP GQSPKLLIY***W AS***TRHTGVPD
Mu mAb ---------- ---------- ---------- ---------- ----------- ---------

GL RFTGSGSGTD FTLTISNVQS EDLADYFCQQ ***YSSYPL***TFGA GSKLELK
Mu mAb ---------- ---------- ----------- ***-N***------- -------

FIGURE 2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100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
100,000.00
90,000.00
80,000.00
70,000.00
60,000.00
50,000.00
40,000.00
30,000.00
20,000.00
10,000.00
0.00
BAP058-hum01
BAP058-hum02
BAP058-hum03
BAP058-hum04
BAP058-hum05
BAP058-hum06
BAP058-hum07
BAP058-hum08
BAP058-hum09
BAP058-hum10
BAP058-hum11
positive control
200 ng/ml
100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
80,000.00
70,000.00
60,000.00
50,000.00
40,000.00
30,000.00
20,000.00
10,000.00
0.00
BAP058-hum12
BAP058-hum13
BAP058-hum14
BAP058-hum15
BAP058-hum16
BAP058-hum17
positive control

FIGURE 3

Clone No.	Concentration µg/mL	Sequence					
		HC			LC		
		FW1	FW2	FW3	FW1	FW2	FW3
		9 unique HC			9 unique LC		
1	22.0	a	a	a	c	c	c
2	21.2	a	a	a	d	c	d
3	16.8	c	a	b	a	c	e
4	30.5	b	a'	c	a	c	b
5	30.3	c	c	d	a	c	b
6	31.3	b	b	b	a	c	b
7	25.2	a	c	a	e	c	f
8	1.4	b	d	d	b	a	a
9	30.6	b	b	b	c	c	c
10	0.5	d	e	b	b	a	a
11	18.6	c	a	b	b	a	a
12	21.5	b	a'	c	d	a	b
13	47.6	c	d	e	f	c	g
14	33.5	a	a	a	a	a	a
15	20.1	b	b	b	a	a	a
16	31.7	a	c	a	a	a	a
17	44.7	b	d	d	a	a	a

FIGURE 4

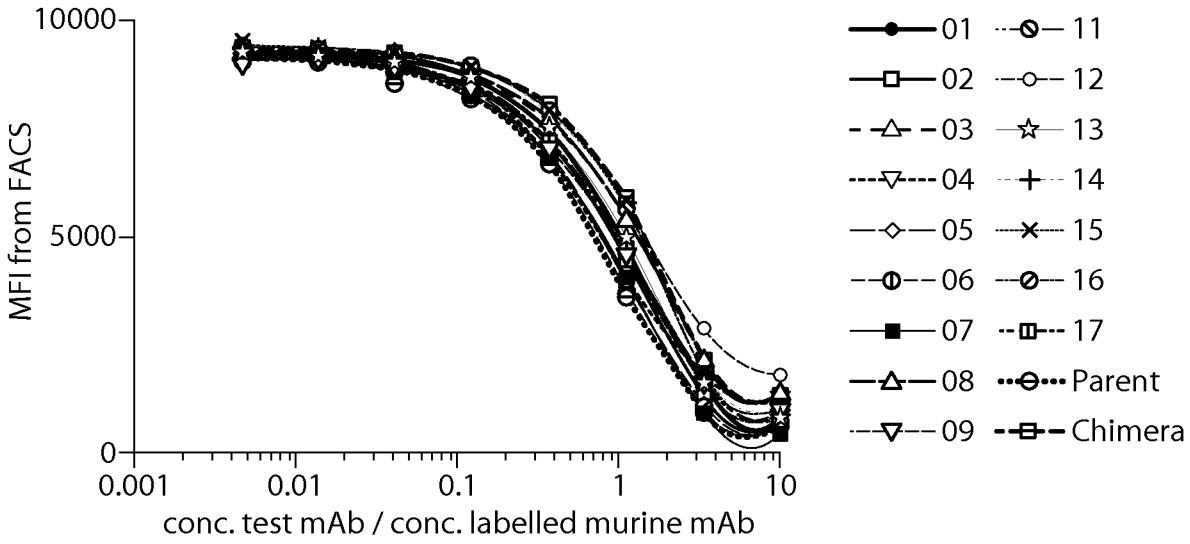
10000
5000
0
MFI from FACS
0.001
0.01
0.1
1
10
conc. test mAb / conc. labelled murine mAb
01
02
03
04
05
06
07
08
09
11
12
13
14
15
16
17
Parent
Chimera

FIGURE 5

Clone No.	Conc. µg/mL	Sequence						Rank	Comp. binding
		HC			LC				
		FW1	FW2	FW3	FW1	FW2	FW3		
		9 unique HC			9 unique LC				
1	22.0	a	a	a	c	c	c	17	2.56
2	21.2	a	a	a	d	c	d	17	2.14
3	16.8	c	a	b	a	c	e	1	1.87
4	30.5	b	a'	c	a	c	b	3	1.13
5	30.3	c	c	d	a	c	b	2	1.71
6	31.3	b	b	b	a	c	b	2	1.39
7	25.2	a	c	a	e	c	f	2	1.8
8	1.4	b	d	d	b	a	a	17	3.38
9	30.6	b	b	b	c	c	c	3	1.96
10	0.5	d	e	b	b	a	a	4	n.b.
11	18.6	c	a	b	b	a	a	4	1.3
12	21.5	b	a'	c	d	a	b	4	2.27
13	47.6	c	d	e	f	c	g	2	2.91
14	33.5	a	a	a	a	a	a	4	4.59
15	20.1	b	b	b	a	a	a	17	4.64
16	31.7	a	c	a	a	a	a	4	2.47
17	44.7	b	d	d	a	a	a	4	2.16

FIGURE 6

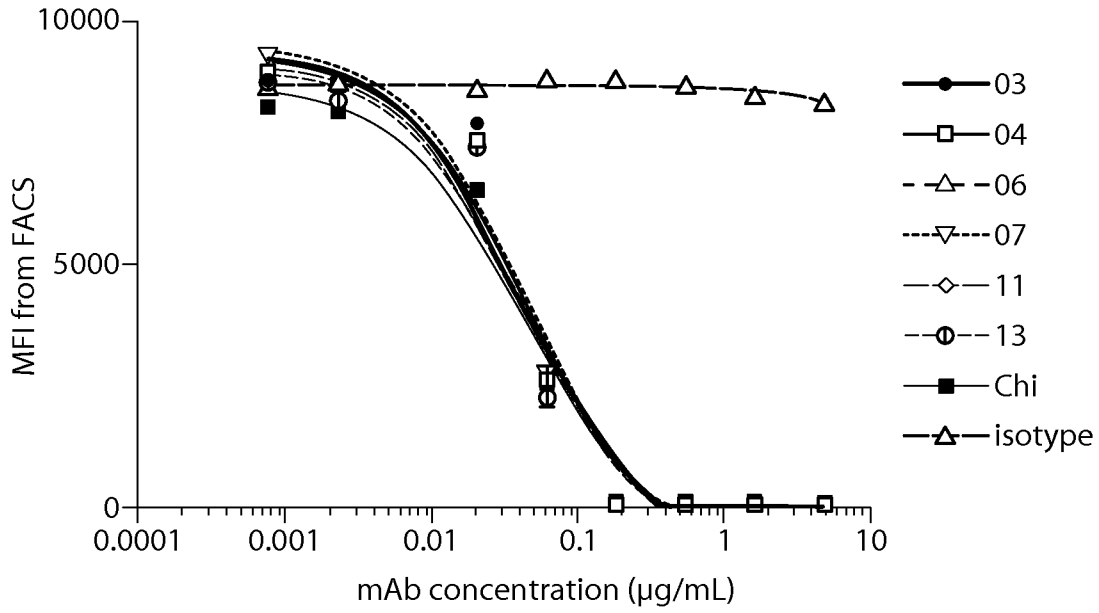
10000
5000
0
MFI from FACS
0.0001
0.001
0.01
0.1
1
10
mAb concentration (µg/mL)
03
04
06
07
11
13
Chi
isotype

