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(54) **Titre : MOLECULES D'ANTICORPS ANTI-LAG-3 ET LEURS UTILISATIONS**
(54) **Title: ANTIBODY MOLECULES TO LAG-3 AND USES THEREOF**

(57) **Abrégé/Abstract:**
Antibody molecules that specifically bind to LAG-3 are disclosed. The anti-LAG-3 antibody molecules can be used to treat, prevent and/or diagnose cancerous or infectious disorders.

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(54) Title: ANTIBODY MOLECULES TO LAG-3 AND USES THEREOF

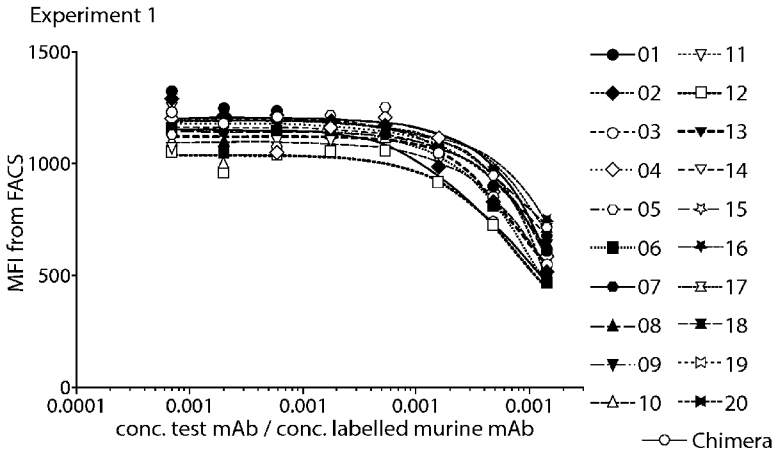

FIGURE 5A

(57) Abstract: Antibody molecules that specifically bind to LAG-3 are disclosed. The anti-LAG-3 antibody molecules can be used to treat, prevent and/or diagnose cancerous or infectious disorders.

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ANTIBODY MOLECULES TO LAG-3 AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/953,536, filed March 14, 2014, U.S. Provisional Application No. 62/059,690, filed October 3, 2014, and U.S. Provisional Application No. 62/094,889, filed December 19, 2014.

BACKGROUND

Lymphocyte Activation Gene-3, or LAG-3 (also known as CD223), is a member of the immunoglobulin supergene family, and is expressed on activated T cells (Huard *et al.* (1994) *Immunogenetics* 39:213), NK cells (Triebel *et al.* (1990) *J. Exp. Med.* 171:1393-1405), regulatory T cells (Huang *et al.* (2004) *Immunity* 21:503-513; Camisaschi *et al.* (2010) *J Immunol.* 184:6545-6551; Gagliani *et al.* (2013) *Nat Med* 19:739-746), and plasmacytoid dendritic cells (DCs) (Workman *et al.* (2009) *J Immunol* 182:1885-1891). LAG-3 is a membrane protein encoded by a gene located on chromosome 12, and is structurally and genetically related to CD4.

Similar to CD4, LAG-3 can interact with MHC class II molecules on the cell surface (Baixeras *et al.* (1992) *J. Exp. Med.* 176:327-337; Huard *et al.* (1996) *Eur. J. Immunol.* 26:1180-1186). It has been suggested that the direct binding of LAG-3 to MHC class II plays a role in down-regulating antigen-dependent stimulation of $CD4^+$ T lymphocytes (Huard *et al.* (1994) *Eur. J. Immunol.* 24:3216-3221) and LAG-3 blockade has also been shown to reinvigorate $CD8^+$ lymphocytes in both tumor or self-antigen (Gross *et al.* (2007) *J Clin Invest.* 117:3383-3392) and viral models (Blackburn *et al.* (2009) *Nat. Immunol.* 10:29-37). Further, the intra-cytoplasmic region of LAG-3 can interact with LAP (LAG-3-associated protein), which is a signal

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transduction molecule involved in the downregulation of the CD3/TCR activation pathway (Iouzalen *et al.* (2001) *Eur. J. Immunol.* 31:2885-2891). Moreover, $CD4^+CD25^+$ regulatory T cells (T_{reg}) have been shown to express LAG-3 upon activation, which contributes to the suppressor activity of T_{reg} cells (Huang, C. *et al.* (2004) *Immunity* 21:503-513). LAG-3 can also negatively regulate T cell homeostasis by T_{reg} cells in both T cell-dependent and independent mechanisms (Workman, C. J. and Vignali, D. A. (2005) *J. Immunol.* 174:688-695).

Given the importance of LAG-3 in downregulating an immune response, the need exists for developing novel agents that modulate its activity to activate 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 Lymphocyte Activation Gene-3 (LAG-3) with high affinity and specificity. In one embodiment, the anti-LAG-3 antibody molecules include 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-LAG-3 antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose cancerous disorders (*e.g.,* solid and soft-tissue tumors), as well as infectious diseases. Thus, compositions and methods for detecting LAG-3, as well as methods for treating various disorders, including cancer and/or infectious diseases using the anti-LAG-3 antibody molecules 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 LAG-3, *e.g.,* human LAG-3, 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) binds to LAG-3, *e.g.*, a LAG-3-CHO transfectant, with a K_D of less than: 5 nM, 4 nM, 3 nM, 2nM, 1 nM, *e.g.*, 1 to 3 nM (*e.g.*, about 1.92 nM or about 2.3 nM);

(iii) does not substantially bind to CD4;

(iv) inhibits binding of LAG-3 to a major histocompatibility (MHC) class II molecule, *e.g.*, shows an IC_{50} of about 1 to 20 nM, 5 to 15 nM, *e.g.*, 5.5 nM;

(v) binds to the D1 domain of LAG-3 (*e.g.*, human LAG-3), *e.g.*, binds to the D1 domain, but does not bind to the extra loop region of the D1 domain;

(vi) modulates (*e.g.*, stimulates, enhances, or restores) an immune response, *e.g.*, an antigen-specific T cell response or anti-tumor response;

(vii) binds specifically to an epitope on LAG-3, *e.g.*, the same or similar epitope as the epitope recognized by murine monoclonal antibody BAP050 or chimeric antibody BAP050-chi;

(viii) binds to a different epitope on LAG-3 than the one recognized by antibody BMS-986016;

(ix) shows the same or similar binding affinity or specificity, or both, as any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J.

(x) 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;

(xi) 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;

(xii) 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;

(xiii) inhibits, *e.g.,* competitively inhibits, the binding of a second antibody molecule to LAG-3, wherein the second antibody molecule is an antibody molecule described herein, *e.g.,* an antibody molecule chosen from, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J;

(xiv) binds the same or an overlapping epitope with a second antibody molecule to LAG-3, wherein the second antibody molecule is an antibody molecule described herein, *e.g.,* an antibody molecule chosen from, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J;

(xv) competes for binding, and/or binds the same epitope, with a second antibody molecule to LAG-3, *e.g.,* as measured by a Biacore method, a FACS method, or both, wherein the second antibody molecule is an antibody molecule described herein, *e.g.,* an antibody molecule chosen from, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03,

BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J;

(xvi) has one or more biological properties of an antibody molecule described herein, *e.g.,* an antibody molecule chosen from, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J;

(xvii) has one or more pharmacokinetic properties of an antibody molecule described herein, *e.g.,* an antibody molecule chosen from, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser),

BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; or

(xviii) inhibits one or more activities of LAG-3, *e.g.,* results in one or more of: an increase in antigen-dependent stimulation of $CD4^+$ T lymphocytes; an increase in T cell proliferation; an increase in expression of an activation antigen, *e.g.,* CD25; an increase in expression of a cytokine, *e.g.,* interferon-gamma (IFN-γ), interleukin-2 (IL-2), or interleukin-4 (IL-4); an increase in expression of a chemokine, *e.g.,* CCL3, CCL4, or CCL5; a decrease in the suppressor activity of T_{reg} cells; an increase in T cell homeostasis; an increase in tumor infiltrating lymphocytes; or a decrease in immune evasion by the cancerous cells.

As used herein, "huBAP050(Ser)" refers to a humanized BAP050 antibody molecule, *e.g.,* any of the humanized BAP050 antibody molecule described herein, *e.g.,* as described in Table 1, that has a Cys to Ser substitution at position 84 of the heavy chain framework region 3 (VHFW3). In some embodiments, the huBAP050(Ser) antibody molecule is chosen from BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser.

In some embodiments, the anti-LAG-3 antibody molecule binds to LAG-3 with high affinity, *e.g.,* with a dissociation equilibrium constant (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-LAG-3 antibody molecule, *e.g.,* a murine or chimeric anti-LAG-3 antibody molecule described herein. In one embodiment, the anti-LAG-3 antibody molecule binds to LAG-3, *e.g.*, a LAG-3-CHO transfectant, with a K_D of less than: 5 nM, 4 nM, 3 nM, 2nM, *e.g.*, 1 to 3 nM (*e.g.*, about 1.92 nM or about 2.3 nM).

In some embodiments, the expression level of the anti-LAG-3 antibody molecule is about the same, higher or lower, *e.g.,* at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10-fold higher or lower, than the expression level of a murine or chimeric antibody molecule, *e.g.,* a murine or chimeric anti-LAG-3 antibody molecule described herein. In some embodiments, the antibody molecule is expressed in CHO cells.

In some embodiments, the anti-LAG-3 antibody molecule reduces one or more LAG-3-associated activities with an IC_{50} (concentration at 50% inhibition) that is about the same, higher or lower, *e.g.,* at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% higher or lower, than the IC_{50} of a murine or chimeric anti-LAG-3 antibody molecule, *e.g.,* a murine or chimeric anti-LAG-3 antibody molecule described herein. In some embodiments, the LAG-3-associated activity is the binding of an MHC class II molecule to LAG-3. In some embodiments, the LAG-3-associated activity is the binding of L-SECtin to LAG-3. In one embodiment, the anti-LAG-3 antibody has an IC_{50} of about 1 to 20 nM, 5 to 15 nM, 5.5 nM (*e.g.*, detected by inhibition of MHC class II or L-SECtin binding).

In some embodiments, the anti-LAG-3 antibody molecule has about the same or 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-LAG-3 antibody molecule, *e.g.,* a murine or chimeric anti-LAG-3 antibody molecule described herein.

In one embodiment, the anti-LAG-3 antibody molecule is a humanized antibody molecule and has a risk score based on T cell epitope analysis of 800 to 1200, 850 to 1150, 900 to 1100, 950 to 1050, or a risk score as described herein.

In another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 one embodiment, the antibody molecule includes a substitution (*e.g.*, a Cys to Ser substitution at position 84) in the heavy chain framework region 3 (VHFW3) (*e.g.*, as shown in Tables 1 and 2).

In yet another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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-LAG-3 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 according to EU numbering (*e.g.,* a Ser to Pro substitution). In still another embodiment, the anti-LAG-3 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 according to EU numbering (*e.g.,* an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265 according to EU numbering, a substitution at position 329 according to EU numbering, or both (*e.g.,* an Asp to Ala substitution at position 265 according to EU numbering and/or a Pro to Ala substitution at position 329 according to EU numbering). In one embodiment, the human IgG1 includes a substitution at position 234 according to EU numbering, a substitution at position 235 according to EU numbering, or both (*e.g.,* a Leu to Ala substitution at position 234 according to EU numbering and/or a Leu to Ala substitution at position 235 according to EU numbering). 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-LAG-3 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-LAG-3 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 one embodiment, the constant region is a mutated IgG4, *e.g.,* a mutated human IgG4 (*e.g.,* has a mutation at position 228 according to EU numbering (*e.g.,* a S228P mutation). In yet another embodiment, the anti-LAG-3 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 according to EU numbering (*e.g.,* an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265 according to EU numbering, a substitution at position 329 according to EU numbering, or both (*e.g.,* an Asp to Ala substitution at position 265 according to EU numbering and/or a Pro to Ala substitution at position 329 according to EU numbering). In one embodiment, the human IgG1 includes a substitution at position 234 according to EU numbering, a substitution at position 235 according to EU numbering, or both (*e.g.,* a Leu to Ala substitution at position 234 according to EU numbering and/or a Leu to Ala substitution at position 235 according to EU numbering).

In another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18,

BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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-LAG-3 antibody molecule, optionally, comprises a leader sequence from a heavy chain, a light chain, or both, as shown in Table 4; or a sequence substantially identical thereto.

In yet another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 shown in Table 1.

In one embodiment, the anti-LAG-3 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-LAG-3 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 shown in Table 1.

In yet another embodiment, the anti-LAG-3 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 shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.
In another embodiment, the anti-LAG-3 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 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 shown in Table 1, or encoded by a nucleotide sequence shown 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 shown in Table 1.

In another embodiment, the anti-LAG-3 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-LAG-3 antibody molecule includes all six CDRs from an antibody described herein, *e.g.,* an antibody chosen from any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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) relative to one, two, three, four, five, or six CDRs shown in Table 1. In one embodiment, the anti-LAG-3 antibody molecule may include any CDR described herein.

In one embodiment, the anti-LAG-3 antibody molecule includes at least one, two or three CDRs according to Kabat (*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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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 shown in Table 1.

In one embodiment, the anti-LAG-3 antibody molecule includes at least one, two or three CDRs according to Kabat (*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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 shown in Table 1.

In yet another embodiment, the anti-LAG-3 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Kabat (*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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 at least one, two, three, four, five, or six CDRs according to Kabat *et al.* shown in Table 1. In one embodiment, the anti-LAG-3 antibody molecule may include any CDR described herein.

In yet another embodiment, the anti-LAG-3 antibody molecule includes all six CDRs according to Kabat (*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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-

hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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-LAG-3 antibody molecule may include any CDR described herein.

In another embodiment, the anti-LAG-3 antibody molecule includes at least one, two or three 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, according to Chothia (*e.g.*, at least one, two, or three hypervariable loops according to the 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 hypervariable loops according to Chothia shown in Table 1.

In another embodiment, the anti-LAG-3 antibody molecule includes at least one, two or three hypervariable loops according to Chothia (*e.g.,* at least one, two, or three CDRs according to the Chothia 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J,; 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 hypervariable loops according to Chothia shown in Table 1.

In yet another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H,

BAP050-Clone-I, or BAP050-Clone-J; 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 LAG-3. In one embodiment, the anti-LAG-3 antibody molecule includes at least one, two, three, four, five, or six Chothia hypervariable loops of Table 1.

In one embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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) relative to all six hypervariable loops shown in Table 1. In one embodiment, the anti-LAG-3 antibody molecule may include any hypervariable loop described herein.

In still another embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser,

BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, *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-LAG-3 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-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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- LAG-3 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 GFTLTNYGMN (SEQ ID NO: 286), 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- LAG-3 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- LAG-3antibody 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- LAG-3 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-LAG-3 antibody molecule can contain any combination of CDRs or hypervariable loops according to the Kabat and Chothia definitions. In one embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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, CDR (*e.g.*, CDR or Kabat CDR), or other sequence referred to herein, *e.g.*, in Table 1, the antibody molecule is a monospecific antibody molecule, a bispecifc antibody molecule, or is an antibody molecule that

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

In one embodiment, the anti-LAG-3 antibody 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: 286; 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: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

In another embodiment, the anti-LAG-3 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: 286; 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: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15.

In one embodiment, the anti-LAG-3 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 1. In another embodiment, the anti-LAG-3 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 4. In yet another embodiment, the anti-LAG-3 antibody molecule comprises the VHCDR1 amino acid sequence of SEQ ID NO: 286.

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-LAG-3 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-LAG-3 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 BAP050-chi-HC, *e.g.,* the amino acid sequence of the FR region in the entire variable region, *e.g.,* shown in Figures. 9A-9B, or SEQ ID NO: 20 or 22. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain variable domain having one or more of: E at position 1, V at position 2, A at position 9, V at position 11, A at position 16, S at position 17, L at position 18, R at position 19, V at position 20, V or G at position 24, I at position 37, A or S at position 40, R or T at position 41, S at position 42, Q or R at position 43, R at position 44, E at position 46, I or L at position 48, V at position 68, V or T at position 69, I at position 70, A at position 72, D at position 73, K at position 74, V or I at position 76, Y at position 80, W at position 83, C or S at position 84, S or T at position 85, A at position 88, E or S at position 89, V or M at position 93, or Y at position 95 of amino acid sequence of BAP050-chi-HC, *e.g.,* the amino acid sequence of the FR in the entire variable region, *e.g.,* shown in Figures. 9A-9B, or SEQ ID NO: 20 or 22. In one embodiment, the antibody molecule includes a substitution (*e.g.,* a Cys to Ser substitution at position 84) in the heavy chain framework region 3 (VHFW3) (*e.g.,* as shown in Table 2).

Alternatively, or in combination with the heavy chain substitutions of BAP050-chi-HC described herein, the anti-LAG-3 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 BAP050-chi-LC, *e.g.,* the amino acid sequence shown in Figures. 10A-10B, or SEQ ID NO: 24 or 26. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain variable domain having one or more of: E or A at position 1, V at position 3, L at position 4, S at position 7, P at

position 8, A or L or D at position 9, T or F at position 10, Q at position 11, P at position 12, V or L at position 13, T at position 14, V or P at position 15, K at position 16, Q or E at position 17, T or P or K at position 18, A at position 19, S at position 20, L at position 21, T at position 22, L at position 37, G at position 41, K or Q at position 42, A or S at position 43, P at position 44, R or Q at position 45, L at position 46, I at position 58, P or D at position 60, Y at position 67, E at position 70, F at position 71, T at position 72, F at position 73, N at position 76, S or R at position 77, I at position 78, Q at position 79, A or S or P at position 80, D at position 81, A or F at position 83, Y or V at position 85, or F at position 87 of the amino acid sequence of BAP050-chi-LC, *e.g.,* the amino acid sequence shown in Figures. 10A-10B, or SEQ ID NO: 24 or 26.

In other embodiments, the anti-LAG-3 antibody molecule includes one, two, three, or four heavy chain framework regions (*e.g.,* a VHFW amino acid or nucleotide sequence shown in Table 2, or encoded by the nucleotide sequence shown in Table 2), 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 antibody molecule includes a substitution (*e.g.,* a Cys to Ser substitution at position 84) in the heavy chain framework region 3 (VHFW3) (*e.g.,* as shown in Table 2).

In yet other embodiments, the anti-LAG-3 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 (*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 other embodiments, the anti-LAG-3 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 sequence 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-LAG-3 antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum14, BAP050-hum15, BAP050-hum18, BAP050-hum19, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-Clone-F, or BAP050-Clone-G (*e.g.,* SEQ ID NO: 187). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, or BAP050-hum20, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone J (*e.g.,* SEQ ID NO: 190). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP050-hum16 (*e.g.,* SEQ ID NO: 194). In some embodiments, the antibody molecule comprises the heavy chain framework region 1 (VHFW1) of BAP050-hum17 (*e.g.,* SEQ ID NO: 196). In other embodiments, the antibody molecule comprises a heavy chain framework region 1 (VHFW1) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum13, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum13-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-Clone-F, BAP050-Clone-G, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 198). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum20, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum20-Ser, or BAP050-Clone-I (*e.g.,* SEQ ID NO: 202). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP050-hum14,

BAP050-hum15, BAP050-hum14-Ser, or BAP050-hum15-Ser (*e.g.*, SEQ ID NO: 206). In some embodiments, the antibody molecule comprises the heavy chain framework region 2 (VHFW2) of BAP050-hum16 (*e.g.*, SEQ ID NO: 208). In other embodiments, the antibody molecule comprises a heavy chain framework region 2 (VHFW2) having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum18, BAP050-hum19, or BAP050-hum20 (*e.g.*, SEQ ID NO: 210). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-hum20-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.*, SEQ ID NO: 212). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP050-hum16 (*e.g.*, SEQ ID NO: 217). In some embodiments, the antibody molecule comprises the heavy chain framework region 3 (VHFW3) of BAP050-hum17 (*e.g.*, SEQ ID NO: 219). In other embodiments, the antibody molecule comprises a heavy chain framework region 3 (VHFW3) having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework region 4 (VHFW4) of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, or

BAP050-hum20, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-hum20-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 221). In other embodiments, the antibody molecule comprises a heavy chain framework region 4 (VHFW4) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum01, BAP050-hum02, BAP050-hum04, BAP050-hum07, BAP050-hum09, BAP050-hum11, BAP050-hum13, BAP050-hum17, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum04-Ser, BAP050-hum07-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum13-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 226). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum03, BAP050-hum10, BAP050-hum14, BAP050-hum03-Ser, BAP050-hum10-Ser, or BAP050-hum14-Ser (*e.g.,* SEQ ID NO: 230). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum05 or BAP050-hum05-Ser (*e.g.,* SEQ ID NO: 232). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum06, BAP050-hum20, BAP050-hum06-Ser, or BAP050-hum20-Ser (*e.g.,* SEQ ID NO: 234). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum08, BAP050-hum12, BAP050-hum15, BAP050-hum16, BAP050-hum19, BAP050-hum08-Ser, BAP050-hum12-Ser, BAP050-hum15-Ser, or BAP050-hum19-Ser (*e.g.,* SEQ ID NO: 236). In some embodiments, the antibody molecule comprises the light chain framework region 1 (VLFW1) of BAP050-hum18 or BAP050-hum18-Ser (*e.g.,* SEQ ID NO: 238). In other embodiments, the antibody molecule comprises a light chain framework region 1 (VLFW1) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or

more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP050-hum01, BAP050-hum02, BAP050-hum05, BAP050-hum09, BAP050-hum13, BAP050-hum17, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum13-Ser, BAP050-hum17-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 240). In some embodiments, the antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP050-hum03, BAP050-hum06, BAP050-hum08, BAP050-hum10, BAP050-hum12, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum18, BAP050-hum19, BAP050-hum20, BAP050-hum03-Ser, BAP050-hum06-Ser, BAP050-hum08-Ser, BAP050-hum10-Ser, BAP050-hum12-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser (*e.g.,* SEQ ID NO: 244). In some embodiments, the antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP050-hum04 or BAP050-hum04-Ser (*e.g.,* SEQ ID NO: 246). In some embodiments, the antibody molecule comprises the light chain framework region 2 (VLFW2) of BAP050-hum07, BAP050-hum11, BAP050-hum07-Ser, or BAP050-hum11-Ser (*e.g.,* SEQ ID NO: 248). In other embodiments, the antibody molecule comprises a light chain framework region 2 (VLFW2) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum01, BAP050-hum03, BAP050-hum05, BAP050-hum10, BAP050-hum14, BAP050-hum19, BAP050-hum01-Ser, BAP050-hum03-Ser, BAP050-hum05-Ser, BAP050-hum10-Ser, BAP050-hum14-Ser, BAP050-hum19-Ser, or BAP050-Clone-F (*e.g.,* SEQ ID NO: 252). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum02, BAP050-hum09, BAP050-hum13, BAP050-hum02-Ser, BAP050-hum09-Ser, BAP050-hum13-Ser, BAP050-Clone-G, BAP050-Clone-H, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 255). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum04 or BAP050-hum04-Ser (*e.g.,* SEQ ID NO: 259). In some embodiments, the antibody molecule

comprises the light chain framework region 3 (VLFW3) of BAP050-hum06, BAP050-hum07, BAP050-hum11, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum11-Ser, or BAP050-Clone-I (*e.g.,* SEQ ID NO: 261). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum08, BAP050-hum12, BAP050-hum15, BAP050-hum16, BAP050-hum18, BAP050-hum08-Ser, BAP050-hum12-Ser, BAP050-hum15-Ser, or BAP050-hum18-Ser (*e.g.,* SEQ ID NO: 265). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum17 (*e.g.,* SEQ ID NO: 267). In some embodiments, the antibody molecule comprises the light chain framework region 3 (VLFW3) of BAP050-hum20 or BAP050-hum20-Ser (*e.g.,* SEQ ID NO: 269). In other embodiments, the antibody molecule comprises a light chain framework region 3 (VHLW3) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the light chain framework region 4 (VLFW4) of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-hum20-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.,* SEQ ID NO: 271). In other embodiments, the antibody molecule comprises a light chain framework region 4 (VLFW4) having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum18,

BAP050-hum19 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum20 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum13 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum14 or BAP050-hum15 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 210 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum16 (*e.g.*, SEQ ID NO: 194 (VHFW1), SEQ ID NO: 208 (VHFW2), and SEQ ID NO: 217 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum17 (*e.g.*, SEQ ID NO: 196 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 219 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-Clone-F, or BAP050-Clone-G (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum20-Ser, BAP050-Clone-H, or BAP050-Clone I (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum13-Ser or BAP050-Clone-J (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)). In some embodiments, the antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum14-Ser or BAP050-hum15-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 212 (VHFW3)). In some embodiments, the antibody molecule further comprises the heavy chain framework region 4 of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14,

BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum13-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.*, SEQ ID NO: 221). In other embodiments, the antibody molecule comprises a heavy chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum01, BAP050-hum01-Ser, or BAP050-Clone-F (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum02, BAP050-hum09, BAP050-hum13, BAP050-hum02-Ser, BAP050-hum09-Ser, BAP050-hum13-Ser, BAP050-Clone-G, BAP050-Clone-H, or BAP050-Clone-J (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 255 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum03, BAP050-hum10, BAP050-hum14, BAP050-hum03-Ser, BAP050-hum10-Ser, or BAP050-hum14-Ser (*e.g.*, SEQ ID NO: 230 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum04 or BAP050-hum04-Ser (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 246 (VLFW2), and SEQ ID NO: 259 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum05 or BAP050-hum05-Ser (*e.g.*, SEQ ID NO: 232 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum06 or BAP050-hum06-Ser (*e.g.*, SEQ ID NO: 234 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 261 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum07, BAP050-hum11, BAP050-hum07-Ser, BAP050-hum11-Ser, or BAP050-Clone-I (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 248 (VLFW2), and SEQ ID NO: 261 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum08, BAP050-hum12, BAP050-hum15, BAP050-hum16,

BAP050-hum08-Ser, BAP050-hum12-Ser, or BAP050-hum15-Ser (*e.g.*, SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum17 (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 267 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum18 or BAP050-hum18-Ser (*e.g.*, SEQ ID NO: 238 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum19 or BAP050-hum19-Ser (*e.g.*, SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In some embodiments, the antibody molecule comprises the light chain framework regions 1-3 of BAP050-hum20 or BAP050-hum20-Ser (*e.g.*, SEQ ID NO: 234 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 269 (VLFW3)). In some embodiments, the antibody molecule further comprises the heavy chain framework region 4 of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, BAP050-hum20-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J (*e.g.*, SEQ ID NO: 271). In other embodiments, the antibody molecule comprises a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum01 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum01-Ser or BAP050-Clone-F (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198

(VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum01, BAP050-hum01-Ser, or BAP050-Clone-F (*e.g.,* SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum02 (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum02-Ser or BAP050-Clone-G (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum02, BAP050-hum02-Ser, or BAP050-Clone-G (*e.g.,* SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 255 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum03 (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum03-Ser (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum03 (*e.g.,* SEQ ID NO: 230 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum04 (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198

(VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum04-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum04 (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 246 (VLFW2), and SEQ ID NO: 259 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum05 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)) or BAP050-hum05-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum05 or BAP050-hum05-Ser (*e.g.*, SEQ ID NO: 232 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum06 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum06-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum06 (*e.g.*, SEQ ID NO: 234 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 261 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum07 (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum07-Ser (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum07 (*e.g.,* SEQ ID NO: 226 (VLFW1), SEQ ID NO: 248 (VLFW2), and SEQ ID NO: 261 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum08 (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum08-Ser (*e.g.,* SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum08 (*e.g.,* SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.,* conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum09 (*e.g.,* SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or BAP050-hum09-Ser or BAP050-Clone-H (*e.g.,* SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum09, BAP050-hum09-Ser, or BAP050-Clone-H (*e.g.,* SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 255 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid

sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum10 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum10-Ser (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum10 (*e.g.*, SEQ ID NO: 230 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum11 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or BAP050-hum11-Ser, or BAP050-Clone-I (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum11, BAP050-hum11-Ser, or BAP050-Clone-I (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 248 (VLFW2), and SEQ ID NO: 261 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum12 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)) or BAP050-hum12-Ser (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum12 or BAP050-hum12-Ser (*e.g.*, SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework

region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum13 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum13-Ser or BAP050-Clone-J (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum13, BAP050-hum13-Ser, or BAP050-Clone-J (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 255 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum14 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum14-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 210 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum14 (*e.g.*, SEQ ID NO: 230 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum15 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum15-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 206 (VHFW2), and SEQ ID NO: 210 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum15 (*e.g.*,

SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum16 (*e.g.*, SEQ ID NO: 194 (VHFW1), SEQ ID NO: 208 (VHFW2), and SEQ ID NO: 217 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum16 (*e.g.*, SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum17 (*e.g.*, SEQ ID NO: 196 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 219 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum17 (*e.g.*, SEQ ID NO: 226 (VLFW1), SEQ ID NO: 240 (VLFW2), and SEQ ID NO: 267 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum18 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum18-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum18 (*e.g.*, SEQ ID NO: 238 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 265 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework

region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum19 (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or the heavy chain framework regions 1-3 of BAP050-hum18-Ser (*e.g.*, SEQ ID NO: 187 (VHFW1), SEQ ID NO: 198 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum19 (*e.g.*, SEQ ID NO: 236 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 252 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises the heavy chain framework regions 1-3 of BAP050-hum20 (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 210 (VHFW3)), or BAP050-hum20-Ser (*e.g.*, SEQ ID NO: 190 (VHFW1), SEQ ID NO: 202 (VHFW2), and SEQ ID NO: 212 (VHFW3)); and the light chain framework regions 1-3 of BAP050-hum20 (*e.g.*, SEQ ID NO: 234 (VLFW1), SEQ ID NO: 244 (VLFW2), and SEQ ID NO: 269 (VLFW3)). In other embodiments, the antibody molecule comprises a heavy chain and a light chain framework region having a sequence, or encoded by a sequence, substantially identical (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical) to any of the aforesaid sequences, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-LAG-3 antibody molecule comprises a heavy chain framework region having a combination of framework regions FW1, FW2 and FW3 as shown in Figures. 4 or 6. In other embodiment, antibody molecule comprises a light chain framework region having a combination of framework regions FW1, FW2 and FW3 as shown in Figures. 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 shown in Figures. 4

or 6, and a light chain framework region having a combination of framework regions FW1, FW2 and FW3 as shown in Figures. 4 or 6.

