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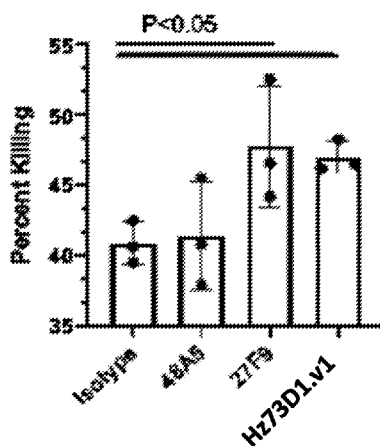
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(54) Title: **ILT-BINDING AGENTS AND METHODS OF USE THEREOF**

Figure 22



(57) Abstract: The present disclosure provides binding agents, such as antibodies, that specifically bind ILT2, ILT4, or both ILT2 and ILT4, as well as compositions comprising the binding agents, and methods of their use. The disclosure also provides related polynucleotides and vectors encoding the binding agents and cells comprising the binding agents.



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## **ILT-BINDING AGENTS AND METHODS OF USE THEREOF**

### **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of priority of U.S. Provisional Appl. No. 63/019,068, filed May 1, 2020; and U.S. Provisional Appl. No. 63/122,848, filed December 8, 2020; the contents of both of which are incorporated herein by reference in their entirety.

### **SEQUENCE LISTING**

The present specification is being filed with a computer readable form (CRF) copy of the Sequence Listing. The CRF entitled 47702-0094WO1\_SL.txt, which was created on April 26, 2021 and is 181,988 bytes in size, is incorporated herein by reference in its entirety.

### **FIELD OF THE DISCLOSURE**

[0001] The present disclosure generally relates to agents that bind immunoglobulin-like transcript (ILT) proteins, particularly antibodies that bind to human ILT2, human ILT4, and both human ILT2 and human ILT4, as well as compositions comprising the ILT-binding agents and methods of using the binding agents and compositions.

### **BACKGROUND**

[0002] The basis for immunotherapy is the manipulation and/or modulation of the immune system, including both innate immune responses and adaptive immune responses. The general aim of immunotherapy is to treat diseases by controlling the immune response to a "foreign agent", for example a pathogen or a tumor cell. However, in some instances immunotherapy is used to treat autoimmune diseases which may arise from an abnormal immune response against proteins, molecules, and/or

tissues normally present in the body. Immunotherapy may include methods to induce or enhance specific immune responses or to inhibit or reduce specific immune responses.

[0003] The immune system is a highly complex system made up of a great number of cell types, including but not limited to, T-cells, T-cell subsets, B-cells, natural killer cells, antigen-presenting cells, dendritic cells, monocytes, and macrophages. These cells possess complex and subtle systems for controlling their interactions and responses. The cells utilize both activating and inhibitory mechanisms and feedback loops to keep responses in check and not allow negative consequences of an uncontrolled immune response (*e.g.*, autoimmune diseases or a cytokine storm).

[0004] Some of the inhibitory mechanisms of the immune system use proteins from the leukocyte Ig-like receptor (LILR) family. The leukocyte Ig-like receptor subfamily B (LILRB) is a group of type I transmembrane glycoproteins with extracellular Ig-like domains and cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). This group of ITIM-containing receptors includes 5 members: LILRB1 (also known as CD85J, LIR1, ILT2), LILRB2 (also known as CD85D, LIR2, ILT4), LILRB3 (also known as CD85A, LIR3, ILT5), LILRB4 (also known as CD85K, LIR5, ILT3), and LILRB5 (also known as CD85C, LIR8). The biological functions and clinical significance of many of these LILRBs (ILTs) are still being investigated. There is also a LILR subfamily A (LILRA) that is a group of type I transmembrane glycoproteins with extracellular Ig-like domains and cytoplasmic immunoreceptor tyrosine-based activating motifs (ITAMs). This group of ITAM-containing receptors includes 6 members: LILRA1 (also known as CD85I, LIR6), LILRA2 (also known as CD85H, LIR7, ILT1), LILRA3 (also known as CD85E, LIR4, ILT6, monocyte inhibitory receptor HM43/31), LILRA4 (also known as CD85G, ILT7), LILRA5 (also known as CD85F, LIR9, ILT11), and LILRA6 (also known as ILT8). The inhibitory and activating proteins of the LILR family appear to work in concert to modulate immune homeostasis.

[0005] The concept of cancer immunosurveillance is based on the theory that the immune system can recognize tumor cells, mount an immune response, and suppress

the development and/or growth of a tumor. However, it is clear that many cancerous/tumor cells have developed mechanisms and/or hijacked normal inhibitory mechanisms to evade the immune system which can allow for uninhibited growth of tumor cells. Cancer/tumor immunotherapy (immuno-oncology) focuses on the development of new and novel agents that can activate and/or boost the immune system to achieve a more effective attack against cancer/tumor cells resulting in increased killing of cancer/tumor cells and/or inhibition of cancer/tumor growth.

### **BRIEF SUMMARY**

[0006] The present disclosure provides agents that bind immunoglobulin-like transcript 2 (ILT2) and/or immunoglobulin-like transcript 4 (ILT4). Although the LILRB family members are referred to by many names in publications, the terms “ILT2” (LILRB1) and “ILT4” (LILRB2) will be used herein. The agents include, but are not limited to, polypeptides such as antibodies that specifically bind ILT2, ILT4, or both ILT2 and ILT4. Generally, the agents referred to herein as “ILT-binding agents” encompass ILT2-binding agents, ILT4-binding agents, and agents binding to both ILT2 and ILT4 (referred to as “ILT2/ILT4-binding agents”). In some embodiments, an ILT-binding agent inhibits ILT2 and/or ILT4 activity. In some embodiments, an ILT-binding agent enhances an immune response. In some embodiments, an ILT-binding agent reverses suppression of an immune cell activity. The disclosure provides methods of using an ILT-binding agent, for example, in treating cancer (e.g., an advanced solid tumor). In some embodiments, an ILT-binding agent is used in combination therapy in, for example, treating cancer. In some embodiments, an ILT-binding agent is used in combination with at least one additional therapeutic agent in, for example, treating cancer.

[0007] In some instances, the ILT-binding agents described herein have one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) of the following properties in any combination or permutation:

- (1) binds human ILT2;

- (2) binds human ILT4;
- (3) binds rhesus ILT2;
- (4) binds cyno ILT2;
- (5) does not bind ILT3, ILT5, and LILRB5;
- (6) does not bind LILRA2, LILRA4, LILRA5, and LILRA6;
- (7) is an ILT2 antagonist;
- (8) is an ILT4 antagonist;
- (9) inhibits ILT2 activity;
- (10) inhibits ILT4 activity;
- (11) inhibits ILT2 signaling in cells that express ILT2;
- (12) inhibits ILT4 signaling in cells that express ILT4;
- (13) inhibits binding of ILT2 to MHC I molecules;
- (14) inhibits binding of ILT4 to MHC I molecules;
- (15) inhibits ILT2-induced suppression of myeloid cells;
- (16) inhibits ILT4-induced suppression of myeloid cells;
- (17) inhibits ILT2-induced suppression of myeloid cell activity;
- (18) inhibits ILT4-induced suppression of myeloid cell activity;
- (19) restores FcR activation in myeloid cells;
- (20) enhances NK cell activity;
- (21) enhances cytotoxic T lymphocyte (CTL) activity;
- (22) enhances macrophage phagocytosis; and
- (23) inhibits MDSC mediated suppression of immune cells.

[0008] The disclosure also provides compositions comprising the ILT-binding agents described herein. In some embodiments, the disclosure provides pharmaceutical compositions comprising the ILT-binding agents and a pharmaceutically acceptable carrier. Polynucleotides and/or vectors encoding the ILT-binding agents are provided. Cells comprising the polynucleotides and/or the vectors described herein are also provided. Cells comprising or producing the ILT-binding agents described herein are

provided. Methods of making the ILT-binding agents described herein are also provided.

**[0009]** In one aspect, the present disclosure provides ILT-binding agents that bind ILT2. In some embodiments, ILT-binding agents bind human ILT2. In some embodiments, the ILT-binding agents bind rhesus monkey (“rhesus”) ILT2. In some embodiments, the ILT-binding agents bind cynomolgus monkey (“cyno”) ILT2. In some embodiments, the ILT-binding agents bind human ILT2 and rhesus ILT2. In some embodiments, the ILT-binding agents bind human ILT2 and cyno ILT2. In some embodiments, the ILT-binding agents bind human ILT2, rhesus ILT2, and cyno ILT2. In some embodiments, the ILT-binding agents bind SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and/or SEQ ID NO:7. In some embodiments, the ILT-binding agents bind SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, and/or SEQ ID NO:21. In some embodiments, the ILT-binding agents bind SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, and/or SEQ ID NO:172. In some embodiments, the ILT-binding agents are antibodies. In some embodiments, the ILT-binding agents are antibody fragments.

**[0010]** In some embodiments, the ILT-binding agents bind within the extracellular domain of ILT2. In some embodiments, the ILT-binding agents bind SEQ ID NO:3. In some embodiments, the ILT-binding agents bind within amino acids 24-461 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 27-115 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 116-221 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 222-312 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 313-409 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 27-221 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 116-312 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind within amino acids 222-409 of SEQ ID NO:1. In some embodiments, the ILT-binding agents bind a conformational

epitope within the extracellular domain of ILT2. In some embodiments, the ILT-binding agents bind a conformational epitope within one of the Ig-like C2-type domains of ILT2 (*e.g.*, D1, D2, D3, or D4). In some embodiments, the ILT-binding agents bind a conformational epitope within two or more of the Ig-like C2-type domains of ILT2 (D1, D2, D3, and/or D4). In some embodiments, the ILT-binding agents bind a conformational epitope within the D4-stem region of ILT2.

**[0011]** In another aspect, the present disclosure provides ILT-binding agents that bind ILT4. In some embodiments, the ILT-binding agents bind human ILT4. In some embodiments, the ILT-binding agents bind SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, and/or SEQ ID NO:14. In some embodiments, the ILT-binding agents are antibodies. In some embodiments, the ILT-binding agents are antibody fragments.

**[0012]** In some embodiments, the ILT-binding agents bind within the extracellular domain of ILT4. In some embodiments, an agent binds SEQ ID NO:10. In some embodiments, ILT-binding agents bind within amino acids 22-461 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 27-110 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 111-229 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 230-318 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 330-419 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 27-229 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 111-318 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind within amino acids 230-419 of SEQ ID NO:8. In some embodiments, ILT-binding agents bind a conformational epitope within the extracellular domain of ILT4. In some embodiments, ILT-binding agents bind a conformational epitope within one of the Ig-like C2-type domains of ILT4 (*e.g.*, D1, D2, D3, or D4). In some embodiments, ILT-binding agents bind a conformational epitope within two or more of the Ig-like C2-type domains of ILT4 (D1, D2, D3, and/or

D4). In some embodiments, ILT-binding agents bind a conformational epitope within the D4-stem region of ILT4.

[0013] In one aspect, the present disclosure provides ILT-binding agents that bind human ILT2, human ILT4, or both human ILT2 and ILT4 and have at least one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19) of the following properties: (1) binds rhesus ILT2; (2) binds cyno ILT2; (3) does not bind ILT3, ILT5, and LILRB5; (4) does not bind LILRA2, LILRA4, LILRA5, and LILRA6; (5) is an ILT2 antagonist; (6) is an ILT4 antagonist, (7) inhibits ILT2 activity; (8) inhibits ILT4 activity; (9) inhibits ILT2 signaling in cells that express ILT2; (10) inhibits ILT4 signaling in cells that express ILT4; (11) inhibits binding of ILT2 to one or more MHC I molecules; (12) inhibits binding of ILT4 to one or more MHC I molecules; (13) inhibits ILT2-induced suppression of myeloid cells; (14) inhibits ILT4-induced suppression of myeloid cells; (15) inhibits ILT2-induced suppression of myeloid cell activity; (16) inhibits ILT4-induced suppression of myeloid cell activity; (17) restores FcR activation in myeloid cells; (18) enhances NK cell activity; and/or (19) enhances CTL activity. In some embodiments, the myeloid cells are monocytes. In some embodiments, the myeloid cells are macrophages. In some embodiments, the myeloid cells are dendritic cells. In some embodiments, the myeloid cells are tolerogenic dendritic cells. In some embodiments, the myeloid cells are antigen-presenting cells (APCs). In some embodiments, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

[0014] In one aspect, the present disclosure provides agents that specifically bind human ILT2. In some embodiments, the present disclosure provides an ILT2-binding agent, wherein the binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and/or (b) a light chain variable region comprising a light chain variable region

CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27). The present disclosure also provides an ILT2-binding agent that comprises the six CDRs of any of the CDR definitions provided in Table 1.

**[0015]** In some embodiments, an ILT2-binding agent comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:125; and/or (b) a light chain variable region having at least 80% sequence identity to SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:125 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region of SEQ ID NO:125 and/or a light chain variable region of SEQ ID NO:126. In some embodiments, the ILT2-binding agent comprises a heavy chain variable region of SEQ ID NO:125 and a light chain variable region of SEQ ID NO:126.

**[0016]** In some embodiments, an ILT2-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:125 and a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:125 and a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:126.

**[0017]** In some embodiments, an ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39),

and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43). The present disclosure also provides an ILT2-binding agent that comprises the six CDRs of any of the CDR definitions provided in Table 2.

**[0018]** In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:127 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:127 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:127 and/or a light chain variable region of SEQ ID NO:128. In some embodiments, the ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:127 and a light chain variable region of SEQ ID NO:128.

**[0019]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:127 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:127 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:128.

[0020] In some embodiments, an ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGAPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59). The present disclosure also provides an ILT2-binding agent that comprises the six CDRs of any of the CDR definitions provided in Table 3.

[0021] In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:129 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:129 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:129 and/or a light chain variable region of SEQ ID NO:130. In some embodiments, the ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:129 and a light chain variable region of SEQ ID NO:130.

[0022] In some embodiments, an ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:129 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region

CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:129 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:130.

[0023] In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYSLSYFDY (SEQ ID NO:72), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). The present disclosure also provides an ILT2/ILT4 binding agent that comprises the six CDRs of any of the CDR definitions provided in Tables 4A and 4B.

[0024] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:131 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:131 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:131 and/or a light chain variable region of SEQ ID NO:132. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:131 and a light chain variable region of SEQ ID NO:132.

[0025] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:133 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:133 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:133 and/or a light chain variable region of SEQ ID NO:134. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:133 and a light chain variable region of SEQ ID NO:134.

[0026] In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:131 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:131 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:133 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:133 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:134.

[0027] In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYGTMYYYAMDY (SEQ ID NO:88), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). The present disclosure also provides an ILT2/ILT4 binding agent that comprises the six CDRs of any of the CDR definitions provided in Table 5.

[0028] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:135 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:135 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:135 and/or a light chain variable region of SEQ ID NO:136. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:135 and a light chain variable region of SEQ ID NO:136.

[0029] In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:135 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region

CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:135 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:136.

**[0030]** In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYDTMYYYAMDY (SEQ ID NO:102), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASEVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). The present disclosure also provides an ILT2/ILT4 binding agent that comprises the six CDRs of any of the CDR definitions provided in Tables 6A and 6B.

**[0031]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:137 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:137 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:137 and/or a light chain variable region of SEQ ID NO:138. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:137 and a light chain variable region of SEQ ID NO:138.

**[0032]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:139 and/or (b) a light

chain variable region having at least 80% identity to SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:139 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:139 and/or a light chain variable region of SEQ ID NO:140. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:139 and a light chain variable region of SEQ ID NO:140.

[0033] In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:137 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:137 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:139 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:139 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:140.

[0034] In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region

CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). The present disclosure also provides an ILT2/ILT4 binding agent that comprises the six CDRs of any of the CDR definitions provided in Table 7.

**[0035]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:141 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:141 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:141 and/or a light chain variable region of SEQ ID NO:142. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:141 and a light chain variable region of SEQ ID NO:142.

**[0036]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:141 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:141 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:142.

[0037] In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYAMDY (SEQ ID NO:107), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). The present disclosure also provides an ILT2/ILT4 binding agent that comprises the six CDRs of any of the CDR definitions provided in Tables 8A and 8B.

[0038] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:143 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:143 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:143 and/or a light chain variable region of SEQ ID NO:142. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:143 and a light chain variable region of SEQ ID NO:142.

[0039] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region having at least 80% identity to SEQ ID NO:144 and/or (b) a light chain variable region having at least 80% identity to SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%,

at least 98%, or at least 99% sequence identity to SEQ ID NO:144 and/or a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:144 and/or a light chain variable region of SEQ ID NO:145. In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region of SEQ ID NO:144 and a light chain variable region of SEQ ID NO:145.

**[0040]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:143 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:143 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:144 and/or a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:144 and/or a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from the amino acid sequence of SEQ ID NO:145.

**[0041]** In another aspect of the disclosure, provided herein is an agent that competes for binding to ILT2, ILT4, or ILT2/ILT4 with any of the ILT-binding agents described herein. In some embodiments, the agent competes for binding to both human ILT2 and human ILT4 with any of the ILT-binding agents described herein. In some embodiments, the agent competes for binding to human ILT2 with any of the ILT-binding agents described herein. In some embodiments, the agent competes for binding

to human ILT4 with any of the ILT-binding agents described herein. In some embodiments, the agent is antibody. In some embodiment, the agent is an antibody fragment.

[0042] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the ILT-binding agents are antibodies. In some embodiments, the antibodies are recombinant antibodies. In some embodiments, the antibodies are humanized antibodies. In some embodiments, the antibodies are human antibodies. In some embodiments, the antibody are chimeric antibodies. In some embodiments, the antibody are whole or intact antibodies. In some embodiments, the antibodies are bispecific antibodies or a multispecific antibodies. In some embodiments, the antibodies are antibody fragments comprising at least one antigen-binding site. In some embodiments, the antibodies are a Fab, Fab', F(ab')<sub>2</sub>, Fv, scFv, (scFv)<sub>2</sub>, single chain antibody, dual variable region antibody, single variable region antibody, linear antibody, diabody, nanobody, or a V region antibody. In some embodiments, the antibodies are IgG antibodies. In some embodiments, the antibodies are IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, or IgG4 antibodies. In some embodiments, the antibodies each comprises a kappa light chain. In some embodiments, the antibodies each comprises a lambda light chain. In some instances, the antibodies each comprises a human IgG1 constant region. In some instances, the antibodies each comprises a human kappa light chain constant region. In some instances, the antibodies each comprises a human IgG1 constant region and a human kappa light chain constant region. In certain instances, the human IgG1 constant region comprises one or more mutations that reduce or eliminate Fc effector functions. In certain instances, the human IgG1 constant region comprises a N297G mutation that reduces effector function.

[0043] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the ILT-binding agents each is attached (either directly or indirectly) to a half-life extending moiety.

[0044] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the ILT-binding agents described herein are antagonists of ILT2. In some embodiments, the ILT-binding agents inhibit ILT2 activity. In some embodiments, the ILT-binding agents are antagonistic antibodies. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT2-induced immune cell suppression. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT2-induced myeloid cell suppression.

[0045] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the ILT-binding agents described herein are antagonists of ILT4. In some embodiments, the ILT-binding agents inhibit ILT4 activity. In some embodiments, the ILT-binding agents are antagonistic antibodies. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT4-induced immune cell suppression. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT4-induced myeloid cell suppression.

[0046] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the ILT-binding agents described herein are antagonists of human ILT2 and ILT4. In some embodiments, the ILT-binding agents inhibit ILT2 activity and ILT4 activity. In some embodiments, the ILT-binding agents are antagonistic antibodies. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT2-induced and ILT4-induced immune cell suppression. In some embodiments, the ILT-binding agents are antibodies that inhibit ILT2-induced and ILT4-induced myeloid cell suppression.

[0047] In some embodiments, the ILT-binding agents are antibodies that reactivate tolerogenic dendritic cells. In some embodiments, the ILT-binding agents are antibodies that inhibit the activity of myeloid-derived suppressor cells (MDSCs). In some embodiments, the ILT-binding agents are antibodies that enhance cytolytic T-cell lymphocyte (CTL) activity. In some embodiments, the ILT-binding agents are

antibodies that enhances CD8<sup>+</sup> T-cell cytolytic activity. In some embodiments, the ILT-binding agents are antibodies that enhance natural killer (NK) cell activity. In some embodiments, the ILT-binding agents are antibodies that enhance macrophage phagocytosis. In some embodiments, the ILT-binding agents desuppress or activate Fc receptor signaling in myeloid cells. In some embodiments, the ILT-binding agents act synergistically with an immune checkpoint inhibitor.

**[0048]** In another aspect, the disclosure provides compositions comprising an ILT-binding agent described herein. In some embodiments, a composition comprises an anti-ILT antibody described herein. In some embodiments, a composition comprises a recombinant anti-ILT antibody described herein. In some embodiments, a composition comprises the anti-ILT2 antibody 27F9. In some embodiments, a composition comprises the anti-ILT4 antibody 47C8 or antibody 48A5. In some embodiments, a composition comprises an anti-ILT2/ILT4 antibody selected from the group consisting of: 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, and Hz73D1.v1.

**[0049]** In some instances, pharmaceutical compositions are provided, which comprise (a) a means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I (e.g., on tumor cells); and (b) a pharmaceutically acceptable carrier. In some embodiments, the means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I comprises an antibody comprising a heavy chain variable region comprising VH-CDR1, VH-CDR2, and VH-CDR3 and a light chain variable region comprising VL-CDR1, VL-CDR2, and VL-CDR3 from any one of 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, and Hz73D1.v1.

**[0050]** In some embodiments of each of the aforementioned aspects, as well as other aspects and/or embodiments described elsewhere herein, the ILT-binding agent is isolated. In some embodiments, the ILT-binding agent is substantially pure.

**[0051]** In another aspect, the disclosure provides polynucleotides comprising a polynucleotide that encodes an ILT-binding agent described herein. In some embodiments, a polynucleotide encodes an anti-ILT2 antibody described herein. In

some embodiments, a polynucleotide encodes an anti-ILT4 antibody described herein. In some embodiments, a polynucleotide encodes an anti-ILT2/ILT4 antibody described herein. In some embodiments, the polynucleotide is isolated. In some embodiments, a vector comprises a polynucleotide that encodes an ILT-binding agent described herein. In some embodiments, an isolated cell comprises a polynucleotide that encodes an ILT-binding agent described herein. In some embodiments, an isolated cell comprises a vector comprising a polynucleotide that encodes an ILT-binding agent described herein. In some embodiments, a cell comprises an ILT-binding agent described herein. In some embodiments, a cell produces an ILT-binding agent described herein. In some embodiments, a cell produces an anti-ILT antibody described herein. In some embodiments, a cell is a monoclonal cell line. In some embodiments, a cell is a hybridoma.

[0052] In another aspect, the disclosure provides methods of using the ILT-binding agents described herein. In some embodiments, the methods comprise using a composition comprising an ILT2-binding agent described herein. In some embodiments, the methods comprise using a composition comprising an ILT4-binding agent described herein. In some embodiments, the methods comprise using a composition comprising an ILT2/ILT4-binding agent described herein. In some embodiments, the methods comprise using a pharmaceutical composition comprising an ILT2-binding agent described herein. In some embodiments, the methods comprise using a pharmaceutical composition comprising an ILT4-binding agent described herein. In some embodiments, the methods comprise using a pharmaceutical composition comprising an ILT2/ILT4-binding agent described herein.

[0053] In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to a ligand and/or binding partner is provided. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to one or more MHC I molecules is provided. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to a MHC

I molecule in a mixture of cells comprises contacting the cells with an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein.

[0054] In some embodiments, a method of disrupting, inhibiting, or blocking ILT2 and/or ILT4 activity is provided. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2 activity in a mixture of cells comprises contacting the cells with an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT4 activity in a mixture of cells comprises contacting the cells with an ILT4-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2 and ILT4 activity in a mixture of cells comprises contacting the cells with an ILT2/ILT4-binding agent described herein.

[0055] In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity is provided. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 activity in a mixture of cells comprises contacting the cells with an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT4 activity in a mixture of cells comprises contacting the cells with an ILT4-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and ILT4 activity in a mixture of cells comprises contacting the cells with an ILT2/ILT4-binding agent described herein. In some embodiments, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

[0056] In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cells is provided. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cells comprises contacting the myeloid cells with an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced suppression of myeloid cells comprises contacting the myeloid cells with

an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT4-induced suppression of myeloid cells comprises contacting the myeloid cells with an ILT4-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and ILT4-induced suppression of myeloid cells comprises contacting the myeloid cells with an ILT2/ILT4-binding agent described herein.

[0057] In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cell activity comprises contacting the myeloid cell with an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced or ILT4-induced suppression of myeloid cell activity comprises contacting the myeloid cell with an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cell activity restores FcR activity in myeloid cells. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid activity enhances, increases, or restores chemokine/cytokine production in myeloid cells. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cell activity enhances, increases, or restores myeloid cell proliferation activity. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cell activity enhances, increases, or restores phagocytic activity of the myeloid cell. In some embodiments, the myeloid cells are monocytes. In some embodiments, the myeloid cells are macrophages. In some embodiments, the myeloid cells are dendritic cells. In some embodiments, the myeloid cells are tolerogenic dendritic cells. In some embodiments, the myeloid cells are APCs.

[0058] In some embodiments, a method of enhancing or increasing NK cell activity is provided. In some embodiments, a method of enhancing or increasing NK cell activity

comprises contacting the NK cell with an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing NK cell activity comprises contacting the NK cell with an ILT2/ILT4-binding agent described herein.

[0059] In some embodiments, a method of enhancing or increasing cytotoxic T lymphocyte (CTL) activity is provided. In some embodiments, a method of enhancing or increasing CTL activity comprises contacting the CTL with an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing CTL activity comprises contacting the CTL with an ILT2/ILT4-binding agent described herein.

[0060] In some embodiments, a method of enhancing or increasing macrophage phagocytosis is provided. In some embodiments, a method of enhancing or increasing phagocytosis comprises contacting the macrophage with an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing phagocytosis comprises contacting the macrophage with an ILT2/ILT4-binding agent described herein.

[0061] In some embodiments, a method of inhibiting the activity of myeloid-derived suppressor cells (MDSCs) is provided. In some embodiments, a method of inhibiting the activity of MDSCs comprises contacting the MDSCs with an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of inhibiting the activity of MDSCs comprises contacting the MDSCs with an ILT2/ILT4-binding agent described herein.

[0062] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the methods can be *in vitro*, *ex vivo*, or *in vivo*.