FIGURE 7

```
                                10        20        30        40        50        60
BAP-chi HC                      ....|....|....|....|....|....|....|....|....|....|....|....|
                                EVQLQQSGAELVKPGASVKLSCKASGYTFTSYWMYWVKQGPGRGLEWIGRIDPNSGSTKY
BAP058-hum01-HC                 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
BAP058-hum02-HC                 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
BAP058-hum14-HC                 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
BAP058-hum06-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWIRQPPGKGLEWIGRIDPNSGSTKY
BAP058-hum09-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWIRQPPGKGLEWIGRIDPNSGSTKY
BAP058-hum15-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWIRQPPGKGLEWIGRIDPNSGSTKY
BAP058-hum03-HC                 EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
BAP058-hum11-HC                 EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
BAP058-hum04-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWVRQAPGQGLEWMGRIDPNSGSTKY
BAP058-hum12-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWVRQAPGQGLEWMGRIDPNSGSTKY
BAP058-hum07-HC                 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWIRQSPSRGLEWLGRIDPNSGSTKY
BAP058-hum16-HC                 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWIRQSPSRGLEWLGRIDPNSGSTKY
BAP058-hum08-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWVRQARGQRLEWLGRIDPNSGSTKY
BAP058-hum17-HC                 EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMYWVRQARGQRLEWLGRIDPNSGSTKY
BAP058-hum05-HC                 EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWIRQSPSRGLEWIGRIDPNSGSTKY
BAP058-hum10-HC                 QITLKESGPTLVKPTQTLTLTCTFSGYTFTSYWMYWVRQAPGKGLEWVSRIDPNSGSTKY
BAP058-hum13-HC                 EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWIRQARGQRLEWIGRIDPNSGSTKY

                                70        80        90        100       110
BAP-chi HC                      ....|....|....|....|....|....|....|....|....|....|...
                                NEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARDYRKGLYAMDYWGQG
BAP058-hum01-HC                 NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum02-HC                 NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum14-HC                 NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum06-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum09-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum15-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum03-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum11-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum04-HC                 NEKFKNRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum12-HC                 NEKFKNRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum07-HC                 NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum16-HC                 NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum08-HC                 NEKFKNRLTISKDTSKNQVVLTMTNMDPVDTATYYCARDYRKGLYAMDYWGQG
BAP058-hum17-HC                 NEKFKNRLTISKDTSKNQVVLTMTNMDPVDTATYYCARDYRKGLYAMDYWGQG
BAP058-hum05-HC                 NEKFKNRLTISKDTSKNQVVLTMTNMDPVDTATYYCARDYRKGLYAMDYWGQG
BAP058-hum10-HC                 NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQG
BAP058-hum13-HC                 NEKFKNRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDYRKGLYAMDYWGQG
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FIGURE 8A

```
                        10        20        30        40        50        60
BAP-chi HC      ....|....|....|....|....|....|....|....|....|....|....|....|
                EVQLQQSGAELVKPGASVKLSCKASGYTFTSYWMYWVKQGPGRGLEWIGRIDPNSGSTKY
BAP058-hum01-HC Q...V.....VK.......V..................R.AT.Q....M.....
BAP058-hum02-HC Q...V.....VK.......V..................R.AT.Q....M.....
BAP058-hum14-HC Q...V.....VK.......V..................R.AT.Q....M.....
BAP058-hum06-HC ....V.....VK...E.LRI...G.............IR.P..K.....
BAP058-hum09-HC ....V.....VK...E.LRI...G.............IR.P..K.....
BAP058-hum15-HC ....V.....VK...E.LRI...G.............IR.P..K.....
BAP058-hum03-HC ....V.....VK....T..I...V.............R.AT.Q....M.....
BAP058-hum11-HC ....V.....VK....T..I...V.............R.AT.Q....M.....
BAP058-hum04-HC ....V.....VK...E.LRI...G.............R.A..Q....M.....
BAP058-hum12-HC ....V.....VK...E.LRI...G.............R.A..Q....M.....
BAP058-hum07-HC Q...V.....VK.......V..................IR.S.S.....L.....
BAP058-hum16-HC Q...V.....VK.......V..................IR.S.S.....L.....
BAP058-hum08-HC ....V.....VK...E.LRI...G.............R.AR.QR.....
BAP058-hum17-HC ....V.....VK...E.LRI...G.............R.AR.QR.....
BAP058-hum05-HC ....V.....VK....T..I...V.............IR.S.S.....L.....
BAP058-hum10-HC QIT.KE..PT....TQTLT.T.TF.............R.A..K....VS.....
BAP058-hum13-HC ....V.....VK....T..I...V.............R.AR.QR.....

                        70        80        90        100       110
BAP-chi HC      ....|....|....|....|....|....|....|....|....|....|...
                NEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARDYRKGLYAMDYWGQG
BAP058-hum01-HC ......RF.ISR.D.KN...L.MN..KT..T.....
BAP058-hum02-HC ......RF.ISR.D.KN...L.MN..KT..T.....
BAP058-hum14-HC ......RF.ISR.D.KN...L.MN..KT..T.....
BAP058-hum06-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum09-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum15-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum03-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum11-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum04-HC ......RV.IS..T.KNQFSLK...V.AA.T.....
BAP058-hum12-HC ......RV.IS..T.KNQFSLK...V.AA.T.....
BAP058-hum07-HC ......RF.ISR.D.KN...L.MN..KT..T.....
BAP058-hum16-HC ......RF.ISR.D.KN...L.MN..KT..T.....
BAP058-hum08-HC ......RL.ISK.T.KNQVVLTMTNMDPV.T.T.....
BAP058-hum17-HC ......RL.ISK.T.KNQVVLTMTNMDPV.T.T.....
BAP058-hum05-HC ......RL.ISK.T.KNQVVLTMTNMDPV.T.T.....
BAP058-hum10-HC ......RV.I.A...T.....E....R...T.....
BAP058-hum13-HC ......RF.ISR.N.KN.LYL.MN..RA..T.....
```

FIGURE 8B

```
                        10        20        30        40        50        60
                ....|....|....|....|....|....|....|....|....|....|....|....|
BAP-chi LC      DIMMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHTGVPD
BAP058-hum14-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum15-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum16-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum17-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum04-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPS
BAP058-hum05-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPS
BAP058-hum06-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPS
BAP058-hum08-LC DVVMTQSPLSLPVTLGQPASISCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum10-LC DVVMTQSPLSLPVTLGQPASISCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum11-LC DVVMTQSPLSLPVTLGQPASISCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS
BAP058-hum01-LC DIVMTQTPLSLPVTPGEPASISCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGIPA
BAP058-hum09-LC DIVMTQTPLSLPVTPGEPASISCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGIPA
BAP058-hum02-LC DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPS
BAP058-hum03-LC EIVLTQSPDFQSVTPKEKVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPD
BAP058-hum07-LC EIVLTQSPATLSLSPGERATLSCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGIPP
BAP058-hum13-LC AIQLTQSPSSLSASVGDRVTITCKASQDVGTAVAWYLQKPGQSPQLLIYWASTRHTGVPS
BAP058-hum12-LC DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYQQKPGQAPRLLIYWASTRHTGVPS