In one embodiment, the heavy or light chain variable domain, or both, of the of the anti-LAG-3 antibody molecule includes an amino acid sequence, which is substantially identical to an amino acid disclosed herein, *e.g.,* at least 70%, 75%, 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 of the anti-LAG-3 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 specific nucleic acid sequence or a nucleic acid sequence that encodes an amino acid sequence described herein, *e.g.,* 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-LAG-3 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-LAG-3 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 70%, 75%, 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-LAG-3 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-LAG-3 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-LAG-3 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, at least one, two, three, four, five or six CDR is defined according to Kabat, *e.g.,* as shown in Table 1. In another embodiment, at least one, two, three, four, five or six CDR is defined according to Chothia, *e.g.,* as shown in Table 1.

In one embodiment, the anti-LAG-3 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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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-LAG-3 antibody molecule comprises at least one, two, or three CDRs from a light chain variable region having an amino acid sequence of an antibody described herein, *e.g.,* an antibody chosen from any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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-LAG-3antibody molecule comprises all six CDRs and/or hypervariable loops described herein, *e.g.,* described in Table 1.

In one embodiment, the anti-LAG-3 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-LAG-3 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-LAG-3 antibody molecule is a monoclonal antibody or an antibody with single specificity. The anti-LAG-3 antibody molecule can also be a humanized, chimeric, camelid, shark, or *in vitro*-generated antibody molecules. In one embodiment, the anti-LAG-3 antibody molecule thereof is a humanized antibody molecule. The heavy and light chains of the anti-LAG-3 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 or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In certain embodiments, the anti-LAG-3 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 LAG-3 and a second binding specifity for PD-1, TIM-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), PD-L1 or PD-L2. In one embodiment, the bispecific antibody molecule binds to LAG-3 and PD-1. In another embodiment, the bispecific antibody molecule binds to LAG-3 and TIM-3. In another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5). In another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM-1. In yet another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM-5. In another embodiment, the bispecific antibody molecule binds to LAG-3 and PD-L1. In yet another embodiment, the bispecific antibody molecule binds to LAG-3 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 LAG-3, and a second and third binding specificity to one or more of: PD-1, TIM-3, CEACAM (*e.g.*, CEACAM-1 or CEACAM-5), PD-L1 or PD-L2.

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

In yet other embodiments, the anti-LAG-3 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, IgG2 or IgG4 (*e.g.*, human IgG1, IgG2 or IgG4). In one embodiment, the heavy chain constant region is human IgG1 or human IgG4. In another embodiment, the anti-LAG-3 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-LAG-3 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 according to EU numbering (*e.g.,* S to P), *e.g.,* as shown in Table 3. In certain embodiments, the anti-LAG-3 antibody molecules comprises a human IgG4 mutated at position 228 according to EU numbering (*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 according to EU numbering (*e.g.,* N to A), position 265 according to EU numbering (*e.g.,* D to A), position 329 according to EU numbering (*e.g.,* P to A), position 234 according to EU numbering (*e.g.,* L to A), or position 235 according to EU numbering (*e.g.,* L to A), *e.g.,* as shown in Table 3. In certain embodiments, the anti-LAG-3 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-LAG-3 antibody molecule is isolated or recombinant.

In one embodiment, the anti-LAG-3 antibody molecule is a humanized antibody molecule.

In one embodiment, the anti-LAG-3 antibody molecule has a risk score based on T cell epitope analysis of less than 1200, 1150, 1100, 1050, 1000, 950, 900, 850, or 800.

In one embodiment, the anti-LAG-3 antibody molecule is a humanized antibody molecule and has a risk score based on T cell epitope analysis of 800 to 1200, 850 to 1150, 900 to 1100, 950 to 1050, or a risk score as described herein.

The invention also features a nucleic acid molecule that comprises one or more nucleotide sequences that encode heavy and light chain variable regions, CDRs, hypervariable loops, and/or framework regions of the anti-LAG-3 antibody molecules, as described herein. In certain embodiments, the nucleotide sequence that encodes the anti-LAG-3 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-LAG-3 antibody molecule chosen from one or more of, *e.g.,* any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-

hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, 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 a heavy chain constant region comprising the amino acid sequence of BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 other embodiments, the nucleic acid comprises a nucleotide sequence that encodes a light chain variable domain and/or a light chain constant region comprising the amino acid sequence of BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; 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 aforesaid nucleotide sequences encoding the anti-LAG-3 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, *e.g.,* a leader sequence as shown in Table 4, or a sequence substantially identical thereto.

In certain embodiments, the nucleic acid molecule comprise 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 comprise 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 can comprise 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 one embodiment, the nucleic acid molecule includes a nucleotide sequence encoding an anti-LAG-3 antibody molecule that includes a substitution (*e.g.,* a Cys to Ser substitution at position 84) in the heavy chain framework region 3 (VHFW3) (*e.g.,* as shown in Tables 1 and 2).

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 b), VHFW2 (type c), VHFW2 (type d), VHFW3 (type a), VHFW3 (type a'), VHFW3 (type b), VHFW3 (type c), or VHFW4, or any combination thereof, *e.g.*, a framework combination as described herein) for any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.,* BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-

hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP049-Clone-F, BAP049-Clone-G, BAP049-Clone-H, BAP049-Clone-I, or BAP049-Clone-J, 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 b), VLFW2 (type c), VLFW2 (type d),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 BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP049-Clone-F, BAP049-Clone-G, BAP049-Clone-H, BAP049-Clone-I, or BAP049-Clone-J, as summarized in Tables 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), human Per C6 cell line (*e.g.,* PER C6 cells from Crucell), 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 LAG-3 antigen (*e.g.,* an antigen comprising at least a portion of a LAG-3 epitope); obtaining an antibody molecule that specifically binds to the LAG-3 polypeptide; and evaluating if the antibody molecule specifically binds to the LAG-3 polypeptide, or evaluating efficacy of the antibody molecule in modulating, *e.g.,* inhibiting, the activity of the LAG-3. 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 anti-LAG3 antibody molecule described herein. In one embodiment, the composition, *e.g.,* the pharmaceutical composition, includes a combination of the anti-LAG-3 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 antibody molecules disclosed herein can inhibit, reduce or neutralize one or more activities of LAG-3. In one embodiment, the anti-LAG-3 antibody molecule results in one or

more of: an increase in antigen-dependent stimulation of $CD4^+$ T lymphocytes or $CD8^+$ T lymphocytes, an increase in T cell proliferation; an increase in expression of an activation antigen, *e.g.,* CD25; an increase in expression of a cytokine, *e.g.,* interferon-gamma (IFN-γ),interleukin-2 (IL-2), interleukin-4 (IL-4), chemokine (C-C motif) ligand 3 (CCL3), chemokine (C-C motif) ligand 4 (CCL4), or chemokine (C-C motif) ligand 5 (CCL5); a decrease in the suppressor activity of T_{reg} cells, an increase in T cell homeostasis, an increase in tumor infiltrating lymphocytes, or a decrease in immune evasion by the cancerous cells. Thus, such antibody molecules can be used, alone or in combination, to treat or prevent disorders where enhancing an immune response in a subject is desired.

Uses of the Anti-LAG-3 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 antibody molecule disclosed herein (*e.g.,* a therapeutically effective amount of an anti-LAG-3 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 restores, enhances, stimulates or increases an 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 some embodiments, the anti-LAG-3 antibody molecule restores, enhances or stimulates an antigen-specific T cell response, *e.g.,* interleukin-2 (IL-2) or interferon-gamma (IFN-γ) production in an antigen-specific T cell response, in the subject. In some embodiments, the immune response is an anti-tumor 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 tumor in a subject is provided. The method comprises administering to the subject an anti-LAG-3 antibody molecule described herein, *e.g.,* a therapeutically effective

amount of an anti-LAG-3 antibody molecule, alone, *e.g.*, as a monotherapy, or in combination, *e.g.*, with one or more agents or procedures. In certain embodiments, the anti-LAG-3 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 one embodiment, the anti-LAG-3 antibody molecule is administered in combination with an inhibitor or activator of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 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-CTLA4 antibody).

In certain embodiments, the cancer treated with the anti-LAG-3 antibody molecule, alone or in combination, includes but is not limited to, a solid tumor, a hematological cancer (*e.g.*, leukemia, lymphoma, myeloma), and a metastatic lesion thereof. In one embodiment, the cancer is a solid tumor. Examples of solid tumors include malignancies, *e.g.*, sarcomas and carcinomas (*e.g.*, adenocarcinomas), of the various organ systems, such as those affecting lung, breast, lymphoid, gastrointestinal or colorectal, genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells), pharynx, CNS (*e.g.*, brain, neural or glial cells), skin (*e.g.*, melanoma), head and neck (*e.g.*, head and neck squamous cell carcinoma (HNCC)), and pancreas. For example, melanoma, colon cancers, gastric cancer, rectal cancer, renal-cell carcinoma, 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), liver cancer, a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology) or small cell lung cancer), prostate cancer, cancer of head or neck (*e.g.*, HPV+ squamous cell carcinoma), cancer of the small intestine and cancer of the esophagus. Examples of hematological cancer include, but is not limited to, leukemia (*e.g.*, a myeloid leukemia, lymphoid leukemia, or chronic lymphocytic leukemia (CLL)), lymphoma (*e.g.*, Hogdkin lymphoma (HL), non-Hogdkin lymphoma (NHL), Diffuse large B-cell lymphoma (DLBCL), T-cell lymphoma, or mantle cell lymphoma (MCL)), and myeloma, *e.g.*, multiple myeloma. The cancer may be at an early, intermediate, late stage or metastatic cancer.

In some embodiments, the cancer is chosen from a colorectal cancer (*e.g.*, CRC), melanoma, *e.g.*, advanced stage melanoma (*e.g.*, stage II-IV melanoma) or HLA-A2 positive-

melanoma; a pancreatic cancer, *e.g.*, advanced pancreatic cancer; a breast cancer, *e.g.*, metastatic breast carcinoma or triple negative breast cancer; a head and neck cancer (*e.g.*, HNSCC); an esophageal cancer; a renal cell carcinoma (RCC), *e.g.*, clear renal cell carcinoma (ccRCC) or metastatic renal cell carcinoma (MRCC); a lung cancer (*e.g.*, NSCLC); a cervical cancer; bladder cancer; or a hematologic malignancy, *e.g.*, a leukemia (*e.g.*, a lymphocytic leukemia), or a lymphoma (*e.g.*, a Hogdkin's lymphoma (HL), a non-Hogdkin's lymphoma (NHL), a diffuse large B-cell lymphoma (DLBCL), a mantle cell lymphoma (MCL), or a CLL, *e.g.*, a relapsed or refractory chronic lymphocytic leukemia).

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-LAG-3 antibody molecule is alone (*e.g.*, as a monotherapy), or in combination with one or more second agents (*e.g.*, a BRAF inhibitor). In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with (*e.g.*, before or after treatment or simultaneously with) an inhibitor of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor, a PD-L1 inhibitor, a TIM-3 inhibitor, a CEACAM (*e.g.*, CEACAM1 and/or CEACAM5) inhibitor, or a CTLA4 inhibitor (*e.g.*, an anti-CLA4 antibody, *e.g.*, ipilimumab)) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib) to treat a melanoma. In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a PD-1 or a PD-L1 inhibitor, *e.g.*, an anti-PD-1 or an anti-PD-L1 antibody molecule, to treat a melanoma as described herein.

In one embodiment, the anti-LAG-3 antibody molecule is administered alone, *e.g.*, as a monotherapy, or in combination with an inhibitor of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule), a CEACAM (*e.g.*, CEACAM1 and/or CEACAM5) inhibitor (*e.g.*, an anti-CEACAM antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA4 antibody) to treat a head and neck cancer (*e.g.*, HNSCC). In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a PD-1 or a PD-L1 inhibitor, *e.g.*, an anti-PD-1 or anti-PD-L1 antibody molecule, to treat a head and neck cancer as described herein.

In one embodiment, the anti-LAG-3 antibody molecule is administered alone, *e.g.*, as a monotherapy, or in combination with an inhibitor or activator of an immune checkpoint

modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a TIM-3 modulator (*e.g.*, a TIM-3 activator or inhibitor, *e.g.*, an anti-TIM-3 antibody molecule), a CEACAM (*e.g.*, CEACAM1 and/or CEACAM5) inhibitor (*e.g.*, an anti-CEACAM antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA4 antibody) to treat a lung cancer (*e.g.*, a NSCLC). In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a PD-1 or a PD-L1 inhibitor, *e.g.*, an anti-PD-1 or anti-PD-L1 antibody molecule, to treat a lung cancer (*e.g.*, a NSCLC) as described herein.

In one embodiment, the anti-LAG-3 antibody molecule is administered alone, *e.g.*, as a monotherapy, or in combination with an inhibitor of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule), a CEACAM (*e.g.*, CEACAM1 and/or CEACAM5) inhibitor (*e.g.*, an anti-CEACAM antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA4 antibody) to treat a gastric cancer. In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a PD-1 or a PD-L1 inhibitor, *e.g.*, an anti-PD-1 or anti-PD-L1 antibody molecule, to treat a gastric cancer as described herein.

In one embodiment, the anti-LAG-3 antibody molecule is administered alone, *e.g.*, as a monotherapy, or in combination with an inhibitor of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule), a CEACAM (*e.g.*, CEACAM1 and/or CEACAM5) inhibitor (*e.g.*, an anti-CEACAM antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA4 antibody) to treat a lymphoma (*e.g.*, Hogdkin's lymphoma (HL), non-Hogdkin's lymphoma (NHL), Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or CLL, *e.g.*, a relapsed or refractory chronic lymphocytic leukemia). In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a PD-1 or a PD-L1 inhibitor, *e.g.*, an anti-PD-1 or anti-PD-L1 antibody molecule, to treat a lymphoma as described herein.

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 some embodiments, the anti-LAG-3 antibody molecule is administered, alone or in combination with a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule) or a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), to treat a subject who 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.

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.

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-LAG-3 antibody molecule described herein, alone or in combination with one or more agents or procedures. The antibodies of the invention are preferred for use in the method although other anti-LAG-3 antibodies, or antigen-binding fragments thereof, can be used instead (or in combination with an anti-LAG-3 antibody molecule described herein).

In one embodiment, the infectious disease is hepatitis (*e.g.*, hepatitis B infection). In certain embodiment, the anti-LAG-3 antibody molecule is administered in combination with a hepatitis B antigen or vaccine, and optionally in combination with an aluminum-containing adjuvant.

In another embodiment, the infectious disease is influenza. In certain embodiment, the anti-LAG-3 antibody molecule is administered in combination with an influenza antigen or vaccine.

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-LAG-3 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-LAG-3 antibody molecule, alone or in combination, 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-LAG-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-LAG-3 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 10 mg/kg, or about 1 mg/kg, 3 mg/kg, or 10 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-LAG-3 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week. In one embodiment, the anti-LAG-3 antibody molecule is administered (*e.g.*, intravenously) at a dose from about 3 to 800 mg, *e.g.*, about 3, 20,

80, 240, or 800 mg. In certain embodiments, the anti-LAG-3 antibody molecule is administered alone at a dose from about 20 to 800 mg, *e.g.,* about 3, 20, 80, 240, or 800 mg. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose from about 3 to 240 mg, *e.g.,* about 3, 20, 80, or 240 mg, when it is combined with a second agent or therapeutic modality, *e.g.,* a second agent or therapeutic modality described herein. In one embodiment, the anti-LAG-3 antibody molecule is administered every 2 weeks (*e.g.,* during weeks 1, 3, 5, 7) during each 8 week cycle, *e.g.,* up to 96 weeks.

The antibody molecules described herein are preferred for use in the methods described herein, although other anti-LAG-3 antibodies can be used instead, or in combination with an anti-LAG-3 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-LAG-3 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-LAG-3 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-LAG-3 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) and/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.*, 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. Exemplary other antibody molecules that can be administered in combination include, but are not limited to, checkpoint inhibitors (*e.g.*, anti-PD-1, anti-PD-L1); antibodies that stimulate an immune cell (*e.g.*, agonistic GITR or CD137 antibodies); anti-cancer antibodies (*e.g.*, rituximab (Rituxan® or MabThera®), trastuzumab (Herceptin®), cetuximab (Erbitux®), among others.

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 immunoinhibitory 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-LAG-3 antibody molecules include the following.

In certain embodiments, the anti-LAG-3 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).

In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a modulator, *e.g.*, an 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 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-LAG-3 antibody molecule is administered in combination with an inhibitor of an inhibitory (or immune checkpoint) molecule chosen from PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CEACAM (*e.g.*, CEACAM-1 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 antibody fragment, 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-L1, PD-L2 or CTLA-4.

For example, the anti-LAG-3 antibody molecule can be administered in combination with an inhibitor of, *e.g.*, an antibody or antibody fragment that binds to, PD-1, PD-L1, PD-L2 or CTLA-4, to treat a cancer (*e.g.*, a cancer chosen from: a colorectal cancer (*e.g.*, CRC); a melanoma, *e.g.*, advanced stage melanoma (*e.g.*, stage II-IV melanoma) or HLA-A2 positive-melanoma; a pancreatic cancer, *e.g.*, advanced pancreatic cancer; a breast cancer, *e.g.*, metastatic breast carcinoma or triple negative breast cancer; a head and neck cancer (*e.g.*, HNSCC); an esophageal cancer; a renal cell carcinoma (RCC), *e.g.*, clear renal cell carcinoma (ccRCC) or metastatic renal cell carcinoma (MRCC); a lung cancer (*e.g.*, NSCLC); a cervical cancer; a bladder cancer; or a hematologic malignancy, *e.g.*, a leukemia (*e.g.*, a lymphocytic leukemia), or a lymphoma (*e.g.*, a Hogdkin's lymphoma (HL), a non-Hogdkin's lymphoma (NHL), a diffuse large B-cell lymphoma (DLBCL), a mantle cell lymphoma (MCL), or a CLL, *e.g.*, a relapsed or refractory chronic lymphocytic leukemia).

In one embodiment, the anti-LAG-3-1 antibody molecule is administered in combination with (*e.g.*, before, with, or after) treatment with an anti-CTLA4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

In another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody (*e.g.*, Nivolumab or Pembrokizumab) or antigen-binding fragment thereof. In another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof. In still another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-L1 antibody or antigen-binding fragment thereof. In yet other embodiments, the

anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody and an anti-TIM-3 antibody (or antigen-binding fragments thereof). In certain embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody and an anti-PD-L1 antibody (or antigen-binding fragments thereof). In certain embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-TIM-3 antibody and an anti-PD-L1 antibody (or antigen-binding fragments thereof).

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

In yet other embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-CEACAM (*e.g.*, anti-CEACAM-1 and/or anti-CEACAM-5) antibody molecule and an anti-PD-1 antibody molecule. In yet other embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-CEACAM (*e.g.*, anti-CEACAM-1 and/or anti-CEACAM-5) antibody molecule and an anti-TIM-3 antibody molecule. In yet other embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-CEACAM (*e.g.*, anti-CEACAM-1 and/or anti-CEACAM-5) antibody molecule and an anti-PD-L1 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-LAG-3 antibody molecule and one of: an anti-TIM-3 antibody, anti- CEACAM (*e.g.*, anti-CEACAM-1 and/or anti-CEACAM-5) antibody, anti-PD-L1 antibody, or anti-PD-1 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 hematolgocial malignancy). In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 or anti-PD-L1 antibody to treat a solid tumor.

In other embodiments, the anti-LAG-3 antibody molecule is administered in combination with a cytokine. The cytokine can be administered as a fusion molecule to the anti- LAG-3

antibody molecule, or as separate compositions. In one embodiment, the anti- LAG-3 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-12, 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 LAG-3), a second binding specificity to a second target (*e.g.,* PD-1, TIM-3, or PD-L1), and is optionally linked to an interleukin (*e.g.,* IL-12) domain e.g., full length IL-12 or a portion thereof. In certain embodiments, the combination of anti-LAG-3 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 other embodiments, the anti-LAG-3 antibody molecule is administered in combination with a vaccine, *e.g.,* a therapeutic cancer vaccine, or other forms of cellular immunotherapy. 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 cancer vaccine comprises an adjuvant (*e.g.*, aluminium phosphate or aluminum hydroxide). In some embodiments, the methods described herein are administered in combination with one or more of surgical removal of a tissue, chemotherapy, or other anti-cancer therapy and the primary or sole target will be metastatic lesions, *e.g.,* metastases in the bone marrow or lymph nodes.

In one embodiment, the cancer is a melanoma, *e.g.,* an advanced stage melanoma (*e.g.,* stage II-IV melanoma) or HLA-A2 positive melanoma. In certain embodiment, the anti-LAG-3 antibody molecule is administered in combination with a tumor antigenic peptide, *e.g.,* one or more HLA-A2 peptides, and optionally in combination with an adjuvant, *e.g.,* Montanide™. Exemplary tumor peptides that can be administered in combination with the anti-LAG-3 antibody molecule include one or more of Tyrosinase.A2, MAGE-C2.A2, NY-ESO-1b.A2, MAGE-4.A2, MAGE-3.A2, MAGE-1.A2, NA17.A2 (GnTV), and MAGE-10.A2.

In another embodiment, the cancer is a pancreatic cancer, *e.g.,* advanced pancreatic cancer. In certain embodiment, the antibody molecule can be administered in combination with a chemotherapeutic agent, *e.g.,* gemcitabine.

In another embodiment, the cancer is a breast cancer, *e.g.,* metastatic breast carcinoma or triple negative breast cancer. In certain embodiment, the antibody molecule can be administered in combination with a chemotherapeutic agent, *e.g.,* paclitaxel.

In another embodiment, the cancer is a renal cell carcinoma, *e.g.,* clear cell carcimoma, advanced (*e.g.,* stage IV) or metastatic renal cell carcinoma (MRCC).

In another embodiment, the cancer is a cancer of head or neck, *e.g.,* HPV+ squamous cell carcinoma.

In another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an antigen. For example, the anti-LAG-3 antibody molecule can be combined with a hepatitis B antigen (*e.g.*, Engerix B). In other embodiments, the anti-LAG-3 antibody molecule is administered in combination with a flu antigen.

The anti-LAG-3 antibody molecule can be used alone in unconjugated form, or 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.

Additional Combination Therapies

The methods and compositions described herein (*e.g.*, LAG-3 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 7. In one embodiment, the methods described herein include administering to the subject an anti-LAG-3 antibody molecule as described herein (optionally in combination with one or more inhibitors of PD-1, PD-L1, TIM-3, CEACAM (*e.g.*, CEACAM-1 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 7, 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-LAG-3 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-LAG-3 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-

LAG-3 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 7. 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 7. 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 7.

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 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-LAG-3 antibody molecule than when the second therapeutic agent is administered individually. In certain embodiments, the concentration of the anti-LAG-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the anti-LAG-3 antibody molecule is administered in combination with the second therapeutic agent than when the anti-LAG-3 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-LAG-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the anti-PD-1 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.

Detection

In another aspect, the invention features methods for detecting the presence of LAG-3 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 anti-LAG-3 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 LAG-3, and can indicate the suitability or need for a treatment described herein. The method can involve an immunohistochemistry, immunocytochemistry, flow cytometry (*e.g.*, FACS), antibody molecule complexed magnetic beads, ELISA assays, PCR-techniques (*e.g.*, RT-PCR).

Typically, the anti-LAG-3 antibody molecule used in the *in vivo* and *in vitro* diagnostic 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.

Additional embodiments provide a method of treating a cancer, comprising: identifying in 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-LAG-3 antibody (*e.g.*, an anti-LAG-3 antibody described herein), alone or incombination with an anti-PD-1 antibody molecule, an anti-PD-L1 antibody molecule, or both, to the subject, optionally in combination with one or more other agents, thereby treating the cancer. 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 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-LAG-3 antibody (*e.g.*, an anti-LAG-3 antibody described herein), alone or incombination with an anti-PD-1 antibody molecule, an anti-PD-L1 antibody molecule, or both, 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).

In another aspect, the invention features diagnostic or therapeutic kits that include the anti-LAG-3 antibody molecules described herein and instructions for use.

In an embodiment, there is provided an isolated antibody molecule that binds specifically to human Lymphocyte Activation Gene-3 (LAG-3), comprising: (a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 4, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15; (b) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 1, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12; (c) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15; or (d) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

In an embodiment, there is provided a pharmaceutical composition comprising the isolated antibody molecule as described herein and a pharmaceutically acceptable carrier, excipient or stabilizer.

In an embodiment, there is provided an isolated nucleic acid encoding heavy chain CDRs 1-3 used for making the antibody molecule as described herein, wherein the nucleic acid comprises one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 140-144, 151-155, 162-166, 173-177, 184-186, and 287.

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In an embodiment, there is provided an isolated nucleic acid encoding one or more light chain CDRs 1-3 used for making the antibody molecule as described herein, wherein the nucleic acid comprises one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 145-150, 156-161, 167-172, and 178-183.

In an embodiment, there is provided an isolated nucleic acid encoding the antibody heavy and/or light chain variable region of the antibody molecule as described herein.

In an embodiment, there is provided an expression vector comprising the nucleic acid as described herein.

In an embodiment, there is provided a host cell comprising the nucleic acid as described herein, for use in making the antibody molecule as described herein.

In an embodiment, there is provided a method of producing an antibody molecule, comprising culturing the host cell as described herein under conditions suitable for gene expression.