[0063] In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 or ILT4 to a MHC I molecule in a subject, comprises administering to the subject an effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of

disrupting, inhibiting, or blocking the binding of ILT2 or ILT4 to a MHC I molecule in a subject, comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments of the methods described herein, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

**[0064]** In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity in a subject, comprises administering to the subject an effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 activity in a subject, comprises administering to the subject an effective amount of an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT4 activity in a subject, comprises administering to the subject an effective amount of an ILT4-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity in a subject, comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments of the methods described herein, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

**[0065]** In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced suppression of myeloid cells in a subject, comprises administering to the subject an effective amount of an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT4-induced suppression of myeloid cell activity in a subject, comprises administering to the subject an effective amount of an ILT4-binding agent or an ILT2/ILT4-binding agent described herein.

**[0066]** In some embodiments, a method of inhibiting or decreasing MDSC activity in a subject comprises administering to the subject an effective amount of an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein.

[0067] In some embodiments, a method of enhancing or increasing NK cell activity in a subject comprises administering to the subject an effective amount of an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing NK cell activity in a subject comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein.

[0068] In some embodiments, a method of enhancing or increasing CTL activity in a subject comprises administering to the subject an effective amount of an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing CTL activity in a subject comprises administering to the subject an ILT2/ILT4-binding agent described herein.

[0069] In some embodiments, a method of enhancing or increasing macrophage phagocytosis in a subject comprises administering to the subject an effective amount of an ILT2-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of enhancing or increasing macrophage phagocytosis in a subject comprises administering to the subject an ILT2/ILT4-binding agent described herein.

[0070] In some embodiments, a method of treating cancer in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the cancer is mesothelioma, glioblastoma, renal cell carcinoma (including cancer arising from the clear cell type and papillary cell type), non-small cell lung cancer, melanoma, pancreatic ductal adenocarcinoma, gastric cancer, squamous cell carcinoma of the head and neck, biliary duct cancer, breast cancer, ovarian cancer, cervical cancer, endocervical cancer, colorectal cancer, or esophageal cancer. In some embodiments, the cancer is an advanced solid tumor.

[0071] In some embodiments, the cancer is pancreatic cancer, lung cancer, head and neck cancer, prostate cancer, skin cancer, stomach cancer, intestinal cancer, ovarian cancer, cervical cancer, uterine cancer, endometrial cancer, urinary bladder cancer, brain cancer, liver cancer, kidney cancer, or testicular cancer. In some embodiments, the

cancer is a hematologic cancer. In some embodiments, the cancer is a myelogenous leukemia. In some embodiments, the myelogenous cancer is acute myeloid leukemia (AML). In some embodiments, the myelogenous cancer is a chronic myeloid leukemia. In some embodiments, the cancer is a myelodysplastic syndrome. Myelodysplastic syndromes (MDS) are a group of cancers in which immature blood cells in the bone marrow do not mature and therefore do not become healthy blood cells. In some embodiments, myelodysplastic syndrome develops into AML.

[0072] In some embodiments, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of increasing or enhancing an immune response to a tumor or tumor cells in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of activating or enhancing a persistent or long-term immune response to a tumor or tumor cells in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of inhibiting tumor relapse or tumor regrowth in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments a method of inducing a persistent or long-term immunity that inhibits tumor relapse or tumor regrowth in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the tumor is a pancreatic tumor, a breast tumor, a lung tumor, a non-small cell lung tumor, a head and neck tumor, a colorectal tumor, a prostate tumor, a skin tumor, a melanoma, a gastric tumor, a colorectal tumor, an ovarian tumor, a cervical tumor, a uterine tumor, an endometrial tumor, an endocervical tumor, a bladder tumor, a brain tumor, an esophageal tumor, a liver tumor, a kidney

tumor, a renal tumor, mesothelioma, glioblastoma, a biliary duct tumor, or a testicular tumor.

[0073] In some embodiments, a method of activating myeloid cells in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the myeloid cells are primary dendritic cells or tolerogenic dendritic cells. In some embodiments, the myeloid cells are monocytes or macrophages.

[0074] In some embodiments, a method of reactivating tolerogenic dendritic cells in a subject comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the tolerogenic dendritic cells are found in the tumor microenvironment.

[0075] In some embodiments of all the methods described herein, the ILT-binding agent is administered to a subject as part of a combination therapy. In some embodiments, the combination therapy comprises at least one additional therapeutic agent. In some embodiments, the combination therapy comprises an immune checkpoint inhibitor, such as an anti-PD-1 antibody or an anti-PD-L1 antibody. In some embodiments, the anti-PD-1 antibody is Pembrolizumab (MK-3475; KEYTRUDA), Pidilizumab (CT-011), Nivolumab (OPDIVO), Durvalumab (MEDI0680), Cemiplimab (REGN2810), Tislelizumab (BGB-A317), Spartalizumab (PDR-001), or STI-A1110.

[0076] Also disclosed is the use of an ILT-binding agent described herein in the manufacture of a medicament for the treatment of cancer. In some embodiments, an ILT-binding agent described herein is for use in the treatment of cancer. In some embodiments, an ILT-binding agent described herein is for use in inhibition of tumor growth.

[0077] In some embodiments of all the aforementioned methods, the subject is human.

[0078] Where aspects or embodiments of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present disclosure encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present disclosure also envisages the explicit exclusion of one or more of any of the group members in the claimed disclosure.

### **BRIEF DESCRIPTION OF THE FIGURES**

[0079] Figure 1. Expression of ILT2 and ILT4 in various immune cells assayed by flow cytometry.

[0080] Figure 2. Inhibition of the interaction between ILT2 or ILT4 and MHC I molecules by anti-ILT antibodies.

[0081] Figure 3. Binding of anti-ILT2/ILT4 antibodies to monocytes.

[0082] Figure 4A and 4B. Inhibition of the interaction between human ILT2 or ILT4 and MHC I molecules by anti-ILT antibodies.

[0083] Figure 5. Inhibition of the interaction between cyno ILT2 and MHC I molecules by anti-ILT antibodies.

[0084] Figure 6. Effect of anti-ILT antibodies on cytolytic activity of NKL cells.

[0085] Figure 7. Effect of anti-ILT antibodies on activity of human primary NK cells.

[0086] Figure 8. Effect of anti-ILT antibodies on cytolytic activity of primary NK cells.

[0087] Figure 9. Effect of anti-ILT antibodies on cytolytic activity of primary NK cells in ADCC assay with classic MHC-I-expressing target cells.

[0088] Figure 10. Effect of anti-ILT antibodies on MDSC activity in MLR assay.

[0089] Figure 11A-11C. Effect of anti-ILT antibodies on MDSC activity in MLR assay.

[0090] Figure 12. Effect of anti-ILT antibodies on LPS-mediated stimulation of human PBMCs as assessed by cytokine production.

- [0091] Figure 13. Effect of anti-ILT antibodies on LPS-mediated stimulation of cyno PBMCs as assessed by cytokine production.
- [0092] Figure 14. Effect of anti-ILT antibodies on LPS-mediated stimulation of tolerized dendritic cells as assessed by cytokine production.
- [0093] Figure 15. Effect of anti-ILT antibodies on cytokine production from HMGB1-treated cells.
- [0094] Figure 16. Effect of anti-ILT antibodies on cytokine production from STING agonist-treated cells.
- [0095] Figure 17. Effect of anti-ILT antibodies suppression of T-cell mediated stimulation of myeloid cells.
- [0096] Figure 18. Effect of anti-ILT antibodies on macrophage phagocytosis.
- [0097] Figure 19. Effect of anti-ILT antibodies on cytokine production by dendritic cells.
- [0098] Figure 20. Effect of anti-ILT antibodies on cytokine production from human blood cells.
- [0099] Figure 21. Effect of anti-ILT antibodies on cytokine production from cyno blood cells.
- [00100] Figure 22. Effect of anti-ILT antibodies on cytolytic activity of T cells.
- [00101] Figures 23A-23C. Synergetic effects of an anti-ILT2/ILT4 antibody and anti-PD-1 antibody on T cell activation and cytokine release from T cells.
- [00102] Figure 24. Effects of anti-ILT2/ILT4 antibodies on polarization of monocyte-derived macrophages by assaying expression markers via flow cyometry.

#### **DETAILED DESCRIPTION**

[00103] The present disclosure provides novel agents, including but not limited to polypeptides such as antibodies, that bind immunoglobulin-like transcript 2 (ILT2), immunoglobulin-like transcript 4 (ILT4), or both ILT2 and ILT4. As used herein the term “ILT-binding agents” refers to ILT2-binding agents, ILT4-binding agents, and ILT2/ILT4-binding agents. As used herein “ILT2/ILT4-binding agents” refers to agents

that bind both ILT2 and ILT4, and may also be referred to as ILT2/ILT4 dual binders. The ILT-binding agents include, but are not limited to, polypeptides, antibodies (including antigen-binding fragments thereof), scaffold proteins, and heterodimeric molecules. ILT-binding agents include, but are not limited to, antagonists of ILT2 and/or ILT4 activity, inhibitors of ILT2 and/or ILT4 activity, and/or agents that inhibit ILT2 and/or ILT4 suppressive activity. Related polypeptides, polynucleotides, vectors, compositions comprising the agents, cells comprising the related polynucleotides or vectors, and methods of making the agents are also provided. Methods of using the novel ILT-binding agents are also provided.

#### I. Definitions

**[00104]** Unless otherwise defined herein, technical and scientific terms used in the present description have the meanings that are commonly understood by those of ordinary skill in the art. Whenever appropriate, terms used in the singular will also include the plural and vice versa. In the event that any description of a term set forth conflicts with any document incorporated herein by reference, the description of the term set forth below shall control.

**[00105]** The term “binding agent” as used herein refers to a molecule that binds a specific antigen or target (*e.g.*, ILT2 and/or ILT4). A binding agent may comprise a protein, peptide, nucleic acid, carbohydrate, lipid, or small molecular weight compound. In some embodiments, a binding agent comprises a full-length antibody. In some embodiments, a binding agent is an antigen-binding fragment of an antibody. In some embodiments, a binding agent comprises an alternative protein scaffold or artificial scaffold (*e.g.*, a non-immunoglobulin backbone). In some embodiments, a binding agent is a fusion protein comprising an antigen-binding site. In some embodiments, a binding agent is a bispecific or multispecific molecule comprising at least one antigen-binding site.

**[00106]** The term “antibody” is used herein in the broadest sense and encompasses various antibody structures, including but not limited to, an immunoglobulin molecule

that recognizes and binds a target through at least one antigen-binding site, polyclonal antibodies, recombinant antibodies, monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, bispecific antibodies, multispecific antibodies, diabodies, tribodies, tetrabodies, single chain Fv (scFv) antibodies, and antibody fragments as long as they exhibit the desired antigen-binding activity.

**[00107]** The term “intact antibody” or “full-length antibody” refers to an antibody having a structure substantially similar to a native antibody structure. This includes, for example, an antibody comprising two light chains each comprising a variable region and a light chain constant region (CL) and two heavy chains each comprising a variable region and at least heavy chain constant regions CH1, CH2, and CH3. Generally, an intact antibody includes a hinge region (or a portion thereof) between the CH1 and CH2 regions.

**[00108]** The term “antibody fragment” or “antibody fragments” as used herein refers to a molecule other than an intact antibody that comprises a portion of an antibody and generally an antigen-binding site. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')<sub>2</sub>, Fv, single chain antibody molecules (*e.g.*, scFv), sc(Fv)<sub>2</sub>, disulfide-linked scFv (dsscFv), diabodies, tribodies, tetrabodies, minibodies, dual variable domain antibodies (DVD), single variable domain antibodies (*e.g.*, camelid antibodies), and multispecific antibodies formed from antibody fragments.

**[00109]** The term “monoclonal antibody” as used herein refers to a substantially homogenous antibody population involved in the highly specific recognition and binding of a single antigenic determinant or epitope. The term “monoclonal antibody” encompasses intact and full-length monoclonal antibodies as well as antibody fragments (*e.g.*, Fab, Fab', F(ab')<sub>2</sub>, Fv), single chain antibodies (*e.g.*, scFv), fusion proteins comprising an antibody fragment, and any other modified immunoglobulin molecule comprising at least one antigen-binding site. Furthermore, “monoclonal antibody” refers to such antibodies made by any number of techniques, including but not limited to, hybridoma production, phage library display, recombinant expression, and transgenic animals.

[00110] The term “chimeric antibody” refers to an antibody in which a portion of the heavy and/or light chain is derived from a first source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[00111] The term “humanized antibody” as used herein refers to an antibody that comprises a human heavy chain variable region and a light chain variable region wherein the native CDR amino acid residues are replaced by residues from corresponding CDRs from a nonhuman antibody (*e.g.*, mouse, rat, rabbit, or nonhuman primate), wherein the nonhuman antibody has the desired specificity, affinity, and/or activity. In some embodiments, one or more framework region amino acid residues of the human heavy chain or light chain variable regions are replaced by corresponding residues from the nonhuman antibody. Furthermore, humanized antibodies can comprise amino acid residues that are not found in the human antibody or in the nonhuman antibody. In some embodiments, these modifications are made to further refine and/or optimize antibody characteristics. In some embodiments, the humanized antibody comprises at least a portion of a human immunoglobulin constant region (*e.g.*, CH1, CH2, CH3, Fc, and/or hinge region).

[00112] The term “human antibody” as used herein refers to an antibody that possesses an amino acid sequence that corresponds to an antibody produced by a human and/or an antibody that has been made using any of the techniques that are known to those of skill in the art for making human antibodies. These techniques include, but not limited to, phage display libraries, yeast display libraries, transgenic animals, recombinant protein production, and B-cell hybridoma technology.

[00113] The terms “epitope” and “antigenic determinant” are used interchangeably herein and refer to that portion of an antigen or target capable of being recognized and bound by a particular antibody. When the antigen or target is a polypeptide, epitopes can be formed both from contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of the protein. Epitopes formed from contiguous amino acids (also referred to as linear epitopes) are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding (also referred to as conformational

epitopes) are typically lost upon protein denaturing. An epitope typically includes at least 3, and more usually, at least 5, 6, 7, or 8-10 amino acids in a unique spatial conformation. Epitopes can be predicted using any one of a large number of software bioinformatic tools available on the internet. X-ray crystallography may be used to characterize an epitope on a target protein by analyzing the amino acid residue interactions of an antigen/antibody complex.

**[00114]** The term “specifically binds” as used herein refers to an agent that interacts more frequently, more rapidly, with greater duration, with greater affinity, or with some combination of the above to a particular antigen, epitope, protein, or target molecule than with alternative substances. A binding agent that specifically binds an antigen can be identified, for example, by immunoassays, ELISAs, surface plasmon resonance (SPR), or other techniques known to those of skill in the art. In some embodiments, an agent that specifically binds an antigen (*e.g.*, human ILT2) can bind related antigens (*e.g.*, rhesus ILT2 and/or cyno ILT2). In some embodiments, an agent that specifically binds an antigen (*e.g.*, human ILT2) can bind a second antigen (*e.g.*, human ILT4) and is referred to herein as a “dual binder”. In some embodiments, a binding agent that specifically binds an antigen can bind the target antigen at a higher affinity than its affinity for a different antigen. The different antigen can be a related antigen. In some embodiments, a binding agent that specifically binds an antigen can bind the target antigen with an affinity that is at least 20 times greater, at least 30 times greater, at least 40 times greater, at least 50 times greater, at least 60 times greater, at least 70 times greater, at least 80 times greater, at least 90 times greater, or at least 100 times greater, than its affinity for a different antigen. In some embodiments, a binding agent that specifically binds a particular antigen binds a different antigen at such a low affinity that binding cannot be detected using an assay described herein or otherwise known in the art. In some embodiments, affinity is measured using SPR technology in a Biacore system as described herein or as known to those of skill in the art.

**[00115]** The terms “polypeptide” and “peptide” and “protein” are used interchangeably herein and 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 naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid, including but not limited to, unnatural amino acids, as well as other modifications known in the art. It is understood that, because the polypeptides of this disclosure may be based upon antibodies, the term “polypeptide” encompasses polypeptides as a single chain and polypeptides of two or more associated chains.

[00116] The terms “polynucleotide” and “nucleic acid” and “nucleic acid molecule” are used interchangeably herein and refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase.

[00117] The terms “identical” or percent “identity” in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity may be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software that may be used to obtain alignments of amino acid or nucleotide sequences are well-known in the art. These include, but are not limited to, BLAST, ALIGN, Megalign, BestFit, GCG Wisconsin Package, and variants thereof. In some embodiments, two nucleic acids or polypeptides of the disclosure are substantially identical, meaning they have at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, and in some embodiments at least 95%, 96%, 97%, 98%, 99% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using

a sequence comparison algorithm or by visual inspection. In some embodiments, identity exists over a region of the sequences that is at least about 10, at least about 20, at least about 20-40, at least about 40-60, at least about 60-80 nucleotides or amino acid residues in length, or any integral value there between. In some embodiments, identity exists over a longer region than 60-80 nucleotides or amino acid residues, such as at least about 80-100 nucleotides or amino acid residues, and in some embodiments the sequences are substantially identical over the full length of the sequences being compared, for example, (i) the coding region of a nucleotide sequence or (ii) an amino acid sequence.

**[00118]** The phrase “conservative amino acid substitution” as used herein refers to a substitution in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been generally defined in the art, including 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). For example, substitution of an alanine for a valine is considered to be a conservative substitution. Generally, conservative substitutions in the sequences of polypeptides and/or antibodies do not abrogate the binding of the polypeptide or antibody to the target binding site. Methods of identifying nucleotide and amino acid conservative substitutions that do not eliminate binding are well-known in the art.

**[00119]** The term “vector” as used herein means a construct that is capable of delivering, and usually expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid, or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, and DNA or RNA expression vectors encapsulated in liposomes.

[00120] The term “isolated” as used herein refers to a polypeptide, soluble protein, antibody, polynucleotide, vector, cell, or composition that is in a form not found in nature. An “isolated” antibody is substantially free of material from the cellular source from which it is derived. In some embodiments, isolated polypeptides, soluble proteins, antibodies, polynucleotides, vectors, cells, or compositions are those that have been purified to a degree that they are no longer in a form in which they are found in nature. In some embodiments, a polypeptide, soluble protein, antibody, polynucleotide, vector, cell, or composition that is isolated is substantially pure. A polypeptide, soluble protein, antibody, polynucleotide, vector, cell, or composition can be isolated from a natural source (*e.g.*, tissue) or from a source such as an engineered cell line.

[00121] The term “substantially pure” as used herein refers to material that is at least 50% pure (*i.e.*, free from contaminants), at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure.

[00122] The term “subject” refers to any animal (*e.g.*, a mammal), including, but not limited to, humans, non-human primates, canines, felines, rabbits, rodents, and the like.

[00123] The term “pharmaceutically acceptable” as used herein refers to a substance approved or approvable by a regulatory agency or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, including humans.

[00124] The terms “pharmaceutically acceptable excipient, carrier, or adjuvant” or “acceptable pharmaceutical carrier” as used herein refer to an excipient, carrier, or adjuvant that can be administered to a subject, together with at least one therapeutic agent, and that is generally safe, non-toxic, and has no effect on the pharmacological activity of the therapeutic agent. In general, those of skill in the art and government agencies consider a pharmaceutically acceptable excipient, carrier, or adjuvant to be an inactive ingredient of any formulation.

[00125] The term “pharmaceutical formulation” or “pharmaceutical composition” as used herein refers to a preparation that is in such form as to permit the biological activity of the agent to be effective. A pharmaceutical formulation or composition

generally comprises additional components, such as a pharmaceutically acceptable excipient, carrier, adjuvant, buffers, etc.

[00126] The term “effective amount” or “therapeutically effective amount” as used herein refers to the amount of an agent that is sufficient to reduce and/or ameliorate the severity and/or duration of (i) a disease, disorder or condition in a subject, and/or (ii) a symptom in a subject. The term also encompasses an amount of an agent necessary for the (i) reduction or amelioration of the advancement or progression of a given disease, disorder, or condition, (ii) reduction or amelioration of the recurrence, development, or onset of a given disease, disorder, or condition, and/or (iii) the improvement or enhancement of the prophylactic or therapeutic effect(s) of another agent or therapy (*e.g.*, an agent other than the binding agents provided herein).

[00127] The term “therapeutic effect” as used herein refers to the effect and/or ability of an agent to reduce and/or ameliorate the severity and/or duration of (i) a disease, disorder, or condition in a subject, and/or (ii) a symptom in a subject. The term also encompasses the ability of an agent to (i) reduce or ameliorate the advancement or progression of a given disease, disorder, or condition, (ii) reduce or ameliorate the recurrence, development, or onset of a given disease, disorder, or condition, and/or (iii) to improve or enhance the prophylactic or therapeutic effect(s) of another agent or therapy (*e.g.*, an agent other than the binding agents provided herein).

[00128] The term “treat” or “treatment” or “treating” or “to treat” or “alleviate” or “alleviation” or “alleviating” or “to alleviate” as used herein refers to therapeutic measures that aim to slow down, lessen symptoms of, and/or halt progression of a pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder.

[00129] The term “prevent” or “prevention” or “preventing” as used herein refers to the partial or total inhibition of the development, recurrence, onset, or spread of a disease, disorder, or condition, or a symptom thereof in a subject.

[00130] The term “immune response” as used herein includes responses from both the innate immune system and the adaptive immune system. It includes both cell-mediated

and/or humoral immune responses. It includes both T-cell and B-cell responses, as well as responses from other cells of the immune system such as natural killer (NK) cells, monocytes, macrophages, dendritic cells, etc.

**[00131]** As used herein, reference to “about” or “approximately” a value or parameter includes (and describes) embodiments that are directed to that value or parameter. For example, a description referring to “about X” includes description of “X”.

**[00132]** As used in the present disclosure and claims, the singular forms “a”, “an” and “the” include plural forms unless the context clearly dictates otherwise.

**[00133]** It is understood that wherever embodiments are described herein with the term “comprising” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided. It is also understood that wherever embodiments are described herein with the phrase “consisting essentially of” otherwise analogous embodiments described in terms of “consisting of” are also provided.

**[00134]** The term “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

## II. ILT-binding agents

**[00135]** Amino acid (aa) sequences for human ILT2 (UniProtKB No. Q8NHL6), human ILT4 (UniProtKB No. Q8N423), rhesus macaque (“rhesus”) ILT2 (NCBI Ref No. XP\_028694980.1), and cynomolgus monkey (“cyno”) ILT2 (in house sequence has 98% identity to UniProtKB No. A0A2K5VN04) are provided herein as SEQ ID NO:1, SEQ ID NO:8, SEQ ID NO:15, and SEQ ID NO:166, respectively. As used herein, reference to amino acid positions of ILT2 or ILT4 refer to the numbering of amino acid sequences including the signal sequence.

**[00136]** A genomic orthologue for human ILT2 is found in the monkey genome, however, no genomic orthologue for human ILT4 appears to exist. Expression patterns

of the monkey ILT2 orthologue are comparable to the combined expression patterns of human ILT2 and human ILT4. Without being bound by theory, it is believed that the ILT2 orthologue in monkeys may have biological/functional capabilities that are equivalent to a combination of the biological functions of human ILT2 and human ILT4.

[00137] ILT2 is a single pass type I transmembrane protein with a predicted molecular weight of approximately 71 kDa. ILT2 (human, rhesus, and cyno) is characterized by an extracellular domain comprising four Ig-like C2 type domains, a transmembrane domain, and a long cytoplasmic domain containing 4 ITIM domains (see, *e.g.*, Borges *et al.*, 1997, *J. Immunol.*, 159:5192-5196). The four Ig-like C2-type domains may be referred to herein as Domain 1 (D1), Domain 2 (D2), Domain 3 (D3), and Domain 4 (D4). D1 is situated at the N-terminal portion of the protein, then D2, D3, with D4 situated closest to the transmembrane region. As characterized within UniProtKB, human ILT2 is a protein of 650 amino acids (aa) - the signal sequence is aa 1-23, the extracellular domain is aa 24-461, the transmembrane region is aa 462-482, and the cytoplasmic domain is aa 483-650. Within the extracellular domain, D1 is aa 27-115, D2 is aa 116-221, D3 is aa 222-312, D4 is aa 313-409, and the “stem region” is aa 410-461. Within the cytoplasmic domain, ITIMs are aa 531-536, 560-565, 612-617, and 642-647. Rhesus ILT2 is a protein of 639 amino acids (aa) - as compared to structural characterization of human ILT2 the signal sequence is aa 1-23, the extracellular domain is aa 24-460, the transmembrane region is aa 461-481, and the cytoplasmic domain is aa 482-639. Within the extracellular domain, D1 is aa 27-114, D2 is aa 115-220, D3 is aa 221-311, D4 is aa 312-408, and the “stem region” is aa 409-460. Within the cytoplasmic domain, ITIMs are aa 530-535, 559-564, 601-606, and 631-636. Cyno ILT2 is a protein of 651 amino acids (aa) - as compared to structural characterization of human ILT2 the signal sequence is aa 1-23, the extracellular domain is aa 24-461, the transmembrane region is aa 462-482, and the cytoplasmic domain is aa 483-651. Within the extracellular domain, D1 is aa 27-114, D2 is aa 115-220, D3 is aa 221-311, D4 is aa 312-408, and the “stem region” is aa 409-461. Within the cytoplasmic domain,

ITIMs are aa 531-536, 561-566, 613-618, and 643-648. ILT2 is expressed (to varying degrees) on natural killer (NK) cells, monocytes, macrophages, eosinophils, basophils, dendritic cells (DCs), subset of T-cells, and B-cells. Various ligands are known to interact with ILT2, including HLA class I molecules (*e.g.*, HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G). ILT2 appears to bind more strongly with the “non-classical” MHC I molecule HLA-G than to classical HLA class I molecules.