                        70        80        90        100
                ....|....|....|....|....|....|....|....|....|..
BAP-chi LC      RFTGSGSGTDFTLTISNVQSEDLADYFCQQYNSYPLTFGQGTKVEIK
BAP058-hum14-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum15-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum16-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum17-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum04-LC RFSGSGSGTDFTFTISSLQPEDIATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum05-LC RFSGSGSGTDFTFTISSLQPEDIATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum06-LC RFSGSGSGTDFTFTISSLQPEDIATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum08-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum10-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum11-LC RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum01-LC RFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum09-LC RFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum02-LC RFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum03-LC RFSGSGSGTDFTLKISRVEAEDVGVYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum07-LC RFSGSGYGTDFTLTINNIESEDAAYYFCQQYNSYPLTFGQGTKVEIK
BAP058-hum13-LC RFSGSGSGTDFTFTISSLEAEDAATYYCQQYNSYPLTFGQGTKVEIK
BAP058-hum12-LC RFSGSGSGTDFTFTISSLQPEDIATYYCQQYNSYPLTFGQGTKVEIK
```

FIGURE 9A

```
                    10        20        30        40        50        60
                    ....|....|....|....|....|....|....|....|....|....|....|
BAP-chi LC          DIMMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHTGVPD
BAP058-hum14-LC     E.VL...PD.Q.VTPKEK.T.....................A.R.............S
BAP058-hum15-LC     E.VL...PD.Q.VTPKEK.T.....................A.R.............S
BAP058-hum16-LC     E.VL...PD.Q.VTPKEK.T.....................A.R.............S
BAP058-hum17-LC     E.VL...PD.Q.VTPKEK.T.....................A.R.............S
BAP058-hum04-LC     E.VL...PD.Q.VTPKEK.T................L.......Q.............S
BAP058-hum05-LC     E.VL...PD.Q.VTPKEK.T................L.......Q.............S
BAP058-hum06-LC     E.VL...PD.Q.VTPKEK.T................L.......Q.............S
BAP058-hum08-LC     .VV....PLSLPVTL.QPA..S.....................A.R.............S
BAP058-hum10-LC     .VV....PLSLPVTL.QPA..S.....................A.R.............S
BAP058-hum11-LC     .VV....PLSLPVTL.QPA..S.....................A.R.............S
BAP058-hum01-LC     ..V...TPLSLPVTP.EPA..S.............L.......Q...........I.A
BAP058-hum09-LC     ..V...TPLSLPVTP.EPA..S.............L.......Q...........I.A
BAP058-hum02-LC     ..Q....PSSL.A......T................L.......Q.............S
BAP058-hum03-LC     E.VL...PD.Q.VTPKEK.T................L.......Q.............
BAP058-hum07-LC     E.VL...PATL.L.P.E.ATLS..............L.......Q...........I.P
BAP058-hum13-LC     A.QL...PSSL.A......T................L.......Q.............S
BAP058-hum12-LC     ..Q....PSSL.A......T.....................A.R.............S