In an embodiment, there is provided use of the isolated antibody molecule as described herein, or the pharmaceutical composition as described herein for stimulating an immune response in a subject.

In an embodiment, there is provided use of the isolated antibody molecule as described herein, or the pharmaceutical composition as described herein for the treatment of lung cancer, mesothelioma, renal cell carcinoma, breast cancer, or melanoma.

In an embodiment, there is provided a method of detecting LAG-3 in a biological sample, comprising (i) contacting the sample or optionally a reference sample with the isolated antibody molecule as described herein under conditions that allow interaction of the antibody molecule and a LAG-3 polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the LAG-3 polypeptide within the sample or optionally the reference sample.

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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: 16) and heavy (SEQ ID NO: 6) chain variable regions of murine anti-LAG-3 mAb BAP050. The light and heavy chain CDR sequences based on Kabat numbering are underlined. The light and 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 NO: 16) and heavy (SEQ ID NO: 6) chain variable regions of murine anti-LAG-3 mAb BAP050 aligned with the germline sequences (SEQ ID NOs: 290-291, respectively, in order of appearance). The upper and lower sequences are the germline (GL) and BAP050 (Mu mAb) sequences, respectively. The light and heavy chain CDR sequences based on Kabat numbering are underlined. The light and heavy chain CDR sequences based on Chothia numbering are shown in bold italics. "-" means identical amino acid residue.

Figure 3 depicts bar graphs showing the results of FACS binding analysis for the twenty humanized BAP050 clones (BAP050-hum01 to BAP050-hum20) and the chimeric mAb (BAP050-chi). 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 BAP049 clones (a, b, c, d, e, f, g represent various types of framework region sequences). The concentrations of the mAbs in the samples are also shown.

Figure 5A-5B depicts the binding affinity and specificity of humanized mAbs measured in a competition binding assay using a constant concentration of FITC-labeled murine mAb,

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serial dilutions of the test antibodies, and LAG-3-expressing CHO cells. Experiment was performed twice, and the results are shown in Figures 5A and 5B, respectively.

Figure 6 depicts the ranking of humanized BAP050 clones based on FACS data, competition binding and structural analysis. The concentrations of the mAbs in the samples are also shown.

Figure 7 depicts the binding affinity and specificity of huBAP050(Ser) clones measured in a competition binding assay using a constant concentration of FITC-labeled murine mAb, serial dilutions of the test antibodies, and LAG-3-expressing CHO cells. HuBAP050(Ser) clones, such as, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, and BAP050-hum13-Ser, were evaluated. Murine mAb BAP050, chimeric mAb BAP050-chi, and humanized BAP050-hum01, BAP050-hum02, BAP050-hum05, BAP050-hum09, BAP050-hum11, BAP050-hum12, and BAP050-hum13 were also included in the analyses.

Figure 8 depicts blocking of binding of LAG-3-Ig to Daudi cells by huBAP050(Ser) clones. HuBAP050(Ser) clones, such as, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum05-Ser, BAP050-hum09-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, and BAP050-hum13-Ser, were evaluated. Murine mAb BAP050 and chimeric mAb BAP050-chi were also included in the analyses.

Figures 9A-9B depict the alignment of heavy chain variable domain sequences for the twenty humanized BAP050 clones and BAP050 chimera (BAP050-chi). In Figure 9A, all of the sequences are shown (SEQ ID NOs: 20, 28, 28, 28, 28, 28, 28, 28, 28, 28, 28, 64, 64, 64, 64, 64, 68, 72, 72, 76 and 80, respectively, in order of appearance). In Figure 9B, only amino acid sequences that are different from mouse sequence are shown (SEQ ID NOs: 20, 28, 28, 28, 28, 28, 28, 28, 28, 28, 28, 64, 64, 64, 64, 64, 68, 72, 72, 76 and 80, respectively, in order of appearance).

Figures 10A-10B depict the alignment of light chain variable domain sequences for the twenty humanized BAP050 clones and BAP050 chimera (BAP050-chi). In Figure 10A, all of the sequences are shown (SEQ ID NOs: 24, 32, 36, 36, 36, 292, 292, 292, 44, 48, 52, 56, 56, 60, 60, 60, 60, 84, 88, 92 and 96, respectively, in order of appearance). In Figure 10B, only amino acid sequences that are different from mouse sequence are shown (SEQ ID NOs: 24, 32, 36, 36,

36, 292, 292, 292, 44, 48, 52, 56, 56, 60, 60, 60, 60, 84, 88, 92 and 96, respectively, in order of appearance).

Figure 11 shows exemplary cancers having relatively high proportions of patients that are triple-positive for PD-L1/CD8/IFN-γ.

Figure 12 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 13 shows the proportion of exemplary breast cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 14 shows the proportion of exemplary colon cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

BRIEF DESCRIPTION OF THE TABLES

Table 1 is a summary of the amino acid and nucleotide sequences for the murine, chimeric and humanized anti-LAG-3 antibody molecules. The antibody molecules include murine mAb BAP050 and chimeric mAbs BAP050-chi, humanized mAbs BAP050-hum01 to BAP050-hum20, BAP050-hum01-Ser to BAP050-hum15-Ser, BAP050-hum18-Ser to BAP050-hum20-Ser, and BAP050-Clone-F to BAP050-Clone-J. 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 BAP050-hum01 to BAP049-hum20, BAP050-hum01-Ser to BAP050-hum15-Ser, BAP050-hum18-Ser to BAP050-hum20-Ser, and BAP049-Clone-F to BAP049-Clone-J.

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

Table 4 shows the amino acid sequences of the heavy and light chain leader sequences for humanized mAbs BAP050-Clone-F to BAP050-Clone-J.

Table 5 is a summary of yield, titre, monomer content and endotoxin levels for exemplary humanized BAP050 mAbs expressed in CHO cells.

Table 6 shows the charge isoforms as detected by Novex IEF analysis for exemplary humanized BAP050 mAbs expressed in CHO cells.

Table 7 is a summary of selected therapeutic agents that can be administered in combination with the anti-LAG-3 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 7 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.

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. Lymphocyte Activation Gene-3 (LAG-3) has been described as an inhibitory receptor in the immunological synapse (Chen and Flies (2013) *Nat Rev Immunol.* 13(4):227-42). Thus, blocking of LAG-3 can lead to enhancement of antitumor immunity.

Several cell types express LAG-3. For example, LAG-3 is expressed on activated $CD4^+$ and $CD8^+$ T cells, T_{reg} cells, natural killer (NK) cells, and plasmacytoid dendritic cells (DCs). LAG-3 is expressed in tumor-infiltrating lymphocytes, *e.g.*, infiltrating lymphocytes in head and neck squamous cell carcinoma (HNSCC). LAG-3 is expressed on highly suppressive induced and natural Tregs. For example, highly suppressive FoxP3+ nTregs and FoxP3- iTregs are LAG-3 positive in melanoma and colorectal cancer (Camisaschi *et al.* (2010) *J. Immunol.* 184(11):6545-6551; Scurr *et al.* (2014) *Mucosal. Immunol.* 7(2):428-439).

LAG-3 negatively regulates T cell signaling and functions. Ligands for LAG-3 includes, *e.g.*, MHC Class II and L-SECtin. Anti-LSECtin has been shown to inhibit B16 melanoma cell growth (Xu *et al.* (2014) *Cancer Res.* 74(13):3418-3428). Blockade of LAG-3 can restore activities of effector cells, dimish suppressor activity of T_{regs}, and/or enhance anti-PD-1 antitumor activity.

LAG-3 is typically though not exclusively co-expressed on $PD\text{-}1^+$ cells and single blockade can restore *in vitro* activities of the cells. The degree of $CD8^+$ T cell exhaustion, *e.g.*, as shown by the percentages of dual IFN-γ/TNF-α producers, correlates with the number of

inhibitory recptors expressed (Blackburn *et al.* (2009) *Nat. Immunol.* 10(1): 29-37). High PD-1/LAG-3 expression correlates with T cell infiltration in melanoma. Co-blockade of LAG-3 with anti-PD-1 or PD-L1 can result in tumor suppressive activities in preclinical models. For example, anti-LAG-3 and anti-PD-1 blockade show efficacy in Sa1N fibrosarcoma and MC38 colon carcinoma models (Woo *et al.* (2012) *Cancer Res.* 72(4):917-27).

LAG-3 blockade is also efficacious in a lymphocytic choriomeningitis virus (LCMV) model. For example, PD-L1 plus LAG-3 blockade during chronic LCMV infection enhances antiviral CD8+ T cell responses (Blackburn *et al.* (2009) *Nat. Immunol.* 10(1): 29-37).

Accordingly, the present invention provides, at least in part, antibody molecules *(e.g.,* humanized antibody molecules) that bind to Lymphocyte Activation Gene-3 (LAG-3) with high affinity and specificity. In one embodiment, humanized antibodies against LAG-3 are disclosed, which show low immunogenicity. For example, humanized BAP050 antibodies were found to have a risk score of less than 1200, 1150, 1100, 1050, 1000, 950, 900, 850, or 800, according to the T cell epitope assays described herein. In other embodiments, selected combination of framework regions, *e.g.,* as shown in Figures 4 and 6, 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-LAG-3 antibody molecules disclosed herein can be used to treat, prevent and/or diagnose cancerous or malignant disorders (*e.g.,* cancers such melanoma, *e.g.,* advanced stage melanoma; pancreatic cancer, *e.g.,* advanced pancreatic cancer; solid tumors; breast cancer, *e.g.,* metastatic breast carcinoma; renal cell carcinoma, *e.g.,* advanced or metastatic renal cell carcinoma (MRCC) or clear cell renal cell carcinoma), as well as infectious diseases (*e.g.,* hepatitis, *e.g.,* hepatitis B; influenza). Thus, methods for detecting LAG-3, as well as methods for treating various disorders, including cancer and infectious diseases using the anti-LAG-3 antibody molecules, alone or in combination, are disclosed herein.

The term "Lymphocyte Activation Gene-3" or "LAG-3" include all isoforms, mammalian, *e.g.,* human LAG-3, species homologs of human LAG-3, and analogs comprising at least one common epitope with LAG-3. The amino acid and nucleotide sequences of LAG-3, *e.g.,* human LAG-3, is known in the art, *e.g.,* Triebel *et al.* (1990) *J. Exp. Med.* 171:1393-1405.

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.

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 70%, 75%, 80%, 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.

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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 a nucleic acid (SEQ ID NO: 1) 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 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

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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 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, LAG-3. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, (*e.g.*, an epitope as described herein) on LAG-3. In some embodiments, the antibody molecule binds to one or more extracellular Ig-like domains of LAG-3, *e.g.*, the first, second, third or fourth extracellular Ig-like domain of LAG-3.

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 bindng or functional fragment of a full length antibody, or a full length immunoglobulin 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 LAG-3 and the second epitope is located on a PD-1, TIM-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), PD-L1, 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 a 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).

Antibodies of the present invention 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 94/04678, 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), 50-65 (HCDR2), and 95-102 (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), 52-56 (HCDR2), and 95-102 (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), 50-65 (HCDR2), and 95-102 (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-LAG-3 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- LAG-3 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 LAG-3 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 LAG-3 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 "compete" or "cross-compete" are used interchangeably herein to refer to the ability of an antibody molecule to interfere with binding of an anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule provided herein, to a target, *e.g.*, human LAG-3. The interference with binding can be direct or indirect (*e.g.*, through an allosteric modulation of the antibody molecule or the target). The extent to which an antibody molecule is able to interfere with the binding of another antibody molecule to the target, and therefore whether it can be said to compete, can be determined using a competition binding assay, for example, a FACS assay, an ELISA or BIACORE assay. In some embodiments, a competition binding assay is a quantitative competition assay. In some embodiments, a first anti-LAG-3 antibody molecule is said to compete for binding to the target with a second anti-LAG-3 antibody molecule when the binding of the first antibody molecule to the target is reduced by 10% or more, *e.g.*, 20% or more, 30% or more, 40% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, 99% or more in a competition binding assay (*e.g.*, a competition assay described herein).

As used herein, the term "epitope" refers to the moieties of an antigen (*e.g.*, human LAG-3) that specifically interact with an antibody molecule. Such moieties, referred to herein as

epitopic determinants, typically comprise, or are part of, elements such as amino acid side chains or sugar side chains. An epitopic determinate can be defined by methods known in the art or disclosed herein, *e.g.,* by crystallography or by hydrogen-deuterium exchange. At least one or some of the moieties on the antibody moleucle, that specifically interact with an epitopic determinant, are typically located in a CDR(s). Typically an epitope has a specific three dimensional structural characteristics. Typically an epitope has specific charge characteristics. Some epitopes are linear epitopes while others are conformational epitopes.

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 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

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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 LAG-3. 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

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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, the *e.g.*, columns 12-16 of US 5,585,089. Other techniques for 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 an 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.

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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. 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

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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 LAG-3 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.

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.

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 bispecific, 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 further 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-LAG-3 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

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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 LAG-3), a second binding specificity to a second target (*e.g.,* PD-1, TIM-3, or PD-L1), 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 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 molecules, vectors and host cells thereof. The nucleic acid molecule includes but is not limited to RNA, genomic DNA and cDNA.

Exemplary Anti-LAG-3 Antibody Molecules

In certain embodiments, the anti-LAG-3 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: 286; 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: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

In other embodiments, the anti-LAG-3 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: 286; 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: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15.

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: 286.

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: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221, 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: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

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: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

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: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

In other embodiments, the aforesaid antibody molecules comprise a VHFW1 amino acid sequence of SEQ ID NO: 187, 190, 194, or 196, a VHFW2 amino acid sequence of SEQ ID NO: 198, 202, 206, or 208, and a VHFW3 amino acid sequence of SEQ ID NO: 210, 212, 217, or 219, and, optionally, further comprising a VHFW4 amino acid sequence of SEQ ID NO: 221.

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: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271, 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 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

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: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

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: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

In other embodiments, the aforesaid antibody molecules comprise a VLFW1 amino acid sequence of SEQ ID NO: 226, 230, 232, 234, 236, or 2385, a VLFW2 amino acid sequence of SEQ ID NO: 240, 244, 246, or 248, and a VLFW3 amino acid sequence of SEQ ID NO: 252, 255, 259, 261, 265, 267, or 269, and, optionally, further comprising a VLFW4 amino acid sequence of SEQ ID NO: 271.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 8, 28, 64, 68, 72, 76, 80, 100, 104, or 108.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 8, 28, 64, 68, 72, 76, 80, 100, 104, or 108.

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: 32, 36, 40, 44, 48, 52, 56, 60, 84, 88, 92, or 96.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 32, 36, 40, 44, 48, 52, 56, 60, 84, 88, 92, or 96.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 8.

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

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain 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: 30.

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

In other embodiments, the aforesaid antibody molecules comprise a heavy chain 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: 68.

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

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

In other embodiments, the aforesaid antibody molecules comprise a heavy chain 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: 76.

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

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain 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: 82.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 100.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 113.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 104.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 106.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 122.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 108.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 110.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 134.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 90.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 92.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 94.

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

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 98.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 32.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain 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: 28 or SEQ ID NO: 100; and a light chain variable domain 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: 28 or SEQ ID NO: 100; and a light chain variable domain 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 64 or SEQ ID NO: 104; and a light chain variable domain 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 68 or SEQ ID NO: 108; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 72 or SEQ ID NO: 8; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 72 or SEQ ID NO: 8; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 76 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

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

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 100; and a light chain variable domain 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 92.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 64 or SEQ ID NO: 104; and a light chain variable domain 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: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 34.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain 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: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain 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: 30 or SEQ ID NO: 102; and a light chain 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: 30 or SEQ ID NO: 102; and a light chain 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: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain 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: 66 or SEQ ID NO: 106; and a light chain 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: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain 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: 70 or SEQ ID NO: 110; and a light chain 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: 74 or SEQ ID NO: 18; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 or SEQ ID NO: 18; and a light chain 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: 78 and a light chain 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: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 94.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 98.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 113 and a light chain comprising the amino acid sequence of SEQ ID NO: 34.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 113 and a light chain 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: 122 and a light chain 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: 122 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 134 and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

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 according to EU numbering or position 108 of SEQ ID NO: 275 or 277 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 according to EU numbering or position 108 of SEQ ID NO: 275 or 277 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 according to EU numbering or position 180 of SEQ ID NO: 279 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 according to EU numbering or position 148, and Proline to Alanine mutation at position 329 according to EU numbering or position 212 of SEQ ID NO: 280 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 according to EU numbering or position 117 and Leucine to Alanine mutation at position 235 according to EU numbering or position 118 of SEQ ID NO: 281 and a kappa light chain constant region.

In other embodiments, the aforesaid antibody molecules are capable of binding to human LAG-3 with a dissociation constant (K_D) of less than about 0.2 nM.

In some embodiments, the aforesaid antibody molecules bind to human LAG-3 with a K_D of less than about 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.,* about 0.05 nM to 0.15 nM, *e.g.,* about 0.11 nM, *e.g.,* as measured by a Biacore method.

In other embodiments, the aforesaid antibody molecules bind to cynomolgus LAG-3 with a K_D of less than about 0.2 nM, 0.15 nM, 0.1 nM, 0.05 nM, or 0.02 nM, *e.g.,* about 0.05 nM to 0.15 nM, *e.g.,* as measured by a Biacore method.

In certain embodiments, the aforesaid antibody molecules bind to both human LAG-3 and cynomolgus LAG-3 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 a human LAG-3-Ig fusion protein with a K_D of less than about 0.5 nM, 0.2 nM, 0.1 nM, 0.05 nM, 0.025 nM, or 0.01 nM, *e.g.,* as measured by ELISA.

In some embodiments, the aforesaid antibody molecules bind to CHO cells that express human LAG-3 (*e.g.,* human LAG-3-transfected CHO cells) with a K_D of less than about 4 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.75 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, or 0.05 nM, *e.g.,* about 2.3, 1.92 nM or about 0.2 nM, *e.g.,* as measured by FACS analysis.

In some embodiments, the aforesaid antibody molecules bind to human T cells with a K_D of less than about 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, or 0.05 nM, *e.g.,* about 0.26 nM, *e.g.,* as measured by FACS analysis.

In some embodiments, the aforesaid antibody molecules bind to cells that expresse LAG-3 (*e.g.,* human LAG-3-expressing 300.19 cells) with a K_D of less than about 20 nM, 15 nM, 10 nM, 5 nM, 2 nM, or 1 nM, *e.g.,* about 13.6 nM, *e.g.,* as measured by FACS analysis.

In some embodiments, the aforesaid antibody molecules bind to cells that express rhesus LAG-3 (*e.g.,* cells transfected with rhesus LAG-3) with a K_D of less than about 15 nM, 10 nM, 9 nM, 8 nM, 6 nM, 5 nM, 2 nM, or 1 nM, *e.g.,* about 8.03 nM, *e.g.,* as measured by FACS analysis.

In certain embodiments, the aforesaid antibody molecules are not cross-reactive with mouse LAG-3. In some embodiments, the aforesaid antibodies are not cross-reactive with rat LAG-3. In other embodiments, the aforesaid antibodies are cross-reactive with rhesus LAG-3. In some embodiments, the aforesaid antibodies are cross-reactive with rat LAG-3. For example, the cross-reactivity can be measured by a Biacore method or a binding assay using cells that expresses LAG-3 (*e.g.,* human LAG-3-expressing 300.19 cells).

In other embodiments, the aforesaid antibody molecules bind an extracellular Ig-like domain of LAG-3 (*e.g.,* human LAG-3), *e.g.,* any of Domain 1 (D1), Domain 2 (D2), Domain 3 (D3), or Domain 4 (D4). In some embodiments, the aforesaid antibody molecules bind one or

more amino acid residues in D1. In some embodiments, the aforesaid antibody molecules do not bind the extra loop of D1 or a fragment thereof (*e.g.*, as measured by a Biacore method or a FACS method). In some embodiments, the aforesaid antibodies do not bind D2. In some embodiments, the aforesaid antibody molecules bind both D1 and D2. In some embodiments, the aforesaid antibody molecules bind one or more amino acid residues in D1 and/or D2 that bind an MHC class II molecule. In other embodiments, the aforesaid antibody molecules are capable of reducing binding of LAG-3 to a major histocompatibility (MHC) class II molecule, or a cell that expresses an MHC class II molecule. In some embodiments, the aforesaid antibody molecules reduce (*e.g.*, block) LAG-3-Ig binding to a MHC class II molecule, *e.g.*, on Raji cells or Daudi cells, with an IC_{50} of less than about 10 nM, 8 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or 0.5 nM, *e.g.*, between about 8 nM and about 10 nM or between about 2 nM and about 3 nM, *e.g.*, about 5.5 nM or about 2.3 nM.

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

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

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-fold, *e.g.*, about 2 to 3-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 or a human whole blood *ex vivo* assay.

In some embodiments, the aforesaid antibody molecules increase the expression of IFN-γ from T cells stimulated by anti-CD3 (*e.g.*, at 0.1 μg/mL) by at least about 0.5, 1, 2, 3, 4, 5, 6, 7, or 8-fold, *e.g.*, about 0.9 to 5.1-fold, *e.g.*, about 3-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 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-fold, *e.g.*, about 1.2 to

2-fold, *e.g.*, about 1.6-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 do not increase the expression of IL-2 or IFN-γ without T cell receptor activation (*e.g.* in the absence of SEB).

In some embodiments, the aforesaid antibody molecules increase the expression of IFN-γ from T cells activated with an CMV peptide by at least about 2, 3, 4, 5-fold, *e.g.*, about 1.1 to 1.7-fold, *e.g.*, about 1.4-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 increase the proliferation of $CD8^+$ T cells activated with an CMV peptide by at least about 1, 2, 3, 4, 5-fold, *e.g.*, about 1.5-fold, compared to the proliferation of $CD8^+$ T cells when an isotype control (*e.g.*, IgG4) is used, *e.g.*, as measured by the percentage of CD8+ T cells that passed through at least n (*e.g.*, n = 2 or 4) cell divisions.

In certain embodiments, the aforesaid antibody molecules has a Cmax between about 50 μg/mL and about 400 μg/mL, between about 100 μg/mL and about 350 μg/mL, between about 150 μg/mL and about 300 μg/mL, or between about 200 μg/mL and about 250 μg/mL, *e.g.*, about 166 μg/mL, *e.g.*, as measured in an animal.

In certain embodiments, the aforesaid antibody molecules has a $T_{1/2}$ between about 50 hours and about 400 hours, between about 100 hours and about 350 hours, between about 150 hours and about 300 hours, or between about 200 hours and about 250 hours, *e.g.*, about 231.9 hours, *e.g.*, as measured in an animal.

In some embodiments, the aforesaid antibody molecules bind to LAG-3 with a Kd slower than 5×10^{-4}, 1×10^{-4}, 5×10^{-5}, or 1×10^{-5} s^{-1}, *e.g.*, about 7×10^{-5} s^{-1}, *e.g.*, as measured by a Biacore method. In some embodiments, the aforesaid antibodies bind to LAG-3 with a Ka faster than 1×10^{4}, 5×10^{4}, 1×10^{5}, 5×10^{5}, or 1×10^{6} $M^{-1}s^{-1}$, *e.g.*, about 6.41×10^{5} $M^{-1}s^{-1}$, *e.g.*, as measured by a Biacore method.

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

In one embodiment, the isolated nucleic acid encodes 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 encodes heavy chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 140-144, 151-155, 162-166, 173-177, 184-186, or 287.

In another embodiment, the isolated nucleic acid encodes light chain CDRs 1-3, wherein said nucleic acid comprises a nucleotide sequence of SEQ ID NO: 145-150, 156-161, 167-172, or 178-183.

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: 9, 29, 65, 69, 73, 77, 81, 101, 105, 109, 112, 121, 124, 125, 132, or 133.

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: 9, 29, 65, 69, 73, 77, 81, 101, 105, 109, 112, 121, 124, 125, 132, or 133.

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: 19, 31, 67, 71, 75, 79, 83, 103, 107, 111, 114, 123, 126, 127, 135, or 136.

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: 19, 31, 67, 71, 75, 79, 83, 103, 107, 111, 114, 123, 126, 127, 135, or 136.

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: 33, 37, 41, 45, 49, 53, 57, 61, 85, 89, 93, 97, 115, 118, 128, 129, or 137.

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: 33, 37, 41, 45, 49, 53, 57, 61, 85, 89, 93, 97, 115, 118, 128, 129, or 137.

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: 35, 39, 43, 47, 51, 55, 59, 63, 87, 91, 95, 99, 117, 120, 130, 131, 138, or 139.

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: 35, 39, 43, 47, 51, 55, 59, 63, 87, 91, 95, 99, 117, 120, 130, 131, 138, or 139.

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. In one embodiment, the antibody molecule is administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and preferably greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, preferably about 70 to 310 mg/m^2, and more preferably, about 110 to 130 mg/m^2. In another embodiment, the antibody molecule is administered by intravenous infusion at a rate of less than 10mg/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. 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-LAG-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-LAG-3 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-LAG-3 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 preferably greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, preferably about 70 to 310 mg/m^2, and more preferably, 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 one embodiment, the anti-LAG-3 antibody molecule is administered (*e.g.*, intravenously) at a dose from about 3 to 800 mg, *e.g.*, about 3, 20, 80, 240, or 800 mg. In certain embodiments, the anti-LAG-3 antibody molecule is administered alone at a dose from about 20 to 800 mg, *e.g.*, about 3, 20, 80, 240, or 800 mg. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose from about 3 to 240 mg, *e.g.*, about 3, 20, 80, or 240 mg, in combination with a second agent or therapeutic modality, *e.g.*, a second agent or therapeutic modality described herein. In one embodiment, the anti-LAG-3 antibody molecule is administered every 2 weeks (*e.g.*, during weeks 1, 3, 5, 7) during each 8 week cycle, *e.g.*, up to 96 weeks.

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 preferably greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, preferably about 70 to 310 mg/m^2, and more preferably, 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 is 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, and more preferably, about 10 mg/m^2. In some embodiments, the antibody is infused over a period of about 30 min.

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-LAG-3 Antibody Molecules

The anti-LAG-3 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, *e.g., in vivo*, to enhance immunity. In one embodiment, the anti-LAG-3 antibody molecules enhance an immune response in a subject, *e.g.,* by blockade of LAG-3 (*e.g.,* by blockade of LAG-3 binding to an MHC molecule or other ligands).

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 some embodiments, the anti-LAG-3 antibody molecule restores, enhances or stimulates an antigen-specific T cell response, *e.g.*, interleukin-2 (IL-2) or interferon-gamma (IFN-γ), production in an antigen-specific T cell response, in the subject. In some embodiments, the immune response is an anti-tumor response. 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 anti-LAG-3 antibody molecules, alone or in combination, can be administered to a subject to treat, prevent, and/or diagnose a variety of disorders, such as cancers (melanoma or hepatic cancers), or an infectious disorder.

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 LAG-3 functioning. The term "non-human animals" of the invention 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 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. 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. Accordingly, in certain embodiments, any (*e.g.*, one, two, three, or all) of TILs, IFN-γ, CD8, or PD-L1, can be used as biomarkers for the anti-LAG-3 immunotherapies described herein.