**[00138]** ILT4 has a structure very similar to ILT2. It is a single pass type I transmembrane protein with a predicted molecular weight of approximately 65 kDa. ILT4 is characterized by an extracellular domain comprising four Ig-like C2 type domains, a transmembrane domain, and a long cytoplasmic domain containing 3 ITIM domains (see, *e.g.*, Borges *et al.*, 1997, *J. Immunol.*, 159:5192-5196). As described for ILT2, the four Ig-like C2-type domains may be referred to herein as D1, D2, D3, and D4. D1 is situated at the N-terminal portion of the protein, then D2, D3, with D4 situated closest to the transmembrane region. As characterized within UniProtKB, human ILT4 is a protein of 598 amino acids (aa) - the signal sequence is aa 1-21, the extracellular domain is aa 22-461, the transmembrane region is aa 462-482, and the cytoplasmic domain is aa 483-598. Within the extracellular domain, D1 is aa 27-110, D2 is aa 111-229, D3 is aa 230-318, D4 is aa 330-419, and the “stem region” is aa 420-461. Within the cytoplasmic domain, ITIMs are aa 531-536, 560-565, and 590-595. ILT4 is expressed on myeloid cells such as monocytes, macrophages, dendritic cells, but not on lymphoid cells. ILT4 has been observed to bind a variety of ligands, notably HLA class I molecules, ANGPTL proteins, myelin inhibitors, and  $\beta$ -amyloid.

**[00139]** It is understood that the domains of ILT2 or ILT4 (*e.g.*, human ILT2, rhesus ILT2, cyno ILT2, or human ILT4) may be defined differently by those of skill in the art, therefore the N-terminal amino acids and the C-terminal amino acids of any ILT2 or ILT4 domain or region may vary by 1, 2, 3, 4, 5, or more amino acid residues.

**[00140]** The present disclosure provides agents that bind ILT2, ILT4, or ILT2 and ILT4, *i.e.*, ILT-binding agents. The agents that bind both ILT2 and ILT4 (ILT2/ILT4-binding agents) may be referred to herein as “dual binders”. In some embodiments, an

ILT2-binding agent or an ILT2/ILT4-binding agent binds ILT2 or a fragment of ILT2. In some embodiments, a fragment of ILT2 comprises the extracellular domain of ILT2. In some embodiments, a fragment of ILT2 comprises one or more of the Ig-like C2 type domains (*e.g.*, D1, D2, D3, and/or D4). In some embodiments, a fragment of ILT2 comprises D1 and D2. In some embodiments, a fragment of ILT2 comprises D2 and D3. In some embodiments, a fragment of ILT2 comprises D3 and D4. In some embodiments, a fragment of ILT2 comprises D1, D2, and D3. In some embodiments, a fragment of ILT2 comprises D2, D3, and D4. In some embodiments, a fragment of ILT2 comprises one or more of the Ig-like C2 type domains and the stem region. In some embodiments, a fragment of ILT2 comprises D4-stem, D3-D4-stem, or D2-D3-D4-stem.

[00141] In some embodiments, the extracellular domain of human ILT2 comprises amino acids 24-461 of SEQ ID NO:1. In some embodiments, D1 of human ILT2 comprises amino acids 27-115 of SEQ ID NO:1. In some embodiments, D2 of human ILT2 comprises amino acids 116-221 of SEQ ID NO:1. In some embodiments, D3 of human ILT2 comprises amino acids 222-312 of SEQ ID NO:1. In some embodiments, D4 of human ILT2 comprises amino acids 313-409 of SEQ ID NO:1. In some embodiments, D1-D2 of human ILT2 comprises amino acids 27-221 of SEQ ID NO:1. In some embodiments, D2-D3 of human ILT2 comprises amino acids 116-312 of SEQ ID NO:1. In some embodiments, D3-D4 of human ILT2 comprises amino acids 222-409 of SEQ ID NO:1. In some embodiments, D1-D2-D3 of human ILT2 comprises amino acids 27-312 of SEQ ID NO:1. In some embodiments, D2-D3-D4 of human ILT2 comprises amino acids 116-409 of SEQ ID NO:1. In some embodiments, D4-stem of human ILT2 comprises amino acids 313-461 of SEQ ID NO:1. In some embodiments, D3-D4-stem of human ILT2 comprises amino acids 222-461 of SEQ ID NO:1. In some embodiments, D2-D3-D4-stem of human ILT2 comprises amino acids 116-461 of SEQ ID NO:1. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:3. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:4. In some embodiments, a

fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:5. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:6. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:7. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:4 and SEQ ID NO:5. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:5 and SEQ ID NO:6. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:6 and SEQ ID NO:7. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

**[00142]** In some embodiments, the extracellular domain of rhesus ILT2 comprises amino acids 24-460 of SEQ ID NO:15. In some embodiments, D1 of rhesus ILT2 comprises amino acids 27-114 of SEQ ID NO:15. In some embodiments, D2 of rhesus ILT2 comprises amino acids 115-220 of SEQ ID NO:15. In some embodiments, D3 of rhesus ILT2 comprises amino acids 221-311 of SEQ ID NO:15. In some embodiments, D4 of rhesus ILT2 comprises amino acids 312-408 of SEQ ID NO:15. In some embodiments, D1-D2 of rhesus ILT2 comprises amino acids 27-220 of SEQ ID NO:15. In some embodiments, D2-D3 of rhesus ILT2 comprises amino acids 115-311 of SEQ ID NO:15. In some embodiments, D3-D4 of rhesus ILT2 comprises amino acids 221-408 of SEQ ID NO:15. In some embodiments, D1-D2-D3 of rhesus ILT2 comprises amino acids 27-311 of SEQ ID NO:15. In some embodiments, D2-D3-D4 of rhesus ILT2 comprises amino acids 115-408 of SEQ ID NO:15. In some embodiments, D4-stem of rhesus ILT2 comprises amino acids 312-460 of SEQ ID NO:15. In some embodiments, D3-D4-stem of rhesus ILT2 comprises amino acids 221-460 of SEQ ID NO:15. In some embodiments, D2-D3-D4-stem of rhesus ILT2 comprises amino acids 115-460 of SEQ ID NO:15. In some embodiments, a fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:17. In some embodiments, a

fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:18. In some embodiments, a fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:19. In some embodiments, a fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:20. In some embodiments, a fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:21. In some embodiments, a fragment of rhesus ILT2 comprises the amino acid sequence of SEQ ID NO:18 and SEQ ID NO:19. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:19 and SEQ ID NO:20. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:20 and SEQ ID NO:21. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:19, SEQ ID NO:20, and SEQ ID NO:21.

**[00143]** In some embodiments, the extracellular domain of cyno ILT2 comprises amino acids 24-461 of SEQ ID NO:166. In some embodiments, D1 of cyno ILT2 comprises amino acids 27-114 of SEQ ID NO:166. In some embodiments, D2 of cyno ILT2 comprises amino acids 115-220 of SEQ ID NO:166. In some embodiments, D3 of cyno ILT2 comprises amino acids 221-311 of SEQ ID NO:166. In some embodiments, D4 of cyno ILT2 comprises amino acids 312-408 of SEQ ID NO:166. In some embodiments, D1-D2 of cyno ILT2 comprises amino acids 27-220 of SEQ ID NO:166. In some embodiments, D2-D3 of cyno ILT2 comprises amino acids 115-311 of SEQ ID NO:166. In some embodiments, D3-D4 of cyno ILT2 comprises amino acids 221-408 of SEQ ID NO:166. In some embodiments, D1-D2-D3 of cyno ILT2 comprises amino acids 27-311 of SEQ ID NO:166. In some embodiments, D2-D3-D4 of cyno ILT2 comprises amino acids 115-408 of SEQ ID NO:166. In some embodiments, D4-stem of cyno ILT2 comprises amino acids 312-461 of SEQ ID NO:166. In some embodiments, D3-D4-stem of cyno ILT2 comprises amino acids 221-461 of SEQ ID NO:166. In some embodiments, D2-D3-D4-stem of cyno ILT2 comprises amino acids 115-461 of SEQ ID NO:166. In some embodiments, a fragment of cyno ILT2 comprises the amino

acid sequence of SEQ ID NO:168. In some embodiments, a fragment of cyno ILT2 comprises the amino acid sequence of SEQ ID NO:169. In some embodiments, a fragment of cyno ILT2 comprises the amino acid sequence of SEQ ID NO:170. In some embodiments, a fragment of cyno ILT2 comprises the amino acid sequence of SEQ ID NO:171. In some embodiments, a fragment of cyno ILT2 comprises the amino acid sequence of SEQ ID NO:172. In some embodiments, a fragment of cyno ILT2 comprises the amino acid sequence of SEQ ID NO:169 and SEQ ID NO:170. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:170 and SEQ ID NO:171. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:171 and SEQ ID NO:172. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:169, SEQ ID NO:170, and SEQ ID NO:171. In some embodiments, a fragment of human ILT2 comprises the amino acid sequence of SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:172.

**[00144]** In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment of ILT2 (*e.g.*, human ILT2, rhesus ILT2, and/or cyno ILT2). In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within a specific region of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the extracellular domain of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D1 domain of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D2 domain of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D3 domain of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D4 domain of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D4-stem region of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D1-D2 domains of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D2-D3 domains of ILT2. In some

embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D3-D4 domains of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D1-D2-D3 domains of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds within the D2-D3-D4 domains of ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope on ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a conformational epitope on ILT2. In some embodiments, an ILT2-binding agent does not bind other human LILRB proteins (*e.g.*, ILT3, ILT4, ILT5, or LILRB5). In some embodiments, an ILT2/ILT4-binding agent does not bind other human LILRB proteins (*e.g.*, ILT3, ILT5, or LILRB5). In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent does not bind one or more of the human LILRA proteins (*e.g.*, LILRA1, LILRA2, LILRA4, LILRA5, or LILRA6). In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent does not bind LILRA2, LILRA4, LILRA5, or LILRA6.

**[00145]** In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds human ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds cyno ILT2 and/or rhesus ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds human ILT2, cyno ILT2, and rhesus ILT2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:3. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 24-461 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-115 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 116-221 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 222-312 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an

ILT2/ILT4-binding agent binds a fragment comprising amino acids 313-409 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-221 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 116-312 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 222-409 of SEQ ID NO:1. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:4. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:5. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:6. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:7.

[00146] In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:16. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:17. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 24-460 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-114 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 115-220 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 221-311 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 312-408 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-220 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 115-311 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment

comprising amino acids 221-408 of SEQ ID NO:15. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:18. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:19. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:20. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:21.

[00147] In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:167. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:168. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 24-461 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-114 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 115-220 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 221-311 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 312-408 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-220 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 115-311 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 221-408 of SEQ ID NO:166. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:169. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:170. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:171. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:172.

[00148] In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:3. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:4. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:5. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:6. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:7. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:16. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:17. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:18. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:19. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:20. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:21. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:167. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:168. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a

polypeptide comprising the amino acid sequence of SEQ ID NO:169. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:170. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:171. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:172.

**[00149]** In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:2. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:3. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:4. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:5. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:6. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:7. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:16. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:17. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:18. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:19. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:20. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:21. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:167. In

some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:168. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:169. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:170. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:171. In some embodiments, an ILT2-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:172.

**[00150]** In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds ILT4 or a fragment of ILT4. In some embodiments, a fragment of ILT4 comprises the extracellular domain of ILT4. In some embodiments, a fragment of ILT4 comprises one or more of the Ig-like C2 type domains (*e.g.*, D1, D2, D3, and/or D4). In some embodiments, a fragment of ILT4 comprises D1 and D2. In some embodiments, a fragment of ILT4 comprises D2 and D3. In some embodiments, a fragment of ILT4 comprises D3 and D4. In some embodiments, a fragment of ILT4 comprises D1, D2, and D3. In some embodiments, a fragment of ILT4 comprises D2, D3, and D4. In some embodiments, a fragment of ILT4 comprises one or more of the Ig-like C2 type domains and the stem region. In some embodiments, a fragment of ILT4 comprises D4-stem, D3-D4-stem, or D2-D3-D4-stem. In some embodiments, the extracellular domain of human ILT4 comprises amino acids 22-461 of SEQ ID NO:8. In some embodiments, D1 of human ILT4 comprises amino acids 27-110 of SEQ ID NO:8. In some embodiments, D2 of human ILT4 comprises amino acids 111-229 of SEQ ID NO:8. In some embodiments, D3 of human ILT4 comprises amino acids 230-318 of SEQ ID NO:8. In some embodiments, D4 of human ILT4 comprises amino acids 330-419 of SEQ ID NO:8. In some embodiments, D1-D2 of human ILT4 comprises amino acids 27-229 of SEQ ID NO:8. In some embodiments, D2-D3 of human ILT4 comprises amino acids 111-318 of SEQ ID NO:8. In some embodiments, D3-D4 of human ILT4 comprises amino acids 230-419 of SEQ ID NO:8. In some embodiments, D1-D2-D3 of

human ILT4 comprises amino acids 27-318 of SEQ ID NO:8. In some embodiments, D2-D3-D4 of human ILT4 comprises amino acids 111-419 of SEQ ID NO:8. In some embodiments, D4-stem of human ILT4 comprises amino acids 330-461 of SEQ ID NO:8. In some embodiments, D3-D4-stem of human ILT4 comprises amino acids 230-461 of SEQ ID NO:8. In some embodiments, D2-D3-D4-stem of human ILT4 comprises amino acids 111-461 of SEQ ID NO:8.

**[00151]** In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within a specific region of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the extracellular domain of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D1 domain of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D2 domain of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D3 domain of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D4 domain of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D4-stem region of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D1-D2 domains of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D2-D3 domains of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D3-D4 domains of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D1-D2-D3 domains of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds within the D2-D3-D4 domains of ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope on ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a conformational epitope on ILT4. In some embodiments, an ILT4-binding agent does not bind other human LILRB proteins (*e.g.*, ILT2, ILT3, ILT5, or LILRB5). In

some embodiments, an ILT2/ILT4-binding agent does not bind other human LILRB proteins (*e.g.*, ILT3, ILT5, or LILRB5). In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent does not bind one or more of the human LILRA proteins (*e.g.*, LILRA1, LILRA2, LILRA4, LILRA5, or LILRA6). In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent does not bind LILRA2, LILRA4, LILRA5, or LILRA6.

**[00152]** In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds human ILT4. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:9. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:10. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 22-461 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-110 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 111-229 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 230-318 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 330-419 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 27-229 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 111-318 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a fragment comprising amino acids 230-419 of SEQ ID NO:8. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:11. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:12. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:13. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-

binding agent binds SEQ ID NO:14. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:11 and SEQ ID NO:12. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:12 and SEQ ID NO:13. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:13 and SEQ ID NO:14. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14.

**[00153]** In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:9. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:11. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:12. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:13. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds a polypeptide comprising the amino acid sequence of SEQ ID NO:14.

**[00154]** In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:9. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:10. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:11. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:12. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope

comprising amino acids within SEQ ID NO:13. In some embodiments, an ILT4-binding agent or an ILT2/ILT4-binding agent binds an epitope comprising amino acids within SEQ ID NO:14.

**[00155]** In some embodiments, an ILT-binding agent binds human ILT2, human ILT4, or both human ILT2/ILT4, and has at least one or more of the following properties: (i) binds rhesus ILT2; (ii) binds cyno ILT2; (iii) does not bind ILT3, ILT5, and LILRB5; (iv) does not bind LILRA2, LILRA4, LILRA5, and LILRA6; (v) is an ILT2 antagonist; (vi) is an ILT4 antagonist, (vii) inhibits ILT2 activity; (viii) inhibits ILT4 activity; (ix) inhibits ILT2 signaling in cells that express ILT2; (x) inhibits ILT4 signaling in cells that express ILT4; (xi) inhibits binding of ILT2 to MHC I molecules; (xii) inhibits binding of ILT4 to MHC I molecules; (xiii) inhibits ILT2-induced suppression of myeloid cells; (xiv) inhibits ILT4-induced suppression of myeloid cells; (xv) inhibits ILT2-induced suppression of myeloid cell activity; (xvi) inhibits ILT4-induced suppression of myeloid cell activity; (xvii) restores FcR activation in myeloid cells; (xviii) enhances NK cell activity; (xix) enhances CTL activity; and/or (xx) enhances macrophage phagocytosis.

**[00156]** In some embodiments, an ILT-binding agent is an antibody. In some embodiments, an ILT2-binding agent is an antibody. In some embodiments, an ILT4-binding agent is an antibody. In some embodiments, an ILT2/ILT4-binding agent is an antibody. In some embodiments, an ILT-binding agent is an anti-ILT2 antibody. In some embodiments, an ILT-binding agent is an anti-ILT4 antibody. In some embodiments, an ILT-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments, the antibody is a recombinant antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a chimeric antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a human antibody. In some embodiments, the antibody is an IgG antibody. In some embodiments, the antibody is an IgG1 antibody. In some embodiments, the antibody is an IgG2 antibody. In some embodiments, the antibody is an IgG3 antibody. In some embodiments, the antibody is an IgG4 antibody. In some

embodiments, the antibody comprises an IgG heavy chain. In some embodiments, the antibody comprises an IgG1 heavy chain. In some embodiments, the antibody comprises an IgG2 heavy chain. In some embodiments, the antibody comprises an IgG4 heavy chain. In some embodiments, the antibody comprises a human IgG heavy chain. In some embodiments, the antibody comprises a human IgG1 heavy chain. In some embodiments, the antibody comprises a human IgG2 heavy chain. In some embodiments, the antibody comprises a human IgG4 heavy chain. In some embodiments, the antibody comprises a kappa light chain. In some embodiments, the antibody comprises a kappa light chain constant region. In some embodiments, the antibody comprises a human kappa light chain constant region. In some embodiments, the antibody comprises a lambda light chain. In some embodiments, the antibody comprises a lambda light chain constant region. In some embodiments, the antibody comprises a human lambda light chain constant region. In some embodiments, the antibody is an antibody fragment comprising at least one antigen-binding site. In some embodiments, the antibody is a scFv. In some embodiments, the antibody is a disulfide-linked scFv. In some embodiments, the antibody is a disulfide-linked sc(Fv)<sub>2</sub>. In some embodiments, the antibody is a Fab, Fab', or a F(ab)<sub>2</sub> antibody. In some embodiments, the antibody is a diabody. In some embodiments, the antibody is a nanobody. In some embodiments, the antibody is a monospecific antibody. In some embodiments, the antibody is a bispecific antibody. In some embodiments, the antibody is a multispecific antibody. In some embodiments, the antibody is a monovalent antibody. In some embodiments, the antibody is a bivalent antibody. In some embodiments, the antibody is a tetravalent antibody.

[00157] In some embodiments, the antibody is isolated. In some embodiments, the antibody is substantially pure.

[00158] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is a polyclonal antibody.

Polyclonal antibodies can be prepared by any method known to those of skill in the art. In some embodiments, polyclonal antibodies are produced by immunizing an animal

(*e.g.*, a rabbit, rat, mouse, goat, donkey) with an antigen of interest (*e.g.*, a purified peptide fragment, a recombinant protein, or a fusion protein) using multiple subcutaneous or intraperitoneal injections. In some embodiments, the antigen is conjugated to a carrier such as keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor. The antigen (with or without a carrier protein) is diluted in sterile saline and usually combined with an adjuvant (*e.g.*, Complete or Incomplete Freund's Adjuvant) to form a stable emulsion. After a period of time, polyclonal antibodies are recovered from the immunized animal (*e.g.*, from blood or ascites). In some embodiments, the polyclonal antibodies are purified from serum or ascites according to standard methods in the art including, but not limited to, affinity chromatography, ion-exchange chromatography, gel electrophoresis, and/or dialysis.

**[00159]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is a monoclonal antibody. Monoclonal antibodies can be prepared by any method known to those of skill in the art. In some embodiments, monoclonal antibodies are prepared using hybridoma methods known to one of skill in the art. For example, using a hybridoma method, a mouse, rat, rabbit, hamster, or other appropriate host animal, is immunized as described above. In some embodiments, lymphocytes are immunized *in vitro*. In some embodiments, the immunizing antigen is a human protein or a fragment thereof. In some embodiments, the immunizing antigen is a mouse protein or a fragment thereof. In some embodiments, the immunizing antigen is a rhesus protein or a fragment thereof. In some embodiments, the immunizing antigen is a cyno protein or a fragment thereof. In some embodiments, the immunizing antigen is a combination of two or more (*e.g.*, 2, 3, 4) related proteins or fragments thereof.

**[00160]** Following immunization, lymphocytes are isolated and fused with a suitable myeloma cell line using, for example, polyethylene glycol. The hybridoma cells are selected using specialized media as known in the art and unfused lymphocytes and myeloma cells do not survive the selection process. Hybridomas that produce

monoclonal antibodies against a chosen antigen can be identified by a variety of methods including, but not limited to, immunoprecipitation, immunoblotting, and *in vitro* binding assays (*e.g.*, flow cytometry, FACS, ELISA, SPR (*e.g.*, Biacore), and radioimmunoassay). Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution techniques. In some embodiments, high-throughput methods are used to distribute single cell hybridoma cells into plates. The hybridomas can be propagated either in *in vitro* culture using standard methods or *in vivo* as ascites tumors in an animal. The monoclonal antibodies can be purified from the culture medium or ascites fluid according to standard methods in the art including, but not limited to, affinity chromatography, ion-exchange chromatography, gel electrophoresis, and dialysis.

[00161] In some embodiments, monoclonal antibodies are made using recombinant DNA techniques as known to one skilled in the art. For example, the polynucleotides encoding an antibody are isolated from mature B-cells or hybridoma cells, such as by RT-PCR using oligonucleotide primers that specifically amplify the genes encoding the heavy and light chains of the antibody, and their sequence is determined using standard techniques. The isolated polynucleotides encoding the heavy and light chains are then cloned into suitable expression vectors which produce the monoclonal antibodies when transfected into host cells such as *E. coli*, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin proteins.

[00162] In some embodiments, recombinant monoclonal antibodies are isolated from phage display libraries expressing variable domains or CDRs of a desired species. Screening of phage libraries can be accomplished by various techniques known in the art.

[00163] In some embodiments, a monoclonal antibody is modified by using recombinant DNA technology to generate alternative antibodies. In some embodiments, the constant domains of the light chain and heavy chain of a mouse monoclonal antibody are substituted for constant regions of a human antibody to generate a chimeric antibody. In some embodiments, the constant regions are truncated

or removed to generate a desired antibody fragment of a monoclonal antibody. In some embodiments, site-directed or high-density mutagenesis of the variable region(s) is used to optimize specificity and affinity of a monoclonal antibody.

[00164] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is a humanized antibody. Various methods for generating humanized antibodies are known in the art. In some embodiments, a humanized antibody comprises one or more amino acid residues that have been introduced into it from a source that is non-human. In some embodiments, humanization is performed by substituting one or more non-human CDR sequences for the corresponding CDR sequences of a human antibody. In some embodiments, the humanized antibodies are constructed by substituting all six CDRs of a non-human antibody (*e.g.*, a mouse antibody) for the corresponding CDRs of a human antibody.

[00165] The choice of which human heavy chain variable region and/or light chain variable region to use for generating humanized antibodies can be made based on a variety of factors and by a variety of methods known in the art. In some embodiments, the “best-fit” method is used where the sequence of the variable region of a non-human (*e.g.*, rodent) antibody is screened against the entire library of known human variable region sequences. The human sequence that is most similar to that of the non-human (*e.g.*, rodent) sequence is selected as the human variable region framework for the humanized antibody. In some embodiments, a particular variable region framework derived from a consensus sequence of all human antibodies of a particular subgroup of light or heavy chains is selected as the variable region framework. In some embodiments, the variable region framework sequence is derived from the consensus sequences of the most abundant human subclasses. In some embodiments, human germline genes are used as the source of the variable region framework sequences.

[00166] Other methods for humanization include, but are not limited to, a method called “superhumanization” which is described as the direct transfer of CDRs to a human germline framework, a method termed Human String Content (HSC) which is based on a metric of “antibody humanness”, methods based on generation of large

libraries of humanized variants (including phage, ribosomal, and yeast display libraries), and methods based on framework region shuffling.

[00167] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is a human antibody. Human antibodies can be prepared using various techniques known in the art. In some embodiments, human antibodies are generated from immortalized human B lymphocytes immunized *in vitro*. In some embodiments, human antibodies are generated from lymphocytes isolated from an immunized individual. In any case, cells that produce an antibody directed against a target antigen can be generated and isolated. In some embodiments, a human antibody is selected from a phage library, where that phage library expresses human antibodies. Alternatively, phage display technology may be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable region gene repertoires from unimmunized human donors. Techniques for the generation and use of antibody phage libraries are well known in the art. Once antibodies are identified, affinity maturation strategies known in the art, including but not limited to, chain shuffling and site-directed mutagenesis, may be employed to generate higher affinity human antibodies. In some embodiments, human antibodies are produced in transgenic mice that contain human immunoglobulin loci. Upon immunization these mice are capable of producing the full repertoire of human antibodies in the absence of endogenous immunoglobulin production.

[00168] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is an antibody fragment. As used herein, the term “antibody fragment” refers to a molecule other than an intact antibody that comprises a portion of an antibody and generally at least one antigen-binding site. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')<sub>2</sub>, Fv, single chain antibody molecules (*e.g.*, scFv), disulfide-linked scFv (dsscFv), nanobodies, diabodies, tribodies, tetrabodies, minibodies, dual variable domain antibodies (DVD), single variable domain antibodies (*e.g.*, camelid antibodies), and multispecific antibodies formed from antibody fragments.

[00169] In some embodiments, an ILT-binding agent is a scFv antibody. In some embodiments, the scFv is a disulfide-linked scFv (dsscFv), which is a scFv comprising an engineered disulfide bond between the light chain variable region and heavy chain variable region of the scFv. In some embodiments, the disulfide bond increases stability of the scFv molecule. In some embodiments, the disulfide bond increases thermostability of the scFv molecule.

[00170] In some embodiments, an ILT-binding agent is a Fv. In some embodiments, an ILT-binding agent is a Fab. In some embodiments, an ILT-binding agent is a F(ab')<sub>2</sub>. In some embodiments, an ILT-binding agent is a F(ab').

[00171] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody. The antibody fragments described herein can be produced using recombinant technologies known in the art (*e.g.*, *E. coli* or phage expression).

[00172] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) is a bispecific antibody. Bispecific antibodies are capable of recognizing and binding at least two different antigens or epitopes. The different epitopes can either be within the same molecule (*e.g.*, two epitopes on ILT2) or on different molecules (*e.g.*, one epitope on ILT2 and a second epitope on a different target). In some embodiments, a bispecific antibody has enhanced potency as compared to an individual antibody or to a combination of more than one antibody. In some embodiments, a bispecific antibody has reduced toxicity as compared to an individual antibody or to a combination of more than one antibody. It is known to those of skill in the art that any therapeutic agent may have unique pharmacokinetics (PK) (*e.g.*, circulating half-life). In some embodiments, a bispecific antibody has the ability to synchronize the PK of two active binding agents wherein the two individual binding agents have different PK profiles. In some embodiments, a bispecific antibody has the ability to concentrate the actions of two agents in a common area (*e.g.*, tissue) in a subject. In some embodiments, a bispecific antibody has the ability to concentrate the actions of two agents to a common target (*e.g.*, a specific cell

type). In some embodiments, a bispecific antibody has the ability to target the actions of two agents to more than one biological pathway or function. In some embodiments, a bispecific antibody has the ability to target two different cells and bring them closer together.