                    70        80        90        100
                    ....|....|....|....|....|....|....|....|....|..
BAP-chi LC          RFTGSGSGTDFTLTISNVQSEDLADYFCQQYNSYPLTFGQGTKVEIK
BAP058-hum14-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum15-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum16-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum17-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum04-LC     ..S.........F...SL.P..I.T.Y.....................
BAP058-hum05-LC     ..S.........F...SL.P..I.T.Y.....................
BAP058-hum06-LC     ..S.........F...SL.P..I.T.Y.....................
BAP058-hum08-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum10-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum11-LC     ..S......E......SL.PD.F.T.Y.....................
BAP058-hum01-LC     ..S......E......SL....F.V.Y.....................
BAP058-hum09-LC     ..S......E......SL....F.V.Y.....................
BAP058-hum02-LC     ..S............SL.P..F.T.Y.....................
BAP058-hum03-LC     ..S..........K..R.EA..VGV.Y.....................
BAP058-hum07-LC     ..S...Y........N.IE...A.Y.....................
BAP058-hum13-LC     ..S.........F...SLEA..A.T.Y.....................
BAP058-hum12-LC     ..S.........F...SL.P..I.T.Y.....................
```

FIGURE 9B

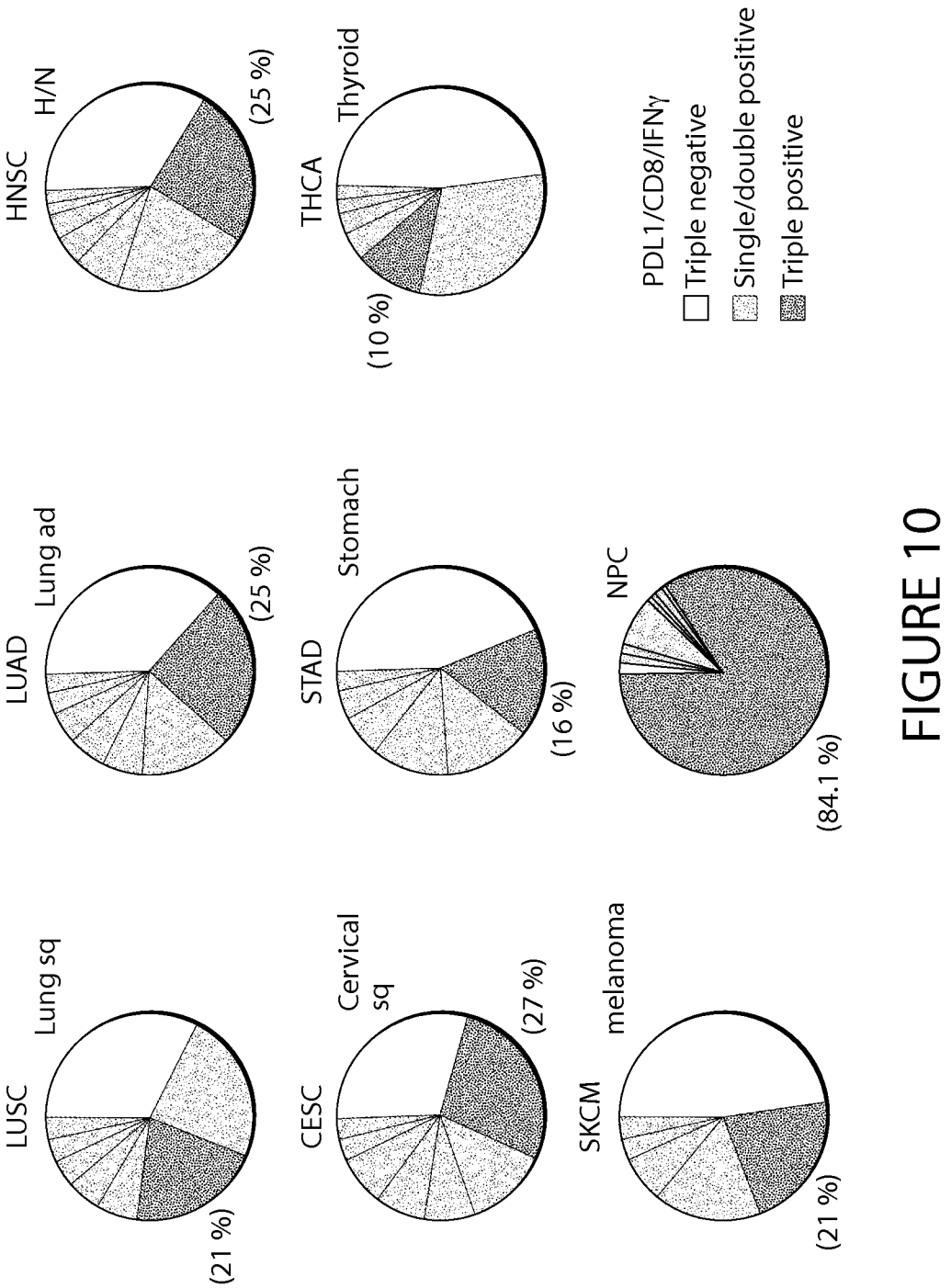

HNSC
H/N
(25 %)
THCA
Thyroid
(10 %)
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive
LUAD
Lung ad
(25 %)
STAD
Stomach
(16 %)
NPC
(84.1 %)
LUSC
Lung sq
(21 %)
CESC
Cervical sq
(27 %)
SKCM
melanoma
(21 %)

FIGURE 10

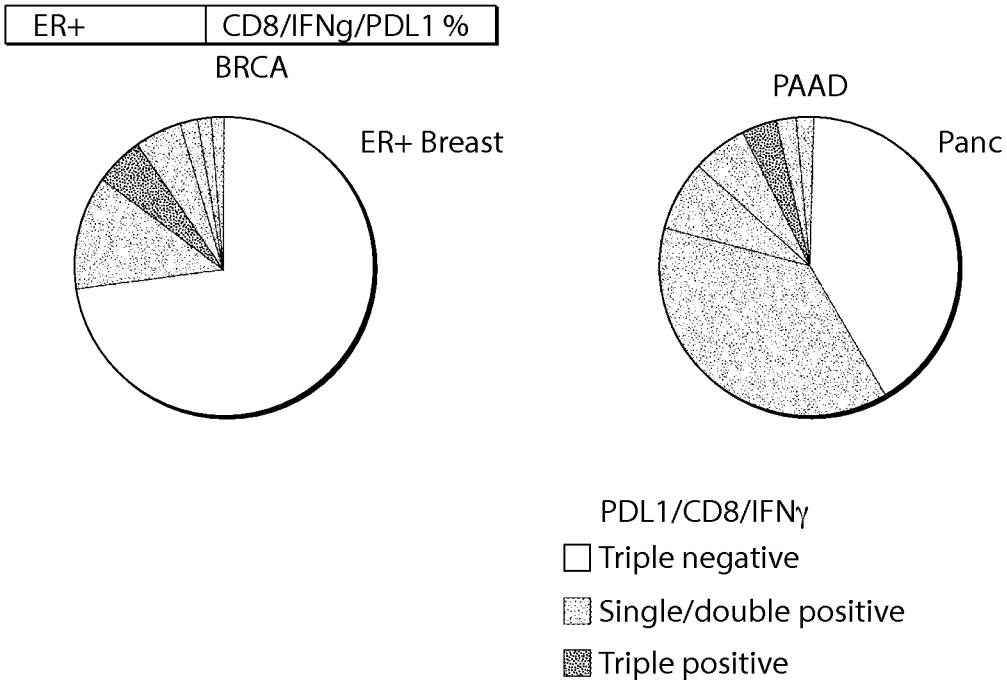

ER+
CD8/IFNg/PDL1 %
BRCA
ER+ Breast
PAAD
Panc
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 11

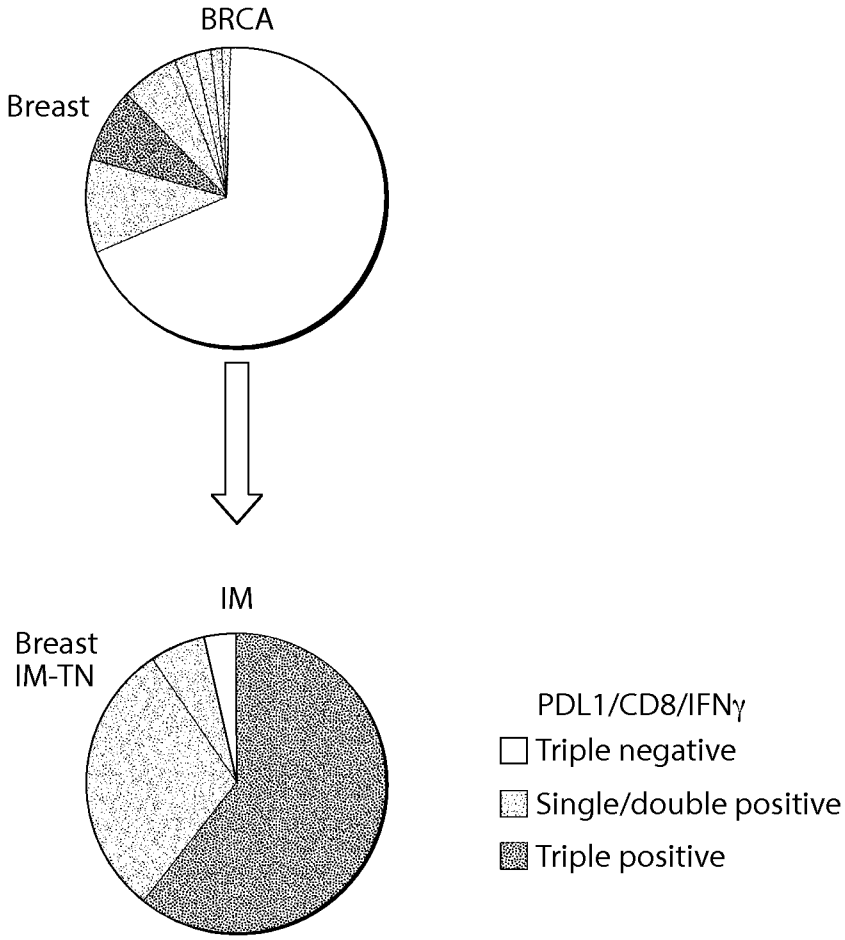