Therapeutic Uses

Cancer

Blockade of LAG-3 by antibodies can enhance an immune response to cancerous cells in a subject. Similar to CD4, LAG-3 interacts with MHC class II molecules but, unlike CD4, LAG-3 does not interact with the human immunodeficiency virus gp120 protein (Baixeras *et al.* (1992) *J. Exp. Med.* 176:327-337). Studies have demonstrated direct and specific binding of LAG-3 to MHC class II on the cell surface (Huard *et al.* (1996) *Eur. J. Immunol.* 26:1180-1186). The LAG-3/MHC class II interaction plays a role in down-regulating antigen-dependent stimulation of $CD4^+$ and $CD8^+$ T lymphocytes. The addition of anti-LAG-3 antibodies can result in increased T cell proliferation, higher expression of activation antigens such as CD25, and higher concentrations of cytokines such as interferon-gamma and interleukin-4 (Huard *et al.* (1994) *Eur. J. Immunol.* 24:3216-3221). The intra-cytoplasmic region of LAG-3 can also interact with LAP, a signal transduction molecule involved in the downregulation of the CD3/TCR activation pathway (Iouzalen *et al.* (2001) *Eur. J. Immunol.* 31:2885-2891). Further, LAG-3 contributes to the suppressor activity of $CD4^+CD25^+$ regulatory T cells (T_{reg}). T_{reg} cells express LAG-3 upon activation and antibodies to LAG-3 inhibit suppression by induced T_{reg} cells (Huang, C. *et al.* (2004) *Immunity* 21:503-513). LAG-3 can also negatively regulate T cell homeostasis by regulatory T cells in both T cell-dependent and independent mechanisms (Workman, C. J. and Vignali, D. A. (2005) *J. Immunol.* 174:688-695). Thus, inhibition of LAG-3 can result in augmenting an immune response.

Accordingly, in one aspect, a method of treating (*e.g.,* reducing or inhibiting) a cancer or tumor in a subject is provided. The method comprises administering to the subject an anti-LAG-3 antibody molecule described herein, *e.g.,* a therapeutically effective amount of an anti-LAG-3 antibody molecule, alone or in combination, *e.g.,* with one or more agents or procedures. In one embodiment, an anti-LAG-3 antibody molecule may be used alone to inhibit the growth of cancerous tumors. Alternatively, an anti-LAG-3 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, 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. In certain embodiments, the anti-LAG-3 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 one embodiment, the methods are suitable for the treatment of cancer *in vivo*. To achieve antigen-specific enhancement of immunity, the anti-LAG-3 antibody molecule can be administered together with an antigen of interest. When antibodies to LAG-3 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 certain embodiments, 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 hematological cancer, soft tissue tumor, or a metastatic lesion, in a subject is provided. The method includes administering to the subject one or more anti-LAG-3 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 such as those affecting the lung, esophagus, skin, head and neck region, oral cavity, anus, and cervix. 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 melanoma (*e.g.*, an advanced stage (*e.g.*, stage II-IV)

melanoma or an HLA-A2 positive melanoma), pancreatic cancer (*e.g.*, advanced pancreatic cancer), solid tumors, breast cancer (*e.g.*, metastatic breast carcinoma, 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), and renal cell carcinoma (*e.g.*, advanced (*e.g.*, stage IV) or metastatic renal cell carcinoma (MRCC)). Additionally, refractory or recurrent malignancies can be treated using the antibody molecules described herein.

Examples of other cancers that can be treated include, *e.g.*, a solid tumor, *e.g.*, prostate cancer (*e.g.*, hormone refractory prostate adenocarcinoma), colon cancer, lung cancer (*e.g.*, non-small cell lung cancer), bone cancer, skin cancer, cancer of the head or neck (*e.g.*, HPV+ squamous cell carcinoma), cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, 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, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, or squamous cell cancer or a hematological malignancy, *e.g.*, 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 (*e.g.*, relapsed or refractory chronic lymphocytic leukemia), solid tumors of childhood, lymphocytic lymphoma, multiple myeloma, myelodisplastic syndromes, cancer of the bladder, 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 MHC class II molecules or LAG-3, can be effected using the antibody molecules described herein.

While not wishing to be bound by theory, in some embodiments, a patient is more likely to respond to treatment with anti-LAG-3, alone or in combination with anti-PD-1 or PD-L1 antibody molecules (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-1 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 LAG-3 antibody, alone or in combination with a PD-1 antibody (*e.g.*, a blocking PD-1 antibody), optionally in combination with one or more other immunomodulators (*e.g.*, an anti-TIM-3 antibody molecule or an anti-PD-L1 antibody molecule) and/or anti-cancer agents, *e.g.*, those listed in Table 7 and disclosed in the publications listed in Table 7.

In some embodiments, the cancer sample is classified as triple-positive for PDL1/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-1 antibody therapy. For instance, many IM-TN (immunomodulatory, triple negative) breast cancer patients are triple-positive for PDL1/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 LAG-3 antibody, *e.g.*, a LAG-3 antibody as described herein, alone or in combination with a PD-1 antibody, (optionally in combination with one or more immunomodulators such as a TIM-3 antibody or a PD-L1 antibody, and one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 7 or in a publication in Table 7) 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 LAG-3 antibody, *e.g.*, a LAG-3 antibody as described herein, alone or in combination with a PD-1 antibody, (optionally in combination with one or more immunomodulators such as a TIM-3 antibody or a PD-L1 antibody, and one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 7 or in a publication in Table 7) 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 LAG-3 antibody, alone or in combination with a PD-1 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 LAG-3antibody, *e.g.*, a LAG-3 antibody as described herein, alone or in combination with a PD-1 antibody, (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 LAG-3 antibody, *e.g.*, a LAG-3 antibody as described herein, *e.g.*, in combination with a PD-1 antibody, 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 LAG-3 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 PDL1/CD8/IFN-γ are also positive for PIK3CA. Accordingly, in some embodiments, a cancer can be treated with a LAG-3 antibody, alone or in combination with an anti-PD1 antibody molecule (optionally in combination with one or more immunomodulators, *e.g.*, an anti-TIM-3 antibody molecule or an anti-PD-L1 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 LAG-3 antibody, alone or in combination with a PD-1 antibody, optionally in combination with a therapeutic that targets one or both of RNF43 and BRAF. For instance, these cancers may be treated with a LAG-3 antibody and a PD-1 antibody, optionally in combination with one or more therapeutics that target one or more of RNF43 and BRAF. In embodiments, the one or more therapeutics include an anti-cancer agent described in

Table 7 or a publication listed in Table 7. PD-1 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 LAG-3 antibody molecule in combination with a therapeutic that targets PD-1, *e.g.*, a PD-1 antibody molecule, and optionally with one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 7 or in a publication in Table 7, or a therapeutic that targets TIM-3, *e.g.*, a TIM-3 antibody.

Based on, *e.g*, Example 4 herein, a patient that has (or is identified as having) a thyroid cancer may be treated with a LAG-3 antibody molecule, alone or in combination 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-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 7 and the publications listed in Table 7.

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 cancer including but is not limited to a leukemia or a lymphoma. For example, the anti-LAG-3 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 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-LAG-3 antibody molecule is administered after treatment with an anti-CTLA4 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-LAG-3 antibodies with cancer vaccines

Antibody molecules to LAG-3 can be combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides (*e.g.*, HLA-A2 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, *e.g.*, 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 virally transduced-based vaccines. The cancer vaccine may be prophylactic or therapeutic.

LAG-3 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).

LAG-3 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 (*e.g.,* 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), Epstein–Barr virus (EBV), and Kaposi's Herpes Sarcoma Virus (KHSV). Another form of tumor specific antigen which may be used in conjunction with LAG-3 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 LAG-3 blockade to activate more potent anti-tumor responses.

In some embodiments, the combination further includes an inhibitor or activator of an immune checkpoint modulator (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a

PD-L1 inhibitor (*e.g.*, an anti-PD-L1 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-CTLA4 antibody), or any combination thereof.

LAG-3 blockade may also be combined with a standard cancer treatment. LAG-3 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-LAG-3 antibody molecules include the following.

In certain embodiments, the anti-LAG-3 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-LAG-3 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 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-LAG-3 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, *e.g.,* 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. One exemplary anti-GITR antibody is TRX518.

In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with an inhibitor of an inhibitory molecule (*e.g.,* an inhibitor 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 TIM-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-L1, PD-L2, CTLA-4, TIM-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CEACAM (*e.g.,* CEACAM-1 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 antibody fragment, that binds to the inhibitory molecule. Exemplary TIM-3 antibody molecules include, but are not limited to,

MBG220, MBG227, and MBG219.Exemplary TIGIT inhibitors include, but are not limited to, 10A7 and 1F4 (Roche).

Further examples of modulators include but are not limited to B7-H5, ENTPD1, ENTPD2, SIGGIR, B7-1, B7-2, VSIG4, TIM-1, CD200, RANKL, and P2X7.

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-L1, PD-L2 or CTLA4. For example, the anti-LAG-3 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, *e.g.,* ipilimumab. Exemplary anti-CTLA4 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-LAG-3 antibody molecule is administered after treatment, *e.g.,* after treatment of a melanoma, with an anti-CTLA4 antibody (*e.g.,* ipilimumab) with or without a BRAF inhibitor (*e.g.,* vemurafenib or dabrafenib). In one embodiment, the anti-CTLA-4 antibody, *e.g.,* ipilimumab, is administered at a dose of about 3 mg/kg. The anti-LAG-3 antibody molecule can be administered in combination at a dose from about 20 to 800 mg, *e.g.,* about 20, 80, 240, or 800 mg. In one embodiment, the anti-LAG-3 antibody molecule is administered every 2 weeks (*e.g.,* during weeks 1, 3, 5, 7) during each 8 week cycle, *e.g.,* up to 96 weeks.

In another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody molecule. Exemplary doses that can be use include a dose of anti-PD-1 antibody molecule of about 1 to 10 mg/kg, *e.g.,* 3 mg/kg. The anti-LAG-3 antibody molecule can be administered in combination at a dose from about 20 to 800 mg, *e.g.,* about 20, 80, 240, or 800 mg. In one embodiment, the anti-LAG-3 antibody molecule is administered every 2 weeks (*e.g.,* during weeks 1, 3, 5, 7) during each 8 week cycle, *e.g.,* up to 96 weeks.

Immune inhibitory molecules, *e.g.,* PD-1 and LAG-3, can regulate, *e.g.,* synergistically, T-cell function to promote tumoral immune escape. In another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-TIM-3 antibody molecule. In still another embodiment, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-L1 antibody molecule. In yet other embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody and an anti-TIM-3 antibody. In certain

embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody and an anti-PD-L1 antibody. In certain embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-TIM-3 antibody and an anti-PD-L1 antibody. 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 another embodiment, the anti- LAG-3 antibody molecule is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1 and/or CEACAM-5 inhibitor), *e.g.*, an anti-CEACAM antibody molecule. In another embodiment, the anti- LAG-3 antibody molecule, is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti- CEACAM-1 antibody molecule. In another embodiment, the anti- LAG-3 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-LAG-3 antibody molecule and an anti-PD-1 or anti-LAG-3 antibody 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. For example, the animal models to test the synergistic effect of anti-LAG-3 and anti-PD-1 are described, *e.g.*, in Woo *et al.* (2012) *Cancer Res.* 72(4):917-27). 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-LAG-3, 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 LAG-3 and PD-1 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-1 antibody molecule and/or PDL1 antibody molecule is continued, and a LAG-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.In other embodiments, the anti-LAG-3 antibody molecule is administered in combination with a cytokine, *e.g.*, interleukin-21, interleukin-2, or interleukin 15. In certain embodiments, the combination of anti-LAG-3 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 the anti-LAG-3 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).

Another example of such a combination is an anti-LAG-3 antibody in combination with decarbazine for the treatment of melanoma. Another example of such a combination is an anti-LAG-3 antibody molecule in combination with interleukin-2 (IL-2) for the treatment of melanoma. In one embodiment the anti-LAG-3 antibody molecule can be combined with IL-21. Without being bound by theory, the combined use of LAG-3 blockade and chemotherapy is that cell death, 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 LAG-3 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 LAG-3 blockade. Inhibition of angiogenesis leads to tumor cell death which may feed tumor antigen into host antigen presentation pathways.

LAG-3 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 LAG-3 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 to each of these entities may be used in combination with anti-LAG-3 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-LAG-3. 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 LAG-3 antibodies (Ito, N. *et al.* (2000) *Immunobiology* 201 (5) 527-40). Activating 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 treatments that can be used in combination with the anti-LAG-3 antibody molecules are described in the section entitled "Combination Therapies" below.

In all of the above methods, LAG-3 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 anti-LAG-3 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-LAG-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-LAG-3 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, or about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, or about 40 mg/kg. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 1-3 mg/kg, or about 3-10 mg/kg. In some embodiments, the anti-LAG-3 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-LAG-3 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

The antibody molecule can be used in unconjugated forms 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 molecule 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.

Additional Combination Therapy

The anti-LAG-3 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. In one embodiment, the anti-LAG-3 antibody is administered in combination with the therapies disclosed herein at a dose from about 20 to 800 mg, *e.g.*, about 20, 80, 240, or 800 mg. In one embodiment, the anti-LAG-3 antibody molecule is administered weekly, every 2 weeks (*e.g.*, during weeks 1, 3, 5, 7) during each 8 week cycle, *e.g.*, up to 96 weeks.

In one embodiment, the compositions described herein are administered in combination with other antibody molecules, *e.g.*, one or more of: an antibody described herein, a chemotherapeutic agent, a cytotoxic agent, surgical and/or radiation procedures. Exemplary chemotherapeutic and/or cytotoxic agents that can be administered in combination with include antimicrotubule agents, topoisomerase inhibitors, antimetabolites, mitotic inhibitors, alkylating agents, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis and radiation. Exemplary other antibody molecules that can be administered in combination include, but are not limited to, checkpoint inhibitors (*e.g.*, PD-1, PD-L1); antibodies that stimulate an immune cell (*e.g.*, agonistic GITR or CD137 antibodies); anti-cancer antibodies (*e.g.*, rituximab (Rituxan® or MabThera®), trastuzumab (Herceptin®), cetuximab (Erbitux®), among others.

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-LAG-3 antibody molecules can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The anti- LAG-3 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. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can

be such that an effect of the first treatment delivered is still detectable when the second is delivered.

Antibody molecules 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.

In certain embodiments, the anti-LAG-3 molecules described herein are administered in combination with one or more 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-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.

In some embodiments, the anti-PD-1 antibody is Nivolumab. Alternative names for Nivolumab include MDX-1106, MDX-1106-04, ONO-4538, or BMS-936558. 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, EP2161336 and WO2006/121168.

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.

Other anti-PD-1 antibodies include AMP 514 (Amplimmune), LZV178, and LZV181, among others, *e.g.*, anti-PD1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

In some embodiments, the anti-PD-L1 antibody is MSB0010718C. MSB0010718C (also referred to as A09-246-2; Merck Serono) is a monoclonal antibody that binds to PD-L1. Pembrolizumab and other humanized anti-PD-L1 antibodies are disclosed in WO2013/079174.

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 PD-1 inhibitor is AMP-224. 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 PD1 and B7-H1.

In some embodiments, the PD-1 inhibitor is MEDI4736.

Cancer Therapies

Exemplary combinations of anti-LAG-3 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-LAG-3 antibody molecule, *e.g.*, the anti-LAG-3 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-LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), include, but are 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-LAG-3 antibody molecule, *e.g.*, the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used 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-LAG-3 antibody molecule, *e.g.*, the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used in combination with a Vascular Endothelial Growth Factor (VEGF) receptor inhibitors, including but not limited to, Bevacizumab (Avastin®), axitinib (Inlyta®); Brivanib alaninate (BMS-582664, (*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Sorafenib (Nexavar®); Pazopanib (Votrient®); Sunitinib malate (Sutent®); Cediranib (AZD2171, CAS 288383-20-1); Vargatef (BIBF1120, CAS 928326-83-4); Foretinib (GSK1363089); Telatinib (BAY57-9352, CAS 332012-40-5); Apatinib (YN968D1, CAS 811803-05-1); Imatinib (Gleevec®); Ponatinib (AP24534, CAS 943319-70-8); Tivozanib (AV951, CAS 475108-18-0); Regorafenib (BAY73-4506, CAS 755037-03-7); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); Brivanib (BMS-540215, CAS 649735-46-6); Vandetanib (Caprelsa® or AZD6474); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); Linfanib (ABT869, CAS 796967-16-3); Cabozantinib (XL184, CAS 849217-68-1); Lestaurtinib (CAS 111358-88-4); N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS38703, CAS 345627-80-7); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); 4-Methyl-3-[[1-methyl-6-(3-pyridinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]amino]-*N*-[3-(trifluoromethyl)phenyl]-benzamide (BHG712, CAS 940310-85-0); and Aflibercept (Eylea®).

Exemplary anti-VEGF antibodies include, but are not limited to, a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709; a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta *et al.* (1997) *Cancer Res.* 57:4593-4599. In one embodiment, the anti-VEGF antibody is Bevacizumab (BV), also known as rhuMAb VEGF or AVASTIN®. It comprises mutated human IgG1 framework regions and antigen-binding complementarity-

determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005. Additional antibodies include the G6 or B20 series antibodies (*e.g.*, G6-31, B20-4.1), as described in PCT Publication No. WO2005/012359, PCT Publication No. WO2005/044853. For additional antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020, 6,054,297; W098/45332; WO 96/30046; WO94/10202; EP 0666868B1; U.S. Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov *et al*, Journal of Immunological Methods 288: 149-164 (2004). Other antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, Ml 8, D19, Y21, Y25, Q89, 191 , Kl 01, El 03, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, 183 and Q89.

In some embodiments, the anti-LAG-3 antibody molecule, *e.g.*, the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used 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 in, *e.g.*, WO 2010/036380; WO 2010/006086, WO 09/114870, WO 05/113556. Exemplary PI3K inhibitors that can be used in combination include, *e.g.*, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL756, XL147, PF-46915032, BKM 120, CAL-101, CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (*e.g.*, Novartis BEZ235).

In some embodiments, the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used in combination with a mTOR inhibitor, *e.g.*, one or more mTOR inhibitors chosen from one or more of rapamycin, temsirolimus (TORISEL®), AZD8055, BEZ235, BGT226, XL765, PF-4691502, GDC0980, SF1126, OSI-027, GSK1059615, KU-0063794, WYE-354, Palomid 529 (P529), PF-04691502, or PKI-587. ridaforolimus (formally known as deferolimus, (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-

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16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); everolimus (Afinitor® or RAD001); rapamycin (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-Bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502, CAS 1013101-36-4); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine-, inner salt (SF1126, CAS 936487-67-1), and XL765.

In some embodiments, the anti-LAG-3 antibody molecule, *e.g.,* the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used in combination with a BRAF inhibitor, *e.g.,* GSK2118436, RG7204, PLX4032, GDC-0879, PLX4720, and sorafenib tosylate (Bay 43-9006).

In some embodiments, the anti-LAG-3 antibody molecule, *e.g.,* the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used in combination with a MEK inhibitor. In some embodiments, the combination of the anti-LAG-3 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 AZD6244 orselumetinib), 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 another embodiment, the anti-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 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, the combination further includes a VEGF inhibitor (*e.g.*, a VEGF inhibitor as disclosed herein). In some embodiments, the combination of the anti-LAG-3 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 some embodiments, the anti-LAG-3 antibody molecule, *e.g.*, the anti-LAG-3 antibody molecule described herein, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used in combination with a JAK2 inhibitor, *e.g.*, CEP-701, INCB18424, CP-690550 (tasocitinib).

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

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permanent or temporary interstitial brachytherapy. The term "brachytherapy," refers to radiation 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-LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used with an antibody against a Killer-cell Immunoglobulin-like Receptor (also referred to herein as an "anti-KIR antibody"), a pan-KIR antibody, an anti-NKG2D antibody, and an anti-MICA antibody. In certain embodiments, the combination of anti-LAG-3 antibody molecule, anti-PD-1 antibody molecule and anti-KIR antibody, pan-KIR antibody, anti-MICA antibody, or 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used with a cellular immunotherapy (*e.g.*, Provenge (*e.g.*, Sipuleucel)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination of anti-LAG-3 antibody molecule, anti-PD-1 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, anti-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), is used with a vaccine, *e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine. In certain embodiments, the combination of anti-LAG-3 antibody molecule, anti-PD-1 antibody molecule and/or 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)).

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

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

L1 or anti-TIM-3 antibody molecule), described herein 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-1 antibody molecules described herein.

An example of suitable therapeutics for use in combination with the anti-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 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: 293)-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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-TIM3 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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-LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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 LAG-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or TIM-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 LAG-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or TIM-3 antibody molecule) is administered. The LAG-3 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 LAG-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or TIM-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 LAG-3 antibody molecule (*e.g.*, as a monotherapy, or in combination with a PD-1 antibody molecule or TIM-3 antibody molecule) but not Compound A8 or cetuximab.

In other embodiments, the three compounds (Compound A8, cetuximab, and a LAG-3 antibody molecule, optionally in combination with a PD-1 antibody molecule or TIM-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 LAG-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or TIM-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 LAG-3 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 LAG-3 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 LAG-3 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 LAG-3 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 LAG-3 antibody molecule than when the cetuximab is administered individually. In certain embodiments, the concentration of the LAG-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the LAG-3 antibody molecule is administered in combination with one

or both of the cetuximab and Compound A8 than when the LAG-3 antibody molecule is administered individually.

Additionally disclosed herein is a method of treating cancer with the anti- LAG-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.*, an anti-PD-1, anti-PD-L1 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- LAG-3 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- LAG-3 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- LAG-3 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-LAG-3 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-LAG-3 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-LAG-3 antibody molecules (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) 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-LAG-3 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 LAG-3 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 Hepatitis (A, B, and C), Influenza, HIV, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa. LAG-3 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 LAG-3 administration, thus provoking a strong T cell response that is not dampened by negative signals through LAG-3.

Viruses

For infections resulting from viral causes, the anti-LAG-3 antibody molecules (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) 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 hepatitis (A, B, or C), influenza virus (A, B, or C), HIV, herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, CMV, Epstein Barr virus), adenovirus, 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 one embodiment, the anti-LAG-3 antibody molecule is administered in combination with an influenza antigen or vaccine.

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-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for hepatitis B infections for therapeutic advantage. In one embodiment, the anti-LAG-3 antibody molecule is administered in combination with a hepatitis B antigen or vaccine, and optionally in combination with an aluminum-containing adjuvant.

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-LAG-3 antibody molecule can be administered as a monotherapy (or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule), or all of the foregoing can be combined with the standard of care for hepatitis C infection. For example, the anti-LAG-3 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 (*e.g.*, 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-LAG-3 antibody molecules 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-LAG-3 antibody molecules to specifically treat Hepatitis C infection include those described in US 2013/0045202.

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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 entire body. Because infection also suppresses cellular immunity, the host is at greater risk for developing bacterial superinfections, including otitis media, pneumonia and postinfectious encephalomyelitis. Acute infection is associated with significant morbidity and mortality, especially in malnourished adolescents.

Treatment for measles includes the passive administration of pooled human IgG, which can prevent infection in non-immune subjects, even if given up to one week after exposure. However, prior immunization with live, attenuated virus is the most effective treatment and prevents disease in more than 95% of those immunized. As there is one serotype of this virus, a single immunization or infection typically results in protection for life from subsequent infection.

In a small proportion of infected hosts, measles can develop into SSPE, which is a chronic progressive neurologic disorder resulting from a persistent infection of the central nervous system. SSPE is caused by clonal variants of measles virus with defects that interfere with virion assembly and budding. For these patients, reactivation of T-cells with the anti-LAG-3 antibody molecule so as to facilitate viral clearance would be desirable.

In another embodiment, the infection is HIV. HIV attacks CD4+ cells, including T-lymphocytes, monocyte-macrophages, follicular dendritic cells and Langerhan's cells, and CD4+ helper/inducer cells are depleted. As a result, the host acquires a severe defect in cell-mediated immunity. Infection with HIV results in AIDS in at least 50% of individuals, and is transmitted via sexual contact, administration of infected blood or blood products, artificial insemination with infected semen, exposure to blood-containing needles or syringes and transmission from an infected mother to infant during childbirth.

A host infected with HIV may be asymptomatic, or may develop an acute illness that resembling mononucleosis—fever, headache, sore throat, malaise and rash. Symptoms can progress to progressive immune dysfunction, including persistent fever, night sweats, weight loss, unexplained diarrhea, eczema, psoriasis, seborrheic dermatitis, herpes zoster, oral candidiasis and oral hairy leukoplakia. Opportunistic infections by a host of parasites are common in patients whose infections develop into AIDS.

Treatments for HIV include antiviral therapies including nucleoside analogs, zidovudine (AST) either alone or in combination with didanosine or zalcitabine, dideoxyinosine, dideoxycytidine, lamidvudine, stavudine; reverse transcriptive inhibitors such as delavirdine, nevirapine, loviride, and proteinase inhibitors such as saquinavir, ritonavir, indinavir and nelfinavir. The anti-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for HIV infections for therapeutic advantage.

In another embodiment, the infection is a Cytomegalovirus (CMV). CMV infection is often associated with persistent, latent and recurrent infection. CMV infects and remains latent in monocytes and granulocyte-monocyte progenitor cells. The clinical symptoms of CMV include mononucleosis-like symptoms (*i.e.*, fever, swollen glands, malaise), and a tendancy to develop allergic skin rashes to antibiotics. The virus is spread by direct contact. The virus is shed in the urine, saliva, semen and to a lesser extent in other body fluids. Transmission can also occur from an infected mother to her fetus or newborn and by blood transfusion and organ transplants. CMV infection results in general impairment of cellular immunity, characterized by impaired blastogenic responses to nonspecific mitogens and specific CMV antigens, diminished cytotoxic ability and elevation of CD8 lymphocyte number of CD4+ lymphocytes.

Treatments of CMV infection include the anti-virals ganciclovir, foscarnet and cidovir, but these druges are typically only prescribed in immunocompromised patients. The anti-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for cytomegalovirus infections for therapeutic advantage.

In another embodiment, the infection is Epstein-Barr virus (EBV). EBV can establish persistent and latent infections and primarily attacks B cells. Infection with EBV results in the clinical condition of infectious mononucleosis, which includes fever, sore throat, often with exudate, generalized lymphadenopathy and splenomegaly. Hepatitis is also present, which can develop into jaundice.

While typical treatments for EBV infections are palliative of symptoms, EBV is associated with the development of certain cancers such as Burkitt's lymphoma and nasopharyngeal cancer. Thus, clearance of viral infection before these complications result would be of great benefit. The anti-LAG-3 antibody molecule (alone or in combination with an

anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for Epstein-Barr virus infections for therapeutic advantage.

In another embodiment, the infection is Herpes simplex virus (HSV). HSV is transmitted by direct contact with an infected host. A direct infection may be asymptomatic, but typically result in blisters containing infectious particles. The disease manifests as cycles of active periods of disease, in which lesions appear and disappear as the viral latently infect the nerve ganglion for subsequent outbreaks. Lesions may be on the face, genitals, eyes and/or hands. In some case, an infection can also cause encephalitis.

Treatments for herpes infections are directed primarily to resolving the symptomatic outbreaks, and include systemic antiviral medicines such as: acyclovir (*e.g.*, Zovirax®), valaciclovir, famciclovir, penciclovir, and topical medications such as docosanol (Abreva®), tromantadine and zilactin. The clearance of latent infections of herpes would be of great clinical benefit. The anti-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for herpes virus infections for therapeutic advantage.

In another embodiment, the infection is Human T-lymphotrophic virus (HTLV-1, HTLV-2). HTLV is transmitted via sexual contact, breast feeding or exposure to contaminated blood. The virus activates a subset of T_H cells called Th1 cells, resulting in their overproliferation and overproduction of Th1 related cytokines (*e.g.*, IFN-γ and TNF-α). This in turn results in a suppression of Th2 lymphocytes and reduction of Th2 cytokine production (*e.g.*, IL-4, IL-5, IL-10 and IL-13), causing a reduction in the ability of an infected host to mount an adequate immune response to invading organisms requiring a Th2-dependent response for clearnance (*e.g.*, parasitic infections, production of mucosal and humoral antibodies).

HTLV infections cause lead to opportunistic infections resulting in bronchiectasis, dermatitis and superinfections with *Staphylococcus* spp. and *Strongyloides* spp. resulting in death from polymicrobial sepsis. HTLV infection can also lead directly to adult T-cell leukemia/lymphoma and progressive demyelinating upper motor neuron disease known as HAM/TSP. The clearance of HTLV latent infections would be of great clinical benefit. The anti-LAG-3 antibody molecules (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for HTLV infections for therapeutic advantage.