[00173] In some embodiments, a bispecific antibody has decreased toxicity and/or side effects. In some embodiments, a bispecific antibody has decreased toxicity and/or side effects as compared to a mixture of the two individual antibodies or the antibodies as single agents. In some embodiments, a bispecific antibody has an increased therapeutic index. In some embodiments, a bispecific antibody has an increased therapeutic index as compared to a mixture of the two individual antibodies or the antibodies as single agents.

[00174] Many techniques for making bispecific antibodies are known to those skilled in the art. In some embodiments, a bispecific antibody comprises heavy chain constant regions with modifications in the amino acids that are part of the interface between the two heavy chains. These modifications are made to enhance heterodimer formation and generally reduce or eliminate homodimer formation. In some embodiments, the bispecific antibody is generated using a knobs-into-holes (KIH) strategy. In some embodiments, the bispecific antibody comprises variant hinge regions incapable of forming disulfide linkages between identical heavy chains (*e.g.*, reduce homodimer formation). In some embodiments, the bispecific antibody comprises heavy chains with changes in amino acids that result in altered electrostatic interactions. In some embodiments, the bispecific antibodies comprise heavy chains with changes in amino acids that result in altered hydrophobic/hydrophilic interactions.

[00175] Bispecific antibodies can be intact antibodies or antibody fragments comprising antigen-binding sites.

[00176] In some embodiments, an ILT-binding agent is an antibody that binds ILT2. In some embodiments, an anti-ILT antibody binds human ILT2. In some embodiments, an anti-ILT antibody binds cyno ILT2. In some embodiments, an anti-ILT antibody binds rhesus ILT2. In some embodiments, an anti-ILT antibody binds human ILT2 and

cyno ILT2. In some embodiments, an anti-ILT antibody binds human ILT2 and rhesus ILT2. In some embodiments, an anti-ILT antibody binds human ILT2, rhesus ILT2, and cyno ILT2. In some embodiments, an anti-ILT2 antibody binds an ILT2 epitope. In some embodiments, an anti-ILT2 antibody binds an ILT2 epitope within the extracellular domain of human ILT2. In some embodiments, an anti-ILT2 antibody binds an ILT2 epitope within the extracellular domain of cyno ILT2. In some embodiments, an anti-ILT2 antibody binds an ILT2 epitope within the extracellular domain of rhesus ILT2. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 24-461 of SEQ ID NO:1. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 27-115 of SEQ ID NO:1. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 116-221 of SEQ ID NO:1. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 222-312 of SEQ ID NO:1. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 313-409 of SEQ ID NO:1. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:3. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:4. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:5. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:6. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:7. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 24-460 of SEQ ID NO:15. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 27-114 of SEQ ID NO:15. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one

amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 115-220 of SEQ ID NO:15. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 221-311 of SEQ ID NO:15. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 312-408 of SEQ ID NO:15. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:17. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:18. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:19. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:20. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:21. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 24-461 of SEQ ID NO:166. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 27-114 of SEQ ID NO:166. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 115-220 of SEQ ID NO:166. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 221-311 of SEQ ID NO:166. In some embodiments, an anti-ILT2 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 312-408 of SEQ ID NO:166. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:168. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:169. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:170. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within SEQ ID NO:171. In some embodiments, an anti-ILT2 antibody binds an epitope comprising amino acids within

SEQ ID NO:172. In some embodiments, the epitope is a conformational epitope. In some embodiments, the epitope is a linear epitope.

[00177] In some embodiments, an ILT-binding agent is an antibody that binds ILT4. In some embodiments, an anti-ILT antibody binds human ILT4. In some embodiments, an anti-ILT4 antibody binds an ILT4 epitope. In some embodiments, an anti-ILT4 antibody binds an ILT4 epitope within the extracellular domain of human ILT4. In some embodiments, an anti-ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 22-461 of SEQ ID NO:8. In some embodiments, an anti-ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 27-110 of SEQ ID NO:8. In some embodiments, an anti-ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 111-229 of SEQ ID NO:8. In some embodiments, an anti-ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 230-318 of SEQ ID NO:8. In some embodiments, an anti-ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 330-419 of SEQ ID NO:8. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:9. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:10. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:11. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:12. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:13. In some embodiments, an anti-ILT4 antibody binds an epitope comprising amino acids within SEQ ID NO:14. In some embodiments, the epitope is a conformational epitope. In some embodiments, the epitope is a linear epitope.

[00178] In some embodiments, an ILT-binding agent is an antibody that binds ILT2 and ILT4. It is understood by those of skill in the art that an antibody that binds ILT2 and ILT4, described as a dual binder, comprises at least one antigen-binding site that

binds an epitope on both ILT2 and ILT4, in contrast to a bispecific antibody which would comprise one antigen-binding site that binds an epitope on ILT2 and a second antigen-binding site that binds a different epitope on ILT4. In some embodiments, an anti-ILT2/ILT4 antibody binds human ILT2 and human ILT4. In some embodiments, anti-ILT2/ILT4 antibody binds human ILT2, human ILT4, cyno ILT2, and rhesus ILT2. In some embodiments, an anti-ILT2/ILT4 antibody binds an ILT2 epitope and ILT4 epitope. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope within the extracellular domain of human ILT2 and an epitope within the extracellular domain of human ILT4, wherein the ILT2 epitope and the ILT4 epitope are the same or essentially the same. In some embodiments, an anti-ILT2/ILT4 antibody binds an ILT2 epitope within the extracellular domain of human ILT2, an ILT4 epitope within the extracellular domain of human ILT4, an ILT2 epitope within the extracellular domain of cyno ILT2, and an ILT2 epitope within the extracellular domain of rhesus ILT2. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 24-461 of SEQ ID NO:1 and the same or essentially the same epitope within amino acids 22-461 of SEQ ID NO:8. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 27-115 of SEQ ID NO:1 and the same or essentially the same epitope within amino acids 27-110 of SEQ ID NO:8. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 116-221 of SEQ ID NO:1 and the same or essentially the same epitope within amino acids 111-229 of SEQ ID NO:8. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 222-312 of SEQ ID NO:1 and the same or essentially the same epitope within amino acids 230-318 of SEQ ID NO:8. In some embodiments, an anti-ILT2/ILT4 antibody binds an epitope comprising at least one amino acid (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9) within amino acids 313-409 of SEQ ID NO:1 and the same or essentially the same epitope within amino acids 330-419 of SEQ ID NO:8. In some embodiments, the

epitope is a conformational epitope. In some embodiments, the epitope is a linear epitope.

[00179] In some embodiments, an ILT-binding agent is an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody described herein. In some embodiments, the ILT-binding agent is a variant of an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody described herein. In some embodiments, a variant of an anti-ILT antibody comprises one to thirty amino acid substitutions. In some embodiments, a variant of the anti-ILT antibody comprises one to twenty-five amino acid substitutions. In some embodiments, a variant of the anti-ILT antibody comprises one to twenty amino acid substitutions. In some embodiments, a variant of the anti-ILT antibody comprises one to fifteen amino acid substitutions. In some embodiments, a variant of the anti-ILT antibody comprises one to ten amino acid substitutions. In some embodiments, a variant of the anti-ILT antibody comprises one to five amino acid substitutions. In some embodiments, the variant of the anti-ILT antibody comprises one to three amino acid substitutions. In some embodiments, the amino acid substitution(s) is in a CDR of the antibody. In some embodiments, the amino acid substitution(s) is not in a CDR of the antibody. In some embodiments, the amino acid substitution(s) is in a framework region of the antibody. In some embodiments, the amino acid substitution(s) is a conservative amino acid substitution.

[00180] CDRs of an antibody are defined using a variety of methods/systems by those skilled in the art. These systems and/or definitions have been developed and refined over a number of years and include Kabat, Chothia, IMGT, AbM, and Contact. The Kabat definition is based on sequence variability and is commonly used. The Chothia definition is based on the location of the structural loop regions. The IMGT system is based on sequence variability and location within the structure of the variable domain. The AbM definition is a compromise between Kabat and Chothia. The Contact definition is based on analyses of the available antibody crystal structures. An Exemplary system is a combination of Kabat and Chothia. Software programs (*e.g.*,

abYsis) are available and known to those of skill in the art for analysis of antibody sequence and determination of CDRs.

**[00181]** The specific CDR sequences defined herein are generally based on a combination of Kabat and Chothia definitions (Exemplary definition). However, it will be understood that reference to a heavy chain variable region CDR or CDRs and/or a light chain variable region CDR or CDRs of a specific antibody will encompass all CDR definitions as known to those of skill in the art.

**[00182]** In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the Kabat definition. In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the Chothia definition. In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the AbM definition. In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the IMGT definition. In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the Contact definition. In some embodiments, an anti-ILT antibody described herein comprises the six CDRs of antibody 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, or Hz73D1.v1 based on the Exemplary definition.

**[00183]** In some embodiments, an ILT-binding agent is an anti-ILT antibody (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) that comprises one, two, three, four, five, and/or six CDRs of any one of the antibodies described herein. In some embodiments, an anti-ILT2 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 1, and/or (ii) a light chain variable region comprising one, two,

and/or three light chain variable region CDRs from Table 1. In some embodiments, an anti-ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 2, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 2. In some embodiments, an anti-ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 3, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 3. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 4A or Table 4B, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 4A or Table 4B. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 5, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 5. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 6A or Table 6B, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 6A or Table 6B. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 7, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 7. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising one, two, and/or three heavy chain variable region CDRs from Table 8A or Table 8B, and/or (ii) a light chain variable region comprising one, two, and/or three light chain variable region CDRs from Table 8A or Table 8B. In some embodiments, an anti-ILT2 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 1, and (ii) a light chain variable region comprising three light chain variable

region CDRs from Table 1. In some embodiments, an anti-ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 2, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 2. In some embodiments, an anti-ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 3, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 3. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 4A, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 4A. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 4B, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 4B. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 5, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 5. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 6A, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 6A. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 6B, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 6B. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 7, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 7. In some embodiments, an anti-ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 8A, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 8B. In some embodiments, an anti-

ILT2/ILT4 antibody comprises (i) a heavy chain variable region comprising three heavy chain variable region CDRs from Table 8B, and (ii) a light chain variable region comprising three light chain variable region CDRs from Table 8B.

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Table 1: Anti-ILT2 Antibody 27F9 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GFSLTNYGVS (SEQ ID NO:22)	GFSLTNY (SEQ ID NO:28)	GFSLTNYGVS (SEQ ID NO:22)	NYGVS (SEQ ID NO:31)	TNYGVS (SEQ ID NO:32)
Heavy Chain variable region CDR2	IIWGDGGS (SEQ ID NO:23)	WGDGS (SEQ ID NO:29)	IIWGDGGS (SEQ ID NO:30)	IIWGDGGS (SEQ ID NO:23)	WLGIIWGDGGS (SEQ ID NO:33)
Heavy Chain variable region CDR3	PNWDTYAMDF (SEQ ID NO:24)	PNWDTYAMDF (SEQ ID NO:24)	PNWDTYAMDF (SEQ ID NO:24)	PNWDTYAMDF (SEQ ID NO:24)	AKPNWDTYAMD (SEQ ID NO:34)
Light Chain variable region CDR1	RASQDISNFLN (SEQ ID NO:25)	RASQDISNFLN (SEQ ID NO:25)	RASQDISNFLN (SEQ ID NO:25)	RASQDISNFLN (SEQ ID NO:25)	SNFLN (SEQ ID NO:35)
Light Chain variable region CDR2	CTSKLHS (SEQ ID NO:26)	CTSKLHS (SEQ ID NO:26)	CTSKLHS (SEQ ID NO:26)	CTSKLHS (SEQ ID NO:26)	LLIYCTSKLH (SEQ ID NO:36)
Light Chain variable region CDR3	QQGNTLPPT (SEQ ID NO:27)	QQGNTLPPT (SEQ ID NO:27)	QQGNTLPPT (SEQ ID NO:27)	QQGNTLPPT (SEQ ID NO:27)	QQGNTLP (SEQ ID NO:27)
27F9 Heavy chain variable region (SEQ ID NO:125)					
QVQLKESGPGLVAPPSQSLSITCTVSGFSLTNYGVS WRQPPKGLGLEWLGIIWGDGGS TNYH SALISRLSISKDNSKQVFLKLNLSLQADDTATYYCAKPNWDTYAMDFWGGGTSVTVSS					

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27F9 Light chain variable region (SEQ ID NO:126)  
 DIQMTQTSSLSASLGDRTVTISCRASQDISNFLNWWYQQKPDGTVKLLIYCTSKLHSGVPS  
 RFGSGSETDYSLTISNLEQEDIAFYFCQQGNTLPTFFGGGKLEII

Table 2: Anti-ILT4 Antibody 47C8 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYSFTGYMH (SEQ ID NO:38)	GYSFTGY (SEQ ID NO:44)	GYSFTGYMH (SEQ ID NO:38)	GYMH (SEQ ID NO:47)	TGYMH (SEQ ID NO:48)
Heavy Chain variable region CDR2	RVYPNNGDTSYNQKF KV (SEQ ID NO:39)	YPNGD (SEQ ID NO:45)	RVYPNNGDTS (SEQ ID NO:46)	RVYPNNGDTSYNQKF KV (SEQ ID NO:39)	WGRVYPNNGDTS (SEQ ID NO:49)
Heavy Chain variable region CDR3	GATVVESELFAY (SEQ ID NO:40)	GATVVESELFAY (SEQ ID NO:40)	GATVVESELFAY (SEQ ID NO:40)	GATVVESELFAY (SEQ ID NO:40)	ARGATVVESELFAY (SEQ ID NO:50)
Light Chain variable region CDR1	RASESVDNYGNNFLH (SEQ ID NO:41)	RASESVDNYGNNFLH H (SEQ ID NO:41)	RASESVDNYGNNFLH H (SEQ ID NO:41)	RASESVDNYGNNFLH (SEQ ID NO:41)	DNYGNNFLHWY (SEQ ID NO:51)
Light Chain variable region CDR2	RTSNLES (SEQ ID NO:42)	RTSNLES (SEQ ID NO:42)	RTSNLES (SEQ ID NO:42)	RTSNLES (SEQ ID NO:42)	LLIYRTSNI (SEQ ID NO:52)
Light Chain variable region CDR3	QQSNEDPYT (SEQ ID NO:43)	QQSNEDPYT (SEQ ID NO:43)	QQSNEDPYT (SEQ ID NO:43)	QQSNEDPYT (SEQ ID NO:43)	QQSNEDP (SEQ ID NO:53)

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47C8 Heavy chain variable region (SEQ ID NO:127) EVQLQSSGPDLVKPGASVKISCKASGYSTGYMHWVKQSHGKSLIEWIGRVYPNNGDTSY NQFKVKAILTVDKSSSTAYMELRSLTSEDSAVYYCARGATVVESLFA YWGQGTLLVTVSA
47C8 Light chain variable region (SEQ ID NO:128) DIVLTQSPASLAVSLGQRATISCRASESVDNYGNNFHLHWYQQKPGQPPKLLIYRTSNLES GIPARFSGSRTDFTLTINPVEADDVATYYCCQQSNEDPYTFGGGKLEIK

Table 3: Anti-ILT4 Antibody 48A5 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTNYGMN (SEQ ID NO:54)	GYTFTNY (SEQ ID NO:60)	GYTFTNYGMN (SEQ ID NO:54)	NYGMN (SEQ ID NO:63)	TNYGMN (SEQ ID NO:64)
Heavy Chain variable region CDR2	WINTYIGEPIYADDFK G (SEQ ID NO:55)	NTYIGE (SEQ ID NO:61)	WINTYIGEPI (SEQ ID NO:62)	WINTYIGEPIYADDFK G (SEQ ID NO:55)	WMGWINTYIGEPI (SEQ ID NO:65)
Heavy Chain variable region CDR3	RSDYDGYAMDY (SEQ ID NO:56)	RSDYDGYAMDY (SEQ ID NO:56)	RSDYDGYAMDY (SEQ ID NO:56)	RSDYDGYAMDY (SEQ ID NO:56)	ARRSDYDGYAMD (SEQ ID NO:66)
Light Chain variable region CDR1	KSSQSLLYSGNQKNY LA (SEQ ID NO:57)	LA (SEQ ID NO:57)	LA (SEQ ID NO:57)	KSSQSLLYSGNQKNY LA (SEQ ID NO:57)	LYSGNQKNYLAWY (SEQ ID NO:67)
Light Chain variable region CDR2	WASTRES (SEQ ID NO:58)	WASTRES (SEQ ID NO:58)	WASTRES (SEQ ID NO:58)	WASTRES (SEQ ID NO:58)	LLIYWASTRE (SEQ ID NO:68)
Light Chain variable region CDR3	QQHDSYPT (SEQ ID NO:59)	QQHDSYPT (SEQ ID NO:59)	QQHDSYPT (SEQ ID NO:59)	QQHDSYPT (SEQ ID NO:59)	QQHDSYF (SEQ ID NO:69)
48A5 Heavy chain variable region (SEQ ID NO:129)					
QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNWKQAPGKGLKWMGWINTYIGEPIY ADDFKGRFAFSLTSASTAYLQINNLKNEEDMATYFCARRSDYDGYAMDYWGQGTSTVTVSS					
48A5 Light chain variable region (SEQ ID NO:130)					
DIVMSQSPSSLAVSVGERVTMSCKSSQSLLYSGNQKNYLAWYQQKPGQSPKLLIYWASTR					

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ESGVDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQHDSYPTFGGGSRLLEIK

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Table 4A: Anti-IL2/ILT4 Antibody 47H6 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTDY YMN (SEQ ID NO:70)	GYTFTDY (SEQ ID NO:76)	GYTFTDY YMN (SEQ ID NO:70)	DYYMN (SEQ ID NO:79)	TDYYMN (SEQ ID NO:80)
Heavy Chain variable region CDR2	DFNPNGGTTYNQKF EG (SEQ ID NO:71)	NPNGG (SEQ ID NO:77)	DFNPNGGTT (SEQ ID NO:78)	DFNPNGGTTYNQKFE G (SEQ ID NO:71)	WIGDFNPNGGTT (SEQ ID NO:81)
Heavy Chain variable region CDR3	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	ARGRFYYGSLYSFD (SEQ ID NO:82)
Light Chain variable region CDR1	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	HNYLAWY (SEQ ID NO:83)
Light Chain variable region CDR2	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	LLVYNAKTLA (SEQ ID NO:84)
Light Chain variable region CDR3	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSI (SEQ ID NO:85)
47H6 Heavy chain variable region (SEQ ID NO:131)					
EVQLQQGPELVKPGASVKISCKASGYTFTDY YMNWVKQSHGKSLWIGDFNPNGGTTY NQKFEKGATLTVDKSSNTAYMDLRSLTSEDSAVYYCARGRFYYGSLYSFDYWGQGTTLTIVSS					

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47H6 Light chain variable region (SEQ ID NO:132)

DIQMTQSPASLSASVGETVTITCRASGNIHNLYLAWYQQKQKSPHLLVYNAKTLADGVPS  
RFSGSGGTQYSLKINNLQPEDEFGSYVCQHFWTSTITFGAGTKLDLK

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Table 4B: Anti-IL2/IL T4 Antibody Hz47H6.v2 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTDYMN (SEQ ID NO:70)	GYTFTDY (SEQ ID NO:76)	GYTFTDYMN (SEQ ID NO:70)	DYYMN (SEQ ID NO:79)	TDYYMN (SEQ ID NO:80)
Heavy Chain variable region CDR2	DFNPNNAGTTYNQK EG (SEQ ID NO:118)	NPNNAG (SEQ ID NO:119)	DFNPNNAGTT (SEQ ID NO:120)	DFNPNNAGTTYNQKFE G (SEQ ID NO:118)	WIGDFNPNNAGTT (SEQ ID NO:121)
Heavy Chain variable region CDR3	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	GRFYYGSLYSFDY (SEQ ID NO:72)	ARGRFYYGSLYSFD (SEQ ID NO:82)
Light Chain variable region CDR1	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	RASGNIHNYLA (SEQ ID NO:73)	HNYLAWY (SEQ ID NO:83)
Light Chain variable region CDR2	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	NAKTLAD (SEQ ID NO:74)	LLIYNAKTLA (SEQ ID NO:122)
Light Chain variable region CDR3	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSIT (SEQ ID NO:75)	QHFWTSI (SEQ ID NO:8)
Hz47H6.v2 Heavy chain variable region (SEQ ID NO:133) QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYMNWVRQAPGQRLEWIGDFNPNNAGTTYN QKFEGRVITITVDKSASTAYMELSSLRSEDTAVYYCARGRFYYGSLYSFDYWGQGLTVTVSS					

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Hz47H6.v2 Light chain variable region (SEQ ID NO:134)

DIQMTQSPSSLSASVGDRVTITCRASGNIHNHNYLAWYQQKPKAPKLLIYNNAKTLADGVPSR  
FSGSGGTDFTLTISSLQPEDFATYYCQHFVTSITFGPGTKVDIK

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Table 5: Anti-IL2/ILT4 Antibody 51A1 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GFTFNTYAMH (SEQ ID NO:86)	GFTFNTY (SEQ ID NO:92)	GFTFNTYAMH (SEQ ID NO:86)	TYAMH (SEQ ID NO:95)	NTYAMH (SEQ ID NO:96)
Heavy Chain variable region CDR2	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	RSKSSNYA (SEQ ID NO:93)	RIRSKSSNYATY (SEQ ID NO:94)	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	WVARIRSKSSNYATY (SEQ ID NO:97)
Heavy Chain variable region CDR3	DGIYYGTMYYAM DY (SEQ ID NO:88)	DGIYYGTMYYAM DY (SEQ ID NO:88)	DGIYYGTMYYA MDY (SEQ ID NO:88)	DGIYYGTMYYAM Y (SEQ ID NO:88)	VRDGIYYGTMYY AMID (SEQ ID NO:98)
Light Chain variable region CDR1	RASEVDYYGNSFMY (SEQ ID NO:89)	RASEVDYYGNSFMY (SEQ ID NO:89)	RASEVDYYGNSFM Y (SEQ ID NO:89)	RASEVDYYGNSFMY (SEQ ID NO:89)	DYYGNSFMYWY (SEQ ID NO:99)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASNLE (SEQ ID NO:100)
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEI (SEQ ID NO:101)
51A1 Heavy chain variable region (SEQ ID NO:135)					
EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMHWVRQAPGKGLEWVARIRSKSSNYAT YYADSVKDRFTISRDDSQSMLYLQMNLLKIEDTAMYYCVRDGIYYGTMYYAMDYWGQGTSTVYS					
51A1 Light chain variable region (SEQ ID NO:136)					
NIVLTQSPASLAVSLGQRATISCRASESVDYYGNSFMYWYQQKPKPPKLLIYFASNLES GVPARFSGSRDFTLTIDPVEAADAASYCQQNNEDPWTFCGGTKLEIK					

Attorney Docket No. 47702-0094WO1

Table 6A: Anti-IL2/ILT4 Antibody 64A12 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GFTFNTYAMH (SEQ ID NO:86)	GFTFNTY (SEQ ID NO:92)	GFTFNTYAMH (SEQ ID NO:86)	TYAMH (SEQ ID NO:95)	NTYAMH (SEQ ID NO:96)
Heavy Chain variable region CDR2	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	RSKSSNYA (SEQ ID NO:93)	RIRSKSSNYATY (SEQ ID NO:94)	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	WVARIRSKSSNYATY (SEQ ID NO:97)
Heavy Chain variable region CDR3	DGIYYDITMYYAM DY (SEQ ID NO:102)	DGIYYDITMYYA MDY (SEQ ID NO:102)	DGIYYDITMYYAM DY (SEQ ID NO:102)	DGIYYDITMYYAMD Y (SEQ ID NO:102)	VRDGIYYDITMYYA MD (SEQ ID NO:104)
Light Chain variable region CDR1	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	DYYGNSFIYWY (SEQ ID NO:105)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASN <sup>T</sup> * (SEQ ID NO: )
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDP (SEQ ID NO: )
64A12 Heavy chain variable region (SEQ ID NO:137)					
EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMHWVRQAPGKGLWEVVARIRSKSSNYAT YYADSVKDRFTISRDDSSQSMLYLQMNNLKTEDTAMYYCVRDGIYYDITMYYAMDYWGQGTSTVTVSS					

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64A12 Light chain variable region (SEQ ID NO:138)

NIVLTQSPASLA VSLGQRATISCRASESVDYYGNSFIYWYQQKPGQPPKLLIYFASNLES  
GVPARFSGSGSR TDFTLTIDPVEAADAASYYCQQNNEDPWTFGGGKLEIK

Attorney Docket No. 47702-0094WO1

Table 6B: Anti-IL2/ILT4 Antibody Hz64A12 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GFTFNTYAMH (SEQ ID NO:86)	GFTFNTY (SEQ ID NO:92)	GFTFNTYAMH (SEQ ID NO:86)	TYAMH (SEQ ID NO:95)	NTYAMH (SEQ ID NO:96)
Heavy Chain variable region CDR2	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	RSKSSNYA (SEQ ID NO:93)	RIRSKSSNYATY (SEQ ID NO:94)	RIRSKSSNYATYYADS VKD (SEQ ID NO:87)	WVARIRSKSSNYATY (SEQ ID NO:97)
Heavy Chain variable region CDR3	DGIYYDVTMYYYAM DY (SEQ ID NO:102)	DGIYYDVTMYYYA MDY (SEQ ID NO:102)	DGIYYDVTMYYYAM DY (SEQ ID NO:102)	DGIYYDVTMYYYAM Y (SEQ ID NO:102)	ARDGIYYDVTMYYYA MD (SEQ ID NO:123)
Light Chain variable region CDR1	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	RASEVDYYGNSFIY (SEQ ID NO:103)	DYYGNSFIYWY (SEQ ID NO:105)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASNLE (SEQ ID NO:100)
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDP (SEQ ID NO:)
Hz64A12 Heavy chain variable region (SEQ ID NO:139)					
EVQLVESGGGLVQPGGSLRLSCAASGFTFTNTYAMHWVVRQAPGKGLWVARIRSKSSNYAT YYADSVKDRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARDGIYYDVTMYYYAMDYWGQGTLVTVSS					
Hz64A12 Light chain variable region (SEQ ID NO:140)					
NIVLTQSPDSLAVSLGERATINCRASESDYYGNSFIYWYQQKPGQPPLLIYFASNLES GVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQNNEDPWTFTGGGKVEIK					

Attorney Docket No. 47702-0094WO1

Table 7: Anti-IL2/ILT4 Antibody 73C4 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTDYVMN (SEQ ID NO:70)	GYTFTDY (SEQ ID NO:76)	GYTFTDYVMN (SEQ ID NO:70)	DYYMN (SEQ ID NO:79)	TDYYMN (SEQ ID NO:80)
Heavy Chain variable region CDR2	NVNPNGGTSYNQK FKG (SEQ ID NO:106)	NPNGG (SEQ ID NO:77)	NVNPNGGTS (SEQ ID NO:108)	NVNPNGGTSYNQK KG (SEQ ID NO:106)	WIGNVNPNGGTS (SEQ ID NO:109)
Heavy Chain variable region CDR3	REIFYGTIYYAMD Y (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAMDY (SEQ ID NO:107)	ARREIFYGTIYYA MD (SEQ ID NO:110)
Light Chain variable region CDR1	RASEVDYYGNSFM Y (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSFMY (SEQ ID NO:89)	DYYGNSFMYWY (SEQ ID NO:99)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASNLE (SEQ ID NO:100)
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPW (SEQ ID NO:10)
73C4 Heavy chain variable region (SEQ ID NO:141)					
AVQLQQSGPELVKPGASVKISCKASGYTFTDYVMNWVKQSHGKSLIEWIGNVNPNGGTSY NQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARREIFYGTIYYAMDYWGQGSTVTVSS					
73C4 Light chain variable region (SEQ ID NO:142)					
DIVLTQSPASLAVSLGQRATISCRASESVDYYGNSFMYWYQQKPKRPPNLLIYFASNLES					

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GVPARFSGSRTDFLTIDPVEADDAATYYCQNNEDPWTFGGGKLEIK

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Table 8A: Anti-ILT2/ILT4 Antibody 73D1 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTDYIN (SEQ ID NO:111)	GYTFTDY (SEQ ID NO:76)	GYTFTDYIN (SEQ ID NO:111)	DYYIN (SEQ ID NO:115)	TDYYIN (SEQ ID NO:116)
Heavy Chain variable region CDR2	NVNPNDGGTTYNQKF KG (SEQ ID NO:112)	NPNDGG (SEQ ID NO:113)	NVNPNDGGTT (SEQ ID NO:114)	NVNPNDGGTTYNQKF KG (SEQ ID NO:112)	WIGNVNPNDGGTT (SEQ ID NO:117)
Heavy Chain variable region CDR3	REIFYGTIYYAMD Y (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAMDY (SEQ ID NO:107)	ARREIFYGTIYY AMD (SEQ ID NO:110)
Light Chain variable region CDR1	RASEVDYYGNSFMY (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSFMY (SEQ ID NO:89)	DYYGNSFMYWY (SEQ ID NO:99)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASNLE (SEQ ID NO:100)
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDP* (SEQ ID NO:1
73D1 Heavy chain variable region (SEQ ID NO:143)					
AVLQQSGPELVKPGASVKISCKASGYTFTDYINWVKQSHGKSLQWIGNVNPNDGGTTY NQKFKGKATLVDKSSSTAYMELRSLTSEDSAVYYCARREIFYGTIYYAMDYWGQGTSVTVSS					

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73D1 Light chain variable region (SEQ ID NO:142)

DIVLTQSPASLAVSLGQRATISCRASESDYDYYGNSFMYYQQKPGRPPNLLIYFASNLES  
GVPARFSGSGSRTDFTLTIDPVEADDAATYYCQQNNEDPWTFGGGKLEIK

Attorney Docket No. 47702-0094WO1

Table 8B: Anti-IL2/IL T4 Antibody Hz73D1.v1 Sequences

	Exemplary	Chothia	AbM	Kabat	Contact
Heavy Chain variable region CDR1	GYTFTDYYIN (SEQ ID NO:111)	GYTFTDY (SEQ ID NO:76)	GYTFTDYYIN (SEQ ID NO:111)	DYYIN (SEQ ID NO:115)	TDYYIN (SEQ ID NO:116)
Heavy Chain variable region CDR2	NVNPNDGGTYYNQKF KG (SEQ ID NO:112)	NPNDGG (SEQ ID NO:113)	NVNPNDGGTT (SEQ ID NO:114)	NVNPNDGGTYYNQKF KG (SEQ ID NO:112)	WMGNVNPNDGGTT (SEQ ID NO:124)
Heavy Chain variable region CDR3	REIFYGTIYYAMD Y (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAM DY (SEQ ID NO:107)	REIFYGTIYYAMDY (SEQ ID NO:107)	ARREIFYGTIYY AMD (SEQ ID NO:110)
Light Chain variable region CDR1	RASEVDYYGNSFMY (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSF MY (SEQ ID NO:89)	RASEVDYYGNSFMY (SEQ ID NO:89)	DYYGNSFMYWY (SEQ ID NO:99)
Light Chain variable region CDR2	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	FASNLES (SEQ ID NO:90)	LLIYFASNLE (SEQ ID NO:100)
Light Chain variable region CDR3	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDPWT (SEQ ID NO:91)	QQNNEDP* (SEQ ID NO:1
Hz73D1.v1 Heavy chain variable region (SEQ ID NO:144)					
QQQLVQSGAEVKKPGASVKV/SCKASGYFTFDYYINWVRQAPGQGLEWMGNVNPNDGGTTY NQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARREIFYGTIYYAMDYWGQGTLVTVSS					

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Hz73D1.v1 Light chain variable region (SEQ ID NO:145)

DIQLTQSPSFLSASVGDRTITCRASESVDYYGNSFMYWYQQKPKAPKLLIYFASNLES  
GVPSRFSGSGGTEFTLTISSLQPEDFATYYCQQNNEDPWTFGGGKVEIK

[00187] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from an antibody described herein. In some embodiments, an ILT-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from an antibody described herein. In some embodiments, an ILT-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, CDR2, and CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, CDR2, and CDR3 from an antibody described herein.

[00188] In some embodiments, an ILT-binding agent (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) comprises one or more (*e.g.*, 1, 2, 3, 4, etc.) amino acid substitutions in a CDR of an antibody described herein. In some embodiments, the amino acid substitutions are conservative substitutions. In some embodiments, a CDR comprises one amino acid substitution. In some embodiments, a CDR comprises two amino acid substitutions. In some embodiments, a CDR comprises three amino acid substitutions. In some embodiments, a CDR comprises four amino acid substitutions. In some embodiments, the CDR is a heavy chain variable region CDR1. In some embodiments, the CDR is a heavy chain variable region CDR2. In some embodiment, the CDR is a heavy chain variable region CDR3. In some embodiments, the CDR is a light chain variable region CDR1. In some embodiments, the CDR is a light chain variable region CDR2. In some embodiments, the CDR is a light chain variable region CDR3. In some embodiments, the substitutions are made as part of a humanization process. In some embodiments, the substitutions are made as part of a germline humanization process. In some embodiments, the substitutions are made as part of an affinity maturation process. In some embodiments, the substitutions are made as part of an optimization process.

[00189] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) comprises one or more heavy

chain variable region CDRs or light chain variable region CDRs that have been modified to reduce deamidation within the CDR sequence. Deamidation is a chemical reaction in which an amide functional group in the side chain of the amino acids asparagine (Asn or N) or glutamine (Gln or Q) is removed or converted to another functional group. Generally, asparagine is converted to aspartic acid or isoaspartic acid and glutamine is converted to glutamic acid or polyglutamic acid. In some situations, deamidation may change the structure, function, and/or stability of a polypeptide, potentially resulting in decreased biological activity. In some embodiments, the heavy chain variable region CDR1, CDR2, and/or CDR3 of an antibody described herein is modified to reduce deamidation. In some embodiments, the light chain variable region CDR1, CDR2, and/or CDR3 of an antibody described herein is modified to reduce deamidation.

**[00190]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) comprises one or more heavy chain variable region CDRs or light chain variable region CDRs that have been modified to reduce isomerization. Isomerization is a chemical process by which a compound is transformed into any of its isomeric forms, *i.e.*, forms with the same chemical composition but with different structure or configuration and, potentially with different physical and chemical properties. Studies have shown that asparatate (Asp or D) isomerization within a CDR can impact antibody binding and/or stability. In some embodiments, the heavy chain variable region CDR1, CDR2, and/or CDR3 of an antibody described herein is modified to reduce isomerization. In some embodiments, the light chain variable region CDR1, CDR2, and/or CDR3 is modified to reduce isomerization.

**[00191]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4 binding agent) comprises one or more heavy chain variable region CDRs or light chain variable region CDRs that have been modified to reduce oxidation. Oxidation is a chemical process by which an oxygen is added to an atom, for example, methionine is converted to methionine sulfoxide by

addition of an oxygen to the sulfur atom. Oxidation of one or more amino acids can potentially affect the physical and chemical properties of a protein. Studies have shown that oxidation of methionine (Met or M) within a CDR has the potential to impact antibody binding and/or stability. In some embodiments, the heavy chain variable region CDR1, CDR2, and/or CDR3 of an antibody described herein is modified to reduce oxidation (*e.g.*, methionine oxidation). In some embodiments, the light chain variable region CDR1, CDR2, and/or CDR3 of an antibody described herein is modified to reduce oxidation (*e.g.*, methionine oxidation).

**[00192]** In some embodiments, an ILT2-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 27F9, a humanized version thereof, or variants thereof. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 27F9. In other embodiments, an ILT2-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 27F9. In some embodiments, an ILT2-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 27F9. In some embodiments, an ILT2-binding agent is a humanized version of antibody 27F9. In some embodiments, an ILT2-binding agent is a variant of antibody 27F9 or humanized 27F9.

**[00193]** In some embodiments, an ILT2-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence

PNWDTYAMDF (SEQ ID NO:24), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNY (SEQ ID NO:28), a heavy chain variable region CDR2 comprising the amino acid sequence WGDGS (SEQ ID NO:29), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTN (SEQ ID NO:30), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence NYGVS (SEQ ID NO:31), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the

amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TNYGVS (SEQ ID NO:32), a heavy chain variable region CDR2 comprising the amino acid sequence WLGIIWGDGSTN (SEQ ID NO:33), and a heavy chain variable region CDR3 comprising the amino acid sequence AKPNWDTYAMD (SEQ ID NO:34), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence SNFLNWY (SEQ ID NO:35), a light chain variable region CDR2 comprising the amino acid sequence LLIYCTSKLH (SEQ ID NO:36), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPP (SEQ ID NO:37).

**[00194]** In some embodiments, an ILT2-binding agent comprises: (a) a heavy chain variable region comprising heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27). In some embodiments, the ILT2-binding agent comprises a heavy chain variable region comprising heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24). In some embodiments, the ILT2-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2

comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27). In some embodiments, the ILT2-binding agent comprises: (a) a heavy chain variable region comprising heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27).

**[00195]** In some embodiments, an anti-ILT2 binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 27F9 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:125 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 27F9 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:126.

**[00196]** In some embodiments, an ILT2-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:125. In some embodiments, an ILT2-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID

NO:125. In some embodiments, an ILT2-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:126.

[00197] In some embodiments, an ILT2-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:125 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:125 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:125 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:126. In some embodiments, an ILT2-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:125 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:126.

[00198] In some embodiments, an ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 47C8, a humanized version thereof, or variants thereof. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 47C8. In other embodiments, an ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 47C8. In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 47C8. In some embodiments, an ILT4-binding agent is a

humanized version of antibody 47C8. In some embodiments, an ILT4-binding agent is a variant of antibody 47C8 or humanized 47C8.

[00199] In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGY (SEQ ID NO:44), a heavy chain variable region CDR2 comprising the amino acid sequence YPNNGD (SEQ ID NO:45), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTS (SEQ ID NO:46), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain

variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYYMH (SEQ ID NO:47), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TGYMH (SEQ ID NO:48), a heavy chain variable region CDR2 comprising the amino acid sequence WIGRVYPNNGDTS (SEQ ID NO:49), and a heavy chain variable region CDR3 comprising the amino acid sequence ARGATVVESLFA (SEQ ID NO:50), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence DNYGNNFLHWY (SEQ ID NO:51), a light chain variable region CDR2 comprising the amino acid sequence LLIYRTSNLE (SEQ ID NO:52), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:53).

**[00200]** In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain

variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43). In some embodiments, the ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40). In some embodiments, the ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43). In some embodiments, the ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPDT (SEQ ID NO:43).

**[00201]** In some embodiments, an anti-ILT4 binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 47C8 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:127 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 47C8 and which has at least 75%, at least 80%, at least 85%, at

least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:128.

**[00202]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:127. In some embodiments, an ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:127. In some embodiments, an ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:128.

**[00203]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:127 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:127 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:127 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:128. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:127 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:128.

**[00204]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 48A5, a humanized version thereof, or variants thereof. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 48A5. In other

embodiments, an ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 48A5. In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 48A5. In some embodiments, an ILT4-binding agent is a humanized version of antibody 48A5. In some embodiments, an ILT4-binding agent is a variant of antibody 48A5 or humanized 48A5.

**[00205]** In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNY (SEQ ID NO:60), a heavy chain variable region CDR2 comprising the amino acid sequence NTYIGE (SEQ ID NO:61), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID

NO:59); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPI (SEQ ID NO:62), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence NYGMN (SEQ ID NO:63), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TNYGMN (SEQ ID NO:64), a heavy chain variable region CDR2 comprising the amino acid sequence WMGWINTYIGEPI (SEQ ID NO:65), and a heavy chain variable region CDR3 comprising the amino acid sequence ARRSYDGYAMD (SEQ ID NO:66), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence LYSQKKNYLA (SEQ ID NO:67), a light chain variable region CDR2 comprising the amino acid sequence LLIYWASTRE (SEQ ID NO:68), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYP (SEQ ID NO:69).

[00206] In some embodiments, an ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59). In some embodiments, the ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56). In some embodiments, the ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59). In some embodiments, the ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID

NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59).

**[00207]** In some embodiments, an anti-ILT4 binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 48A5 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:129 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 48A5 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:130.

**[00208]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:129. In some embodiments, an ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:129. In some embodiments, an ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:130.

**[00209]** In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:129 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:129 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:130. In some embodiments, an ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:129 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:130. In some embodiments, an

ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:129 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:130.

**[00210]** In some embodiments, an ILT2/ILT4-binding agent (*e.g.*, a dual binder) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 47H6, a humanized version thereof (*e.g.*, Hz47H6.v2), or variants thereof. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 47H6 or antibody Hz47H6.v2. In other embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 47H6 or antibody Hz47H6.v2. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 47H6. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody Hz47H6.v2. In some embodiments, an ILT2/ILT4-binding agent is a humanized version of antibody 47H6. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody 47H6. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody Hz47H6.v2.

**[00211]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region

CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDY (SEQ ID NO:76), a heavy chain variable region CDR2 comprising the amino acid sequence NPNNGG (SEQ ID NO:77) or the amino acid sequence NPNNAG (SEQ ID NO:119), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTT (SEQ ID NO:78) or the amino acid sequence DFNPNAGTT (SEQ ID NO:120), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence DYYMN (SEQ ID NO:79), a heavy chain variable region CDR2 comprising the amino acid sequence

DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TDYYMN (SEQ ID NO:80), a heavy chain variable region CDR2 comprising the amino acid sequence WIGDFNPNNGGTT (SEQ ID NO:81) or the amino acid sequence WIGDFNPNNAGTT (SEQ ID NO:121), and a heavy chain variable region CDR3 comprising the amino acid sequence ARGRFYYGSLYSFD (SEQ ID NO:82), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence HNYLAWY (SEQ ID NO:83), a light chain variable region CDR2 comprising the amino acid sequence LLVYNAKTLA (SEQ ID NO:84) or the amino acid sequence LLIYNAKTLA (SEQ ID NO:122), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSI (SEQ ID NO:85).

**[00212]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments, the ILT2/ILT4-binding agent

comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72). In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72). In some embodiments, the ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNAGTTYNQKFEG (SEQ ID NO:118),

and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75).

**[00213]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 47H6 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:131 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 47H6 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:132.

**[00214]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:131. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:131. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:132.

**[00215]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:131 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable

region having at least 90% sequence identity to SEQ ID NO:131 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:131 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:132. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:131 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:132.

**[00216]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody Hz47H6.v2 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:133 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody Hz47H6.v2 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:134.

**[00217]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:133. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:133. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:134.

**[00218]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:133 and a light

chain variable region having at least 80% sequence identity to SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:133 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:133 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:134. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:133 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:134.

[00219] In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable region CDR1 comprising GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:148, and wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable region CDR1 comprising GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence

GRFYYGSLYSFDY (SEQ ID NO:72), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75), wherein the heavy chain comprises at least 95% identity to the sequence of SEQ ID NO:148, and wherein the light chain comprises at least 95% identity to the sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:148 and (b) a light chain comprising a light chain variable region CDR1 comprising RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75), wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:148 and (b) a light chain comprising a light chain variable region CDR1 comprising RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising a heavy chain variable region CDR1 comprising GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:148, and (b) a light chain comprising the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-

binding agent comprises (a) a heavy chain comprising a heavy chain variable region CDR1 comprising GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYSLSYFDY (SEQ ID NO:72), and (b) a light chain comprising the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent is an antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:148 and a light chain comprising the amino acid sequence of SEQ ID NO:149.

**[00220]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:148. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:148 and a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:148. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:148 and a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:148. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain comprising the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:148 and a light chain

comprising the amino acid sequence of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:148 and/or a light chain of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:148. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a light chain of SEQ ID NO:149. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:148 and a light chain of SEQ ID NO:149.

[00221] In some embodiments, an ILT2/ILT4-binding agent (*e.g.*, a dual binder) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 51A1, a humanized version thereof, or variants thereof. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 51A1. In other embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 51A1. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 51A1. In some embodiments, an ILT2/ILT4-binding agent is a humanized version of antibody 51A1. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody 51A1 or humanized 51A1.

[00222] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence

DGIYYYYGTMYYYYAMDY (SEQ ID NO:88), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTY (SEQ ID NO:92), a heavy chain variable region CDR2 comprising the amino acid sequence RSKSSNYA (SEQ ID NO:93), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYGTMYYYYAMDY (SEQ ID NO:88), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATY (SEQ ID NO:94), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYGTMYYYYAMDY (SEQ ID NO:88), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TYAMH (SEQ ID NO:95), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYGTMYYYYAMDY (SEQ ID NO:88), and a light chain variable region comprising a light chain variable region

CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence NTYAMH (SEQ ID NO:96), a heavy chain variable region CDR2 comprising the amino acid sequence WVARIRSKSSNYATY (SEQ ID NO:97), and a heavy chain variable region CDR3 comprising the amino acid sequence VRDGIYYYYGTMYYYAMD (SEQ ID NO:98), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence DYYGNSFMYWY (SEQ ID NO:99), a light chain variable region CDR2 comprising the amino acid sequence LLIYFASNLE (SEQ ID NO:100), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPW (SEQ ID NO:101).

**[00223]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYGTMYYYAMDY (SEQ ID NO:88), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYGTMYYYAMDY (SEQ ID NO:88). In some embodiments, the ILT2/ILT4-

binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYGTMYYYAMDY (SEQ ID NO:88), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91).

**[00224]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 51A1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:135 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 51A1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:136.

**[00225]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:135. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region

having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:135. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:136.

**[00226]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:135 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:135 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:135 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:136. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:135 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:136.

**[00227]** In some embodiments, an ILT2/ILT4-binding agent (*e.g.*, a dual binder) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 64A12, a humanized version thereof (*e.g.*, Hz64A12), or variants thereof. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 64A12 or Hz64A12. In other embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 64A12 or Hz64A12. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a

heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 64A12 or Hz64A12. In some embodiments, an ILT2/ILT4-binding agent is a humanized version of antibody 64A12. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody 64A12. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody Hz64A12.

**[00228]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYD(TM)YYYAMDY (SEQ ID NO:102), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTY (SEQ ID NO:92), a heavy chain variable region CDR2 comprising the amino acid sequence RSKSSNYA (SEQ ID NO:93), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYD(TM)YYYAMDY (SEQ ID NO:102), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATY

(SEQ ID NO:94), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYDTMYYYAMDY (SEQ ID NO:102), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TYAMH (SEQ ID NO:95), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYDTMYYYAMDY (SEQ ID NO:102), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence NTYAMH (SEQ ID NO:96), a heavy chain variable region CDR2 comprising the amino acid sequence WVARIRSKSSNYATY (SEQ ID NO:97), and a heavy chain variable region CDR3 comprising the amino acid sequence VRDGIYYYDTMYYYAMD (SEQ ID NO:104), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence DYYGNSFIYWY (SEQ ID NO:105), a light chain variable region CDR2 comprising the amino acid sequence LLIYFASNLE (SEQ ID NO:100), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPW (SEQ ID NO:101).

[00229] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID

NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYDYDTMYYYAMDY (SEQ ID NO:102), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYDYDTMYYYAMDY (SEQ ID NO:102). In some embodiments, the ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYDYDTMYYYAMDY (SEQ ID NO:102), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91).

**[00230]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 64A12 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:137 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 64A12 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:138.

**[00231]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:137. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:137. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:138.

**[00232]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:137 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:137 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:137 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:138. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region

comprising an amino acid sequence of SEQ ID NO:137 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:138.

**[00233]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody Hz64A12 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:139 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody Hz64A12 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:140.

**[00234]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:139. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:139. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:140.

**[00235]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:139 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:139 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:139 and a light chain variable

region having at least 95% sequence identity to SEQ ID NO:140. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:139 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:140.

**[00236]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYDTMYYYAMDY (SEQ ID NO:102), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:152, and wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYDTMYYYAMDY (SEQ ID NO:102), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain comprises at least 95% identity to the sequence of

SEQ ID NO:152, and wherein the light chain comprises at least 95% identity to the sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:152 and (b) a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:152 and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYYDTMYYYAMDY (SEQ ID NO:102), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:152, and (b) a light chain comprising the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence

DGIYYDYDTMYYYAMDY (SEQ ID NO:102), and (b) a light chain comprising the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent is an antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:152 and a light chain comprising the amino acid sequence of SEQ ID NO:153.

[00237] In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:152. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:152 and a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:152. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:152 and a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:152. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain comprising the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:152 and a light chain comprising the amino acid sequence of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:152 and/or a light chain of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:152. In some

embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a light chain of SEQ ID NO:153. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:152 and a light chain of SEQ ID NO:153.

[00238] In some embodiments, an ILT2/ILT4-binding agent (*e.g.*, a dual binder) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 73C4, a humanized version thereof, or variants thereof. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 73C4. In other embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 73C4. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 73C4. In some embodiments, an ILT2/ILT4-binding agent is a humanized version of antibody 73C4. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody 73C4 or humanized 73C4.

[00239] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain

variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDY (SEQ ID NO:76), a heavy chain variable region CDR2 comprising the amino acid sequence NPNNGG (SEQ ID NO:77), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTS (SEQ ID NO:108), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence DYYMN (SEQ ID NO:79), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); or (e) a heavy chain variable region

comprising a heavy chain variable region CDR1 comprising the amino acid sequence TDYYMN (SEQ ID NO:80), a heavy chain variable region CDR2 comprising the amino acid sequence WIGNVNPNGGTS (SEQ ID NO:109), and a heavy chain variable region CDR3 comprising the amino acid sequence ARREIFYFGTIYYYAMD (SEQ ID NO:110), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence DYYGNSFMWY (SEQ ID NO:99), a light chain variable region CDR2 comprising the amino acid sequence LLIYFASNLE (SEQ ID NO:100), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPW (SEQ ID NO:101).

**[00240]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYYAMDY (SEQ ID NO:107), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMWY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYYAMDY (SEQ ID NO:107). In some embodiments, the ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMWY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the

amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91).

**[00241]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 73C4 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:141 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 73C4 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:142.

**[00242]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:141. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:141. In some embodiments, an ILT2/ILT4-binding agent

comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:142.

**[00243]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:141 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:141 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:141 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:141 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:142.

**[00244]** In some embodiments, an ILT2/ILT4-binding agent (*e.g.*, a dual binder) comprises a heavy chain variable region CDR1, CDR2, and CDR3 and/or a light chain variable region CDR1, CDR2, and CDR3 from antibody 73D1, a humanized version thereof (*e.g.*, Hz73D1), or variants thereof. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, and a heavy chain variable region CDR3 from antibody 73D1 or antibody Hz73D1.v1. In other embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 73D1 or antibody Hz73D1.v1. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3; and (b) a light chain variable region comprising a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 from antibody 73D1 or antibody Hz73D1.v1. In some

embodiments, an ILT2/ILT4-binding agent is a humanized version of antibody 73D1. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody 73D1. In some embodiments, an ILT2/ILT4-binding agent is a variant of antibody Hz73D1.v1.

[00245] In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDY (SEQ ID NO:76), a heavy chain variable region CDR2 comprising the amino acid sequence NPNDGG (SEQ ID NO:113), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTT (SEQ ID NO:114), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region

CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence DYYIN (SEQ ID NO:115), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91); or (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence TDYYIN (SEQ ID NO:116), a heavy chain variable region CDR2 comprising the amino acid sequence WIGNVNPNDGGTT (SEQ ID NO:117) or the amino acid sequence WMGNVNPNDGGTT (SEQ ID NO:124), and a heavy chain variable region CDR3 comprising the amino acid sequence ARREIYFYGTIYYYAMD (SEQ ID NO:110), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence DYYGNSFMYWY (SEQ ID NO:99), a light chain variable region CDR2 comprising the amino acid sequence LLIYFASNLE (SEQ ID NO:100), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPW (SEQ ID NO:101).

**[00246]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and/or (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence

RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYYAMDY (SEQ ID NO:107). In some embodiments, the ILT2/ILT4-binding agent comprises a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, the ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91).

**[00247]** In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112),

or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions.

**[00248]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody 73D1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:143 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody 73D1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:142.

**[00249]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:143. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:143. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:142.

**[00250]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:143 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:143 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:143 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:143 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:142.

**[00251]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising the amino acid sequence of heavy chain variable region CDR1, CDR2, and CDR3 of antibody Hz73D1.v1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:144 and a light chain variable region comprising the amino acid sequence of light chain variable region CDR1, CDR2, and CDR3 of antibody Hz73D1.v1 and which has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:145.