BRCA
Breast
IM
Breast
IM-TN
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 12

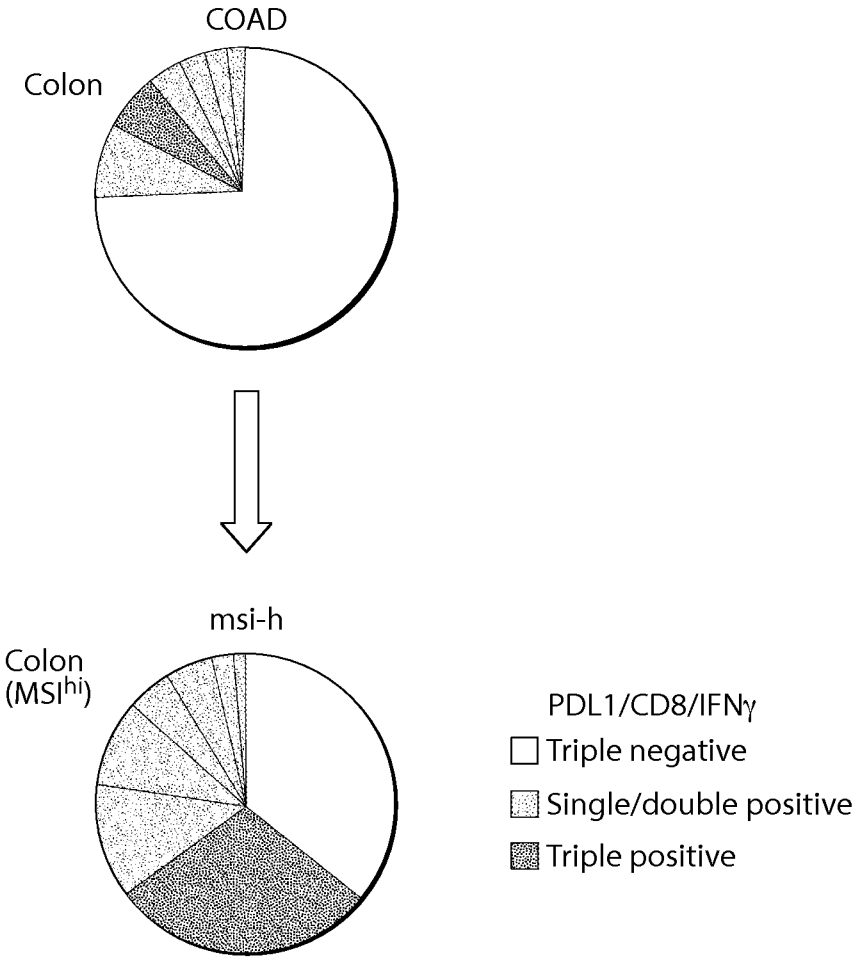

COAD
Colon
msi-h
Colon
(MSI^hi)
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 13

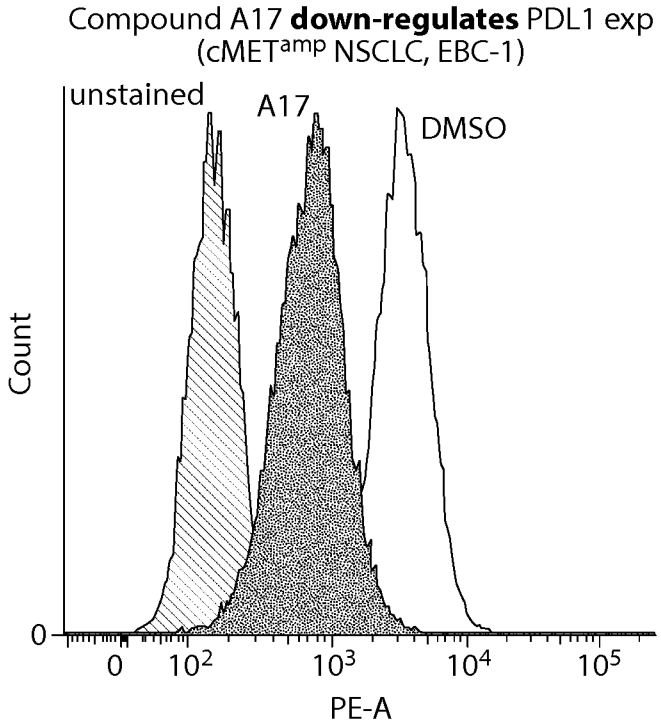

Compound A17 down-regulates PDL1 exp
(cMET^amp NSCLC, EBC-1)
unstained
A17
DMSO
Count
0
0
10^2
10^3
10^4
10^5
PE-A
PDL1 expression by Flow Cytometry

FIGURE 14

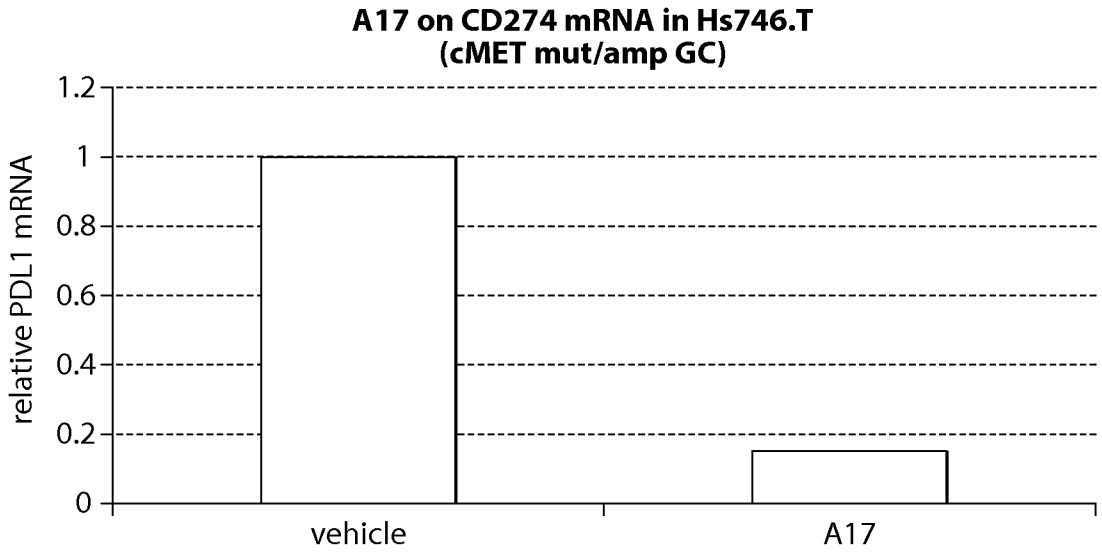


FIGURE 15

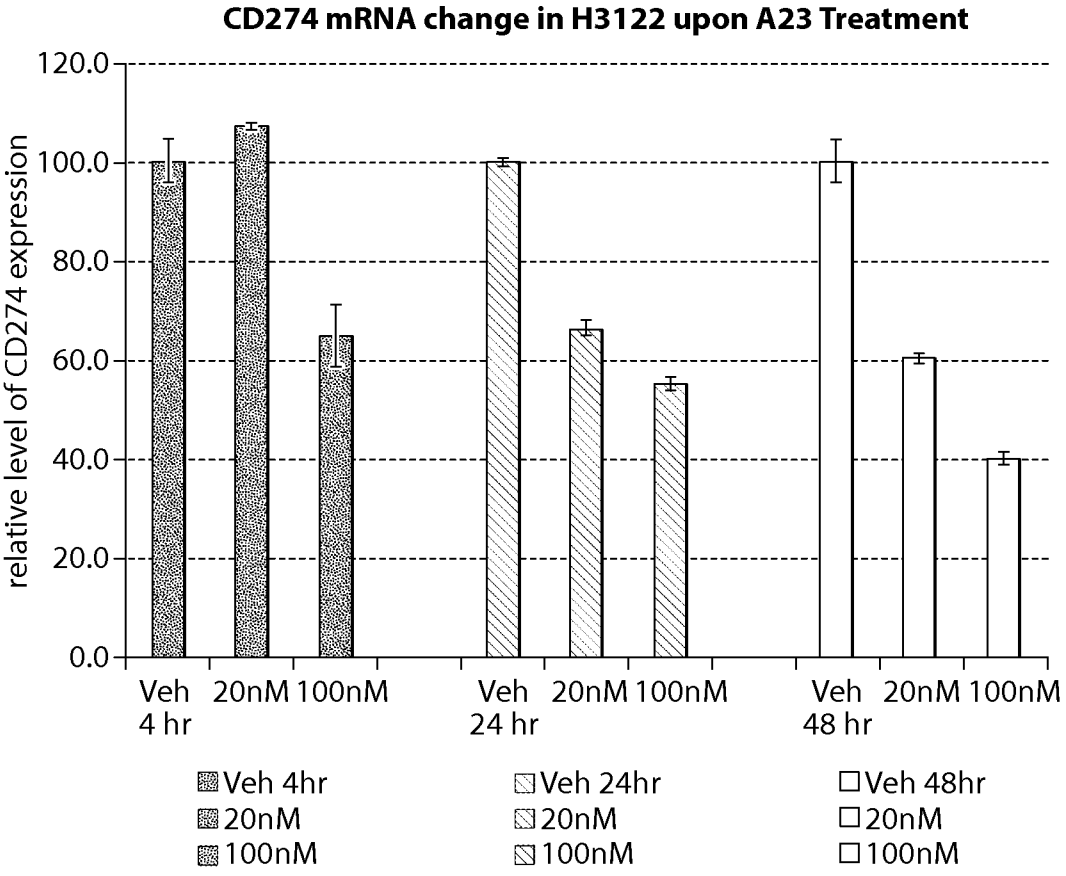


FIGURE 16

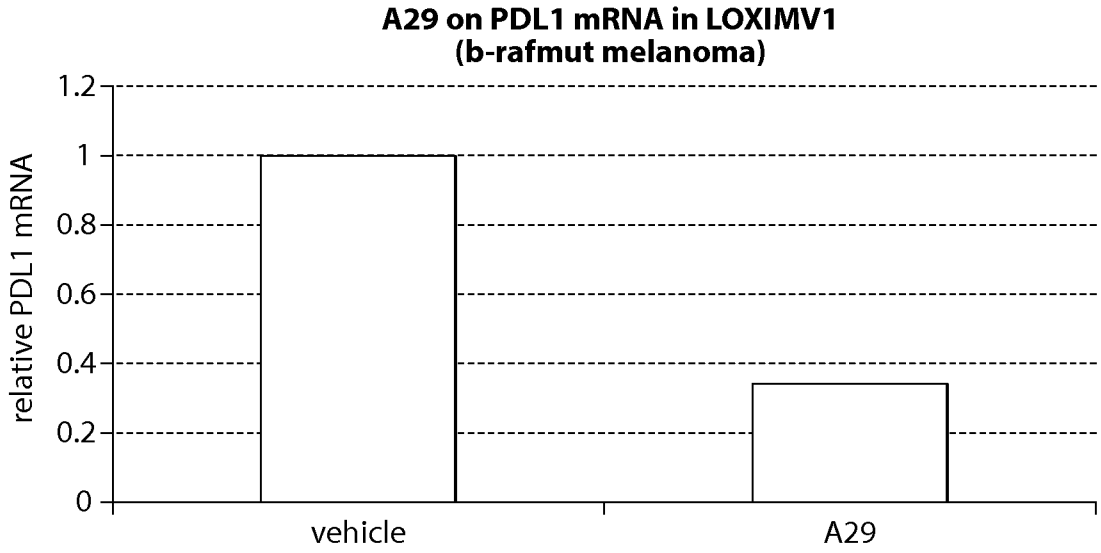


FIGURE 17

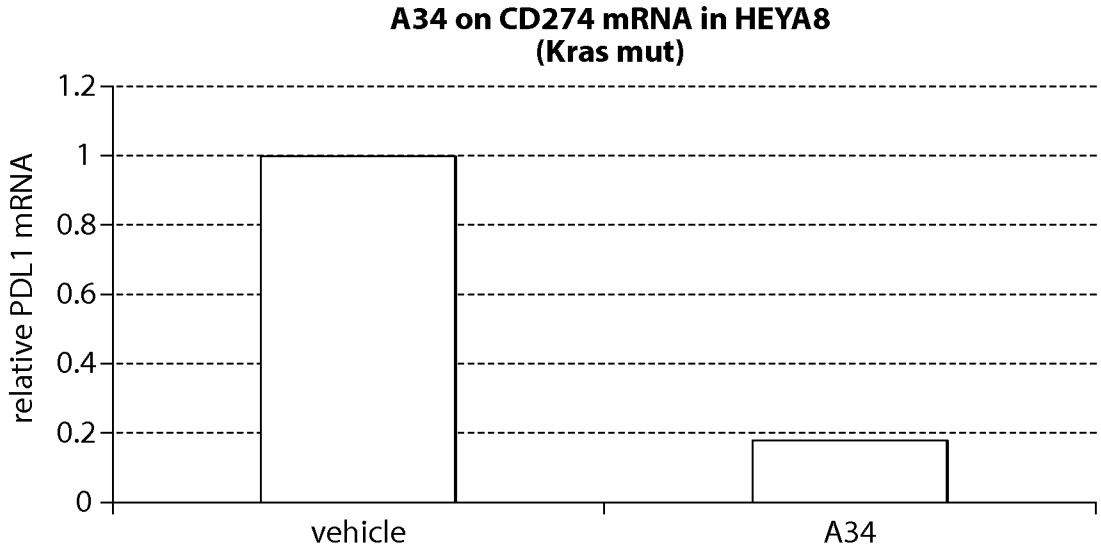


FIGURE 18

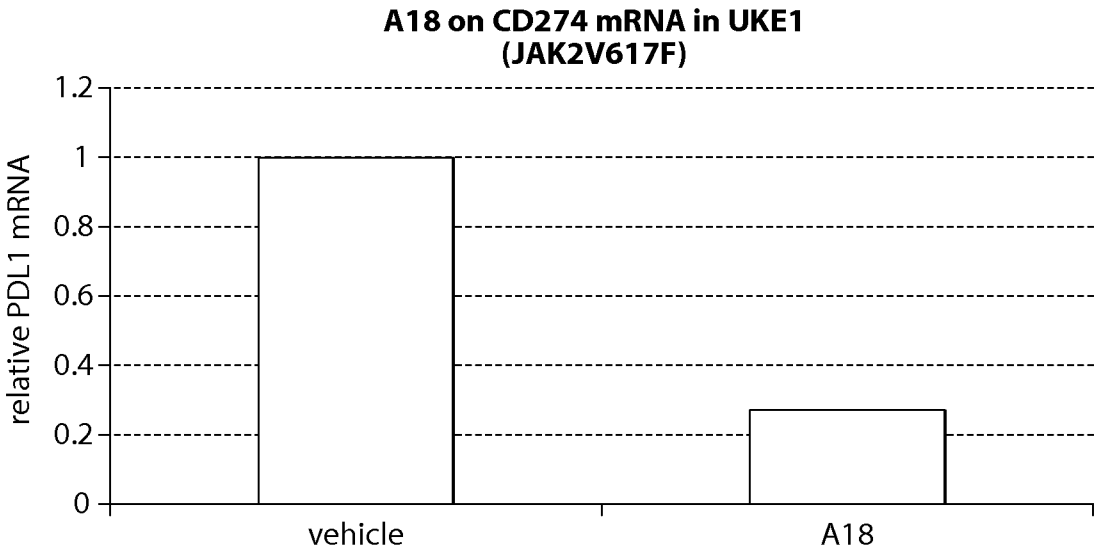

A18 on CD274 mRNA in UKE1
(JAK2V617F)
relative PDL1 mRNA
1.2
1
0.8
0.6
0.4
0.2
0
vehicle
A18

FIGURE 19

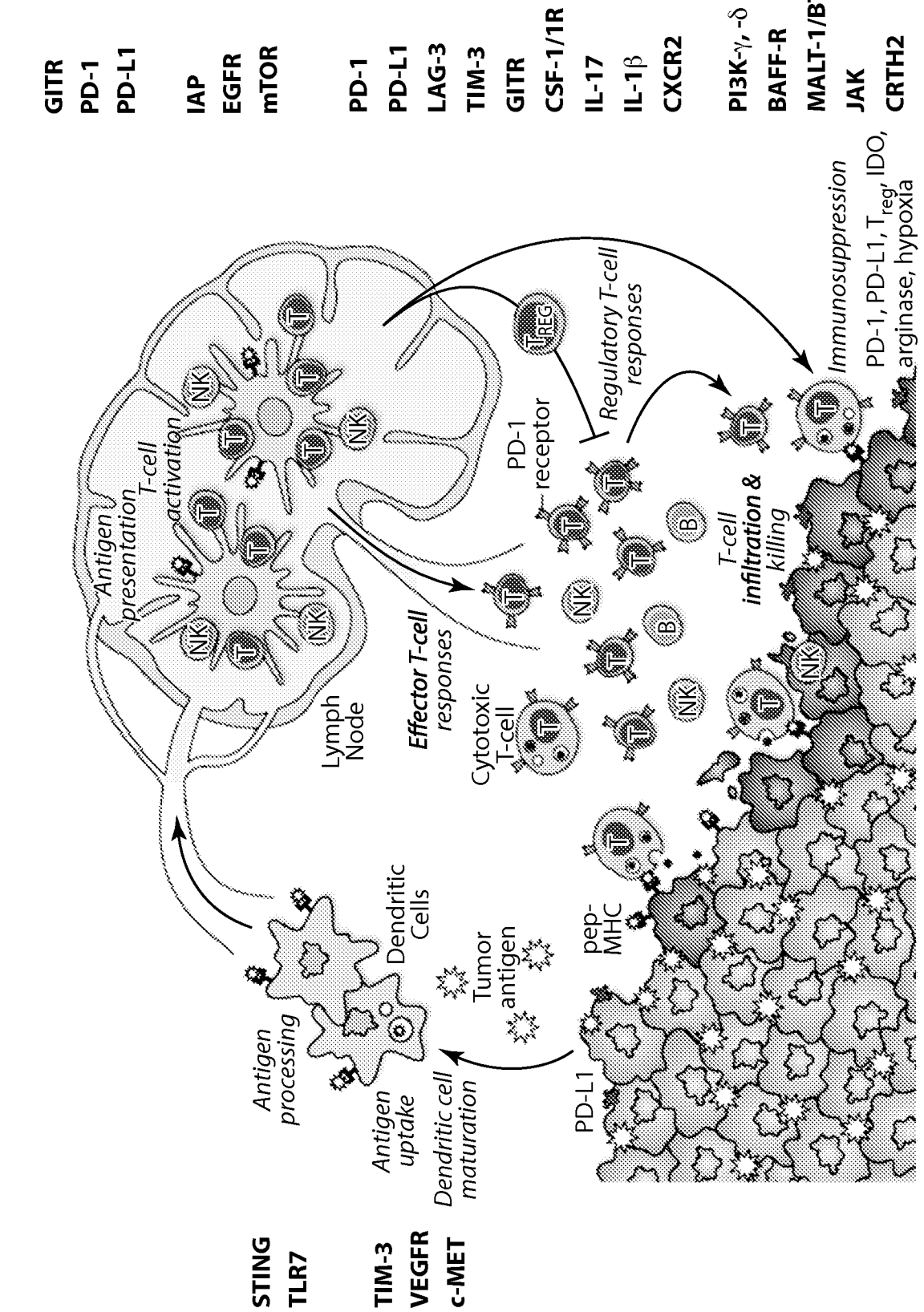

GITR
PD-1
PD-L1
IAP
EGFR
mTOR
PD-1
PD-L1
LAG-3