In another embodiment, the infection is Human papilloma virus (HPV). HPV primarily affects keratinocytes and occurs in two forms: cutaneous and genital. Transmission it believed to occur through direct contact and/or sexual activity. Both cutaneous and genital HPV infection, can result in warts and latent infections and sometimes recurring infections, which are controlled by host immunity which controls the symptoms and blocks the appearance of warts, but leaves the host capable of transmitting the infection to others.

Infection with HPV can also lead to certain cancers, such as cervical, anal, vulvar, penile and oropharynial cancer. There are no known cures for HPV infection, but current treatment is topical application of Imiquimod, which stimulates the immune system to attack the affected area. The clearance of HPV latent infections would be of great clinical benefit. The anti-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) may be combined with conventional treatments for HPV infections for therapeutic advantage.

Bacterial Infections

Some examples of pathogenic bacteria causing infections treatable by methods of the invention include syphilis, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lymes disease bacteria. The anti-LAG-3 antibody molecule (alone or in combination with an anti-PD-1, anti-PD-L1 or anti-TIM-3 antibody molecule) can be used in combination with existing treatment modalities for the aforesaid infections. For example, Treatments for syphilis include penicillin (*e.g.*, penicillin G.), tetracycline, doxycycline, ceftriaxone and azithromycin.

Lyme disease, caused by *Borrelia burgdorferi* is transmitted into humans through tick bites. The disease manifests initially as a localized rash, followed by flu-like symptoms including malaise, fever, headache, stiff neck and arthralgias. Later manifestations can include migratory and polyarticular arthritis, neurologic and cardiac involvement with cranial nerve palsies and radiculopathy, myocarditis and arrhythmias. Some cases of Lyme disease become persistent, resulting in irreversible damage analogous to tertiary syphilis. Current therapy for Lyme disease includes primarily the administration of antibiotics. Antibiotic-resistant strains may be treated

with hydroxychloroquine or methotrexate. Antibiotic refractory patients with neuropathic pain can be treated with gabapentin. Minocycline may be helpful in late/chronic Lyme disease with neurological or other inflammatory manifestations.

Other forms of borreliois, such as those resulting from *B. recurentis, B. hermsii, B. turicatae, B. parikeri., B. hispanica, B. duttonii* and *B. persica*, as well leptospirosis (*E.g., L. interrogans*), typically resolve spontaneously unless blood titers reach concentrations to cause intrahepatic obstruction.

Fungi and Parasites

Some examples of pathogenic fungi causing infections treatable by methods of the invention include *Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis* and *Histoplasma capsulatum.*

Some examples of pathogenic parasites causing infections treatable by methods of the invention include *Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi*, and *Nippostrongylus brasiliensis.*

Additional Combination Therapies

Combinations of anti-LAG-3 antibody molecules with one or more second therapeutics are provided herein. Many of the combinations in this section are useful in treating cancer, but other indications are also described. This section focuses on combinations of anti-LAG-3 antibody molecules, optionally in combination with one or more immunomodulators (e.g., an anti-PD-1 antibody molecule, an anti-TIM-3 antibody molecule, or an anti-PD-L1 antibody molecule), with one or more of the agents described in Table 7. In the combinations herein below, in one embodiment, the anti-LAG-3 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: 286; 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 VLCDR amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

In one embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PKC inhibitor, Sotrastaurin (Compound A1), or a compound disclosed in PCT Publication No. WO 2005/039549, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PKC inhibitor is Sotrastaurin (Compound A1) or a compound disclosed in PCT Publication No. WO 2005/039549. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Sotrastaurin (Compound A1), or a compound as described in PCT Publication No. WO 2005/039549, to treat a disorder such as a cancer, a melanoma, a non-Hodgkin lymphoma, an inflammatory bowel disease, transplant rejection, an ophthalmic disorder, or psoriasis.

In certain embodiments, Sotrastaurin (Compound A1) is administered at a dose of about 20 to 600 mg, *e.g.*, about 200 to about 600 mg, about 50 mg to about 450 mg, about 100 mg to 400 mg, about 150 mg to 350 mg, or about 200 mg to 300 mg, *e.g.*, about 50 mg, 100 mg, 150mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg. The dosing schedule can vary from *e.g.*, every other day to daily, twice or three times a day.

In one embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BCR-ABL inhibitor, TASIGNA (Compound A2, or a compound disclosed in PCT Publication No. WO 2004/005281, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the BCR-ABL inhibitor is TASIGNA, or a compound disclosed in PCT Publication No. WO 2004/005281. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with TASIGNA (Compound A2), or a compound as described in PCT Publication No. WO 2004/005281, to treat a disorder such as a lymphocytic leukemia, Parkinson's Disease, a neurologic cancer, a melanoma, a digestive/gastrointestinal cancer, a colorectal cancer, a myeloid leukemia, a head and neck cancer, or pulmonary hypertension.

In one embodiment, the BCR-ABL inhibitor or TASIGNA is administered at a dose of about 300 mg (*e.g.*, twice daily, *e.g.*, for newly diagnosed Ph+ CML-CP), or about 400 mg, *e.g.*,

twice daily, *e.g.*, for resistant or intolerant Ph+ CML-CP and CML-AP). BCR-ABL inhibitor or a Compound A2 is administered at a dose of about 300-400 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an HSP90 inhibitor, such as 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound disclosed in PCT Publication No. WO 2010/060937 or WO 2004/072051, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the HSP90 inhibitor is 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound disclosed in PCT Publication No. WO 2010/060937 or WO 2004/072051. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound as described in PCT Publication No. WO 2010/060937 or WO 2004/072051, to treat a disorder such as a cancer, a multiple myeloma, a non-small cell lung cancer, a lymphoma, a gastric cancer, a breast cancer, a digestive/gastrointestinal cancer, a pancreatic cancer, a colorectal cancer, a solid tumor, or a hematopoiesis disorder.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of PI3K and/or mTOR, Dactolisib (Compound A4) or 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound disclosed in PCT Publication No. WO 2006/122806, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K and/or mTOR inhibitor is Dactolisib (Compound A4), 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound disclosed in PCT Publication No. WO 2006/122806. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Dactolisib (Compound A4), 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound described in PCT Publication No. WO 2006/122806 , to treat a disorder such as a cancer, a prostate cancer, a leukemia (*e.g.*, lymphocytic leukemia), a breast cancer, a

brain cancer, a bladder cancer, a pancreatic cancer, a renal cancer, a solid tumor, or a liver cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an FGFR inhibitor, 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) or a compound disclosed in US Patent 8,552,002, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the FGFR inhibitor is 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) or a compound disclosed in US Patent 8,552,002. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Compound A5, or a compound as described in US 8,552,002, to treat a disorder such as a digestive/gastrointestinal cancer, a hematological cancer, or a solid tumor.

In one embodiment, the FGFR inhibitor or 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) is administered at a dose of about 100-125 mg (*e.g.*, per day), *e.g.*, about 100 mg or about 125 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PI3K inhibitor, Buparlisib (Compound A6), or a compound disclosed in PCT Publication No. WO 2007/084786, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K inhibitor is Buparlisib (Compound A6) or a compound disclosed in PCT Publication No. WO 2007/084786. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Buparlisib (Compound A6), or a compound disclosed in PCT Publication No. WO 2007/084786, to treat a disorder such as, a prostate cancer, a non-small cell lung cancer, an endocrine cancer, a leukemia, an ovarian cancer, a melanoma, a bladder cancer, a breast cancer, a female reproductive system cancer, a digestive/gastrointestinal cancer, a colorectal cancer, a glioblastoma multiforme, a solid tumor, a non-Hodgkin lymphoma, a hematopoiesis disorder, or a head and neck cancer.

In one embodiment, the PI3K inhibitor or Buparlisib (Compound A6) is administered at a dose of about 100 mg (*e.g.*, per day).

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an FGFR inhibitor, 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide (Compound A7) or a compound disclosed in PCT Publication No. WO 2009/141386 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the FGFR inhibitor is 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7) or a compound disclosed in a PCT Publication No. WO 2009/141386. In one embodiment, the FGFR inhibitor is 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7). In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7), or a compound disclosed in PCT Publication No. WO 2009/141386, to treat a disorder such as a cancer characterized by angiogenesis.

In one embodiment, the FGFR inhibitor or 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide (Compound A7) is administered at a dose of *e.g.*, from approximately 3 mg to approximately 5 g, more preferably from approximately 10 mg to approximately 1.5 g per person per day, optionally divided into 1 to 3 single doses which may, for example, be of the same size.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PI3K inhibitor, (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) or a compound disclosed PCT Publication No. WO 2010/029082 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K inhibitor is (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) or a compound disclosed PCT Publication No. WO 2010/029082. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8), or a compound disclosed PCT Publication

No. WO 2010/029082, to treat a disorder such as a gastric cancer, a breast cancer, a pancreatic cancer, a digestive/ gastrointestinal cancer, a solid tumor, and a head and neck cancer.

In one embodiment, the PI3K inhibitor or (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) is administered at a dose of about 150-300, 200-300, 200-400, or 300-400 mg (*e.g.*, per day), *e.g.*, about 200, 300, or 400 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of cytochrome P450 (*e.g.*, a CYP17 inhibitor) or a compound disclosed in PCT Publication No. WO 2010/149755, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the cytochrome P450 inhibitor (*e.g.*, the CYP17 inhibitor) is a compound disclosed in PCT Publication No. WO 2010/149755. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with a compound disclosed in PCT Publication No. WO 2010/149755, to treat prostate cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an HDM2 inhibitor, (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one(Compound A10) or a compound disclosed in PCT Publication No. WO 2011/076786 to treat a disorder, *e.g.*, a disorder described herein). In one embodiment, the HDM2 inhibitor is (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10) or a compound disclosed in PCT Publication No. WO 2011/076786. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10), or a compound disclosed in PCT Publication No. WO 2011/076786, to treat a disorder such as a solid tumor.

In one embodiment, the HDM2 inhibitor or (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-

yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10) is administered at a dose of about 400 to 700 mg, *e.g.*, administered three times weekly, 2 weeks on and one week off. In some embodiments, the dose is about 400, 500, 600, or 700 mg; about 400-500, 500-600, or 600-700 mg, *e.g.*, administered three times weekly.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an iron chelating agent, Deferasirox (also known as EXJADE; Compound A11), or a compound disclosed in PCT Publication No. WO 1997/049395 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the iron chelating agent is Deferasirox or a compound disclosed in PCT Publication No. WO 1997/049395. In one embodiment, the iron chelating agent is Deferasirox (Compound A11). In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Deferasirox (Compound A11), or a compound disclosed in PCT Publication No. WO 1997/049395, to treat iron overload, hemochromatosis, or myelodysplasia.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an aromatase inhibitor, Letrozole (also known as FEMARA; Compound A12), or a compound disclosed in US 4,978,672 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the aromatase inhibitor is Letrozole (Compound A12) or a compound disclosed in US Patent 4,978,672. In one embodiment, an LAG-3 antibody molecule is used in combination with Letrozole (Compound A12), or a compound disclosed in US Patent 4,978,672, to treat a disorder such as a cancer, a leiomyosarcoma, an endometrium cancer, a breast cancer, a female reproductive system cancer, or a hormone deficiency.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PI3K inhibitor, *e.g.*, a pan-PI3K inhibitor, (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13) or a compound disclosed in PCT Publication No. WO2013/124826 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K inhibitor is (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-

bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13) or a compound disclosed in PCT Publication No. WO2013/124826. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13), or a compound disclosed in PCT Publication No. WO2013/124826, to treat a disorder such as a cancer or an advanced solid tumor.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of p53 and/or a p53/Mdm2 interaction, (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14), or a compound disclosed in PCT Publication No. WO2013/111105 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the p53 and/or a p53/Mdm2 interaction inhibitor is (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14) or a compound disclosed in PCT Publication No. WO2013/111105. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14), or a compound disclosed in PCT Publication No. WO2013/111105, to treat a disorder such as a cancer or a soft tissue sarcoma.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a CSF-1R tyrosine kinase inhibitor, 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A15), or a compound disclosed in PCT Publication No. WO 2005/073224 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the CSF-1R tyrosine kinase inhibitor is 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A15) or a compound disclosed in PCT Publication No. WO 2005/073224. In one embodiment, a LAG-3 antibody molecule is used in combination with 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide

(Compound A15) or a compound disclosed in PCT Publication No. WO 2005/073224, to treat a disorder such as cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an apoptosis inducer and/or an angiogenesis inhibitor, such as Imatinib mesylate (also known as GLEEVEC; Compound A16) or a compound disclosed in PCT Publication No. WO1999/003854 to treat a disorder, *e.g.*, a disorder described. In one embodiment, the apoptosis inducer and/or an angiogenesis inhibitor is Imatinib mesylate (Compound A16) or a compound disclosed in PCT Publication No. WO1999/003854. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Imatinib mesylate (Compound A16), or a compound disclosed in PCT Publication No. WO1999/003854, to treat a disorder such as a cancer, a multiple myeloma, a prostate cancer, a non-small cell lung cancer, a lymphoma, a gastric cancer, a melanoma, a breast cancer, a pancreatic cancer, a digestive/gastrointestinal cancer, a colorectal cancer, a glioblastoma multiforme, a liver cancer, a head and neck cancer, asthma, multiple sclerosis, allergy, Alzheimer's dementia, amyotrophic lateral sclerosis, or rheumatoid arthritis.

In certain embodiments, Imatinib mesylate (Compound A16) is administered at a dose of about 100 to 1000 mg, *e.g.*, about 200 mg to 800 mg, about 300 mg to 700 mg, or about 400 mg to 600 mg, *e.g.*, about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, or 700 mg. The dosing schedule can vary from *e.g.*, every other day to daily, twice or three times a day. In one embodiment, Imatinib mesylate is administered at an oral dose from about 100 mg to 600 mg daily, *e.g.*, about 100 mg, 200 mg, 260 mg, 300 mg, 400 mg, or 600 mg daily.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK inhibitor, 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK inhibitor is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514. In one embodiment, an LAG-3 antibody molecule is used in combination

with 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder such as colorectal cancer, myeloid leukemia, hematological cancer, autoimmune disease, non-Hodgkin lymphoma, or thrombocythemia.

In one embodiment, the JAK inhibitor or a 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof is administered at a dose of about 400-600 mg (*e.g.*, per day), *e.g.*, about 400, 500, or 600 mg, or about 400-500 or 500-600 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK inhibitor, Ruxolitinib Phosphate (also known as JAKAFI; Compound A18) or a compound disclosed in PCT Publication No. WO 2007/070514 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK inhibitor is Ruxolitinib Phosphate (Compound A18) or a compound disclosed in PCT Publication No. WO 2007/070514. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Ruxolitinib Phosphate (Compound A18), or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder such as a prostate cancer, a lymphocytic leukemia, a multiple myeloma, a lymphoma, a lung cancer, a leukemia, cachexia, a breast cancer, a pancreatic cancer, rheumatoid arthritis, psoriasis, a colorectal cancer, a myeloid leukemia, a hematological cancer, an autoimmune disease, a non-Hodgkin lymphoma, or thrombocythemia.

In one embodiment, the JAK inhibitor or Ruxolitinib Phosphate (Compound A18) is administered at a dose of about 15-25 mg, *e.g.*, twice daily. In some embodiments, the dose is about 15, 20, or 25 mg, or about 15-20 or 20-25 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a deacetylase (DAC) inhibitor, Panobinostat (Compound A19), or a compound disclosed in PCT Publication No. WO 2014/072493 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the DAC inhibitor is Panobinostat (Compound A19) or a compound disclosed in PCT Publication No. WO 2014/072493. In one embodiment, an anti-LAG-3 antibody molecule is used in combination

with Panobinostat (Compound A19), a compound disclosed in PCT Publication No. WO 2014/072493, to treat a disorder such as a small cell lung cancer, a respiratory/thoracic cancer, a prostate cancer, a multiple myeloma, myelodysplastic syndrome, a bone cancer, a non-small cell lung cancer, an endocrine cancer, a lymphoma, a neurologic cancer, a leukemia, HIV/AIDS, an immune disorder, transplant rejection, a gastric cancer, a melanoma, a breast cancer, a pancreatic cancer, a colorectal cancer, a glioblastoma multiforme, a myeloid leukemia, a hematological cancer, a renal cancer, a non-Hodgkin lymphoma, a head and neck cancer, a hematopoiesis disorders, or a liver cancer.

In one embodiment, the DAC inhibitor or Panobinostat (Compound A19) is administered at a dose of about 20 mg (*e.g.*, per day).

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of one or more of cytochrome P450 (*e.g.*, 11B2), aldosterone or angiogenesis, Osilodrostat (Compound A20), or a compound disclosed in PCT Publication No. WO2007/024945 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the inhibitor of one or more of cytochrome P450 (*e.g.*, 11B2), aldosterone or angiogenesis is Osilodrostat (Compound A20) or a compound disclosed in PCT Publication No. WO2007/024945. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Osilodrostat (Compound A20), or a compound disclosed in PCT Publication No. WO2007/024945, to treat a disorder such as Cushing's syndrome, hypertension, or heart failure therapy.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a IAP inhibitor, (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US 8,552,003 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the IAP inhibitor is (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US Patent 8,552,003. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide

(Compound A21), or a compound disclosed in US Patent 8,552,003, to treat a disorder such as a multiple myeloma, a breast cancer, an ovarian cancer, a pancreatic cancer, or a hematopoiesis disorder.

In one embodiment, the IAP inhibitor or (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US 8,552,003 is administered at a dose of approximately 1800 mg, *e.g.*, once weekly.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a Smoothened (SMO) inhibitor, Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the SMO inhibitor is Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120 to treat a disorder such as a cancer, a medulloblastoma, a small cell lung cancer, a prostate cancer, a basal cell carcinoma, a pancreatic cancer, or an inflammation.

In certain embodiments, Sonidegib phosphate (Compound A22) is administered at a dose of about 20 to 500 mg, *e.g.,* about 40 mg to 400 mg, about 50 mg to 300 mg, or about 100 mg to 200 mg, *e.g.,* about 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg. The dosing schedule can vary from *e.g.,* every other day to daily, twice or three times a day.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an Alk inhibitor, ceritinib (also known as ZYKADIA; Compound A23) or a compound disclosed in PCT Publication No. WO 2007/131201 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the Alk

inhibitor is ceritinib (Compound A23) or a compound disclosed in PCT Publication No. WO 2007/131201. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with ceritinib (Compound A23), or a compound disclosed in PCT Publication No. WO 2007/131201, to treat a disorder such as non-small cell lung cancer or solid tumors.

In one embodiment, the Alk inhibitor or ceritinib (Compound A23) is administered at a dose of approximately 750 mg, *e.g.*, once daily.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK and/or CDK4/6 inhibitor, 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24), or a compound disclosed in US Patent 8,415,355 or US Patent 8,685,980 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK and/or CDK4/6 inhibitor is 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24) or a compound disclosed in US Patent 8,415,355 or US Patent 8,685,980. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24), or a compound disclosed in US 8,415,355 or US 8,685,980, to treat a disorder such as a lymphoma, a neurologic cancer, a melanoma, a breast cancer, or a solid tumor.

In one embodiment, the JAK and/or CDK4/6 inhibitor or 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24) is administered at a dose of approximately 200-600 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 200, 300, 400, 500, or 600 mg, or about 200-300, 300-400, 400-500, or 500-600 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a prolactin receptor (PRLR) inhibitor, a human monoclonal antibody molecule (Compound A26) as disclosed in US Patent 7,867,493), to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PRLR inhibitor is a human monoclonal antibody (Compound A26) disclosed in US 7,867,493. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with human monoclonal antibody molecule

(Compound A26) described in US Patent 7,867,493 to treat a disorder such as, a cancer, a prostate cancer, or a breast cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PIM Kinase inhibitor, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27) or a compound disclosed in PCT Publication No. WO 2010/026124 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PIM Kinase inhibitor is N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27) or a compound disclosed in PCT Publication No. WO 2010/026124. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27), or a compound disclosed in PCT Publication No. WO 2010/026124, to treat a disorder such as a multiple myeloma, myelodysplastic syndrome, a myeloid leukemia, or a non-Hodgkin lymphoma.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a Wnt signaling inhibitor, 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) or a compound disclosed in PCT publication No. WO 2010/101849 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the Wnt signaling inhibitor is 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) or a compound disclosed in PCT publication No. WO 2010/101849. In one embodiment, the Wnt signaling inhibitor is 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28). In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28), or a compound disclosed in PCT publication No. WO 2010/101849, to treat a disorder such as a solid tumor (*e.g.*, a head and neck cancer, a squamous cell carcinoma, a breast cancer, a pancreatic cancer, or a colon cancer).

In certain embodiments, 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) is administered at a dose of about 1 to 50 mg, *e.g.*,

about 2 mg to 45 mg, about 3 mg to 40 mg, about 5 mg to 35 mg, 5 mg to 10 mg, or about 10 mg to 30 mg, *e.g.*, about 2 mg, 5 mg, 10 mg, 20 mg, 30 mg, or 40 mg. The dosing schedule can vary from *e.g.*, every other day to daily, twice or three times a day.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BRAF inhibitor, Encorafenib (Compound A29), or a compound disclosed in PCT Publication No. WO 2011/025927 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the BRAF inhibitor is Encorafenib (Compound A29) or a compound disclosed in PCT Publication No. WO 2011/025927. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Encorafenib (Compound A29), or a compound disclosed in PCT Publication No. WO 2011/025927, to treat a disorder such as a non-small cell lung cancer, a melanoma, or a colorectal cancer.

In one embodiment, the BRAF inhibitor or Encorafenib (Compound A29) is administered at a dose of about 200-300, 200-400, or 300-400 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 200, about 300 or about 400 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a CDK4/6 inhibitor, 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30), or a compound disclosed in PCT publication No. WO 2011/101409 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the CDK4/6 inhibitor is 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30) or a compound disclosed in PCT publication No. WO 2011/101409. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30), or a compound disclosed in PCT publication No. WO 2011/101409, to treat a disorder such as a cancer, a mantle cell lymphoma, a liposarcoma, a non-small cell lung cancer, a melanoma, a squamous cell esophageal cancer, or a breast cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a HER3 inhibitor, Compound A31, or a compound disclosed in PCT Publication No. WO 2012/022814, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the HER3 inhibitor is Compound A31 or a compound disclosed in PCT Publication WO 2012/022814. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Compound A31, or a compound disclosed in PCT Publication WO 2012/022814, to treat a disorder such as a gastric cancer, an esophageal cancer, a head and neck cancer, a squamous cell carcinoma, a stomach cancer, a breast cancer (*e.g.*, metastatic breast cancer), or a digestive/gastrointestinal cancer.

In some embodiments, Compound A31 is a human monoclonal antibody molecule.

In one embodiment, the HER3 inhibitor or Compound A31 is administered at a dose of about 3, 10, 20, or 40 mg/kg, *e.g.*, once weekly (QW). In one embodiment, the compound is administered at a dose of about 3-10, 10-20, or 20-40 mg/kg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an FGFR2 and/or FGFR4 inhibitor, Compound A32, or a compound disclosed in a publication PCT Publication No. WO 2014/160160 (*e.g.*, an antibody molecule drug conjugate against an FGFR2 and/or FGFR4, *e.g.*, mAb 12425), to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the FGFR2 and/or FGFR4 inhibitor is Compound A32 or a compound disclosed in a publication PCT Publication No. WO 2014/160160. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Compound A32, or a compound as described in Table 7, to treat a disorder such as a cancer, a gastric cancer, a breast cancer, a rhabdomyosarcoma, a liver cancer, an adrenal cancer, a lung cancer, an esophageal cancer, a colon cancer, or an endometrial cancer.

In some embodiments, Compound A32 is an antibody molecule drug conjugate against an FGFR2 and/or FGFR4, *e.g.*, mAb 12425.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an M-CSF inhibitor, Compound A33, or a compound disclosed in PCT Publication No. WO 2004/045532 (*e.g.*, an antibody molecule or Fab fragment

against M-CSF), to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the M-CSF inhibitor is Compound A33 or a compound disclosed in PCT Publication No. WO 2004/045532. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Compound A33, or a compound as described in PCT Publication No. WO 2004/045532, to treat a disorder such as a cancer, a prostate cancer, a breast cancer, or pigmented villonodular synovitis (PVNS).

In embodiments, Compound A33 is a monoclonal antibody molecule against M-CSF or a fragment (*e.g.*, Fab fragment) thereof. In embodiments, the M-CSF inhibitor or Compound A33 is administered at an average dose of about 10mg/kg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a MEK inhibitor, Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the MEK inhibitor is Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914, to treat a disorder such as a non-small cell lung cancer, a multisystem genetic disorder, a melanoma, an ovarian cancer, a digestive/gastrointestinal cancer, a rheumatoid arthritis, or a colorectal cancer.

In one embodiment, the MEK inhibitor or Binimetinib (Compound A34) is administered at a dose of about 45 mg, *e.g.*, twice daily.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC, Midostaurin (Compound A35) or a compound disclosed in PCT Publication No. WO 2003/037347 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the inhibitor is Midostaurin (Compound A35) or compound disclosed in PCT Publication No. WO 2003/037347. In one embodiment, the inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC is Midostaurin. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Midostaurin (Compound A35), or compound disclosed in PCT Publication No. WO 2003/037347, to treat a

disorder such as a cancer, a colorectal cancer, a myeloid leukemia, myelodysplastic syndrome, an age-related mascular degeration, a diabetic complication, or a dermatologic disorder.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a TOR inhibitor (*e.g.*, mTOR inhibitor), Everolimus (also known as AFINITOR; Compound A36) or a Compound disclosed in PCT Publication No. WO 2014/085318 to treat a disorder, *e.g.*, a disorder described herein). In one embodiment, the TOR inhibitor is Everolimus (Compound A36) or a Compound disclosed in PCT Publication No. WO 2014/085318. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Everolimus (Compound A36) to treat a disorder such as an interstitial lung disease, a small cell lung cancer, a respiratory/thoracic cancer, a prostate cancer, a multiple myeloma, a sarcoma, an age-related macular degeneration,a bone cancer, tuberous sclerosis, a non-small cell lung cancer, an endocrine cancer, a lymphoma, a neurologic disorders, an astrocytoma, a cervical cancer, a neurologic cancer, a leukemia, an immune disorders, transplant rejection, a gastric cancer, a melanoma, epilepsy, a breast cancer, or a bladder cancer.

In one embodiment, the TOR inhibitor or Everolimusis (Compound A36) administered at a dose of about 2.5-20 mg/day. In one embodiment, the compound is administered at a dose of about 2.5, 5, 10, or 20 mg/day, *e.g.*, about 2.5-5, 5-10, or 10-20 mg/day.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an inhibitor of one or more of VEGFR-2, PDGFRbeta, KIT or Raf kinase C, 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-amine (Compound A37) or a compound disclosed in PCT Publication No. WO 2007/030377 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the inhibitor of one or more of VEGFR-2, PDGFRbeta, KIT or Raf kinase C is 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-amine (Compound A37) or a compound disclosed in PCT Publication No. WO 2007/030377. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-

benzo[d]imidazol-2-amine (Compound A37), or a compound disclosed in PCT Publication No. WO 2007/030377, to treat a disorder such as a cancer, a melanoma, or a solid tumor.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a somatostatin agonist and/or growth hormone release inhibitor, Pasireotide diaspartate (also known as SIGNIFOR; Compound A38) or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the somatostatin agonist and/or growth hormone release inhibitor is Pasireotide diaspartate (Compound A38) or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Pasireotide diaspartate (Compound A38), or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761, to treat a disorder such as a prostate cancer, an endocrine cancer, a nurologic cancer, a skin cancer (*e.g.*, a melanoma), a pancreatic cancer, a liver cancer, Cushing's syndrome, a gastrointestinal disorder, acromegaly, a liver and biliary tract disorder, or liver cirrhosis.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a signal transduction modulator and/or angiogenesis inhibitor, Dovitinib (Compound A39) or a compound disclosed in PCT Publication No. WO 2009/115562 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the signal transduction modulator and/or angiogenesis inhibitor is Dovitinib (Compound A39) or a compound disclosed in PCT Publication No. WO 2009/115562. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Dovitinib (Compound A39), or a compound disclosed in PCT Publication No. WO 2009/115562, to treat a disorder such as a cancer, a respiratory/thoracic cancer, a multiple myeloma, a prostate cancer, a non-small cell lung cancer, an endocrine cancer, or a neurological genetic disorder.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide

(Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO 2013/184757, to treat a disorder such as a cancer, *e.g.*, a solid tumor.