**[00252]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:144. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain variable region having at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity to the sequence of SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:144. In some embodiments, an ILT2/ILT4-binding agent

comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:145.

**[00253]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:144 and a light chain variable region having at least 80% sequence identity to SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:144 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:144 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:145. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:144 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:145.

**[00254]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain variable region comprising a heavy chain variable region CDR1 comprising GYTFTDYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYFGTIYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain variable region comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98% identity to the sequence of SEQ ID NO:143, and wherein the light chain variable region comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98% identity to the sequence of SEQ ID NO:142. In some embodiments, an ILT2/ILT4-binding agent comprises a

heavy chain variable region comprising a heavy chain variable region CDR1 comprising GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain variable region comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98% identity to the sequence of SEQ ID NO:144, and wherein the light chain variable region comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98% identity to the sequence of SEQ ID NO:145.

**[00255]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable region CDR1 comprising GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:156, and wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising a heavy chain variable

region CDR1 comprising GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and a light chain comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the heavy chain comprises at least 95% identity to the sequence of SEQ ID NO:156, and wherein the light chain comprises at least 95% identity to the sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:156 and (b) a light chain comprising a light chain variable region CDR1 comprising RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91), wherein the light chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises (a) a heavy chain comprising the amino acids of SEQ ID NO:156 and (b) a light chain comprising a light chain variable region CDR1 comprising RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID

NO:107), wherein the heavy chain comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identity to the sequence of SEQ ID NO:156, and (b) a light chain comprising the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises: (a) a heavy chain comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIFYGTIYYAMDY (SEQ ID NO:107), and (b) a light chain comprising the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent is an antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:156 and a light chain comprising the amino acid sequence of SEQ ID NO:157.

**[00256]** In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:156. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:156 and a light chain having at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:156. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain having at least 90% identity to the amino acid sequence of SEQ ID NO:156 and a light chain having at least 90% identity to the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain

comprising the amino acid sequence of SEQ ID NO:156. In some embodiments, an ILT2/ILT4-binding agent comprises a light chain comprising the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:156 and a light chain comprising the amino acid sequence of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:156 and/or a light chain of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:156. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a light chain of SEQ ID NO:157. In some embodiments, an ILT2/ILT4-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:156 and a light chain of SEQ ID NO:157.

**[00257]** In some embodiments, the ILT2/ILT4-binding agent is antibody 73D1. In some embodiments, the ILT2/ILT4-binding agent is antibody Hz73D1.v1.

**[00258]** Provided herein are agents that compete with one or more of the binding agents described herein for binding to ILT2, ILT4, or both ILT2 and ILT4. In some embodiments, an agent competes with one or more of the antibodies described herein for binding to ILT2, ILT4, or both ILT2 and ILT4. In some embodiments, an agent that competes with one or more of the antibodies described herein is an antibody. In some embodiments, an agent binds the same epitope as one of the antibodies described herein. In some embodiments, an agent binds an epitope overlapping with an epitope bound by one of the antibodies described herein. Antibodies and antigen-binding fragments that compete with or bind the same epitope as the antibodies described herein are expected to show similar functional properties.

**[00259]** In some embodiments, an agent competes for binding to human ILT2, ILT4, or both ILT2 and ILT4 with a reference antibody, wherein the reference antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region

CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an agent competes for binding to human ILT2 with a reference antibody, wherein the reference antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91).

**[00260]** In some embodiments, an agent competes for binding to human ILT2, ILT4, or both ILT2 and ILT4 with a reference antibody, wherein the reference antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some

embodiments, an agent competes for binding to human ILT4 with a reference antibody, wherein the reference antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYSGLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75).

[00261] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4, binding agent, or an ILT2/ILT4 binding agent) described herein comprises an antibody in which at least one or more of the constant regions of the antibody has been modified or deleted. In some embodiments, an antibody comprises one or more modifications to one or more of the three heavy chain constant regions (CH1, CH2 or CH3) and/or to the light chain constant region (CL). In some embodiments, an antibody comprises one or more modifications to the hinge region. In some embodiments, the heavy chain constant region of the modified antibody comprises at least one human constant region. In some embodiments, the heavy chain constant region of the modified antibody comprises more than one human constant region. In some embodiments, modifications to the constant region comprise additions, deletions, or substitutions of one or more amino acids in one or more regions. In some embodiments, one or more regions are partially or entirely deleted from the constant regions of a modified antibody. In some embodiments, the entire CH2 domain has been removed from an antibody ( $\Delta$ CH2 constructs). In some embodiments, one or more regions are partially or entirely deleted from the hinge region of a modified antibody. In some embodiments, a deleted constant region is replaced by a short amino acid spacer that

provides some of the molecular flexibility typically imparted by the absent constant region. In some embodiments, a deleted hinge region is replaced by a short amino acid spacer that provides some of the molecular flexibility typically imparted by the absent hinge region. In some embodiments, a modified antibody comprises a CH3 domain directly fused to the hinge region of the antibody. In some embodiments, a modified antibody comprises a peptide spacer inserted between the hinge region and modified CH2 and/or CH3 domains.

[00262] It is known in the art that the constant region(s) of an antibody mediates several effector functions and these effector functions can vary depending on the isotype of the antibody. For example, binding of the C1 component of complement to the Fc region of IgG or IgM antibodies (bound to antigen) activates the complement system. Activation of complement is important in the opsonization and lysis of cell pathogens. The activation of complement also stimulates the inflammatory response and can be involved in autoimmune hypersensitivity. In addition, the Fc region of an antibody can bind a Fc receptor (FcR) on the surface of a cell. There are a number of Fc receptors that are specific for different classes of antibody, including IgG (gamma receptors), IgE (epsilon receptors), IgA (alpha receptors) and IgM (mu receptors). Binding of antibody to Fc receptors on cell surfaces triggers a number of important and diverse biological responses including engulfment and destruction of antibody-coated particles, clearance of immune complexes, lysis of antibody-coated target cells by killer cells (called antibody-dependent cell cytotoxicity or ADCC), release of inflammatory mediators, placental transfer, and control of immunoglobulin production.

[00263] In some embodiments, an ILT-binding agent comprises a variant Fc region. The amino acid sequences of the Fc region of human IgG1, IgG2, IgG3, and IgG4 are known to those of ordinary skill in the art (*e.g.*, a representative human IgG1 region is SEQ ID NO:158). In some cases, Fc regions with amino acid variations have been identified in native antibodies. In some embodiments, a variant Fc region is engineered with substitutions at specific amino acid positions as compared to a native Fc region.

Variant Fc regions are well-known in the art and include, but are not limited to, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, and SEQ ID NO:163.

**[00264]** In some embodiments, a modified antibody provides for altered effector functions that, in turn, affect the biological profile of the antibody. For example, in some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region reduces Fc receptor binding of a modified antibody as it circulates. In some embodiments, constant region modifications increase the serum half-life of an antibody. In some embodiments, constant region modifications reduce the serum half-life of an antibody. In some embodiments, constant region modifications decrease or remove ADCC and/or complement-dependent cytotoxicity (CDC) of an antibody. In some embodiments, specific amino acid substitutions in a human IgG1 Fc region with corresponding IgG2 or IgG4 residues reduce effector functions (*e.g.*, ADCC and CDC) in a modified antibody. In some embodiments, a modified antibody does not have one or more effector functions. In some embodiments, a modified antibody does not have any detectable effector functions (*e.g.*, “effectorless” antibodies). In some embodiments, a modified antibody has no ADCC activity and/or no CDC activity. In some embodiments, a modified antibody does not bind an Fc receptor and/or complement factors. In some embodiments, a modified antibody has no effector function(s). In some embodiments, constant region modifications increase or enhance ADCC and/or CDC of an antibody. In some embodiments, the constant region is modified to eliminate disulfide linkages or oligosaccharide moieties. In some embodiments, the constant region is modified to add/substitute one or more amino acids to provide one or more cytotoxin, oligosaccharide, or carbohydrate attachment sites.

**[00265]** Modifications to the constant region of antibodies described herein may be made using well-known biochemical or molecular engineering techniques. In some embodiments, antibody variants are prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Using these engineering techniques to modify an antibody it may be possible to disrupt the activity or effector function provided by a specific sequence or

region while substantially maintaining the structure, binding activity, and other desired characteristics of the modified antibody.

[00266] The present disclosure further embraces additional variants and equivalents that are substantially homologous to the recombinant, monoclonal, chimeric, humanized, and human antibodies, or antibody fragments thereof, described herein. In some embodiments, it is desirable to improve the binding affinity of the antibody. In some embodiments, it is desirable to modulate biological properties of the antibody, including but not limited to, specificity, thermostability, expression level, effector function(s), glycosylation, immunogenicity, and/or solubility. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of an antibody, such as changing the number or position of glycosylation sites or altering membrane anchoring characteristics.

[00267] Variations may be generated by the substitution, deletion, or insertion of one or more nucleotides into a polynucleotide encoding the antibody or polypeptide that results in a change in an amino acid or the amino acid sequence as compared with the native antibody or polypeptide sequence. In some embodiments, amino acid substitutions are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine (*i.e.*, conservative amino acid replacements). In some embodiments, the substitution, deletion, or insertion includes less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the parent molecule. In some embodiments, variations in the amino acid sequence that are biologically useful and/or relevant are determined by systematically making insertions, deletions, or substitutions in the sequence and testing the resulting variant proteins for activity as compared to the parental antibody.

[00268] In some embodiments, variants may include addition of amino acid residues at the amino- and/or carboxyl-terminal end of the antibody or polypeptide. The length of

additional amino acids residues may range from one residue to a hundred or more residues. In some embodiments, a variant comprises an N-terminal methionyl residue. In some embodiments, the variant comprises an additional polypeptide/protein to create a fusion protein. In some embodiments, a variant is engineered to be detectable and may comprise a detectable label and/or protein (*e.g.*, a fluorescent tag, a fluorescent protein, or an enzyme).

[00269] In some embodiments, a cysteine residue not involved in maintaining the proper conformation of an antibody is substituted or deleted to modulate the antibody's characteristics, for example, to improve oxidative stability and/or prevent aberrant disulfide crosslinking. Conversely, in some embodiments, one or more cysteine residues are added to create disulfide bond(s) to improve stability.

[00270] In some embodiments, an antibody of the present disclosure is "deimmunized". The deimmunization of antibodies generally consists of introducing specific amino acid mutations (*e.g.*, substitutions, deletions, additions) that result in removal of T-cell epitopes (known or predicted) without significantly reducing the binding affinity or other desired activities of the antibody.

[00271] The variant antibodies or polypeptides described herein may be generated using methods known in the art, including but not limited to, site-directed mutagenesis, alanine scanning mutagenesis, and PCR mutagenesis.

[00272] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein is chemically modified. In some embodiments, an ILT-binding agent is (i) an anti-ILT2 antibody, (ii) an anti-ILT4 antibody, or (iii) an anti-ILT2/ILT4 antibody that is chemically modified by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, and/or linkage to a cellular ligand or other protein. Any of numerous chemical modifications may be carried out by known techniques. In some embodiments, an ILT-binding agent is an antibody fragment (*e.g.*, scFv, Fv, Fab, F(ab')<sub>2</sub>, or F(ab')), wherein the antibody fragment is attached (either directly or indirectly) to a half-life extending moiety including, but not

limited to, polyethylene glycol (PEG), a PEG mimetic, XTEN®, serum albumin, polysialic acid, N-(2-hydroxypropyl)methacrylamide, or dextran.

[00273] The present disclosure encompasses ILT-binding agents built upon non-immunoglobulin backbones, wherein the agents bind the same epitope or essentially the same epitope as an anti-ILT antibody disclosed herein. In some embodiments, a non-immunoglobulin-based binding agent is an agent that competes with (i) an anti-ILT2 antibody, (ii) an anti-ILT4 antibody, and/or (iii) an anti-ILT2/ILT4 antibody described herein in a competitive binding assay. In some embodiments, alternative ILT-binding agents comprise a scaffold protein. Generally, scaffold proteins can be assigned to one of three groups based on the architecture of their backbone (1) scaffolds consisting of  $\alpha$ -helices; (2) small scaffolds with few secondary structures or an irregular architecture of  $\alpha$ -helices and  $\beta$ -sheets; and (3) scaffolds consisting of predominantly  $\beta$ -sheets. Scaffold proteins include, but are not limited to, anticalins, which are based upon the lipocalin scaffold; adnectins, which are based on the 10<sup>th</sup> domain of human fibronectin type 3; affibodies, which are based on the B-domain in the Ig-binding region of *Staphylococcus aureus* protein A; darpins, which are based on ankyrin repeat domain proteins; fynomers, which are based on the SH3 domain of the human Fyn protein kinase; affitins, which are based on Sac7d from *Sulfolobus acidocaldarius*; affilins, which are based on human  $\gamma$ -B-crystallin or human ubiquitin; avimers, which are based on the A-domains of membrane receptor proteins; knottins (cysteine knot miniproteins), which are based upon a stable 30-amino acid anti-parallel  $\beta$ -strand protein fold; and Kunitz domain inhibitor scaffolds, which are based upon a structure that contains three disulfide bonds and three loops.

[00274] In some embodiments, an ILT2-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 1. In some embodiments, an ILT2-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the

amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27). In some embodiments, an ILT2-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 27F9.

[00275] In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 2. In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPYPY (SEQ ID NO:43). In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 47C8.

[00276] In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 3. In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence

GYTFTNYGMN (SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPYADDFKG (SEQ ID NO:55), a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59). In some embodiments, an ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 48A5.

[00277] In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 4A or Table 4B. In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYSLSYFDY (SEQ ID NO:72), a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 47H6 or antibody Hz47H6.v2.

[00278] In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 5. In some

embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYGTMYYYYAMDY (SEQ ID NO:88), a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 51A1.

**[00279]** In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 6A or Table 6B. In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYDTMYYYYAMDY (SEQ ID NO:102), a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 64A12.

[00280] In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 7. In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 73C4.

[00281] In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 shown in Table 8A or Table 8B. In some embodiments, an ILT2/ILT4-binding agent comprises an engineered scaffold protein comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDDGGTTYNQKFKG (SEQ ID NO:112), a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYYAMDY (SEQ ID NO:107), a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments, an ILT2/ILT4-binding agent

comprises an engineered scaffold protein comprising a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 from antibody 73D1 or antibody Hz73D1.v1.

[00282] In some embodiments, a composition comprises an ILT-binding agent described herein. In some embodiments, a composition comprises an ILT2-binding agent described herein. In some embodiments, a composition comprises an ILT4-binding agent described herein. In some embodiments, a composition comprises an ILT2/ILT4-binding agent described herein. In some embodiments, a composition comprises an anti-ILT2 antibody described herein. In some embodiments, a composition comprises a monoclonal anti-ILT2 antibody described herein. In some embodiments, a composition comprises an anti-ILT4 antibody described herein. In some embodiments, a composition comprises a monoclonal anti-ILT4 antibody described herein. In some embodiments, a composition comprises an anti-ILT2/ILT4 antibody described herein. In some embodiments, a composition comprises a monoclonal anti-ILT2/ILT4 antibody described herein. In some embodiments, a composition comprises an antibody selected from the group consisting of: antibody 27F9, antibody 47C8, antibody 48A5, antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or humanized versions thereof.

[00283] In some embodiments, a pharmaceutical composition comprises an ILT-binding agent described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an ILT2-binding agent described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an ILT4-binding agent described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an ILT2/ILT4-binding agent described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an anti-ILT2 antibody described herein and a pharmaceutically acceptable carrier. In some embodiments, a composition comprises a monoclonal anti-ILT2 antibody described herein and a pharmaceutically acceptable carrier. In some

embodiments, a pharmaceutical composition comprises an anti-ILT4 antibody described herein and a pharmaceutically acceptable carrier. In some embodiments, a composition comprises a monoclonal anti-ILT4 antibody described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an anti-ILT2/ILT4 antibody described herein and a pharmaceutically acceptable carrier. In some embodiments, a composition comprises a monoclonal anti-ILT2/ILT4 antibody described herein and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises an antibody selected from the group consisting of: antibody 27F9, antibody 47C8, antibody 48A5, antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or humanized versions thereof and a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition comprises antibody Hz73D1.v1 and a pharmaceutically acceptable carrier.

**[00284]** In some embodiments, an ILT-binding agent is isolated. In some embodiments, an ILT-binding agent is substantially pure.

**[00285]** Generally speaking, antigen-antibody interactions are non-covalent and reversible, formed by a combination of hydrogen bonds, hydrophobic interactions, and electrostatic and van der Waals forces. When describing the strength of an antigen-antibody complex, the terms affinity and/or avidity are commonly used. The binding of an antibody to its antigen is a reversible process, and the affinity of the binding is typically reported as an equilibrium dissociation constant ( $K_D$ ).  $K_D$  is the ratio of an antibody dissociation rate ( $k_{off}$ ) (how quickly it dissociates from its antigen) to the antibody association rate ( $k_{on}$ ) (how quickly it binds to its antigen). In some embodiments,  $K_D$  values are determined by measuring the  $k_{on}$  and  $k_{off}$  rates of a specific antibody/antigen interaction and then using a ratio of these values to calculate the  $K_D$  value.  $K_D$  values may be used to evaluate and rank order the strength of individual antibody/antigen interactions. The lower the  $K_D$  of an antibody, the higher the affinity of the antibody for its target. In some embodiments, affinity is measured using SPR technology (*e.g.*, using a Biacore system). Avidity gives a measure of the overall strength of an antibody-antigen complex. It is dependent on three major parameters: (i)

affinity of the antibody for the target, (ii) valency of both the antibody and antigen, and (iii) structural arrangement of the parts that interact.

[00286] In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a dissociation constant ( $K_D$ ) of 1  $\mu$ M or less, 100 nM or less, 40 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, 50 pM or less, 10 pM or less, or 1 pM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of about 20 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 10 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 5 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 3 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 2 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 1 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 0.5 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 0.1 nM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 50 pM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 25 pM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 10 pM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 1 pM or less. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 0.01 nM to 2.5 nM. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 0.1 nM to 5 nM. In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a  $K_D$  of 1 nM to 5 nM. In some embodiments, the dissociation constant of the binding agent for ILT2 and/or ILT4 is the dissociation constant determined using an ILT protein (*e.g.*, ILT2 or ILT4) immobilized on a Biacore chip and the binding agent flowed over the chip. In some embodiments, the

dissociation constant of the binding agent for ILT2 and/or ILT4 is the dissociation constant determined using the binding agent captured by an anti-human IgG antibody on a Biacore chip and soluble ILT2 or ILT4 flowed over the chip.

**[00287]** In some embodiments, an ILT-binding agent binds ILT2, ILT4, or both ILT2 and ILT4 with a half maximal effective concentration (EC<sub>50</sub>) of 1 μM or less, 100 nM or less, 40 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, or 0.1 nM or less. In some embodiments, an ILT-binding agent binds human ILT2, ILT4, or both ILT2 and ILT4 with an EC<sub>50</sub> of 1 μM or less, 100 nM or less, 40 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, or 0.1 nM or less. In some embodiments, an ILT-binding agent binds cyno or rhesus ILT2 with an EC<sub>50</sub> of 40 nM or less, 20 nM or less, 10 nM or less, 1 nM or less or 0.1 nM or less. In some embodiments, an ILT-binding agent binds ILT2 and/or ILT4 with an EC<sub>50</sub> of 0.1 nM to about 3 nM, 0.1 nM to 2 nM, 0.1 nM to 1 nM, 0.5 nM to 3 nM, 0.5 nM to 2 nM, or 0.5 nM to 1 nM.

**[00288]** In some embodiments, an ILT-binding agent binds human ILT2 and human ILT4 and has at least one or more of the following properties: (i) binds rhesus ILT2/4; (ii) binds cyno ILT2/4; (iii) does not bind ILT3, ILT5, and LILRB5; (iv) does not bind LILRA2, LILRA4, LILRA5, and LILRA6; (v) is an ILT2 antagonist; (vi) is an ILT4 antagonist; (vii) inhibits ILT2 activity; (viii) inhibits ILT4 activity; (ix) inhibits ILT2 signaling in cells that express ILT2; (x) inhibits ILT4 signaling in cells that express ILT4; (xi) inhibits binding of ILT2 to MHC I molecules; (xii) inhibits binding of ILT4 to MHC I molecules; (xiii) inhibits ILT2-induced suppression of myeloid cells; (xiv) inhibits ILT4-induced suppression of myeloid cells; (xv) inhibits ILT2-induced suppression of myeloid cell activity; (xvi) inhibits ILT4-induced suppression of myeloid cell activity; (xvii) restores FcR activation in myeloid cells; (xviii) enhances NK cell activity; (xix) enhances CTL activity; and/or (xx) enhances macrophage phagocytosis.

**[00289]** The ILT-binding agents (*e.g.*, ILT2-binding agents, ILT4-binding agents, or ILT2/ILT4-binding agents) described herein can be produced by any suitable method known in the art. Such methods range from direct protein synthesis methods to constructing a DNA sequence encoding polypeptide sequences and expressing those

sequences in a suitable host. In some embodiments, a DNA sequence is constructed using recombinant technology by isolating or synthesizing a DNA sequence encoding a wild-type protein of interest. Optionally, the sequence can be mutagenized by site-specific mutagenesis to provide functional variants thereof. In some embodiments, a DNA sequence encoding a polypeptide of interest is constructed by chemical synthesis using an oligonucleotide synthesizer. Oligonucleotides can be designed based on the amino acid sequence of the desired polypeptide and selecting those codons that are favored in the host cell in which the recombinant polypeptide of interest will be produced. Standard methods can be applied to synthesize a polynucleotide sequence encoding an isolated polypeptide of interest. For example, a complete amino acid sequence can be used to construct a back-translated gene. Further, a DNA oligomer containing a nucleotide sequence coding for the particular isolated polypeptide can be synthesized. For example, several small oligonucleotides coding for portions of the desired polypeptide can be synthesized and then ligated. The individual oligonucleotides typically contain 5' or 3' overhangs for complementary assembly.

[00290] Once assembled (by synthesis, site-directed mutagenesis, or another method), the polynucleotide sequences encoding a particular polypeptide of interest can be inserted into an expression vector and operatively linked to an expression control sequence appropriate for expression of the protein in a desired host. Proper assembly can be confirmed by nucleotide sequencing, restriction enzyme mapping, and/or expression of a biologically active polypeptide in a suitable host.

[00291] In some embodiments, recombinant expression vectors are used to amplify and express DNA encoding the ILT-binding agents described herein. For example, recombinant expression vectors can be replicable DNA constructs which have synthetic or cDNA-derived DNA fragments encoding a polypeptide chain of an ILT-binding agent, such as an anti-ILT2/ILT4 antibody, or antigen-binding fragment thereof, operatively linked to suitable transcriptional and/or translational regulatory elements derived from mammalian, microbial, viral, or insect genes. A transcriptional unit generally comprises an assembly of (1) a genetic element or elements having a

regulatory role in gene expression, for example, transcriptional promoters and/or enhancers, (2) a structural or coding sequence that is transcribed into mRNA and translated into protein, and (3) appropriate transcription and translation initiation and termination sequences. Regulatory elements can include an operator sequence to control transcription. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants can additionally be incorporated. DNA regions are “operatively linked” when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operatively linked to DNA for a polypeptide if it is expressed as a precursor that participates in the secretion of the polypeptide; a promoter is operatively linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operatively linked to a coding sequence if it is positioned so as to permit translation. In some embodiments, structural elements intended for use in yeast expression systems include a leader sequence enabling extracellular secretion of translated protein by a host cell. In some embodiments, in situations where recombinant protein is expressed without a leader or transport sequence, a polypeptide may include an N-terminal methionine residue. This residue can optionally be subsequently cleaved from the expressed recombinant protein to provide a final product.

[00292] The choice of an expression control sequence and an expression vector generally depends upon the choice of host. A wide variety of expression host/vector combinations can be employed. Useful expression vectors for eukaryotic hosts include, for example, vectors comprising expression control sequences from SV40, bovine papilloma virus, adenovirus, and cytomegalovirus. Useful expression vectors for bacterial hosts include known bacterial plasmids, such as plasmids from *E. coli*, including pCR1, pBR322, pMB9 and their derivatives, and wider host range plasmids, such as M13 and other filamentous single-stranded DNA phages.

[00293] In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) of the present disclosure is expressed from one or more vectors. In some embodiments, a heavy chain variable

region is expressed by one vector and a light chain variable region is expressed by a second vector. In some embodiments, a heavy chain variable region and a light chain variable region are expressed by one vector. In some embodiments, a vector encodes a heavy chain variable region of an ILT-binding agent described herein. In some embodiments, a vector encodes a light chain variable region of an ILT-binding agent described herein. In some embodiments, a vector encodes a heavy chain variable region and a light chain variable region of an ILT-binding agent described herein. In some embodiments, a heavy chain polypeptide is expressed by one vector and a light chain polypeptide is expressed by a second vector. In some embodiments, a heavy chain polypeptide and a light chain polypeptide are expressed by one vector. In some embodiments, a vector encodes a heavy chain polypeptide of an ILT-binding agent described herein. In some embodiments, a vector encodes a light chain polypeptide of an ILT-binding agent described herein. In some embodiments, a vector encodes a heavy chain polypeptide and a light chain polypeptide of an ILT-binding agent described herein.

**[00294]** Suitable host cells for expression of an ILT-binding agent (*e.g.*, ILT2-binding agents, ILT4-binding agents, or ILT2/ILT4-binding agents) or a ILT2 or ILT4 protein or fragment thereof to use as an antigen or immunogen include prokaryotes, yeast cells, insect cells, or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram-negative or gram-positive organisms, for example *E. coli* or *Bacillus*. Higher eukaryotic cells include established cell lines of mammalian origin as described herein. Cell-free translation systems may also be employed. Appropriate cloning vectors and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts, as well as methods of protein production, including antibody production are well known in the art.

**[00295]** Various mammalian culture systems may be used to express recombinant polypeptides. Expression of recombinant proteins in mammalian cells may be desirable because these proteins are generally correctly folded, appropriately modified, and biologically functional. Examples of suitable mammalian host cell lines include, but are

not limited to, COS-7 (monkey kidney-derived), L-929 (murine fibroblast-derived), C127 (murine mammary tumor-derived), 3T3 (murine fibroblast-derived), CHO (Chinese hamster ovary-derived), HeLa (human cervical cancer-derived), BHK (hamster kidney fibroblast-derived), HEK-293 (human embryonic kidney-derived) cell lines and variants thereof. Mammalian expression vectors can comprise non-transcribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, and other 5' or 3' flanking non-transcribed sequences, and 5' or 3' non-translated sequences, such as necessary ribosome binding sites, a polyadenylation site, splice donor and acceptor sites, and transcriptional termination sequences.