TIM-3
GITR
CSF-1/1R
IL-17
IL-1β
CXCR2
PI3K-γ, -δ
BAFF-R
MALT-1/BTK
JAK
CRTH2
VEGFR
STING
TLR7
TIM-3
VEGFR
c-MET
Antigen processing
Antigen uptake
Dendritic cell maturation
Dendritic Cells
Tumor antigen
pep-MHC
PD-L1
Lymph Node
Antigen presentation
T-cell activation
Effector T-cell responses
Cytotoxic T-cell
PD-1 receptor
Regulatory T-cell responses
T-cell infiltration & killing
Immunosuppression
PD-1, PD-L1, T_{reg}, IDO, arginase, hypoxia

FIGURE 20

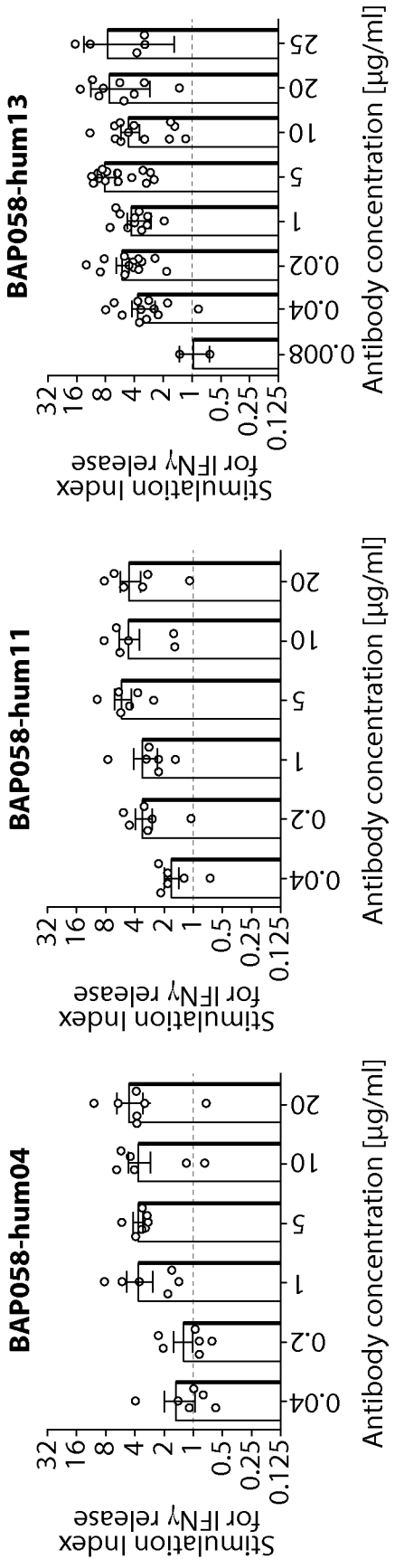

BAP058-hum04
BAP058-hum11
BAP058-hum13
Stimulation Index for IFNγ release
32
16
8
4
2
1
0.5
0.25
0.125
0.04
0.2
1
5
10
20
0.008
0.02
25
Antibody concentration [µg/ml]

FIGURE 21

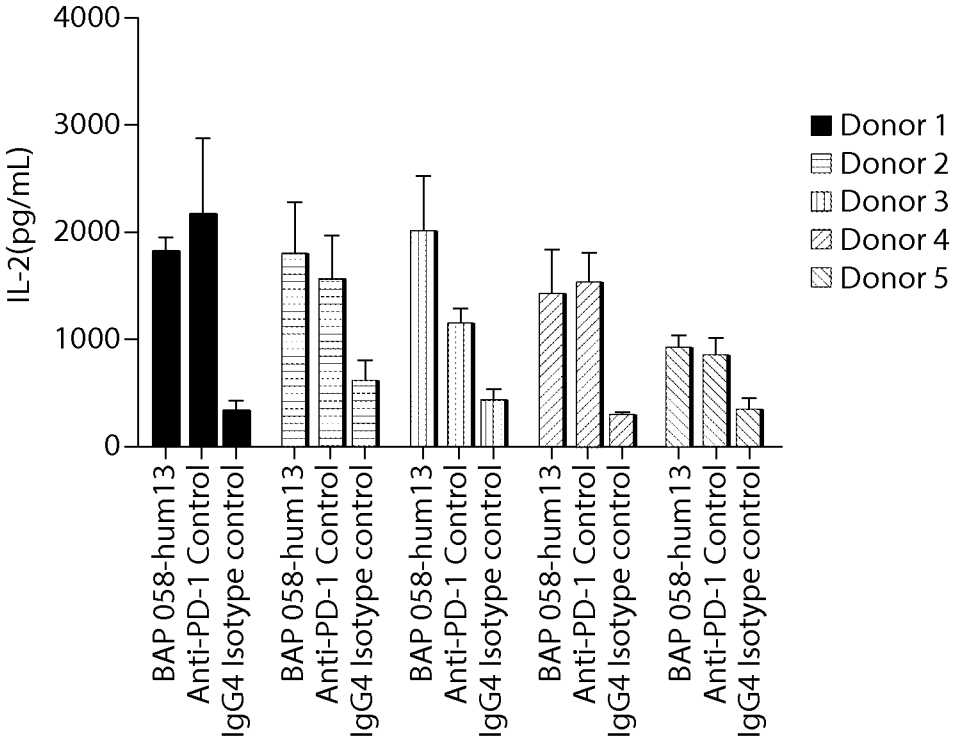
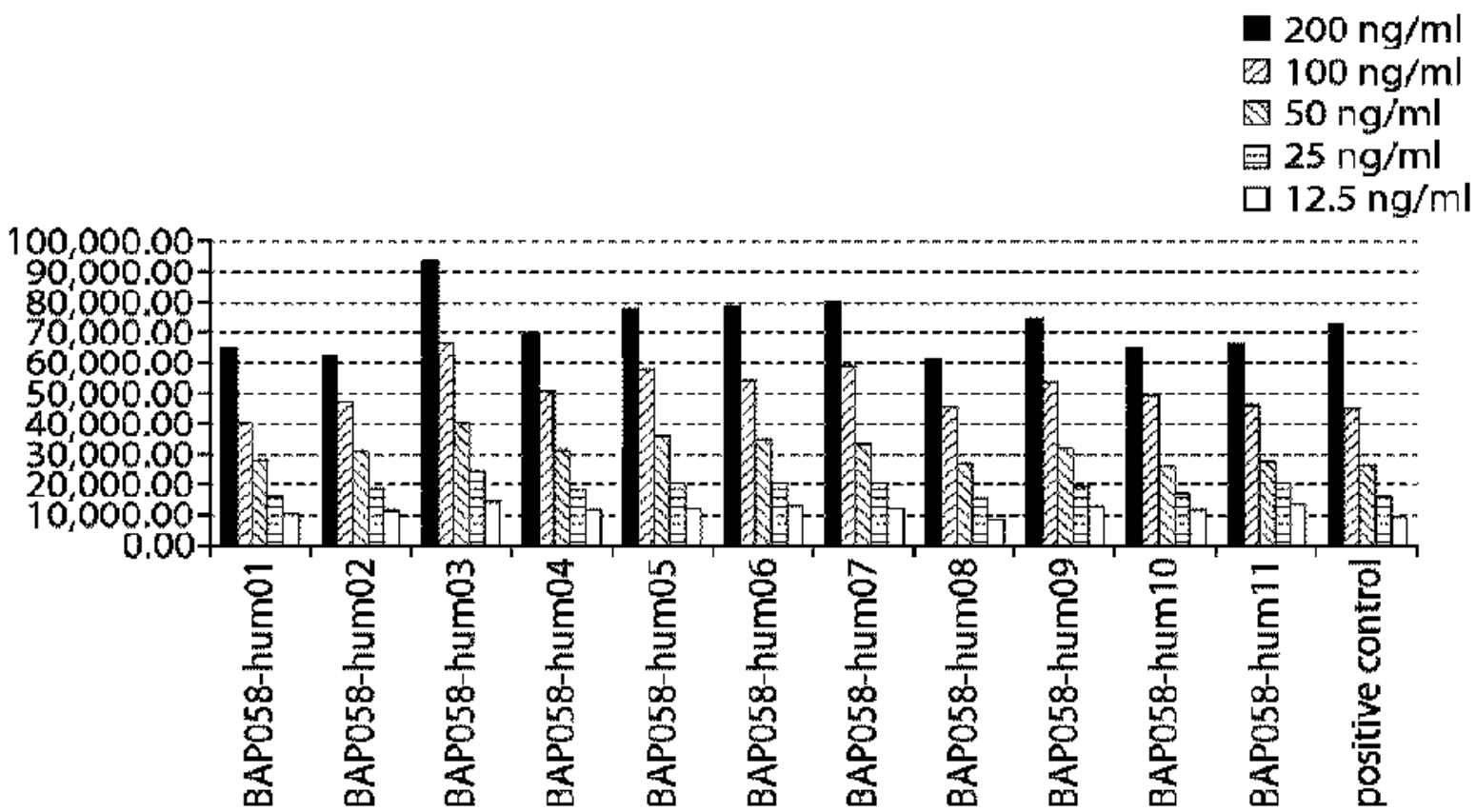
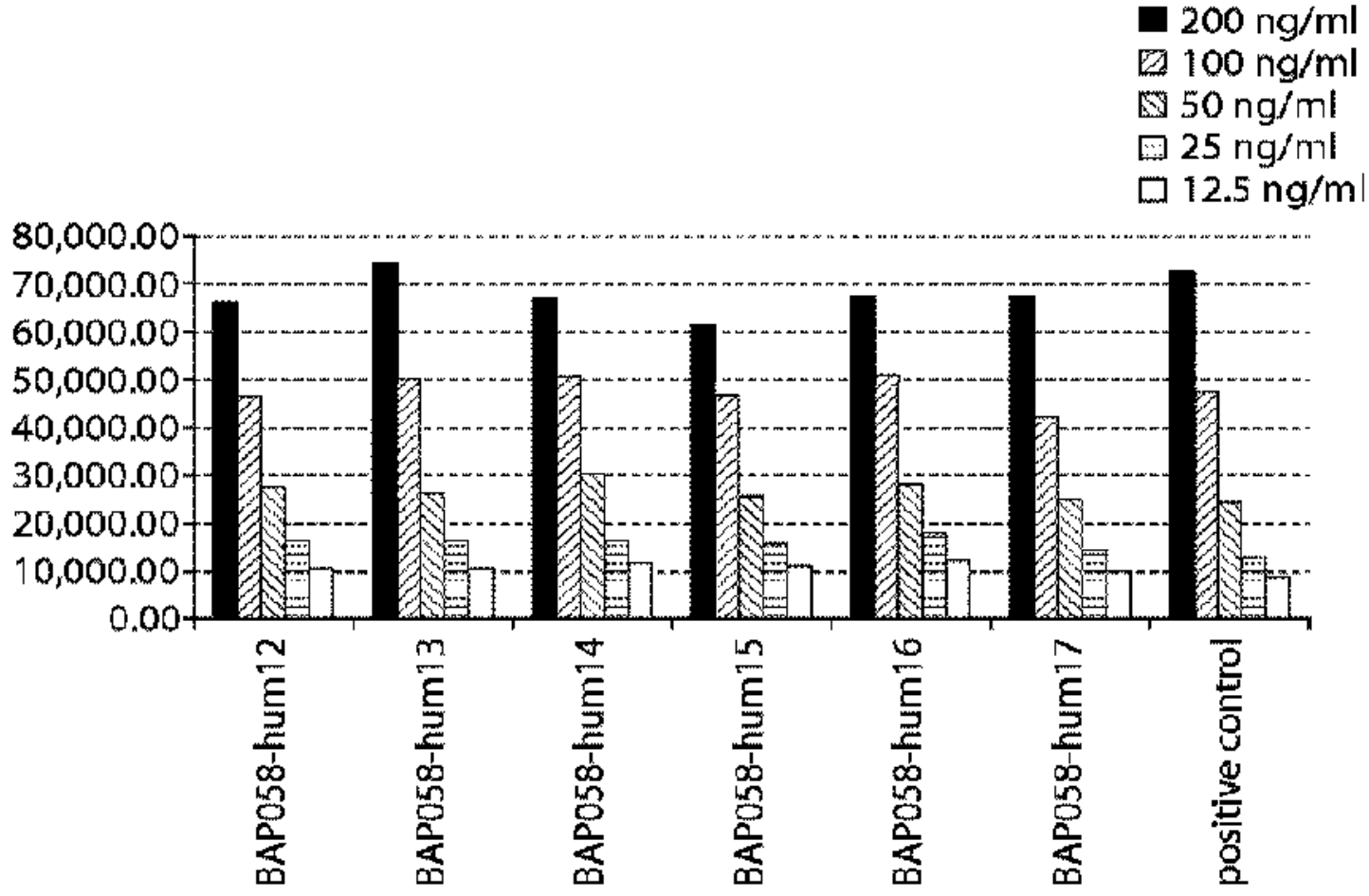

4000
3000
2000
1000
0
IL-2(pg/mL)
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
BAP 058-hum13
Anti-PD-1 Control
IgG4 Isotype control
BAP 058-hum13
Anti-PD-1 Control
IgG4 Isotype control
BAP 058-hum13
Anti-PD-1 Control
IgG4 Isotype control
BAP 058-hum13
Anti-PD-1 Control
IgG4 Isotype control
BAP 058-hum13
Anti-PD-1 Control
IgG4 Isotype control
Ab + SEB

FIGURE 22


200 ng/ml
100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
100,000.00
90,000.00
80,000.00
70,000.00
60,000.00
50,000.00
40,000.00
30,000.00
20,000.00
10,000.00
0.00
BAP058-hum01
BAP058-hum02
BAP058-hum03
BAP058-hum04
BAP058-hum05
BAP058-hum06
BAP058-hum07
BAP058-hum08
BAP058-hum09
BAP058-hum10
BAP058-hum11
positive control


200 ng/ml
100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
80,000.00
70,000.00
60,000.00
50,000.00
40,000.00
30,000.00
20,000.00
10,000.00
0.00
BAP058-hum12
BAP058-hum13
BAP058-hum14
BAP058-hum15
BAP058-hum16
BAP058-hum17
positive control