In one embodiment, the EGFR inhibitor or (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) is administered at a dose of 150-250 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 150, 200, or 250 mg, or about 150-200 or 200-250 mg.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an ALK inhibitor, N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42) or a compound disclosed in PCT Publication No. WO 2008/073687 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the ALK inhibitor is N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42) or a compound disclosed in PCT Publication No. WO 2008/073687. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42), or a compound disclosed in PCT Publication No. WO 2008/073687, to treat a disorder such as a cancer, an anaplastic large-cell lymphoma (ALCL), a non-small cell lung carcinoma (NSCLC), or a neuroblastoma.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an IGF-1R inhibitor, 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-

yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), or 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45) or a compound disclosed in PCT Publication No. WO 2010/002655 to treat a disorder, *e.g.,* a disorder described. In one embodiment, the IGF-1R inhibitor is 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45), or a compound disclosed in PCT Publication No. WO 2010/002655. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45), or a compound disclosed in PCT Publication No. WO 2010/002655, to treat a disorder such as a cancer or a sarcoma.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a P-Glycoprotein 1 inhibitor, Valspodar (also known as AMDRAY; Compound A46) or a compound disclosed in EP 296122 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the P-Glycoprotein 1 inhibitor is Valspodar (Compound A46) or a compound disclosed in EP 296122. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Valspodar (Compound A46), or a compound disclosed in EP 296122, to treat a disorder such as a cancer or a drug-resistant tumor.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination one or more of a VEGFR inhibitor, Vatalanib succinate (Compound A47) or a compound disclosed in EP 296122 to treat a disorder, *e.g.,* a

disorder described herein. In one embodiment, the VEGFR inhibitor is Vatalanib succinate (Compound A47) or a compound disclosed in EP 296122. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Vatalanib succinate (Compound A47), or a compound disclosed in EP 296122, to treat cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an IDH inhibitor or a compound disclosed in WO2014/141104 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the IDH inhibitor is a compound disclosed in PCT Publication No. WO2014/141104. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with a compound disclosed in WO2014/141104 to treat a disorder such as a cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BCL-ABL inhibitor or a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the BCL-ABL inhibitor is a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642 to treat a disorder such as a cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a c-RAF inhibitor or a compound disclosed in PCT Publication No. WO2014/151616 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the c-RAF inhibitor is Compound A50 or a compound disclosed in PCT Publication No. WO2014/151616. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with a compound disclosed in PCT Publication No. WO2014/151616 to treat a disorder such as a cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other

immunomodulators, is used in combination with an ERK1/2 ATP competitive inhibitor or a compound disclosed in International Patent Application No. PCT/US2014/062913 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the ERK1/2 ATP competitive inhibitor is a compound disclosed in International Patent Application No. PCT/US2014/062913. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with Compound A51 or a compound disclosed in International Patent Application No. PCT/US2014/062913 to treat a disorder such as a cancer.

In another embodiment, the anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a tyrosine kinase inhibitor, (Compound A52) or a compound disclosed in PCT Publication No. WO2005/073224 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the tyrosine kinase inhibitor is 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A52) or a compound disclosed in PCT Publication No. WO2005/073224. In one embodiment, an anti-LAG-3 antibody molecule is used in combination with 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A52), or a compound disclosed in PCT Publication No. WO2005/073224, to treat a disorder such as a cancer.

In some embodiments, the anit-LAG-3 antibody molecule is administerd in combination with one or more agents selected from, Compound A8, Compound A17, Compound A23, Compound A24, Compound A27, Compound A29, and Compound A33.

In some embodiments, an anti-LAG-3 antibody molecule is administered in combination with an anti-cancer agent having a known activity in an immune cell assay, *e.g.*, in one or more of a huMLR assay, a T cell proliferation assay, and a B-cell proliferation assay. Exemplary assays are described below. Based on the assay, an IC50 for can be calculated for each test agent. In embodiments, the anti-cancer agent has an IC50 of, *e.g.*, 0-1 μM, 1-4 μM, or greater than 4 μM, *e.g.*, 4-10 μM or 4-20 μM. In 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 Compound A28 (or a compound related to Compound A28) is administered at a dose of approximately 5-10 or 10-30 mg. In some embodiments, the

Compound A22 (or compound related to Compound A22) is administered at a dose of about 200 mg. In some embodiments, the Compound A17 (or compound related to Compound A17) is administered at a dose of approximately 400-600 mg. In some embodiments, the Compound A16 (or compound related to Compound A16) is administered at a dose of approximately 400-600 mg PO qDay. In some embodiments, the Compound A29 (or compound related to Compound A29) is administered at a dose of approximately 200-400 or 300-400 mg. In some embodiments, the Compound A24 (or compound related to Compound A24) is administered at a dose of approximately 200-600 mg. In some embodiments, the Compound A23 (ceritinib) (or compound related to ceritinib) is administered at a dose of approximately 750 mg once daily. In some embodiments, the Compound A8 (or compound related to Compound A8) is administered at a dose of approximately 200-400 or 300-400 mg. In some embodiments, the Compound A5 (or compound related to Compound A5) is administered at a dose of approximately 100-125 mg. In some embodiments, the Compound A6 (or compound related to Compound A6) is administered at a dose of about 100 mg. In some embodiments, the Compound A1 (or compound related to Compound A1) is administered at a dose of approximately 200-300 or 200-600 mg. In some embodiments, the Compound A40 (or compound related to Compound A40) is administered at a dose of approximately 150-250 mg. In some embodiments, the Compound A10 (or compound related to Compound A10) is administered at a dose of approximately 400 to 700 mg, *e.g.*, administered three times weekly, 2 weeks on and one week off. In some embodiments, the BCR-ABL inhibitor is administered at a dose of approximately 20 mg bid-80 mg bid.

Exemplary huMLR assay and B or T cell proliferation assays are provided below.

Human mixed lymphocyte reaction

The Mixed Lymphocyte Reaction (MLR) is a functional assay which measures the proliferative response of lymphocytes from one individual (the responder) to lymphocytes from another individual (the stimulator). To perform an allogeneic MLR, peripheral blood mononuclear cells (PBMC) from three donors were isolated from buffy-coats of unknown HLA type (Kantonspital Blutspendezentrum from Bern and Aarau, Switzerland). The cells were prepared at $2x10^5$ in 0.2mL of culture medium containing RPMI 1640 GlutaMAX™ with 10% fetal calf serum (FCS), 100U penicillin/ 100µg streptomycin, 50µM 2-Mercaptoethanol.

Individual 2-way reactions were set up by mixing PBMC from two different donors at a 1:1 ratio and co-cultures were done in triplicates in flat-bottomed 96-well tissue culture plates for 6 days at 37°C, 5% CO2, in presence or not of an 8-point concentration range of test compounds. Cells were pulsed with 3H-TdR (1 μCi/0.2mL) for the last 16h of culture and incorporated radioactivity was used as a measure of cell proliferation. The concentration that inhibited 50% of the maximal huMLR response (IC50) was calculated for each compound. Cyclosporine was used as a positive control of huMLR inhibition.

Human B cell proliferation assay

PBMC were freshly isolated by Ficoll-Paque density gradient from human blood and subjected to negative B-cell isolation. B cells were resuspended in culture medium (RPMI 1640, HEPES, 10% FCS, 50μg/mL gentamicine, 50μM 2-Mercaptoethanol, 1x ITS (Insulin, Transferrin and Sodium Selenite), 1x Non-Essential Amino-Acids) at a concentration of 9.104 per well in a flat-bottom 96-well culture plate. B cell stimulation was performed by human anti-IgM antibody molecule (30ug/mL) and IL-4 (75ng/mL) or by CD40 ligand (3ug/mL) and IL-4 (75ng/mL) in presence or not of a 7-point concentration range of test compounds. After 72h of culture at 37°C, 10% CO2, cells were pulsed with 3H-TdR (1 μCi/well) for the last 6h of culture. B cells were then harvested and the incorporation of thymidine was measured using a scintillation counter. Of each duplicate treatment, the mean was calculated and these data were plotted in XLfit 4 to determine the respective IC50 values.

Human T cell proliferation assay

PBMC were freshly isolated by Ficoll-Paque density gradient from human blood and subjected to negative isolation of T cells. T cells were prepared in culture medium (RPMI 1640, HEPES, 10% FCS, 50μg/mL gentamicine, 50μM 2-Mercaptoethanol, 1x ITS (Insulin, Transferrin and Sodium Selenite), 1x Non-Essential Amino-Acids) at a concentration of 8.104 per well in a flat-bottom 96-well culture plate. T cell stimulation was performed by human anti-CD3 antibody molecule (10ug/mL) or by human anti-CD3 antibody molecule (5μg/mL) and anti-CD28 antibody molecule (1μg/mL) in presence or not of a 7-point concentration range of test compounds. After 72h of culture at 37°C, 10% CO_2, cells were pulsed with 3H-TdR (1 μCi/well)

for the last 6h of culture. Cell proliferation was measured by the incorporation of thymidine allowing IC50 determination for each tested compound.

Decreasing an Immune Response

Anti-LAG-3 antibodies can be used to modulate, *e.g.,* provoke and amplify, an immune response, *e.g.,* an autoimmune response. For example, anti-LAG-3 blockade in conjunction with various self proteins can be used to devise vaccination protocols to efficiently generate immune responses against these self proteins for disease treatment. Indeed, many anti-tumor responses involve anti-self reactivities (van Elsas *et al.* (2001) *J. Exp. Med.* 194:481-489; Overwijk, *et al.* (1999) *Proc. Natl. Acad. Sci. U.S.A.* 96: 2982-2987; Rosenberg & White (1996) *J. Immunother Emphasis Tumor Immunol* 19 (1): 81-4). Further, Alzheimer's disease involves inappropriate accumulation of Aβ peptide in amyloid deposits in the brain; antibody responses against amyloid are able to clear these amyloid deposits (Schenk *et al.*, (1999) *Nature* 400: 173-177).

Other self proteins can also be used as targets such as IgE for the treatment of allergy and asthma, and TNFc for rheumatoid arthritis. Antibody responses to various hormones can be induced by the use of anti-LAG-3 antibody. Neutralizing antibody responses to reproductive hormones can be used for contraception. Neutralizing antibody response to hormones and other soluble factors that are required for the growth of particular tumors can also be considered as candidate vaccination targets.

Analogous methods as described above for the use of anti-LAG-3 antibody can be used for induction of therapeutic autoimmune responses to treat patients having an inappropriate accumulation of other self-antigens, such as amyloid deposits, including Aβ in Alzheimer's disease, cytokines such as TNFa, and IgE.

In other embodiments, the anti-LAG-3 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-LAG-3 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-LAG-3 antibody molecules. In an additional embodiment, the anti-LAG-3 antibody molecules are administered before or following surgery.

Diagnostic Uses

In one aspect, the present invention provides a diagnostic method for detecting the presence of a LAG-3 protein *in vitro* (*e.g.,* in a biological sample, such as a tissue biopsy, *e.g.,* from a cancerous tissue) or *in vivo* (*e.g., in vivo* imaging in a subject). The method includes: (i) contacting the sample with an antibody molecule described herein , or administering to the subject, the antibody molecule; (optionally) (ii) contacting a reference sample, *e.g.,* a control sample (*e.g.,* a control biological sample, such as plasma, tissue, biopsy) or a control subject)); and (iii) detecting formation of a complex between the antibody molecule, and the sample or subject, or the control sample or subject, wherein a change, *e.g.,* a statistically significant change, in the formation of the complex in the sample or subject relative to the control sample or subject is indicative of the presence of LAG-3 in the sample. The antibody molecule can be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials, as described above and described in more detail below.

The term "sample," as it refers to samples used for detecting polypeptides includes, but is not limited to, cells, cell lysates, proteins or membrane extracts of cells, body fluids, or tissue samples.

Complex formation between the antibody molecule and LAG-3 can be detected by measuring or visualizing either the binding molecule bound to the LAG-3 antigen or unbound binding molecule. Conventional detection assays can be used, *e.g.,* an enzyme-linked immunosorbent assays (ELISA), a radioimmunoassay (RIA) or tissue immunohistochemistry. Alternative to labeling the antibody molecule, the presence of LAG-3 can be assayed in a sample by a competition immunoassay utilizing standards labeled with a detectable substance and an unlabeled antibody molecule. In this assay, the biological sample, the labeled standards and the antibody molecule are combined and the amount of labeled standard bound to the unlabeled binding molecule is determined. The amount of LAG-3 in the sample is inversely proportional to the amount of labeled standard bound to the antibody molecule.

Nucleic Acids

The invention also features nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs of the anti-LAG-3 antibody molecules, as described herein. For example, the invention features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-LAG-3 antibody molecule chosen from one or more of the antibody molecules disclosed herein. The nucleic acid can comprise a nucleotide sequence as set forth in the tables herein, 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 the tables herein.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having an amino acid sequence as set forth in the tables herein, 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 or more substitutions, *e.g.*, conserved substitutions). In other embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having an amino acid sequence as set forth in the tables herein, 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 or more substitutions, *e.g.*, conserved substitutions). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding 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 the tables herein, 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 or more substitutions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having the nucleotide sequence as set forth in the tables herein, a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having the nucleotide sequence as set forth in the tables herein, or a sequence

substantially homologous thereto (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs from heavy and light chain variable regions having the nucleotide sequence as set forth in the tables herein, or a sequence substantially homologous thereto (*e.g.,* a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein).

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, as described in more detail hereinbelow.

Vectors

Further provided herein are vectors comprising nucleotide sequences encoding an antibody molecule described herein. In one embodiment, the vectors comprise nucleotides encoding an antibody molecule described herein. In one embodiment, the vectors comprise the nucleotide sequences described herein. The vectors include, but are not limited to, a virus, plasmid, cosmid, lambda phage or a yeast artificial chromosome (YAC).

Numerous vector systems can be employed. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as, for example, bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (Rous Sarcoma Virus, MMTV or MOMLV) or SV40 virus. Another class of vectors utilizes RNA elements derived from RNA viruses such as Semliki Forest virus, Eastern Equine Encephalitis virus and Flaviviruses.

Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The marker may provide, for example, prototropy to an auxotrophic host, biocide resistance, (*e.g.,* antibiotics), or resistance to heavy metals such as copper, or the like. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for

optimal synthesis of mRNA. These elements may include splice signals, as well as transcriptional promoters, enhancers, and termination signals.

Once the expression vector or DNA sequence containing the constructs has been prepared for expression, the expression vectors may be transfected or introduced into an appropriate host cell. Various techniques may be employed to achieve this, such as, for example, protoplast fusion, calcium phosphate precipitation, electroporation, retroviral transduction, viral transfection, gene gun, lipid based transfection or other conventional techniques. In the case of protoplast fusion, the cells are grown in media and screened for the appropriate activity.

Methods and conditions for culturing the resulting transfected cells and for recovering the antibody molecule produced are known to those skilled in the art, and may be varied or optimized depending upon the specific expression vector and mammalian host cell employed, based upon the present description.

Cells

The invention also provides host cells comprising a nucleic acid encoding an antibody molecule as described herein.

In one embodiment, the host cells are genetically engineered to comprise nucleic acids encoding the antibody molecule.

In one embodiment, the host cells are genetically engineered by using an expression cassette. The phrase "expression cassette," refers to nucleotide sequences, which are capable of affecting expression of a gene in hosts compatible with such sequences. Such cassettes may include a promoter, an open reading frame with or without introns, and a termination signal. Additional factors necessary or helpful in effecting expression may also be used, such as, for example, an inducible promoter.

The invention also provides host cells comprising the vectors described herein.

The cell can be, but is not limited to, a eukaryotic cell, a bacterial cell, an insect cell, or a human cell. Suitable eukaryotic cells include, but are not limited to, Vero cells, HeLa cells, COS cells, CHO cells, HEK293 cells, BHK cells, MDCKII cells and Per C6 cell line (*e.g.*, PER C6 cells from Crucell). Suitable insect cells include, but are not limited to, Sf9 cells.

Table 1. Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb BAP050, chimeric mAbs BAP050-chi, humanized mAbs BAP050-hum01 to BAP050-hum20, humanized mAbs BAP050-hum01-Ser to BAP050-hum15-Ser, BAP050-hum18-Ser to BAP050-hum20-Ser, and humanized mAbs BAP050-Clone-F to BAP050-Clone-J. The amino acid and nucleotide sequences of the heavy and light chain CDRs, the heavy and light chain variable regions, and the heavy and light chains are shown.

BAP050 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 6	VH	QIQLVQSGPELKKPGETVKISCKASGFTLTNYGMN WVRQTPGKGLKWMGWINTDTGEPTYADDFKGRFAF SLETSASTASLQINNLKNADTATYFCARNPPYYYG TNNAEAMDYWGQGTAVTVSS
SEQ ID NO: 7	DNA VH	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAA GAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGAGGCAGACTCCAGGAAAGGGTTTAAAGTG GATGGGCTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGACGGTTTGCCTTC TCTTTGGAGACCTCTGCCAGCACTGCCTCTTTGCA GATCAACAACCTCAAAAATGCGGACACGGCTACAT ATTTCTGTGCAAGAAACCCCCCTTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGTCA AGGAACCGCAGTCACCGTCTCCTCA
BAP050 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 16	VL	DIQMTQTTSSLSASLGDRVTISCSSSQDISNYLNW YQQKPDGTVKVLIYYTSTLHLGVPSRFSGSGSGTD YSLTISNLELEDIATYYCQQYYNLPWTFGGGTKLE IK
SEQ ID NO: 17	DNA VL	GATATCCAGATGACACAGACTACATCCTCCCTGTC TGCCTCTCTGGGAGACAGAGTCACCATCAGTTGCA

		GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGATGGAACTGTTAAAGTCCT GATCTATTACACATCAACCTTACACTTAGGAGTCC CATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGAT TATTCTCTCACCATCAGCAACCTGGAACTCGAAGA TATTGCCACATACTATTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGTGGAGGCACCAAGTTGGAA ATCAAA
BAP050-chi HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 20	VH	QIQLVQSGPELKKPGETVKISCKASGFTLTNYGMN WVRQTPGKGLKWMGWINTDTGEPTYADDFKGRFAF SLETSASTASLQINNLKNADTATYFCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 21	DNA VH	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAA GAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGAGGCAGACTCCAGGAAAGGGTTTAAAGTG GATGGGCTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGACGGTTTGCCTTC TCTTTGGAGACCTCTGCCAGCACTGCCTCTTTGCA GATCAACAACCTCAAAAATGCGGACACGGCTACAT ATTTCTGTGCAAGAAACCCCCCTTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 22	HC	QIQLVQSGPELKKPGETVKISCKASGFTLTNYGMN WVRQTPGKGLKWMGWINTDTGEPTYADDFKGRFAF SLETSASTASLQINNLKNADTATYFCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 23	DNA HC	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAA GAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGAGGCAGACTCCAGGAAAGGGTTTAAAGTG GATGGGCTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGACGGTTTGCCTTC TCTTTGGAGACCTCTGCCAGCACTGCCTCTTTGCA GATCAACAACCTCAAAAATGCGGACACGGCTACAT ATTTCTGTGCAAGAAACCCCCCTTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA

		GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-chi LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 24	VL	DIQMTQTTSSLSASLGDRVTISCSSSQDISNYLNW YQQKPDGTVKVLIYYTSTLHLGVPSRFSGSGSGTD YSLTISNLELEDIATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 25	DNA VL	GATATCCAGATGACACAGACTACATCCTCCCTGTC TGCCTCTCTGGGAGACAGAGTCACCATCAGTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGATGGAACTGTTAAAGTCCT GATCTATTACACATCAACCTTACACTTAGGAGTCC CATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGAT TATTCTCTCACCATCAGCAACCTGGAACTCGAAGA TATTGCCACATACTATTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 26	LC	DIQMTQTTSSLSASLGDRVTISCSSSQDISNYLNW YQQKPDGTVKVLIYYTSTLHLGVPSRFSGSGSGTD YSLTISNLELEDIATYYCQQYYNLPWTFGQGTKVE

		IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 27	DNA LC	GATATCCAGATGACACAGACTACATCCTCCCTGTC TGCCTCTCTGGGAGACAGAGTCACCATCAGTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGATGGAACTGTTAAAGTCCT GATCTATTACACATCAACCTTACACTTAGGAGTCC CATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGAT TATTCTCTCACCATCAGCAACCTGGAACTCGAAGA TATTGCCACATACTATTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum01 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF

		NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum01 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 32	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD

		FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 33	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 34	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 35	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum02 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG

		GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC

		AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum02 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 36	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 37	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 38	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 39	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum03 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN

SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC

		TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum03 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 40	VL	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 41	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 42	LC	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 43	DNA LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA

		TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum04 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC

		TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum04 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 44	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 45	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGAC TTCACTCTCACCATCAGCAGACTGGAGCCTGAAGA TTTTGCAGTGTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA

		ATCAAA
SEQ ID NO: 46	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 47	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGAC TTCACTCTCACCATCAGCAGACTGGAGCCTGAAGA TTTTGCAGTGTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum05 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NIDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS

		RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum05 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS

SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 48	VL	EIVLTQSPATLSLSPGERATLSCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 49	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTC TTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 50	LC	EIVLTQSPATLSLSPGERATLSCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 51	DNA LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTC TTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum06 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA

		GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLIVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG

		TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum06 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 52	VL	DIVMTQTPLSLPVTPGEPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 53	DNA VL	GATATTGTGATGACCCAGACTCCACTCTCCCTGCC CGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 54	LC	DIVMTQTPLSLPVTPGEPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 55	DNA LC	GATATTGTGATGACCCAGACTCCACTCTCCCTGCC CGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT

BAP050-hum07 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA

		GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum07 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 56	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 57	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACTATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 58	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVIKSFN RGEC
SEQ ID NO: 59	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACTATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT

		GATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum08 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC

		TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum08 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 60	VL	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 61	DNA VL	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT

		TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 62	LC	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 63	DNA LC	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum09 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 66	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN

		WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 67	DNA HC	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum09 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT

SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 36	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 37	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 38	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 39	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum10 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF

		SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 66	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 67	DNA HC	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG

		CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum10 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 40	VL	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 41	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 42	LC	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 43	DNA LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA

		GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum11 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 66	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 67	DNA HC	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG

		CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum11 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 56	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 57	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACTATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 58	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YLQKPGQSPQLLIYYTSTLHLGVPSRFSGSGSGTE FTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 59	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC

		TGCATCTGTAGGAGACAGAGTCACTATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum12 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 66	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLIVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO: 67	DNA HC	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum12 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 60	VL	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 61	DNA VL	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG

		TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 62	LC	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 63	DNA LC	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum13 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 68	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 69	DNA VH	CAGGTTCAGCTGGTGCAGTCCGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT

		ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 70	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 71	DNA HC	CAGGTTCAGCTGGTGCAGTCCGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum13 LC		

SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 36	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 37	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 38	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGIPPRFSGSGYGTD FTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 39	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCT GATCTATTACACATCAACCTTACACTTAGGGATCC CACCTCGATTCAGTGGCAGCGGGTATGGAACAGAT TTTACCCTCACAATTAATAACATAGAATCTGAGGA TGCTGCATATTACTTCTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum14 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY

SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 72	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WIRQSPSRGLEWLGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 73	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTG GCTGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 74	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WIRQSPSRGLEWLGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 75	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTG GCTGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC

		CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum14 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 40	VL	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 41	DNA VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 42	LC	EIVLTQSPATLPVTLGQPASISCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 43	DNA LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGCC CGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA

		CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum15 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 72	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WIRQSPSRGLEWLGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 73	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTG GCTGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 74	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WIRQSPSRGLEWLGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 75	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTG GCTGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA

		GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum15 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 60	VL	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 61	DNA VL	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 62	LC	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE

		IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 63	DNA LC	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum16 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 76	VH	EVQLVQSGAEVKKPGESLRISCKGSGFTLTNYGMN WVRQATGQGLEWMGWINTDTGEPTYADDFKGRVTI SADKSISTAYLQWSSLKASDTAMYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 77	DNA VH	GAAGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAA AAAGCCCGGGGAGTCTCTGAGGATCTCCTGTAAGG GTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGAGTCACCATC TCAGCCGACAAGTCCATCAGCACCGCCTACCTGCA GTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 78	HC	EVQLVQSGAEVKKPGESLRISCKGSGFTLTNYGMN WVRQATGQGLEWMGWINTDTGEPTYADDFKGRVTI SADKSISTAYLQWSSLKASDTAMYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF

		NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 79	DNA HC	GAAGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAA AAAGCCCGGGGAGTCTCTGAGGATCTCCTGTAAGG GTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGAGTCACCATC TCAGCCGACAAGTCCATCAGCACCGCCTACCTGCA GTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum16 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 60	VL	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD

		FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 61	DNA VL	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 62	LC	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 63	DNA LC	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum17 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 80	VH	QVQLVQSGSELKKPGASVKVSCKASGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQISTLKAEDTATYFCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 81	DNA VH	CAGGTGCAGCTGGTGCAATCTGGGTCTGAGTTGAA GAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATTCACCCTGACTAACTATGGCATGAAT TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG

		GATGGGATGGATCAACACCGACACTGGGGAGCCAA CGTATGCCGATGACTTCAAGGGACGGTTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCAGCACGCTAAAGGCTGAGGACACTGCTACAT ATTTCTGTGCAAGAAACCCCCCTTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 82	HC	QVQLVQSGSELKKPGASVKVSCKASGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQISTLKAEDTATYFCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 83	DNA HC	CAGGTGCAGCTGGTGCAATCTGGGTCTGAGTTGAA GAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATTCACCCTGACTAACTATGGCATGAAT TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGATGGATCAACACCGACACTGGGGAGCCAA CGTATGCCGATGACTTCAAGGGACGGTTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCAGCACGCTAAAGGCTGAGGACACTGCTACAT ATTTCTGTGCAAGAAACCCCCCTTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GACCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC

		AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum17 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 84	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLQPEDIATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 85	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCT CCTCTAGTCAGGACATTAGCAACTATTTAAATTGG TATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT GATCTACTATACATCCACTTTGCACCTGGGGGTCC CATCAAGGTTCAGTGGAAGTGGATCTGGGACAGAT TTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGA TATTGCAACATATTACTGTCAACAGTATTATAATC TCCCTTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 86	LC	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGKAPKLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLQPEDIATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 87	DNA LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCT CCTCTAGTCAGGACATTAGCAACTATTTAAATTGG TATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT GATCTACTATACATCCACTTTGCACCTGGGGGTCC CATCAAGGTTCAGTGGAAGTGGATCTGGGACAGAT TTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGA TATTGCAACATATTACTGTCAACAGTATTATAATC TCCCTTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum18 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN

SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC

		TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum18 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 88	VL	AIQLTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 89	DNA VL	GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAA
SEQ ID NO: 90	LC	AIQLTQSPSSLSASVGDRVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 91	DNA LC	GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA

		TTTTGCAACTTATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum19 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 28	VH	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 29	DNA VH	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 30	HC	EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMN WVRQAPGQGLEWMGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 31	DNA HC	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCTACAGTGAAAATCTCCTGCAAGG TTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC

		TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum19 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS
SEQ ID NO: 15 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 92	VL	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IK
SEQ ID NO: 93	DNA VL	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA

		ATCAAA
SEQ ID NO: 94	LC	EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNW YQQKPGQAPRLLIYYTSTLHLGVPSRFSGSGSGTD FTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 95	DNA LC	GAAATTGTGCTGACTCAGTCTCCAGACTTTCAGTC TGTGACTCCAAAGGAGAAAGTCACCATCACCTGCA GTTCAAGTCAGGACATCAGCAATTATTTAAACTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATTACACATCAACCTTACACTTAGGGGTCC CCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGAT TTCACCTTTACCATCAGTAGCCTGGAAGCTGAAGA TGCTGCAACATATTACTGTCAGCAGTATTATAACC TTCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAA ATCAAACGTACGGTGGCTGCACCATCTGTCTTCAT CTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTAT CCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC AGGGGAGAGTGT
BAP050-hum20 HC		
SEQ ID NO: 1 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 2 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 3 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 4 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 5 (Chothia)	HCDR2	NIDTGE
SEQ ID NO: 3 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCC
SEQ ID NO: 66	HC	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMN WVRQARGQRLEWIGWINTDTGEPTYADDFKGRFVF SLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYG TNNAEAMDYWGQGTTVTVSSASTKGPSVFPLAPCS

		RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 67	DNA HC	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATTTACCCTCACAAACTATGGAATGAAC TGGGTGCGACAGGCTCGTGGACAACGCCTTGAGTG GATAGGTTGGATAAACACCGACACTGGAGAGCCAA CATATGCTGATGACTTCAAGGGAAGATTTGTCTTC TCCTTGGACACCTCTGTCAGCACGGCATATCTGCA GATCTGCAGCCTAAAGGCTGAGGACACTGCCGTGT ATTACTGTGCAAGAAACCCTCCCTATTACTACGGT ACTAATAACGCGGAGGCTATGGACTACTGGGGCCA GGGCACCACCGTGACCGTGTCCTCCGCTTCCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCC AGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAGCTTGGGCACGAAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGAG AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT GCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTC TTCCTGTTCCCCCCAAAACCCAAGGACACTCTCAT GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG TGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTC AACTGGTACGTGGATGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCAC CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA GGTGTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT TCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGC AGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACACAGA AGAGCCTCTCCCTGTCTCTGGGTAAA
BAP050-hum20 LC		
SEQ ID NO: 10 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 11 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 12 (Kabat)	LCDR3	QQYYNLPWT
SEQ ID NO: 13 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 14 (Chothia)	LCDR2	YTS

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 236

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 236

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS:

1. An isolated antibody molecule that binds specifically to human Lymphocyte Activation Gene-3 (LAG-3), comprising:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 4, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15;

(b) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 1, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12;

(c) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15; or

(d) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

2. The antibody molecule of claim 1, comprising a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 4, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15.