[00296] Expression of recombinant proteins in insect cell culture systems (*e.g.*, baculovirus) also offers a robust method for producing correctly folded and biologically functional proteins. Baculovirus systems for production of heterologous proteins in insect cells are well-known to those of skill in the art.

[00297] Thus, the present disclosure provides cells comprising the ILT-binding agents described herein. In some embodiments, the cells produce the ILT-binding agents described herein. In some embodiments, the cells produce an antibody. In some embodiments, the cells produce an antibody that binds human ILT2. In some embodiments, the cells produce an antibody that binds human ILT4. In some embodiments, the cells produce an antibody that binds human ILT2 and ILT4. In some embodiments, the cells produce an antibody that binds human ILT2 and cyno ILT2. In some embodiments, the cells produce an anti-ILT2 antibody designated 27F9. In some embodiments, the cells produce an anti-ILT4 antibody designated 47C8. In some embodiments, the cells produce an anti-ILT4 antibody designated 48A5. In some embodiments, the cells produce an anti-ILT2/ILT4 antibody designated 47H6. In some embodiments, the cells produce a humanized anti-ILT2/ILT4 antibody designated Hz47H6.v2. In some embodiments, the cells produce an anti-ILT2/ILT4 antibody designated 51A1. In some embodiments, the cells produce an anti-ILT2/ILT4 antibody designated 64A12. In some embodiments, the cells produce a humanized anti-

ILT2/ILT4 antibody designated Hz64A12. In some embodiments, the cells produce an anti-ILT2/ILT4 antibody designated 73C4. In some embodiments, the cells produce an anti-ILT2/ILT4 antibody designated 73D1. In some embodiments, the cells produce a humanized anti-ILT2/ILT4 antibody designated Hz73D1.v1. In some embodiments, the cell is a prokaryotic cell. In some embodiments, the cell is an eukaryotic cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a hybridoma cell.

**[00298]** Proteins produced by a host cell can be purified according to any suitable method. Standard methods include chromatography (*e.g.*, ion exchange, affinity, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for protein purification. Affinity tags such as hexahistidine (His<sub>6</sub>; SEQ ID NO:173), maltose binding domain, influenza coat sequence, and glutathione-S-transferase can be attached to the protein to allow easy purification by passage over an appropriate affinity column. Affinity chromatography methods used for purifying immunoglobulins can include, but are not limited to, Protein A, Protein G, and Protein L chromatography. Isolated proteins can be physically characterized using techniques that include, but are not limited to, proteolysis, size exclusion chromatography (SEC), mass spectrometry (MS), nuclear magnetic resonance (NMR), isoelectric focusing (IEF), high performance liquid chromatography (HPLC), and x-ray crystallography. The purity of isolated proteins can be determined using techniques known to those of skill in the art, including but not limited to, SDS-PAGE, SEC, capillary gel electrophoresis, IEF, and capillary isoelectric focusing (cIEF).

**[00299]** In some embodiments, supernatants from expression systems that secrete recombinant protein into culture media are first concentrated using a commercially available protein concentration filter, for example, an Amicon® or Millipore Pellicon® ultrafiltration unit. Following the concentration step, the concentrate can be applied to a suitable purification matrix. In some embodiments, an anion exchange resin is employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose, or other

types commonly employed in protein purification. In some embodiments, a cation exchange step is employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. In some embodiments, a hydroxyapatite media is employed, including but not limited to, ceramic hydroxyapatite (CHT). In some embodiments, one or more reverse-phase HPLC steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups, are employed to further purify a recombinant protein. In some embodiments, hydrophobic interaction chromatography (HIC) is used to separate recombinant proteins based on their hydrophobicity. HIC is a useful separation technique for purifying proteins while maintaining biological activity due to the use of conditions and matrices that operate under less denaturing conditions than some other techniques. Some or all of the foregoing purification steps, in various combinations, can be employed to provide a homogeneous recombinant protein.

**[00300]** ILT-binding agents (*e.g.*, ILT2-binding agents, ILT4-binding agents, or ILT2/ILT4-binding agents) of the present disclosure may be analyzed for their physical/chemical properties and/or biological activities by various assays known in the art. In some embodiments, an anti-ILT2 antibody is tested for its ability to bind ILT2 (*e.g.*, human ILT2 and/or cyno/rhesus ILT2). In some embodiments, an anti-ILT4 antibody is tested for its ability to bind ILT4 (*e.g.*, human ILT4). In some embodiments, an anti-ILT2/ILT4 antibody is tested for its ability to bind ILT2 and ILT4 (*e.g.*, human ILT2, human ILT4, and cyno/rhesus ILT2). Binding assays include, but are not limited to, SPR (*e.g.*, Biacore), ELISA, and FACS. In some embodiments, an anti-ILT2 antibody is tested for its ability to inhibit, reduce, or block ILT2 binding to MHC class I antigens. In some embodiments, an anti-ILT4 antibody is tested for its ability to inhibit, reduce, or block ILT4 binding to MHC class I antigens. In some embodiments, an anti-ILT2/ILT4 antibody is tested for its ability to inhibit, reduce, or block ILT2 and ILT4 binding to MHC class I antigens. In addition, antibodies may be evaluated for solubility, stability, thermostability, viscosity, expression levels, expression quality, and/or purification efficiency.

[00301] In some embodiments, monoclonal antibodies generated against ILT2, ILT4, or ILT2 and ILT4 are grouped based upon the epitope each individual antibody recognizes, a process known as “epitope binning”. Generally, antibodies are tested in a pairwise combinatorial manner and antibodies that compete with each other are grouped together into bins. For example, in a premix binning assay, a first antibody is immobilized on a surface and a premixed solution of a second antibody and antigen is flowed over the immobilized first antibody. In tandem, the antigen is immobilized on a surface and the two antibodies are flowed over the immobilized antigen and compete to bind. Using these techniques, antibodies that block one another can be identified. A competitive blocking profile is created for each antibody relative to the other antibodies. The blocking results determine which bin each antibody is placed in. High-throughput methods of epitope binning are known in the art and allow for screening and characterization of large numbers of antibodies within a short period of time. Antibodies that bind similar epitopes often share similar functions and/or capabilities. Conversely, antibodies that bind different epitopes may have different functional activities.

[00302] In some embodiments, an epitope bin comprises at least one antibody from the group consisting of: 27F9, 47C8, 48A5, 47H6, 51A1, 64A12, 73C4, and 73D1. In some embodiments, an epitope bin comprises at least antibodies 27F9 and 73D1. In some embodiments, an epitope bin comprises at least antibodies 27F9, 73C4, and 73D1. In some embodiments, an epitope bin comprises at least antibodies 48A5 and 47H6.

[00303] Epitope mapping is the process of identifying the binding site, or epitope on a target protein/antigen where an antibody (or other binding agent) binds. A variety of methods are known in the art for mapping epitopes on target proteins. These methods include (i) mutagenesis, including but not limited to, shotgun mutagenesis, site-directed mutagenesis, and alanine scanning; (ii) domain or fragment scanning; (iii) peptide scanning (*e.g.*, Pepscan technology); (iv) display methods, including but not limited to, phage display, microbial display, and ribosome/mRNA display; (v) methods involving proteolysis and mass spectroscopy; (vi) methods involving amide hydrogen/deuterium

exchange; and (vii) structural determination, including but not limited to, x-ray crystallography and NMR.

[00304] In some embodiments, purified anti-ILT antibodies (*e.g.*, anti-ILT2 antibodies, anti-ILT4 antibodies, or anti-ILT2/ILT4 antibodies) are characterized by assays including, but not limited to, N-terminal sequencing, amino acid analysis, HPLC, mass spectrometry, differential scanning fluorimetry (DSF), nanoDSF, capillary isoelectric focusing (cIEF), ion exchange chromatography, and papain digestion.

[00305] *In vitro* assays that characterize immune cell function include, but are not limited to, cell activation assays (*e.g.*, cell proliferation assays), cytotoxic T-cell (CTL) assays, T-cell suppression assays, MDSC assays, natural killer (NK) cell assays, mixed lymphocyte reaction (MLR) assays, cytokine/chemokine production assays, FcR binding assays, phagocytosis assays, and cell migration assays. In some embodiments, assays are provided for identifying anti-ILT antibodies that affect ILT activity. “Affect or affecting ILT activity” may include, for example, inhibiting, reducing, blocking, antagonizing, suppressing, and/or interfering with ILT2 activity, ILT4 activity, or ILT2 and ILT4 activity. As ILT2 and ILT4 generally act as negative regulator/inhibitory molecules, in some embodiments, inhibiting, reducing, blocking, antagonizing, suppressing, and/or interfering with ILT2 and/or ILT4 activity results in a blockade of ILT2-induced and/or ILT4-induced suppression of a biological function. Those of skill in the art may refer to this ability as “releasing the brake”, for example, anti-ILT antibodies described herein block the signaling of ILT2 and/or ILT4 that would otherwise send a suppressive message. Once the “brakes” are released, the immune system is able to mount a response or a stronger response to, for example, a tumor.

[00306] As described herein, ILT2 is expressed on myeloid cells, such as monocytes, macrophages, dendritic cells (DCs), and APCs, as well as NK cells, B-cells, and CD8<sup>+</sup> T-cells (CTLs). ILT2 activity or ILT2 signaling activity includes, but is not limited to, suppression of myeloid cells, suppression of myeloid cell activity, suppression of tumor-associated myeloid cells, suppression of NK cells, and suppression of cytolytic T-cells (CTLs). In some embodiments, inhibiting, reducing, blocking, antagonizing,

suppressing, and/or interfering with ILT2 activity results in a release of ILT2-induced suppression of an activation signal. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody inhibits ILT2 signaling. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody inhibits ILT2 signaling thereby reversing an ILT2-induced suppressive effect. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody inhibits an ILT2-induced extinction signal. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases myeloid cell activity. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases APC activity. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases macrophage activity. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases macrophage phagocytosis. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases NK cell activity. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody increases CTL activity.

[00307] ILT4 is expressed on myeloid cells, such as monocytes, macrophages, dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and APCs, as well as neutrophils and eosinophils. ILT4 activity or ILT4 signaling activity includes, but is not limited to, suppression of myeloid cells, suppression of myeloid cell activity, and suppression of tumor-associated myeloid cells. In some embodiments, inhibiting, reducing, blocking, antagonizing, suppressing, and/or interfering with ILT4 activity results in a release of ILT4-induced suppression of an activation signal. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody inhibits ILT4 signaling. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody inhibits ILT4 signaling thereby reversing an ILT4-induced suppressive effect. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody inhibits an ILT4-induced extinction signal. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody increases myeloid cell activity. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody increases macrophage activity. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody decreases MDSCs.

In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody decreases suppression by MDSCs. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody induces a switch of MDSCs to activated macrophages.

[00308] In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and activates myeloid cells. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and activates APCs. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and activates dendritic cells. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and activates primary dendritic cells. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and increases NK cell activity. In some embodiments, an anti-ILT2 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and increases CTL activity.

[00309] In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT4 signaling pathway. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT4 signaling pathway and activates myeloid cells. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT4 signaling pathway and activates APCs. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT4 signaling pathway and activates dendritic cells. In some embodiments, an anti-ILT4 antibody or an anti-ILT2/ILT4 antibody disrupts the ILT4 signaling pathway and activates primary dendritic cells.

[00310] In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and activates myeloid cells. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and activates APCs. In some

embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and activates dendritic cells. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and activates primary dendritic cells. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and increases myeloid cell activity. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and increases NK cell activity. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and increases CTL activity. In some embodiments, an anti-ILT2/ILT4 antibody disrupts the ILT2 signaling pathway and the ILT4 signaling pathway and decreases MDSC activity.

**[00311]** In some embodiments, the terms “inhibiting”, “reducing”, “blocking”, “antagonizing”, “suppressing”, and “interfering” are relative to levels and/or activity in the absence of treatment with the ILT-binding agent. In some embodiments, the terms “inhibiting”, “reducing”, “blocking”, “antagonizing”, “suppressing”, and “interfering” are relative to levels and/or activity prior to treatment with the ILT-binding agent.

**[00312]** In some embodiments, the terms “activating”, “promoting”, “increasing”, and “enhancing” are relative to levels and/or activity in the absence of treatment with the ILT-binding agent. In some embodiments, the terms “activating”, “promoting”, “increasing”, and “enhancing” are relative to levels and/or activity prior to treatment with the ILT-binding agent.

**[00313]** In some embodiments, an anti-ILT2 antibody that inhibits ILT2 activity is antibody 27F9. In some embodiments, an anti-ILT4 antibody that inhibits ILT4 activity is antibody 47C8. In some embodiments, an anti-ILT4 antibody that inhibits ILT4 activity is antibody 48A5. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody 47H6. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody Hz47H6.v2. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody 51A1. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2

and ILT4 activity is antibody 64A12. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody Hz64A12. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody 73C4. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody 73D1. In some embodiments, an anti-ILT2/ILT4 antibody that inhibits ILT2 and ILT4 activity is antibody Hz73D1.v1

**[00314]** The present disclosure also provides conjugates comprising an anti-ILT2, an anti-ILT4, or an anti-ILT2/ILT4 antibody described herein. In some embodiments, the antibody is attached to a second molecule. In some embodiments, the antibody is conjugated to a cytotoxic agent or moiety. In some embodiments, the antibody is conjugated to a cytotoxic agent to form an ADC (antibody-drug conjugate). In some embodiments, the cytotoxic agent is a chemotherapeutic agent including, but not limited to, methotrexate, adriamycin/doxorubicin, melphalan, mitomycin C, chlorambucil, duocarmycin, daunorubicin, pyrrolobenzodiazepines (PBDs), or other intercalating agents. In some embodiments, the cytotoxic agent is a microtubule inhibitor including, but not limited to, auristatins, maytansinoids (*e.g.*, DM1 and DM4), and tubulysins. In some embodiments, the cytotoxic agent is an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof, including, but not limited to, diphtheria A chain, non-binding active fragments of diphtheria toxin, exotoxin A chain, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *Momordica charantia* inhibitor, curcin, crotin, *Sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. In some embodiments, an antibody is conjugated to one or more small molecule toxins, such as calicheamicins, maytansinoids, trichothenes, and CC1065. A derivative of any one of these toxins may be used as long as the derivative retains the cytotoxic activity of the parent molecule.

**[00315]** Conjugates comprising an anti-ILT antibody (*e.g.*, an ILT2 antibody, an ILT4 antibody, or an ILT2/ILT4 antibody) described herein may be made using any suitable

method known in the art. In some embodiments, conjugates are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene).

[00316] In some embodiments, an anti-ILT antibody (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) described herein is conjugated to a detectable substance or molecule that allows the antibody to be used for diagnosis and/or detection. In some embodiments, a labeled anti-ILT antibody is used to monitor immune cells in a tumor or in the microenvironment of a tumor. In some embodiments, a labeled anti-ILT antibody is used to monitor immune cells in a tumor or in the microenvironment of a tumor after treatment. A detectable substance can include but is not limited to, enzymes, such as horseradish peroxidase, alkaline phosphatase, beta-galactosidase, and acetylcholinesterase; prosthetic groups, such as biotin and flavine(s); fluorescent materials, such as, umbelliferone, fluorescein, fluorescein isothiocyanate (FITC), rhodamine, tetramethylrhodamine isothiocyanate (TRITC), dichlorotriazinylamine fluorescein, dansyl chloride, cyanine (Cy3), and phycoerythrin; bioluminescent materials, such as luciferase; radioactive materials, such as <sup>212</sup>Bi, <sup>14</sup>C, <sup>57</sup>Co, <sup>51</sup>Cr, <sup>67</sup>Cu, <sup>18</sup>F, <sup>68</sup>Ga, <sup>67</sup>Ga, <sup>153</sup>Gd, <sup>159</sup>Gd, <sup>68</sup>Ge, <sup>3</sup>H, <sup>166</sup>Ho, <sup>131</sup>I, <sup>125</sup>I, <sup>123</sup>I, <sup>121</sup>I, <sup>115</sup>In, <sup>113</sup>In, <sup>112</sup>In, <sup>111</sup>In, <sup>140</sup>La, <sup>177</sup>Lu, <sup>54</sup>Mn, <sup>99</sup>Mo, <sup>32</sup>P, <sup>103</sup>Pd, <sup>149</sup>Pm, <sup>142</sup>Pr, <sup>186</sup>Re, <sup>188</sup>Re, <sup>105</sup>Rh, <sup>97</sup>Ru, <sup>35</sup>S, <sup>47</sup>Sc, <sup>75</sup>Se, <sup>153</sup>Sm, <sup>113</sup>Sn, <sup>117</sup>Sn, <sup>85</sup>Sr, <sup>99m</sup>Tc, <sup>201</sup>Ti, <sup>133</sup>Xe, <sup>90</sup>Y, <sup>69</sup>Yb, <sup>175</sup>Yb, <sup>65</sup>Zn; positron emitting metals; and magnetic metal ions.

[00317] In some embodiments, an anti-ILT antibody (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) described herein is used in an immunoassay. Immunoassays are known to those of skill in the art and include, but are not limited to, ELISA, SPR (*e.g.*, Biacore), FACS, and immunohistochemistry (IHC).

In some embodiments, an anti-ILT antibody described herein is used on a tissue sample or a tumor sample.

[00318] An anti-ILT antibody (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) described herein can also be conjugated to a second antibody to form an antibody heteroconjugate.

[00319] An anti-ILT antibody (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody, or an anti-ILT2/ILT4 antibody) as described herein may be attached to a solid support. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride, or polypropylene. In some embodiments, immobilized anti-ILT antibodies are used in immunoassays. In some embodiments, immobilized anti-ILT antibodies are used in purification of the target antigen.

### III. Polynucleotides

[00320] In some embodiments, the disclosure encompasses polynucleotides comprising polynucleotides that encode a polypeptide (*e.g.*, an ILT-binding agent) described herein. The term “polynucleotides that encode a polypeptide” encompasses a polynucleotide that includes only coding sequences for the polypeptide as well as a polynucleotide that includes additional coding and/or non-coding sequences. The polynucleotides of the disclosure can be in the form of RNA or in the form of DNA. DNA includes cDNA, genomic DNA, and synthetic DNA; and can be double-stranded or single-stranded, and if single stranded can be the coding strand or non-coding (anti-sense) strand.

[00321] In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region and/or a light chain variable region of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain variable region of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy

chain variable region of an ILT2-binding agent described herein and a polynucleotide encoding a light chain variable region of the ILT2-binding agent. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region and/or a light chain variable region of an ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain variable region of an ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region of an ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region of an ILT4-binding agent described herein and a polynucleotide encoding a light chain variable region of the ILT4-binding agent. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region and/or a light chain variable region of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain variable region of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain variable region of an ILT2/ILT4-binding agent described herein and a polynucleotide encoding a light chain variable region of the ILT2/ILT4-binding agent.

**[00322]** In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain and/or a light chain of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain of an ILT2-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT2-binding agent described herein and a polynucleotide encoding a light chain of the ILT2-binding agent. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain and/or a light chain of an ILT4-

binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain of an ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT4-binding agent described herein and a polynucleotide encoding a light chain of the ILT4-binding agent. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain and/or a light chain of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a light chain of an ILT2/ILT4-binding agent described herein. In some embodiments, a polynucleotide comprises a polynucleotide encoding a heavy chain of an ILT2/ILT4-binding agent described herein and a polynucleotide encoding a light chain of the ILT2/ILT4-binding agent.

**[00323]** In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs:125-145. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:125. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:126. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:127. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:128. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:129. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:130. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence

of SEQ ID NO:131. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:132. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:133. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:134. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:135. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:136. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:137. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:138. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:139. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:140. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:141. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:142. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:143. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:144. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:145. [00324] In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs:146-157. In some embodiments, the polynucleotide

comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:146. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:147. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:148. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:149. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:150. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:151. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:152. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:153. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:154. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:155. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:156. In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:157.

**[00325]** In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising more than one amino acid sequence selected from the group consisting of: SEQ ID NOs:125-145. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:125 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:126. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ

ID NO:127 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:128. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:129 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:130. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:131 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:132. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:133 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:134. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:135 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:136. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:137 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:138. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:139 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:140. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:141 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:142. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:143 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:142. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:144 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:145.

[00326] In some embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising more than one amino acid sequence selected from the group consisting of: SEQ ID NOs:146-157. In some embodiments, the

polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:146 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:147. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:148 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:149. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:150 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:151. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:152 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:153. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:154 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:155. In some embodiments, the polynucleotide comprises a polynucleotide encoding (i) a polypeptide comprising an amino acid sequence of SEQ ID NO:156 and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO:157.

**[00327]** The present disclosure also provides variants of the polynucleotides described herein, wherein a variant encodes, for example, a fragment, an analog, and/or a derivative of a polypeptide. In some embodiments, the present disclosure provides a polynucleotide comprising a polynucleotide having a nucleotide sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, and in some embodiments, at least 96%, at least 97%, at least 98%, or at least 99% identical to a polynucleotide encoding a polypeptide described herein.

**[00328]** In some embodiments, a polynucleotide comprises a polynucleotide having a nucleotide sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, and in some embodiments, at least 96%, at least 97%, at least 98%, or at least 99% identical to a polynucleotide encoding an amino acid sequence selected from the group consisting of: SEQ ID NOs:125-157. Also provided is a

polynucleotide that comprises a polynucleotide that hybridizes to a polynucleotide encoding an amino acid sequence selected from the group consisting of: SEQ ID NOs:125-157. In some embodiments, the hybridization is under conditions of high stringency as is known to those skilled in the art.

**[00329]** As used herein, the phrase “a polynucleotide having a nucleotide sequence at least 95% identical to a polynucleotide sequence” is intended to mean that the nucleotide sequence of the polynucleotide is identical to a reference sequence except that the polynucleotide sequence can include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence can be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence can be inserted into the reference sequence. It is understood by those of skill in the art that an appropriate calculation would be made for other “% identical” statements, for example, 90% identical or 85% identical. The mutations of the reference sequence can occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence.

**[00330]** The polynucleotide variants can contain alterations in the coding regions, non-coding regions, or both. In some embodiments, a polynucleotide variant contains alterations that produce silent substitutions, additions, or deletions, but does not alter the properties or activities of the encoded polypeptide. In some embodiments, a polynucleotide variant comprises silent substitutions that results in no change to the amino acid sequence of the polypeptide (due to the degeneracy of the genetic code). In some embodiments, a polynucleotide variant comprises one or more mutated codons comprising one or more (*e.g.*, 1, 2, or 3) substitutions to the codon that change the amino acid encoded by that codon. Methods for introducing one or more substitutions into a codon are known in the art, including but not limited to, PCR mutagenesis and

site-directed mutagenesis. Polynucleotide variants can be produced for a variety of reasons, for example, to optimize codon expression for a particular host (*e.g.*, change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*). In some embodiments, a polynucleotide variant comprises at least one silent mutation in a non-coding or a coding region of the sequence.

[00331] In some embodiments, a polynucleotide variant is produced to modulate or alter expression (or expression levels) of the encoded polypeptide. In some embodiments, a polynucleotide variant is produced to increase expression of the encoded polypeptide. In some embodiments, a polynucleotide variant is produced to decrease expression of the encoded polypeptide. In some embodiments, a polynucleotide variant has increased expression of the encoded polypeptide as compared to a parental polynucleotide sequence. In some embodiments, a polynucleotide variant has decreased expression of the encoded polypeptide as compared to a parental polynucleotide sequence.

[00332] In some embodiments, a polynucleotide comprises the coding sequence for a polypeptide fused in the same reading frame to a polynucleotide that aids in expression and secretion of a polypeptide from a host cell. In some embodiments, the polynucleotide that aids in expression and secretion is a leader sequence that functions as a secretory sequence for controlling transport of a polypeptide. In some embodiments, the polypeptide has a leader sequence cleaved by the host cell to form a “mature” form of the polypeptide.

[00333] In some embodiments, a polynucleotide comprises the coding sequence for a polypeptide fused in the same reading frame to a marker or tag sequence. For example, in some embodiments, a marker sequence is a hexa-histidine tag (HIS-tag; SEQ ID NO:173) that allows for efficient purification of the polypeptide fused to the marker. In some embodiments, a marker sequence is a hemagglutinin (HA) tag derived from the influenza hemagglutinin protein when a mammalian host is used. In some embodiments, the marker sequence is a FLAG™ tag. In some embodiments, a marker may be used in conjunction with other markers or tags.

[00334] In some embodiments, a polynucleotide is isolated. In some embodiments, a polynucleotide is substantially pure.

[00335] Vectors and cells comprising each and every one of the polynucleotides described herein are also provided. In some embodiments, a vector comprises a polynucleotide molecule encoding an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein. In some embodiments, a vector comprises a polynucleotide molecule encoding a polypeptide that is part of an ILT-binding agent described herein. In some embodiments, a cell comprises a vector comprising a polynucleotide molecule encoding an ILT-binding agent described herein. In some embodiments, a cell comprises a vector comprising a polynucleotide molecule encoding a polypeptide that is part of an ILT-binding agent described herein. In some embodiments, a cell comprises a polynucleotide molecule encoding an ILT-binding agent described herein. In some embodiments, a cell comprises one or more polynucleotides encoding an ILT-binding agent described herein. In some embodiments, a cell comprises a single polynucleotide encoding an ILT-binding agent described herein. In some embodiments, a cell comprises a first polynucleotide encoding a heavy chain variable region of an ILT-binding agent described herein and a second polynucleotide encoding a light chain variable region of an ILT-binding agent described herein. In some embodiments, a cell comprises a polynucleotide encoding a heavy chain variable region and a light chain variable region of an ILT-binding agent described herein. In some embodiments, a cell comprises a first polynucleotide encoding a heavy chain of an ILT-binding agent described herein and a second polynucleotide encoding a light chain of an ILT-binding agent described herein. In some embodiments, a cell comprises a polynucleotide encoding a heavy chain and a light chain of an ILT-binding agent described herein. In some embodiments, a cell comprises one or more vectors encoding an ILT-binding agent described herein. In some embodiments, a cell comprises a vector encoding an ILT-binding agent described herein. In some embodiments, a cell comprises a first vector encoding a heavy chain variable region of an ILT-binding agent described herein and a

second vector encoding a light chain variable region of an ILT-binding agent described herein. In some embodiments, a cell comprises a single vector encoding a heavy chain variable region and a light chain variable region of an ILT-binding agent described herein. In some embodiments, a cell comprises a first vector encoding a heavy chain of an ILT-binding agent described herein and a second vector encoding a light chain of an ILT-binding agent described herein. In some embodiments, a cell comprises a single vector encoding a heavy chain and a light chain of an ILT-binding agent described herein.