3. The antibody molecule of claim 1, comprising a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 1, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

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4. The antibody molecule of claim 1, comprising a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15.

5. The antibody molecule of claim 1, comprising a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 286, a VHCDR2 amino acid sequence of SEQ ID NO: 2, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

6. The antibody molecule of any one of claims 1-5, wherein the antibody molecule is a humanized antibody molecule.

7. The antibody molecule of any one of claims 1-6, wherein the antibody molecule is a monospecific antibody molecule.

8. The antibody molecule of any one of claims 1-6, wherein the antibody molecule is a bispecific antibody molecule.

9. The antibody molecule of any one of claims 1-8, which comprises a heavy chain variable region comprising at least one framework (FW) region comprising the amino acid sequence of any one of SEQ ID NOs: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221, 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 one of SEQ ID NOs: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

10. The antibody molecule of any one of claims 1-9, which comprises a heavy chain variable region comprising at least one framework region comprising the amino acid sequence of any one of SEQ ID NOs: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

11. The antibody molecule of any one of claims 1-10, which comprises a heavy chain variable region comprising at least two, three, or four framework regions comprising the amino

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acid sequences of any one of SEQ ID NOs: 187, 190, 194, 196, 198, 202, 206, 208, 210, 212, 217, 219, or 221.

12. The antibody molecule of any one of claims 1-11, which comprises a heavy chain framework region 1 ("VHFW1") amino acid sequence of SEQ ID NO: 187, 190, 194, or 196, a VHFW2 amino acid sequence of SEQ ID NO: 198, 202, 206, or 208, and a VHFW3 amino acid sequence of SEQ ID NO: 210, 212, 217, or 219, and, optionally, further comprising a VHFW4 amino acid sequence of SEQ ID NO: 221.

13. The antibody molecule of any one of claims 1-12, which comprises a light chain variable region comprising at least one framework region comprising the amino acid sequence of any one of SEQ ID NOs: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271, 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 one of SEQ ID NOs: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

14. The antibody molecule of any one of claims 1-13, which comprises a light chain variable region comprising at least one framework region comprising the amino acid sequence of any one of SEQ ID NOs: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

15. The antibody molecule of any one of claims 1-14, which comprises a light chain variable region comprising at least two, three, or four framework regions comprising the amino acid sequences of any one of SEQ ID NOs: 226, 230, 232, 234, 236, 238, 240, 244, 246, 248, 252, 255, 259, 261, 265, 267, 269, or 271.

16. The antibody molecule of any one of claims 1-15, which comprises a light chain framework region 1 ("VLFW1") amino acid sequence of SEQ ID NO: 226, 230, 232, 234, 236, or 238, a VLFW2 amino acid sequence of SEQ ID NO: 240, 244, 246, or 248, and a VLFW3 amino acid sequence of SEQ ID NO: 252, 255, 259, 261, 265, 267, or 269, and, optionally, further comprising a VLFW4 amino acid sequence of SEQ ID NO: 271.

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17. The antibody molecule of any one of claims 1-16, which comprises a heavy chain variable domain comprising an amino acid sequence at least 85% identical to any one of SEQ ID NOs: 8, 28, 64, 68, 72, 76, 80, 100, 104, or 108.

18. The antibody molecule of any one of claims 1-17, which comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 8, 28, 64, 68, 72, 76, 80, 100, 104, or 108.

19. The antibody molecule of any one of claims 1-18, which comprises a light chain variable domain comprising an amino acid sequence at least 85% identical to any one of SEQ ID NOs: 32, 36, 40, 44, 48, 52, 56, 60, 84, 88, 92, or 96.

20. The antibody molecule of any one of claims 1-19, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 32, 36, 40, 44, 48, 52, 56, 60, 84, 88, 92, or 96.

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: 8.

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

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: 28.

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

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: 64.

26. The antibody molecule of any one of claims 1-20 or 25, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66.

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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: 68.

28. The antibody molecule of any one of claims 1-20 or 27, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 70.

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: 72.

30. The antibody molecule of any one of claims 1-20 or 29, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 74.

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: 76.

32. The antibody molecule of any one of claims 1-20 or 31, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 78.

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: 80.

34. The antibody molecule of any one of claims 1-20 or 33, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 82.

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: 100.

36. The antibody molecule of any one of claims 1-20 or 35, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 113.

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: 104.

38. The antibody molecule of any one of claims 1-20 or 37, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 106.

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39. The antibody molecule of any one of claims 1-20 or 37, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 122.

40. 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: 108.

41. The antibody molecule of any one of claims 1-20 or 40, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 110.

42. The antibody molecule of any one of claims 1-20 or 40, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134.

43. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 32.

44. The antibody molecule of any one of claims 1-43, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 34.

45. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

46. The antibody molecule of any one of claims 1-42 or 45, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 38.

47. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

48. The antibody molecule of any one of claims 1-42 or 47, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 42.

49. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 44.

50. The antibody molecule of any one of claims 1-42 or 49, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 46.

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51. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 48.

52. The antibody molecule of any one of claims 1-42 or 51, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 50.

53. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 52.

54. The antibody molecule of any one of claims 1-42 or 53, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 54.

55. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

56. The antibody molecule of any one of claims 1-42 or 55, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 58.

57. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

58. The antibody molecule of any one of claims 1-42 or 57, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 62.

59. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 84.

60. The antibody molecule of any one of claims 1-42 or 59, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 86.

61. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 88.

62. The antibody molecule of any one of claims 1-42 or 61, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 90.

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63. The antibody molecule of any one of claims 1-42, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 92.

64. The antibody molecule of any one of claims 1-40 or 63, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 94.

65. The antibody molecule of any one of claims 1-43, which comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 96.

66. The antibody molecule of any one of claims 1-43 or 65, which comprises a light chain comprising the amino acid sequence of SEQ ID NO: 98.

67. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 32.

68. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

69. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

70. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 44.

71. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 48.

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72. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 52.

73. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

74. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

75. 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

76. 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

77. 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

78. 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

79. 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: 68 or SEQ ID NO: 108; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

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80. 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: 72 or SEQ ID NO: 8; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

81. 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: 72 or SEQ ID NO: 8; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

82. 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: 76 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

83. 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: 80 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 84.

84. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 88.

85. 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: 28 or SEQ ID NO: 100; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 92.

86. 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: 64 or SEQ ID NO: 104; and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 96.

87. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 34.

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88. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

89. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

90. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 46.

91. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 50.

92. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 54.

93. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

94. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 62.

95. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

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96. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

97. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

98. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 62.

99. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 or SEQ ID NO: 110; and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

100. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 or SEQ ID NO: 18; and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

101. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 or SEQ ID NO: 18; and a light chain comprising the amino acid sequence of SEQ ID NO: 62.

102. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 62.

103. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 86.

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104. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 94.

105. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 or SEQ ID NO: 106; and a light chain comprising the amino acid sequence of SEQ ID NO: 98.

106. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 113 and a light chain comprising the amino acid sequence of SEQ ID NO: 34.

107. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 113 and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

108. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 122 and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

109. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 122 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

110. The antibody molecule of any one of claims 1-20, which comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134 and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

111. The antibody molecule of any one of claims 1-110, which is a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv).

112. The antibody molecule of any one of claims 1-110, which comprises a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4.

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113. The antibody molecule of claim 112, which comprises a light chain constant region that is the light chain constant regions of kappa or lambda.

114. The antibody molecule of claim 112 or 113, which comprises a human IgG4 heavy chain constant region with a mutation at position 108 of SEQ ID NO: 275 or 277 and a kappa light chain constant region.

115. The antibody molecule of claim 112 or 113, which comprises a human IgG4 heavy chain constant region of SEQ ID NO: 275 or 277 and a kappa light chain constant region.

116. The antibody molecule of claim 112 or 113, which comprises a human IgG1 heavy chain constant region of SEQ ID NO: 279 and a kappa light chain constant region.

117. The antibody molecule of claim 112 or 113, which comprises the human IgG1 heavy chain constant region of SEQ ID NO: 280 and a kappa light chain constant region.

118. The antibody molecule of claim 112 or 113, which comprises the human IgG1 heavy chain constant region of SEQ ID NO: 281 and a kappa light chain constant region.

119. The antibody molecule of any one of claims 1-118, which binds specifically to human LAG-3 with a dissociation constant (K_D) of less than 0.2 nM.

120. The antibody molecule of any one of claims 1-119, which binds an extracellular Ig-like domain of LAG-3.

121. The antibody molecule of any one of claims 1-120, which inhibits the binding of LAG-3 to a major histocompatibility (MHC) class II molecule, or a cell that expresses an MHC class II molecule.

122. The antibody molecule of any one of claims 1-121, wherein the antibody produces an antigen-specific T cell response.

123. The antibody molecule of any one of claims 1-6 and 8-122, wherein the antibody molecule has a first binding specificity for LAG-3 and a second binding specificity for

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Programmed Death-1 ("PD-1"), T-cell Immunoglobulin and Mucin Domain-3 ("TIM-3"), Carcinoembryonic Antigen-related Adhesion Molecule-1 ("CEACAM-1"), CEACAM-5, Programmed Death-Ligand 1 ("PD-L1") or PD-L2.

124. The antibody molecule of any one of claims 1-122, wherein the antibody molecule comprises an antigen binding fragment of an antibody, wherein the antibody binding fragment retains antigen specific binding abilities of the antibody.

125. A pharmaceutical composition comprising the isolated antibody molecule of any one of claims 1-124 and a pharmaceutically acceptable carrier, excipient or stabilizer.

126. An isolated nucleic acid encoding one or more heavy chain CDRs 1-3 used for making the antibody molecule of any one of claims 1-124, wherein the nucleic acid comprises one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 140-144, 151-155, 162-166, 173-177, 184-186, and 287.

127. An isolated nucleic acid encoding one or more light chain CDRs 1-3 used for making the antibody molecule of any one of claims 1-124, wherein the nucleic acid comprises one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 145-150, 156-161, 167-172, and 178-183.

128. The nucleic acid of claim 126, further comprising a nucleotide sequence encoding a heavy chain variable domain, wherein the nucleotide sequence comprises any one of SEQ ID NO: 9, 29, 65, 69, 73, 77, 81, 101, 105, 109, 112, 121, 124, 125, 132, or 133.

129. The nucleic acid of claim 128, further comprising a nucleotide sequence encoding a heavy chain, wherein the nucleotide sequence comprises any one of SEQ ID NO: 19, 31, 67, 71, 75, 79, 83, 103, 107, 111, 114, 123, 126, 127, 135, or 136.

130. The nucleic acid of claim 127, further comprising a nucleotide sequence encoding a light chain variable domain, wherein the nucleotide sequence comprises any one of SEQ ID NO: 33, 37, 41, 45, 49, 53, 57, 61, 85, 89, 93, 97, 115, 118, 128, 129, or 137.

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131. The nucleic acid of claim 130, further comprising a nucleotide sequence encoding a light chain, wherein the nucleotide sequence comprises any one of SEQ ID NO: 35, 39, 43, 47, 51, 55, 59, 63, 87, 91, 95, 99, 117, 120, 130, 131, 138, or 139.

132. An isolated nucleic acid encoding the antibody heavy and/or light chain variable region of the antibody molecule of any one of claims 1-124.

133. An expression vector comprising the nucleic acid of any one of claims 126-132.

134. A host cell comprising the nucleic acid of any one of claims 126-132, wherein the host cell is used in making the antibody molecule of any one of claims 1-124.

135. A method of producing an antibody molecule, comprising culturing the host cell of claim 134 under conditions suitable for gene expression.

136. Use of the isolated antibody molecule of any one of claims 1-124, or the pharmaceutical composition of claim 125 for stimulating an immune response in a subject.

137. Use of the isolated antibody molecule of any one of claims 1-124, or the pharmaceutical composition of claim 125 for the treatment of lung cancer, mesothelioma, renal cell carcinoma, breast cancer, or melanoma.

138. The use of claim 136 or 137 further comprising the use of a second therapeutic agent or procedure.

139. The use of claim 138, wherein the second therapeutic agent or procedure is one or more of chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, a surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy.

140. The use of claim 138, further comprising the use of an agonist of a costimulatory molecule that is one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1, ICOS, 4-1BB,

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GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

141. The use of claim 140, further comprising the use of an inhibitor of an immune checkpoint that is one or more of PD-1, PD-L1, PD-L2, CTLA4, TIM3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR.

142. A method of detecting LAG-3 in a biological sample, comprising (i) contacting the sample or optionally a reference sample with the isolated antibody molecule of any one of claims 1-124 under conditions that allow interaction of the antibody molecule and a LAG-3 polypeptide to occur, and (ii) detecting formation of a complex between the antibody molecule and the LAG-3 polypeptide within the sample or optionally the reference sample.

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Light chain (murine κ)

FWL1 CDRL1 FWL2 CDRL2 FWL3

DIQMTQTTSS LSASLGDRVT ISCSS***SQDIS NY***LNWYQQKP DGTVKVLIY***Y TS***TLHLGVPS RFSGSGSGTD

CDRL3 FWL4

YSLTISNLEL EDIATYYCQQ ***YYNLPW***TFGG GTKLEIK

Heavy Chain (murine IgG1)

FWH1 CDRH1 FWH2 CDRH2

QIQLVQSGPE LKKPGETVKI SCKAS***GFTLT NY***GMNWVRQT PGKGLKWMGW I***NTDTGE***PTY ADDFKGRFAF

FWH3 CDRH3 FWH4

SLETSASTAS LQINNLKNAD TATYFCAR***NP PYYYGTNWAE AMDY***WGQGTA VTVSS

FIGURE 1

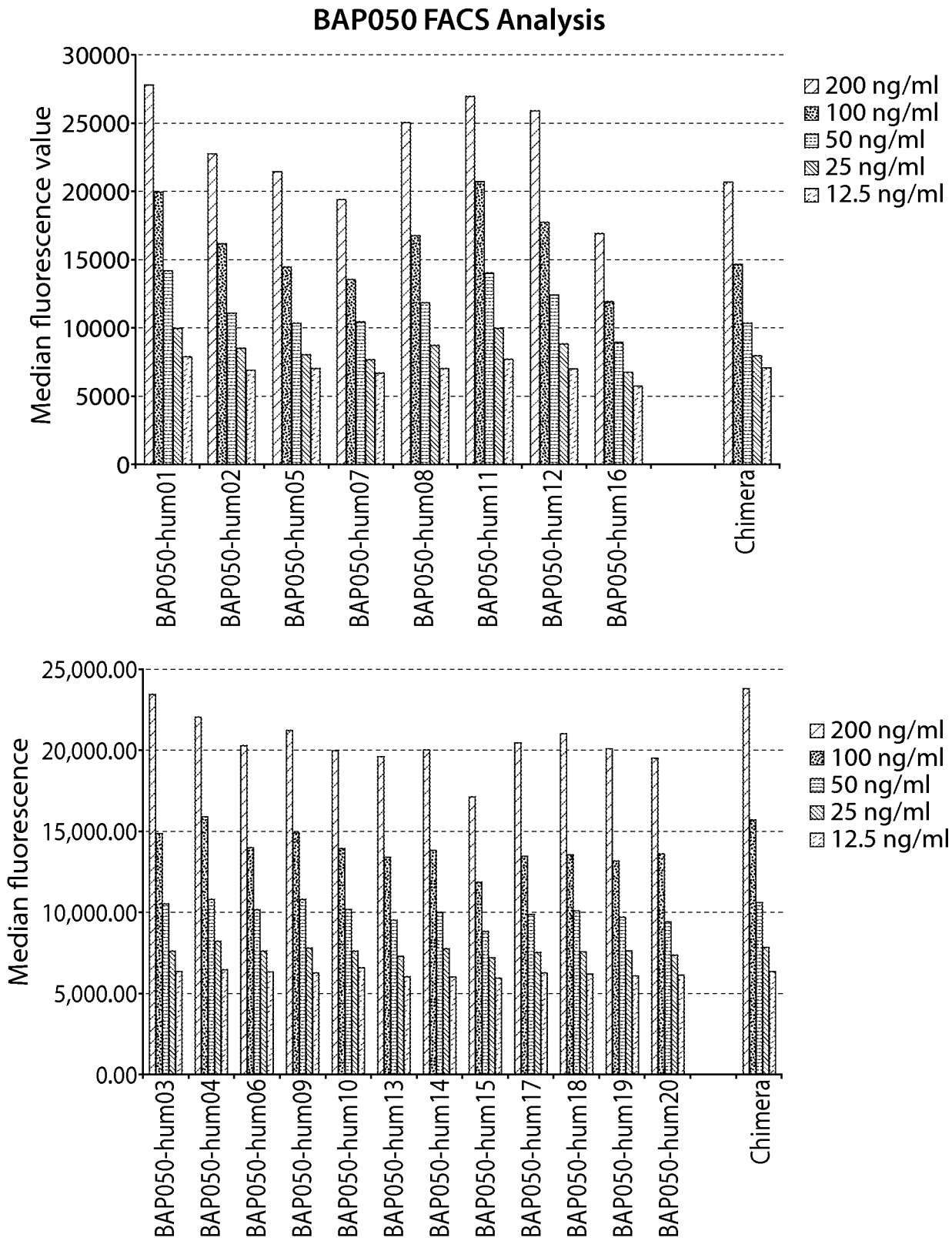
Light chain

```
GL      DIQMTQTTSS LSASLGDRVT ISCSASQGIS NYLNWYQQKP DGTVKLLIYY TSSLHSGVPS
Mu mAb  ----------- ----S--D-- ---------- -----V---- --T--L----
GL      RFSGSGSGTD YSLTISNLEP EDIATYYCQQ YSKLP
Mu mAb  ----------- ----------L ---------- -YN--WTFGG GTKLEIK
```

Heavy chain

```
GL      QIQLVQSGPE LKKPGETVKI SCKASGYTFT NYGMNWVKQA PGKGLKWMGW INTYTGEPTY
Mu mAb  ----------- ---------- ------F-L- -------R-T ---------- ---D------
GL      ADDFKGRFAF SLETSASTAY LQINNLKNED TATYFCAR
Mu mAb  -------A-- ---------S ---------- ---------- NP PYYYGTNWAE AMDYWGQGTA
GL
Mu mAb  VTVSS
```

FIGURE 2


BAP050 FACS Analysis
Median fluorescence value
30000
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20000
15000
10000
5000
0
200 ng/ml
100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
BAP050-hum01
BAP050-hum02
BAP050-hum05
BAP050-hum07
BAP050-hum08
BAP050-hum11
BAP050-hum12
BAP050-hum16
Chimera
Median fluorescence
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100 ng/ml
50 ng/ml
25 ng/ml
12.5 ng/ml
BAP050-hum03
BAP050-hum04
BAP050-hum06
BAP050-hum09
BAP050-hum10
BAP050-hum13
BAP050-hum14
BAP050-hum15
BAP050-hum17
BAP050-hum18
BAP050-hum19
BAP050-hum20
Chimera

FIGURE 3

Clone No.	μg/mL	Sequence					
		HC			LC		
		FW1	FW2	FW3	FW1	FW2	FW3
chimera	31.7	6 unique HC			12 unique LC		
1	35.4	a	a	a	a	a	a
2	25.2	a	a	a	a	a	b
3	3.2	a	a	a	b	b	a
4	26	a	a	a	a	c	c
5	16.9	a	a	a	c	a	a
6	9.1	a	a	a	d	b	d
7	35.8	a	a	a	a	d	d
8	24.7	a	a	a	e	b	e
9	19.9	b	b	a	a	a	b
10	7.7	b	b	a	b	b	a
11	34.9	b	b	a	a	d	d
12	17.9	b	b	a	e	b	e
13	24.9	b	a	a	a	a	b
14	7.5	a	c	a	b	b	a
15	21.9	a	c	a	e	b	e
16	17.7	c	d	b	e	b	e
17	21.2	d	a	c	a	a	f
18	8.1	a	a	a	f	b	e
19	7.5	a	a	a	e	b	a
20	3.2	b	b	a	d	b	g

FIGURE 4

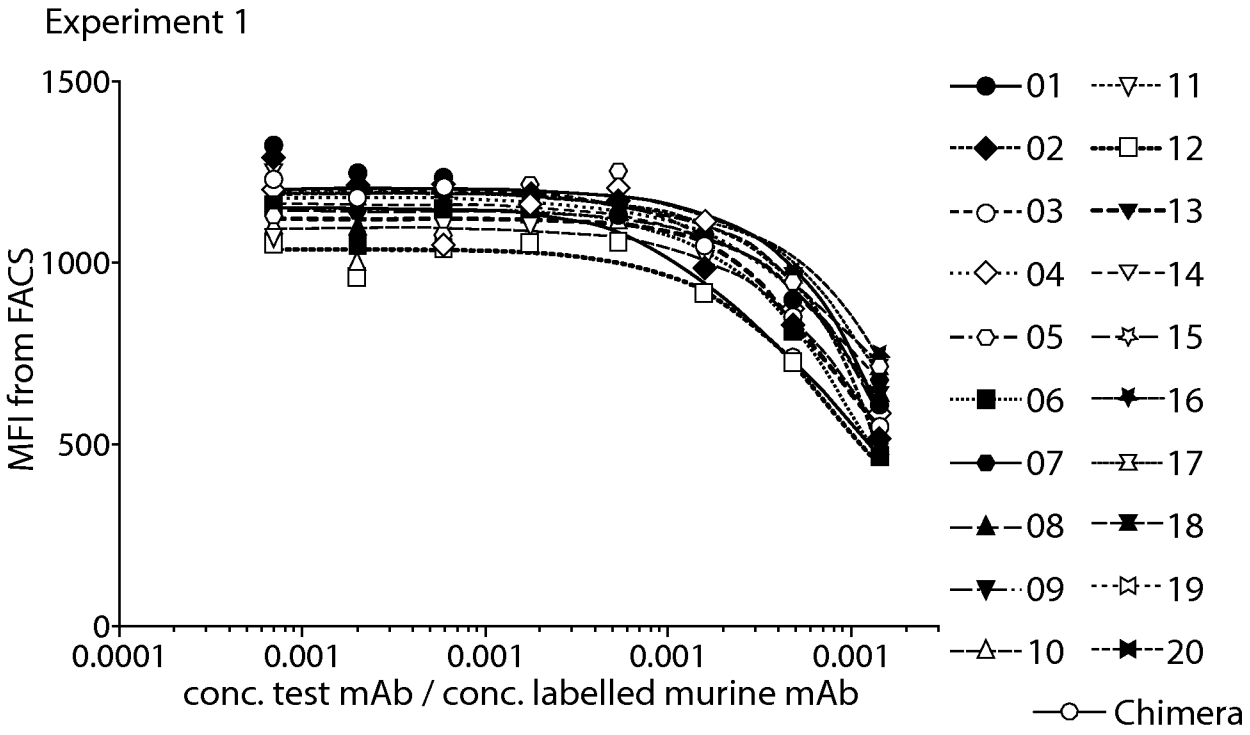

FIGURE 5A

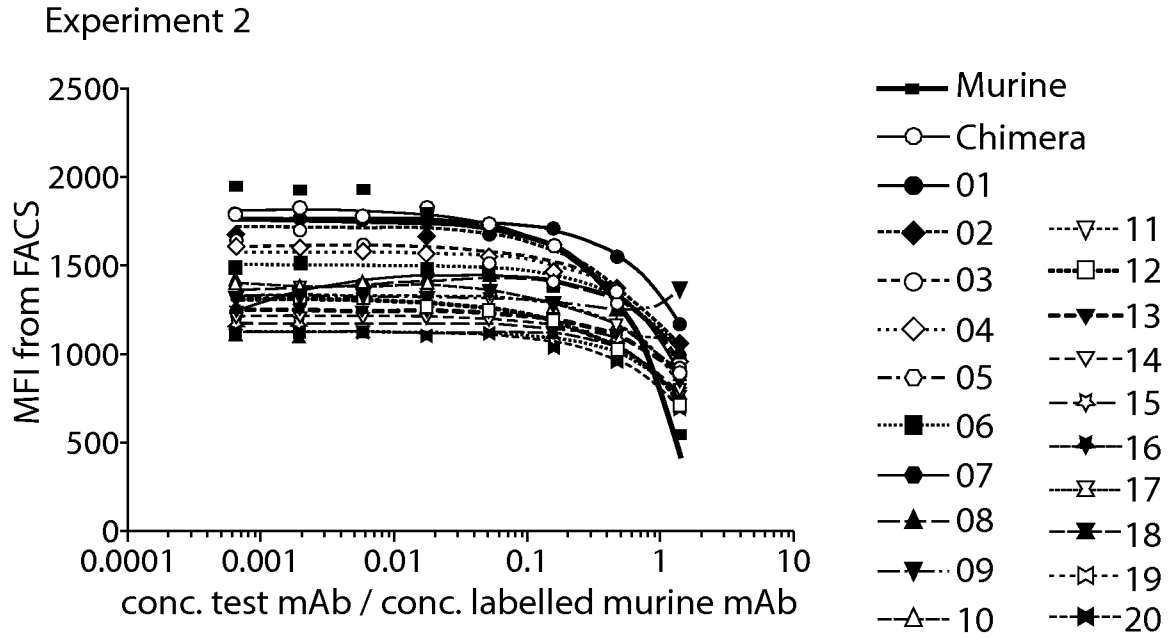

FIGURE 5B

Clone No.	Conc. μg/mL	Sequence						Ranking		Structure
		HC			LC			Binding data	Compet. data	
		FW1	FW2	FW3	FW1	FW2	FW3			
		6 unique HC			12 unique LC				*	
1	35.4	a	a	a	a	a	a	1	2	D
2	25.2	a	a	a	a	a	b	5	1	B
3	3.2	a	a	a	b	b	a	7	1	E
4	26	a	a	a	a	c	c	8	2	E
5	16.9	a	a	a	c	a	a	6		E
6	9.1	a	a	a	d	b	d	9	1	E
7	35.8	a	a	a	a	d	d	8		C
8	24.7	a	a	a	e	b	e	4		E
9	19.9	b	b	a	a	a	b	8	2	B
10	7.7	b	b	a	b	b	a	9	2	E
11	34.9	b	b	a	a	d	d	2	2	C
12	17.9	b	b	a	e	b	e	3	2	E
13	24.9	b	a	a	a	a	b	9	3	A
14	7.5	a	c	a	b	b	a	9		F
15	21.9	a	c	a	e	b	e	20	20	F
16	17.7	c	d	b	e	b	e	20	20	D
17	21.2	d	a	c	a	a	f	9		E
18	8.1	a	a	a	f	b	e	8		C
19	7.5	a	a	a	e	b	a	9		D
20	3.2	b	b	a	d	b	g	9	3	C

*empty boxes means worse than 3.

FIGURE 6

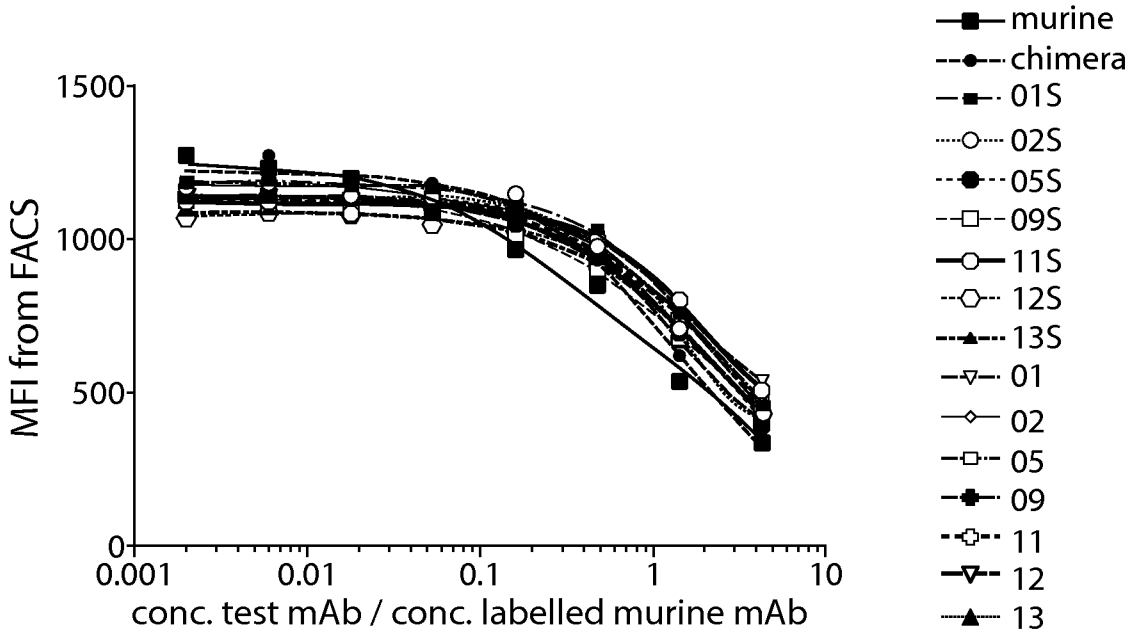

FIGURE 7

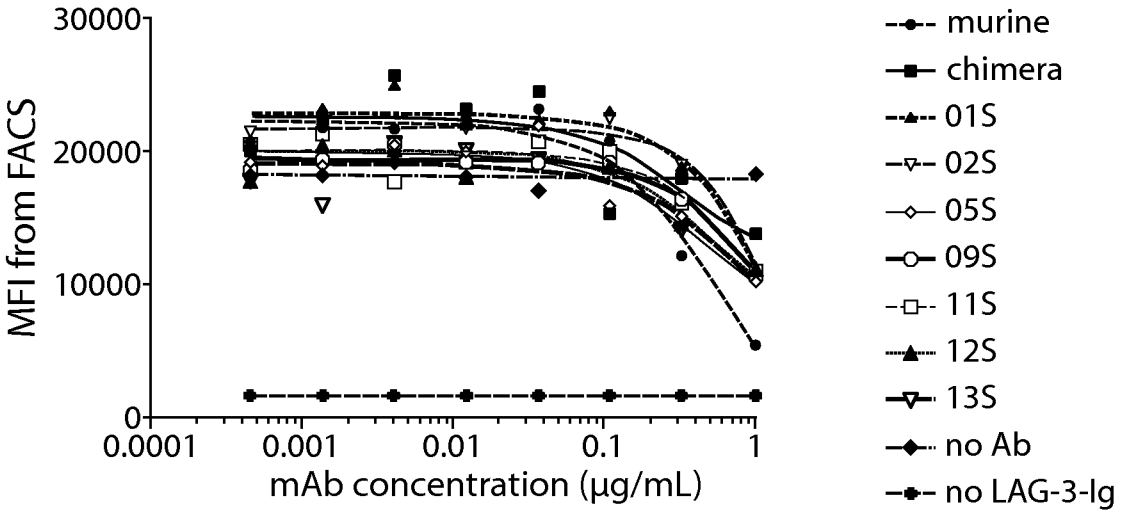

FIGURE 8

```
                        10        20        30        40        50        60
                   ....|....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-HC      QIQLVQSGPELKKPGETVKISCKASGFTLTNYGMNWVRQTPGKGLKWMGWINTDTGEPTY
BAP050-hum01-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum02-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum03-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum04-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum05-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum06-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum07-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum08-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum18-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum19-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum09-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
BAP050-hum10-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
BAP050-hum11-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
BAP050-hum12-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
BAP050-hum20-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
BAP050-hum13-HC    QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
BAP050-hum14-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWIRQSPSRGLEWLGWINTDTGEPTY
BAP050-hum15-HC    EVQLVQSGAEVKKPGATVKISCKVSGFTLTNYGMNWIRQSPSRGLEWLGWINTDTGEPTY
BAP050-hum16-HC    EVQLVQSGAEVKKPGESLRISCKGSGFTLTNYGMNWVRQATGQGLEWMGWINTDTGEPTY
BAP050-hum17-HC    QVQLVQSGSELKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY

                        70        80        90        100       110       120
                   ....|....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-HC      ADDFKGRFAFSLETSASTASLQINNLKNADTATYFCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum01-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum02-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum03-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum04-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum05-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum06-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum07-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum08-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum18-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum19-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum09-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum10-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum11-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum12-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum20-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum13-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum14-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum15-HC    ADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum16-HC    ADDFKGRVTISADKSISTAYLQWSSLKASDTAMYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum17-HC    ADDFKGRFVFSLDTSVSTAYLQISTLKAEDTATYFCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
```

FIGURE 9A

```
                          10        20        30        40        50        60
                  ....|....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-HC     QIQLVQSGPELKKPGETVKISCKASGFTLTNYGMNWVRQTPGKGLKWMGWINTDTGEPTY
BAP050-hum01-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum02-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum03-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum04-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum05-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum06-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum07-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum08-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum18-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum19-HC   EV......A.V....A.......V..............A..Q..E.............
BAP050-hum09-HC   .V......A.V....AS..V..................AR.QR.E.I...........
BAP050-hum10-HC   .V......A.V....AS..V..................AR.QR.E.I...........
BAP050-hum11-HC   .V......A.V....AS..V..................AR.QR.E.I...........
BAP050-hum12-HC   .V......A.V....AS..V..................AR.QR.E.I...........
BAP050-hum20-HC   .V......A.V....AS..V..................AR.QR.E.I...........
BAP050-hum13-HC   .V......A.V....AS..V..................A..Q..E.............
BAP050-hum14-HC   EV......A.V....A.......V...........I..S.SR..E.L...........
BAP050-hum15-HC   EV......A.V....A.......V...........I..S.SR..E.L...........
BAP050-hum16-HC   EV......A.V.....SLR....G..............AT.Q..E.............
BAP050-hum17-HC   .V......S......AS..V..................A..Q..E.............

                          70        80        90        100       110       120
                  ....|....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-HC     ADDFKGRFAFSLETSASTASLQINNLKNADTATYFCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-hum01-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum02-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum03-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum04-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum05-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum06-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum07-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum08-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum18-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum19-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum09-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum10-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum11-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum12-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum20-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum13-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum14-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum15-HC   ........V...D..V...Y...CS..AE...V.Y...........................
BAP050-hum16-HC   .......VTI.ADK.I...Y..WSS..AS...M.Y...........................
BAP050-hum17-HC   ........V...D..V...Y...ST..AE.................................
```

FIGURE 9B

```
                        10        20        30        40        50        60
                  ....|....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-LC     DIQMTQTTSSLSASLGDRVTISCSSSQDISNYLNWYQQKPDGTVKVLIYYTSTLHLGVPS
BAP050-hum01-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGVPS
BAP050-hum02-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGIPP
BAP050-hum13-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGIPP
BAP050-hum09-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGIPP
BAP050-hum03-LC   EIVLTQSPATLPVSLGQTASISCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum10-LC   EIVLTQSPATLPVSLGQTASISCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum14-LC   EIVLTQSPATLPVSLGQTASISCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum04-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGIPD
BAP050-hum05-LC   EIVLTQSPATLSLSPGERATLSCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGVPS
BAP050-hum06-LC   DIVMTQTPLSLPVTPGEPASISCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum07-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGVPS
BAP050-hum11-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGVPS
BAP050-hum08-LC   EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum12-LC   EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum15-LC   EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum16-LC   EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum17-LC   DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGVPS
BAP050-hum18-LC   AIQLTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum19-LC   EIVLTQSPDFQSVTPKEKVTITCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGVPS
BAP050-hum20-LC   DIVMTQTPLSLPVTPGEPASISCSSSQDISNYLNWYQQKPGQAPRLLIYYTSTLHLGIPD

                        70        80        90        100
                  ....|....|....|....|....|....|....|....|..
BAP050-chi-LC     RFSGSGSGTDYSLTISNLELEDIATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum01-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum02-LC   RFSGSGYGTDFTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVEIK
BAP050-hum13-LC   RFSGSGYGTDFTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVEIK
BAP050-hum09-LC   RFSGSGYGTDFTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVEIK
BAP050-hum03-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum10-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum14-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum04-LC   RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum05-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum06-LC   RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum07-LC   RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum11-LC   RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum08-LC   RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum12-LC   RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum15-LC   RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum16-LC   RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum17-LC   RFSGSGSGTDFTFTISSLQPEDIATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum18-LC   RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum19-LC   RFSGSGSGTDFTFTISSLEAEDAATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum20-LC   RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYYNLPWTFGQGTKVEIK
```

FIGURE 10A

```
                        10        20        30        40        50        60
                   ....|....|....|....|....|....|....|....|....|....|....|
BAP050-chi-LC      DIQMTQTTSSLSASLGDRVTISCSSSQDISNYLNWYQQKPDGTVKVLIYYTSTLHLGVPS
BAP050-hum01-LC    ......SP......V......T..................GKAP.L.............
BAP050-hum02-LC    ......SP......V......T..................GKAP.L..........I.P
BAP050-hum13-LC    ......SP......V......T..................GKAP.L..........I.P
BAP050-hum09-LC    ......SP......V......T..................GKAP.L..........I.P
BAP050-hum03-LC    E.VL..SPAT.PV...QTAS.....................GQAPRL.............
BAP050-hum10-LC    E.VL..SPAT.PV...QTAS.....................GQAPRL.............
BAP050-hum14-LC    E.VL..SPAT.PV...QTAS.....................GQAPRL.............
BAP050-hum04-LC    ......SP......V......T.............L...GQSPQL..........I.D
BAP050-hum05-LC    E.VL..SPAT..L.P.E.A.L....................GKAP.L.............
BAP050-hum06-LC    ..V....PL..PVTP.EPAS.....................GQAPRL.............
BAP050-hum07-LC    ......SP......V......T.............L...GQSPQL.............
BAP050-hum11-LC    ......SP......V......T.............L...GQSPQL.............
BAP050-hum08-LC    E.VL..SPDFQ.VTPKEK...T...................GQAPRL.............
BAP050-hum12-LC    E.VL..SPDFQ.VTPKEK...T...................GQAPRL.............
BAP050-hum15-LC    E.VL..SPDFQ.VTPKEK...T...................GQAPRL.............
BAP050-hum16-LC    E.VL..SPDFQ.VTPKEK...T...................GQAPRL.............
BAP050-hum17-LC    ......SP......V......T..................GKAP.L.............
BAP050-hum18-LC    A..L..SP......V......T...................GQAPRL.............
BAP050-hum19-LC    E.VL..SPDFQ.VTPKEK...T...................GQAPRL.............
BAP050-hum20-LC    ..V....PL..PVTP.EPAS.....................GQAPRL..........I.D

                        70        80        90        100
                   ....|....|....|....|....|....|....|....|..
BAP050-chi-LC      RFSGSGSGTDYSLTISNLELEDIATYYCQQYYNLPWTFGQGTKVEIK
BAP050-hum01-LC    ..........FTF...S..A..A.......................
BAP050-hum02-LC    ......Y...FT...N.I.S..A.Y.F...................
BAP050-hum13-LC    ......Y...FT...N.I.S..A.Y.F...................
BAP050-hum09-LC    ......Y...FT...N.I.S..A.Y.F...................
BAP050-hum03-LC    ..........FTF...S..A..A.......................
BAP050-hum10-LC    ..........FTF...S..A..A.......................
BAP050-hum14-LC    ..........FTF...S..A..A.......................
BAP050-hum04-LC    ..........FT....R..P..F.V.....................
BAP050-hum05-LC    ..........FTF...S..A..A.......................
BAP050-hum06-LC    .........EFT....S.QPD.F.......................
BAP050-hum07-LC    .........EFT....S.QPD.F.......................
BAP050-hum11-LC    .........EFT....S.QPD.F.......................
BAP050-hum08-LC    ..........FT....S.QP..F.......................
BAP050-hum12-LC    ..........FT....S.QP..F.......................
BAP050-hum15-LC    ..........FT....S.QP..F.......................
BAP050-hum16-LC    ..........FT....S.QP..F.......................
BAP050-hum17-LC    ..........FTF...S.QP..........................
BAP050-hum18-LC    ..........FT....S.QP..F.......................
BAP050-hum19-LC    ..........FTF...S..A..A.......................
BAP050-hum20-LC    ..........FT....R..P..F.V.....................
```

FIGURE 10B

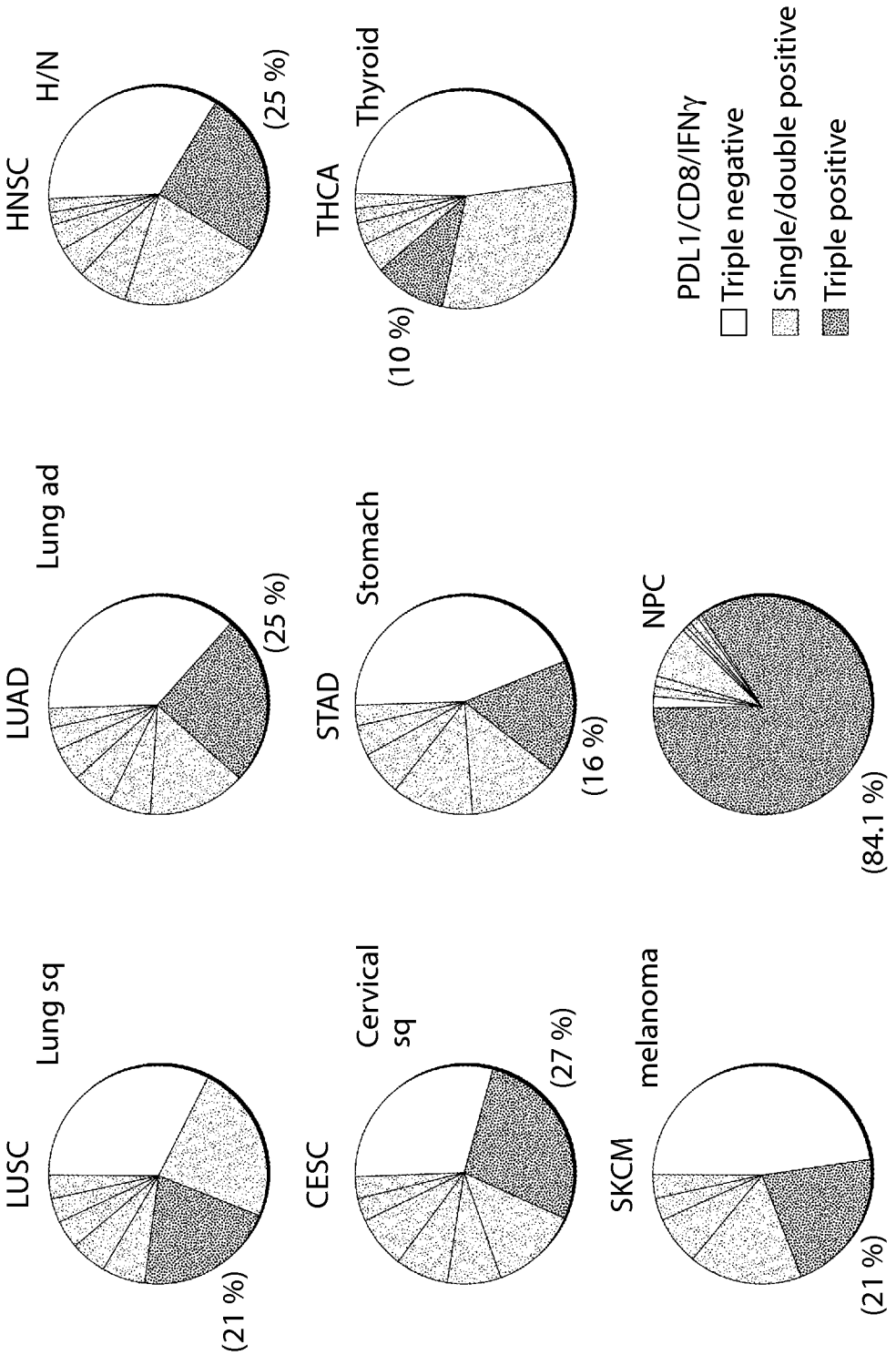
HNSC
H/N
(25 %)
THCA
Thyroid
(10 %)
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive
LUAD
Lung ad
(25 %)
STAD
Stomach
(16 %)
NPC
(84.1 %)
LUSC
Lung sq
(21 %)
CESC
Cervical sq
(27 %)
SKCM
melanoma
(21 %)

FIGURE 11

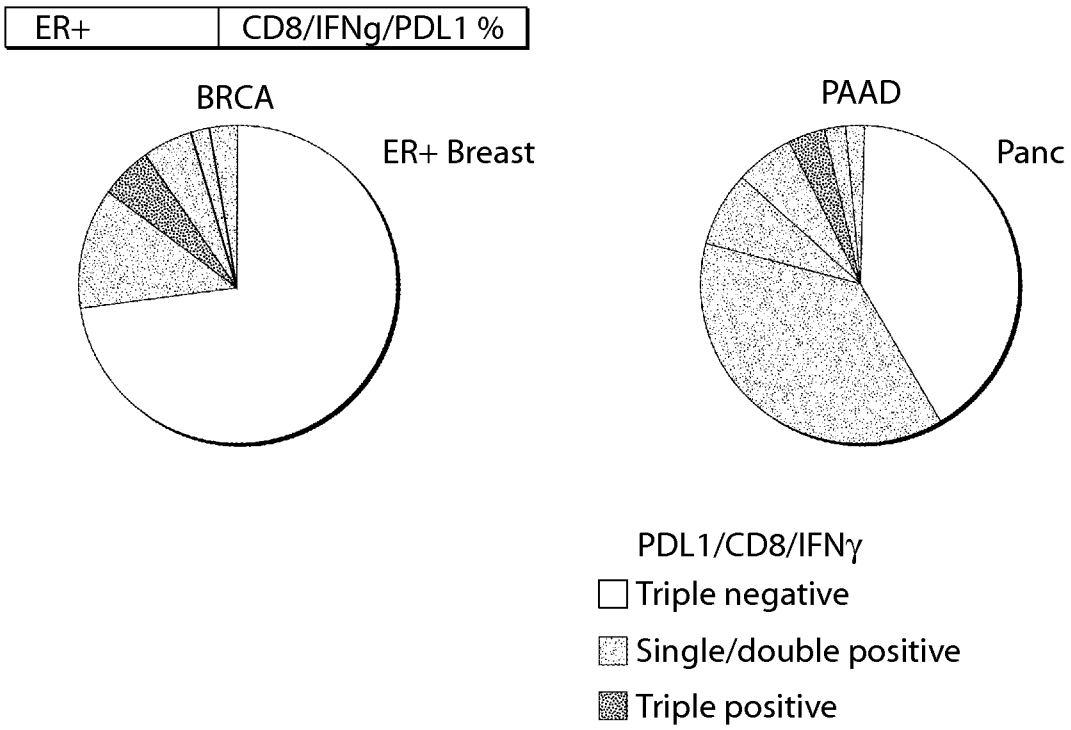
ER+
CD8/IFNg/PDL1 %
BRCA
ER+ Breast
PAAD
Panc
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 12

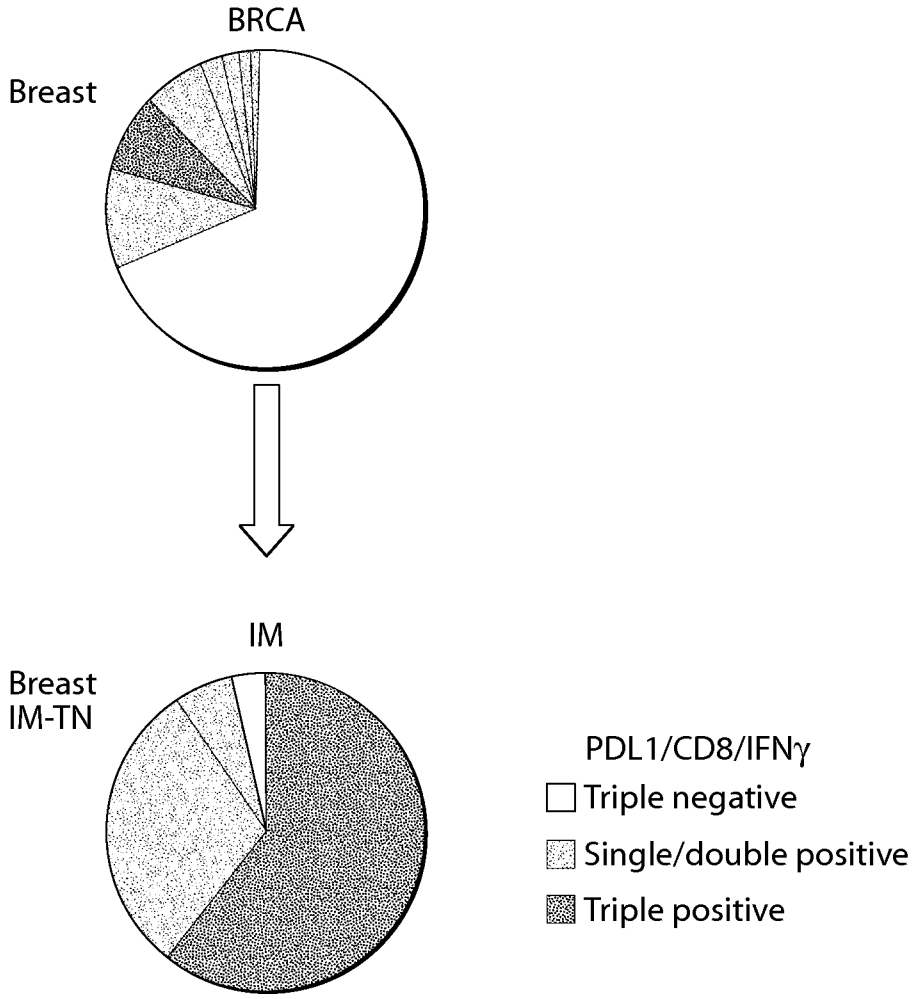
BRCA
Breast
IM
Breast
IM-TN
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 13

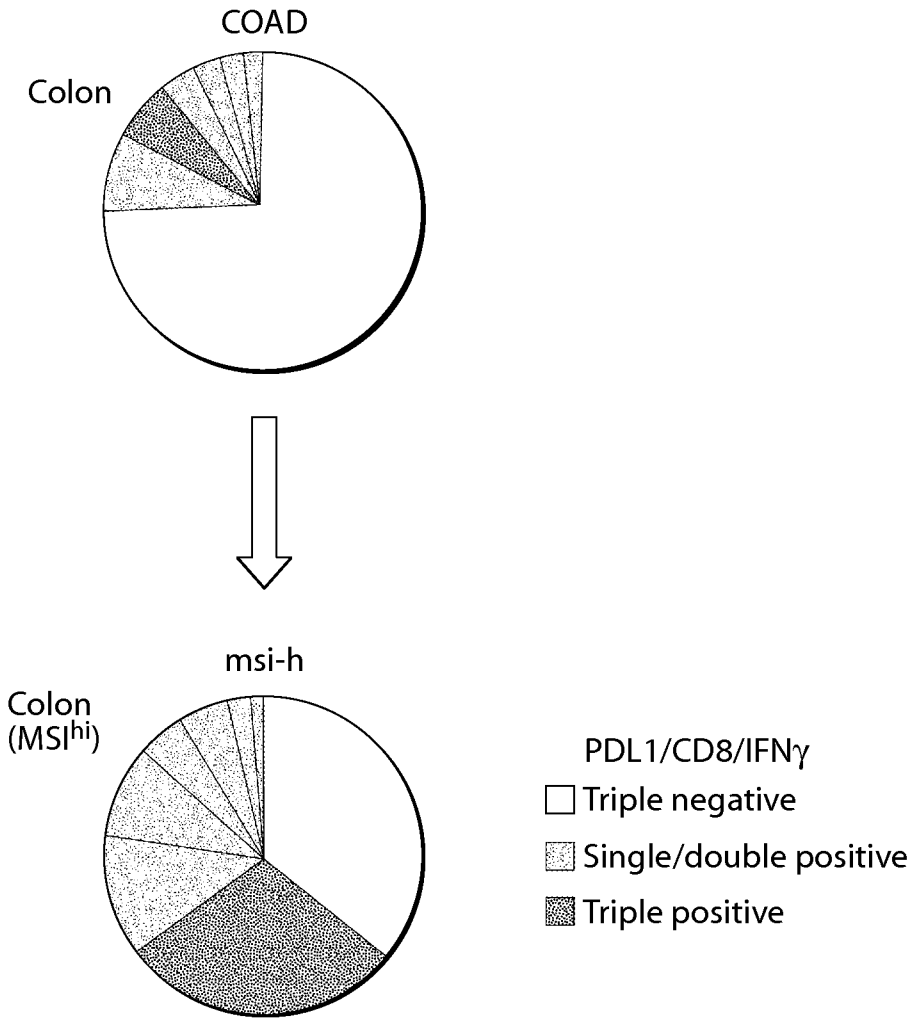
COAD
Colon
msi-h
Colon
(MSI^hi)
PDL1/CD8/IFNγ
Triple negative
Single/double positive
Triple positive

FIGURE 14