#### IV. Methods of Making Binding Agents

[00336] The disclosure provides methods for making the ILT-binding agents (*e.g.*, ILT2-binding agents, ILT4-binding agents, or ILT2/ILT4-binding agents) described herein. In some embodiments, a method comprises providing a cell comprising one or more polynucleotides encoding a heavy chain and/or light chain of an ILT-binding agent described herein, culturing the cell under conditions that permit the expression of the binding agent, and isolating the binding agent. In some embodiments, a method further comprises purifying the binding agent. In some embodiments, a method further comprises formulating the binding agent as a pharmaceutical composition.

[00337] In some embodiments, a cell comprises one or more polynucleotides encoding the heavy chain and the light chain of an ILT-binding agent described herein. In some embodiments, a cell comprises a first polynucleotide encoding the heavy chain of an ILT-binding agent and a second polynucleotide encoding the light chain of an ILT-binding agent. In other embodiments, a cell comprises a polynucleotide encoding the heavy chain and the light chain of an ILT-binding agent described herein. In some embodiments, a polynucleotide encoding an ILT-binding agent described herein is transiently transfected into a cell. In some embodiments, a polynucleotide encoding an ILT-binding agent described herein is stably transfected into a cell.

[00338] In some embodiments, a cell comprises one or more vectors encoding the heavy chain variable region and the light chain variable region of an ILT-binding agent

described herein. In some embodiments, a cell comprises a first vector encoding the heavy chain variable region of an ILT-binding agent and a second vector encoding the light chain variable region of an ILT-binding agent. In other embodiments, a cell comprises a vector encoding the heavy chain variable region and the light chain variable region of an ILT-binding agent. In some embodiments, a cell comprises one or more vectors encoding the heavy chain and the light chain of an ILT-binding agent described herein. In some embodiments, a cell comprises a first vector encoding the heavy chain of an ILT-binding agent and a second vector encoding the light chain of an ILT-binding agent. In other embodiments, a cell comprises a vector encoding the heavy chain and the light chain of an ILT-binding agent described herein.

**[00339]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) is an antibody fragment comprising at least one antigen-binding site and the method involves providing a cell comprising a polynucleotide encoding the fragment of the anti-ILT antibody, incubating the cell under conditions that permit the expression of the antibody fragment, and isolating the antibody fragment. In some embodiments, the cell comprises a polynucleotide encoding an antibody fragment described herein. In some embodiments, the cell comprises a vector encoding an antibody fragment described herein. In some embodiments, the method comprises purifying the antibody fragment. In some embodiments, the antibody fragment is a Fab, Fab', F(ab')<sub>2</sub>, Fv, scFv, (scFv)<sub>2</sub>, single chain antibody, dual variable region antibody, diabody, or nanobody.

**[00340]** In some embodiments, the ILT-binding agent is a scFv and the method involves providing a cell comprising the scFv, incubating the cell under conditions that permit the expression of the scFv, and isolating the scFv. In some embodiments, the cell comprises a vector described herein encoding the scFv. In some embodiments, the cell comprises a polynucleotide described herein encoding the scFv. In some embodiments, the method comprises purifying the scFv.

**[00341]** In some embodiments, the cell used to make an ILT-binding agent is a bacterial cell. In some embodiments, the cell used to make an ILT-binding agent is a

yeast cell. In some embodiments, the cell used to make an ILT-binding agent is a mammalian cell. In some embodiments, the cell used to make an ILT-binding agent is a CHO cell. In other embodiments, the cell used to make an ILT-binding agent is a HEK-293 cell.

#### V. Methods of use and pharmaceutical compositions

[00342] The ILT-binding agents (*e.g.*, ILT2-binding agent, ILT4-binding agents, or ILT2/ILT4-binding agents) of the disclosure are useful in a variety of applications including, but not limited to, therapeutic treatment methods, such as treatment of cancer. In some embodiments, the therapeutic treatment methods comprise immunotherapy for cancer. In some embodiments, an ILT-binding agent described herein is useful for activating, promoting, increasing, and/or enhancing an immune response to cancer or cancer cells. In some embodiments, an ILT-binding agent described herein is useful for activating, promoting, increasing, and/or enhancing an immune response to a tumor or tumor cells. The methods of use may be *in vitro*, *ex vivo*, or *in vivo* methods.

[00343] The present disclosure provides methods of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking MHC I-induced ILT2 activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking ILT2-induced suppression of myeloid cells. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding

agent described herein, wherein the method results in disrupting, inhibiting, or blocking of ILT2-induced suppression of myeloid cell activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules restores FcR signaling activity in myeloid cells. In some embodiments, the myeloid cell is a monocyte. In some embodiments, the myeloid cell is a macrophage. In some embodiments, the myeloid cell is a dendritic cell. In some embodiments, the myeloid cell is an APC. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding agent described herein, wherein the method results in increasing NK cell activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 to one or more MHC I molecules comprises contacting cells with an ILT2-binding agent described herein, wherein the method results in increasing CTL activity. In some embodiments of the methods described herein, the MHC I molecule is a classical MHC I molecule. In some embodiments of the methods described herein, the MHC I molecule is a non-classical MHC I molecule. In some embodiments of the methods described herein, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

**[00344]** The present disclosure provides methods of disrupting, inhibiting, or blocking the binding of ILT4 to one or more MHC I molecules. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT4 to one or more MHC I molecules comprises contacting cells with an ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT4 to one or more MHC I molecules comprises contacting cells with an ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking MHC I-induced ILT4 activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT4 to one or more MHC I molecules comprises contacting cells with an ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking ILT4-induced suppression of myeloid cells. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of

ILT2 to one or more MHC I molecules comprises contacting cells with an ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking of ILT4-induced suppression of myeloid cell activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT4 to one or more MHC I molecules restores FcR signaling activity in myeloid cells. In some embodiments, the myeloid cell is a monocyte. In some embodiments, the myeloid cell is a macrophage. In some embodiments, the myeloid cell is a dendritic cell. In some embodiments, the myeloid cell is an APC. In some embodiments of the methods described herein, the MHC I molecule is a classical MHC I molecule. In some embodiments of the methods described herein, the MHC I molecule is a non-classical MHC I molecule. In some embodiments of the methods described herein, the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

**[00345]** The present disclosure provides methods of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cells. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein, wherein the method results in disrupting, inhibiting, or blocking of ILT2-induced and/or ILT4-induced suppression of myeloid cell activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2

and ILT4 to one or more MHC I molecules restores FcR signaling activity in myeloid cells. In some embodiments, the myeloid cell is a monocyte. In some embodiments, the myeloid cell is a macrophage. In some embodiments, the myeloid cell is a dendritic cell. In some embodiments, the myeloid cell is an APC. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein, wherein the method results in increasing NK cell activity. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and ILT4 to one or more MHC I molecules comprises contacting cells with an ILT2/ILT4-binding agent described herein, wherein the method results in increasing CTL activity.

[00346] The present disclosure provides methods of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to MHC I molecules in a subject. In some embodiments, a method of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to MHC I molecules in a subject, comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity in a subject comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cells in a subject comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of myeloid cell activity in a subject comprises administering to the subject an effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of disrupting, inhibiting, or blocking ILT2-induced and/or ILT4-induced suppression of antigen-presenting cell activity in a subject restores FcR activity in myeloid cells. In some embodiments, the myeloid cell is a monocyte. In some embodiments, the myeloid cell is a macrophage. In some embodiments, the myeloid cell is a dendritic cell. In some embodiments, the myeloid cell is an APC.

[00347] The present disclosure provides methods for activating an immune response in a subject using an ILT2/ILT4-binding agent described herein. In some embodiments, the disclosure provides methods for promoting an immune response in a subject using an ILT2/ILT4-binding agent described herein. In some embodiments, the disclosure provides methods for increasing an immune response in a subject using an ILT2/ILT4-binding agent described herein. In some embodiments, the disclosure provides methods for enhancing an immune response in a subject using an ILT2/ILT4-binding agent described herein. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises stimulating myeloid cells. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises stimulating monocytes. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises stimulating macrophages. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises stimulating dendritic cells. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises stimulating APCs. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises increasing cell-mediated immunity. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises increasing effector T-cell activity. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises increasing CTL activity. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises increasing NK cell activity. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises enhancing NK cell activity. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises inhibiting or decreasing the suppressive activity of Tregs. In some embodiments, the activating, promoting, increasing, and/or enhancing of an immune response comprises inhibiting or decreasing the suppressive activity of MDSCs. In some embodiments, the immune response is a result of antigenic

stimulation. In some embodiments, the antigenic stimulation is a tumor cell. In some embodiments, the antigenic stimulation is cancer.

[00348] The disclosure also provides methods of disrupting and/or inhibiting ILT2 and/or ILT4 signaling in a cell comprising contacting the cell with an effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the method of disrupting and/or inhibiting ILT2 signaling in a cell comprises contacting the cell with an effective amount of antibody 27F9, antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or a humanized version thereof. In some embodiments, the method of disrupting and/or inhibiting ILT4 signaling in a cell comprises contacting the cell with an effective amount of antibody 47C8, antibody 48A5, antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or a humanized version thereof. In some embodiments, the method of disrupting and/or inhibiting ILT2 signaling and ILT4 signaling in a cell comprises contacting the cell with an effective amount of antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or a humanized version thereof. In some embodiments, the method of disrupting and/or inhibiting ILT2 signaling and ILT4 in a cell comprises contacting the cell with an effective amount of antibody Hz47H6.v2. In some embodiments, the method of disrupting and/or inhibiting ILT2 signaling and ILT4 in a cell comprises contacting the cell with an effective amount of antibody Hz64A12. In some embodiments, the method of disrupting and/or inhibiting ILT2 signaling and ILT4 in a cell comprises contacting the cell with an effective amount of antibody Hz73D1.v1. In some embodiments, the disclosure provides use of an ILT2-binding agent described herein in the manufacture or preparation of a medicament for disrupting and/or inhibiting ILT2 signaling in a cell. In some embodiments, the disclosure provides use of an ILT4-binding agent described herein in the manufacture or preparation of a medicament for disrupting and/or inhibiting ILT4 signaling in a cell. In some embodiments, the disclosure provides use of an ILT2/ILT4-binding agent described herein in the manufacture or preparation of a medicament for disrupting and/or inhibiting ILT2 signaling and ILT4 signaling in a cell.

In some embodiments, the cell is a myeloid cell. In some embodiments, the cell is a monocyte. In some embodiments, the cell is a macrophage. In some embodiments, the cell is a dendritic cell. In some embodiments, the cell is an antigen-presenting cell. In some embodiments, the cell is a NK cell. In some embodiments, the cell is a CTL. In some embodiments, the method is an *in vivo* method wherein the step of contacting the cell with the agent comprises administering a therapeutically effective amount of an ILT-binding agent to a subject. In some embodiments, the method is an *in vitro* or *ex vivo* method.

[00349] The present disclosure also provides methods for inhibiting growth of a tumor using an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, the method of inhibiting growth of a tumor comprises using an ILT2-binding agent described herein. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody 27F9 or a humanized version thereof. In some embodiments, the method of inhibiting growth of a tumor comprises using an ILT4-binding agent described herein. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody 47C8 or antibody 48A5, or a humanized version thereof. In some embodiments, the method of inhibiting growth of a tumor comprises using an ILT2/ILT4-binding agent described herein. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or humanized versions thereof. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody Hz47H6.v2. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody Hz64A12. In some embodiments, the method of inhibiting growth of a tumor comprises using antibody Hz73D1.v1. In some embodiments, the method of inhibiting growth of a tumor comprises contacting a cell mixture with an ILT-binding agent *in vitro*. For example, an immortalized cell line or a cancer cell line mixed with immune cells (*e.g.*, a myeloid cell) is cultured in medium to which is added a test agent that binds ILT2 and/or ILT4. In some embodiments, tumor cells are isolated from a patient sample such as, for

example, a tissue biopsy, pleural effusion, or blood sample, mixed with immune cells (*e.g.*, myeloid cells), and cultured in medium to which is added a test agent that binds ILT2 and/or ILT4. In some embodiments, the disclosure provides use of an ILT2-binding agent described herein in the manufacture or preparation of a medicament for inhibiting growth of a tumor or a tumor cell. In some embodiments, the disclosure provides use of an ILT4-binding agent described herein in the manufacture or preparation of a medicament for inhibiting growth of a tumor or a tumor cell. In some embodiments, the disclosure provides use of an ILT2/ILT4-binding agent described herein in the manufacture or preparation of a medicament for inhibiting growth of a tumor or a tumor cell. In some embodiments, an ILT2-binding agent increases, promotes, and/or enhances the activity of effector immune cells. In some embodiments, an ILT2-binding agent inhibits tumor cell growth by increasing, promoting, and/or enhancing the activity of effector immune cells. In some embodiments, an ILT4-binding agent increases, promotes, and/or enhances the activity of effector immune cells. In some embodiments, an ILT4-binding agent inhibits tumor cell growth by increasing, promoting, and/or enhancing the activity of effector immune cells. In some embodiments, an ILT2/ILT4-binding agent increases, promotes, and/or enhances the activity of effector immune cells. In some embodiments, an ILT2/ILT4-binding agent inhibits tumor cell growth by increasing, promoting, and/or enhancing the activity of effector immune cells.

**[00350]** In some embodiments, a method of inhibiting tumor growth comprises contacting the tumor and/or tumor microenvironment with an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein *in vivo*. In some embodiments, contacting a tumor and/or tumor microenvironment with an ILT-binding agent described herein is undertaken in an animal model. For example, a test agent (*e.g.*, an ILT2/ILT4-binding agent) may be administered to mice that have tumors. In some embodiments, an ILT2/ILT4-binding agent increases, promotes, and/or enhances the activity of immune cells in the mice. In some embodiments, an ILT2/ILT4-binding agent inhibits tumor growth. In some

embodiments, an ILT2/ILT4-binding agent causes a tumor to regress. In some embodiments, an ILT2/ILT4-binding agent is administered at the same time or shortly after introduction of tumor cells into the animal to prevent tumor growth (“preventative model”). In some embodiments, an ILT2/ILT4-binding agent is administered after tumors have grown to a specified size or have become “established” for treatment (“therapeutic model”). In some embodiments, an ILT2/ILT4-binding agent is administered to a transgenic animal (*e.g.*, a transgenic mouse) that expresses human ILT2 and/or ILT4, wherein the transgenic animal has a tumor derived from human cells.

[00351] In some embodiments, a method of inhibiting tumor growth comprises administering to a subject a therapeutically effective amount of an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein. In some embodiments, a method of inhibiting tumor growth comprises administering to a subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of increasing or enhancing an immune response to a tumor or tumor cells in a subject comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of activating or enhancing a persistent or long-term immune response to a tumor or tumor cells in a subject comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of inhibiting tumor relapse or tumor regrowth in a subject comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, a method of inducing a persistent or long-term immunity that inhibits tumor relapse or tumor regrowth in a subject comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments of the methods described herein, the tumor is a solid tumor. In some embodiments, the tumor is a pancreatic tumor, a breast tumor, a lung tumor, a non-small cell lung tumor, a head and neck tumor, a colorectal tumor, a prostate tumor, a skin tumor, a melanoma tumor, a

stomach tumor, a gastric tumor, an intestinal tumor, an ovarian tumor, a cervical tumor, an uterine tumor, an endometrial tumor, a bladder tumor, a brain tumor, an esophageal tumor, a liver tumor, a kidney tumor, a renal cell carcinoma, or a testicular tumor. In some embodiments, the tumor is a pancreatic tumor. In some embodiments, the tumor is a non-small cell lung tumor. In some embodiments, the tumor is a renal cell carcinoma (RCC). In some embodiments, the subject has a tumor or the subject had a tumor that was at least partially removed. In some embodiments of the methods described herein, the subject is a human.

**[00352]** In some embodiments, the disclosure provides use of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein in the manufacture or preparation of a medicament for inhibiting growth of a tumor or tumor cell. In some embodiments, the method of inhibiting growth of a tumor comprises administering to a subject a therapeutically effective amount of antibody 27F9, antibody 47C8, antibody 48A5, antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or humanized versions thereof. In some embodiments, the method of inhibiting growth of a tumor comprises administering to a subject a therapeutically effective amount of antibody Hz47H6.v2. In some embodiments, the method of inhibiting growth of a tumor comprises administering to a subject a therapeutically effective amount of antibody Hz64A12. In some embodiments, the method of inhibiting growth of a tumor comprises administering to a subject a therapeutically effective amount of antibody Hz73D1.v1. In some embodiments of the methods described herein, the subject is a human.

**[00353]** The present disclosure provides methods of treating cancer. In some embodiments, a method of treating cancer comprises administering to a subject a therapeutically effective amount of an ILT2-binding agent described herein. In some embodiments, a method of treating cancer comprises administering to a subject a therapeutically effective amount of an ILT4-binding agent described herein. In some embodiments, a method of treating cancer comprises administering to a subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In

some embodiments, an ILT2/ILT4-binding agent binds ILT2 and/or ILT4 and inhibits or reduces growth of the cancer. In some embodiments, an ILT2/ILT4-binding agent binds human ILT2-expressing cells and/or ILT4-expressing cells, enhances an immune response to a cancer, and inhibits or reduces growth of the cancer. In some embodiments, an ILT2/ILT4-binding agent binds human ILT2-expressing cells and/or ILT4-expressing cells, activates myeloid cells, enhances an immune response to a cancer, and inhibits or reduces growth of the cancer. In some embodiments, the subject is a human. In some embodiments, the subject has a cancerous tumor. In some embodiments, the subject has had the cancer at least partially removed.

[00354] In some embodiments, the disclosure provides use of an ILT2-binding agent described herein in the manufacture or preparation of a medicament for the treatment of cancer. In some embodiments, the disclosure provides use of an ILT4-binding agent described herein in the manufacture or preparation of a medicament for the treatment of cancer. In some embodiments, the disclosure provides use of an ILT2/ILT4-binding agent described herein in the manufacture or preparation of a medicament for the treatment of cancer.

[00355] In some embodiments of the methods described herein, the cancer is pancreatic cancer, breast cancer, lung cancer, non-small cell lung cancer (NSCLC), head and neck cancer, colorectal cancer, prostate cancer, skin cancer, melanoma, stomach cancer, gastric cancer, intestinal cancer, ovarian cancer, cervical cancer, uterine cancer, endometrial cancer, bladder cancer, brain cancer, esophageal cancer, liver cancer, kidney cancer, renal cell carcinoma (RCC), or testicular cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the cancer is renal cell carcinoma.

[00356] In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of antibody 27F9 or a humanized version thereof. In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of

antibody 47C8 or antibody 48A5, or a humanized version thereof. In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of antibody 47H6, antibody 51A1, antibody 64A12, antibody 73C4, or antibody 73D1, or a humanized version thereof. In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of antibody Hz47H6.v2. In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of antibody Hz64A12. In some embodiments, a method for treating cancer in a subject comprises administering to the subject a therapeutically effective amount of antibody Hz73D1.v1.

**[00357]** In some embodiments, the disclosure provides methods of activating myeloid cells in the tumor microenvironment. In some embodiments, a method of activating myeloid cells in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of activating myeloid cells in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein. In some embodiments, the myeloid cells are primary dendritic cells. In some embodiments, the myeloid cells are monocytes. In some embodiments, the myeloid cells are macrophages. In some embodiments, the myeloid cells are APCs.

**[00358]** In some embodiments, the disclosure provides methods of activating NK cells in the tumor microenvironment. In some embodiments, a method of activating NK cells in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of activating NK cells in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent described herein. In some embodiments, a method of activating NK cells in the tumor microenvironment

in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein.

**[00359]** In some embodiments, the disclosure provides methods of activating CTLs in the tumor microenvironment. In some embodiments, a method of activating CTLs in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent or an ILT2/ILT4-binding agent described herein. In some embodiments, a method of activating CTLs in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2-binding agent described herein. In some embodiments, a method of activating CTLs in the tumor microenvironment in a subject with a tumor comprises administering to the subject a therapeutically effective amount of an ILT2/ILT4-binding agent described herein.

**[00360]** In some embodiments of the methods described herein, an ILT2-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 27F9.

**[00361]** In some embodiments of the method described herein, an ILT2-binding agent is an anti-ILT2 antibody. In some embodiments of the methods described herein, the anti-ILT2 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFSLTNYGVS (SEQ ID NO:22), a heavy chain variable region CDR2 comprising the amino acid sequence IIWGDGSTNYHSALIS (SEQ ID NO:23), and a heavy chain variable region CDR3 comprising the amino acid sequence PNWDTYAMDF (SEQ ID NO:24), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASQDISNFLN (SEQ ID NO:25), a light chain variable region CDR2 comprising the amino acid sequence CTSKLHS (SEQ ID NO:26), and a light chain variable region CDR3 comprising the amino acid sequence QQGNTLPPT (SEQ ID NO:27). In some embodiments of the methods described herein, the anti-ILT2 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:125 and (b) a light chain variable region of SEQ ID NO:126. In some embodiments of the methods

described herein, the anti-ILT2 antibody is antibody 27F9. In some embodiments of the methods described herein, the anti-ILT2 antibody is a humanized version of 27F9.

**[00362]** In some embodiments of the methods described herein, the ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 47C8.

**[00363]** In some embodiments of the method described herein, an ILT4-binding agent is an anti-ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYSFTGYMH (SEQ ID NO:38), a heavy chain variable region CDR2 comprising the amino acid sequence RVYPNNGDTSYNQKFKV (SEQ ID NO:39), and a heavy chain variable region CDR3 comprising the amino acid sequence GATVVESLFAY (SEQ ID NO:40), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDNYGNNFLH (SEQ ID NO:41), a light chain variable region CDR2 comprising the amino acid sequence RTSNLES (SEQ ID NO:42), and a light chain variable region CDR3 comprising the amino acid sequence QQSNEPYPY (SEQ ID NO:43). In some embodiments of the methods described herein, the anti-ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:127 and (b) a light chain variable region of SEQ ID NO:128. In some embodiments of the methods described herein, the anti-ILT4 antibody is antibody 47C8. In some embodiments of the methods described herein, the anti-ILT4 antibody is a humanized version of antibody 47C8.

**[00364]** In some embodiments of the methods described herein, the ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 48A5.

**[00365]** In some embodiments of the method described herein, an ILT4-binding agent is an anti-ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTNYGMN

(SEQ ID NO:54), a heavy chain variable region CDR2 comprising the amino acid sequence WINTYIGEPIYADDFKG (SEQ ID NO:55), and a heavy chain variable region CDR3 comprising the amino acid sequence RSDYDGYAMDY (SEQ ID NO:56), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence KSSQSLLYSGNQKNYLA (SEQ ID NO:57), a light chain variable region CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO:58), and a light chain variable region CDR3 comprising the amino acid sequence QQHDSYPT (SEQ ID NO:59). In some embodiments of the methods described herein, the anti-ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:129 and (b) a light chain variable region of SEQ ID NO:130. In some embodiments of the methods described herein, the anti-ILT4 antibody is antibody 48A5. In some embodiments of the methods described herein, the anti-ILT4 antibody is a humanized version of antibody 48A5.

**[00366]** In some embodiments of the methods described herein, the ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 47H6 or antibody Hz47H6.v2.

**[00367]** In some embodiments of the method described herein, an ILT2/ILT4-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71) or DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYSLSYFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence

QHFWTSIT (SEQ ID NO:75). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNGGTTYNQKFEG (SEQ ID NO:71), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence DFNPNNAGTTYNQKFEG (SEQ ID NO:118), and a heavy chain variable region CDR3 comprising the amino acid sequence GRFYYGSLYSFDY (SEQ ID NO:72), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASGNIHNYLA (SEQ ID NO:73), a light chain variable region CDR2 comprising the amino acid sequence NAKTLAD (SEQ ID NO:74), and a light chain variable region CDR3 comprising the amino acid sequence QHFWTSIT (SEQ ID NO:75). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:131 and (b) a light chain variable region of SEQ ID NO:132. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:133 and (b) a light chain variable region of SEQ ID NO:134. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain of SEQ ID NO:148 and (b) a light chain of SEQ ID NO:149. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody

47H6. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is a humanized version of antibody 47H6. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody Hz47H6.v2.

**[00368]** In some embodiments of the methods described herein, the ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 51A1 or a humanized version of antibody 51A1.

**[00369]** In some embodiments of the method described herein, an ILT2/ILT4-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYYGTMYYAMDY (SEQ ID NO:88), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:135 and (b) a light chain variable region of SEQ ID NO:136. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody 51A1. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is a humanized version of antibody 51A1.

**[00370]** In some embodiments of the methods described herein, the ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 64A12, a humanized version of antibody 64A12, or antibody Hz64A12.

[00371] In some embodiments of the method described herein, an ILT2/ILT4-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GFTFNTYAMH (SEQ ID NO:86), a heavy chain variable region CDR2 comprising the amino acid sequence RIRSKSSNYATYYADSVKD (SEQ ID NO:87), and a heavy chain variable region CDR3 comprising the amino acid sequence DGIYYDYDTMYYYAMDY (SEQ ID NO:102), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFIY (SEQ ID NO:103), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:137 and (b) a light chain variable region of SEQ ID NO:138. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:139 and (b) a light chain variable region of SEQ ID NO:140. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain of SEQ ID NO:152 and (b) a light chain of SEQ ID NO:153. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody 64A12. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is a humanized version of antibody 64A12. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody Hz64A12.

[00372] In some embodiments of the methods described herein, the ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 73C4 or a humanized version of antibody 73C4.

[00373] In some embodiments of the method described herein, an ILT2/ILT4-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYMN (SEQ ID NO:70), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNNGGTSYNQKFKG (SEQ ID NO:106), and a heavy chain variable region CDR3 comprising the amino acid sequence REIYFYGTIYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASEVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:141 and (b) a light chain variable region of SEQ ID NO:142. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody 73C4. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is a humanized version of antibody 73C4.

[00374] In some embodiments of the methods described herein, the ILT2/ILT4-binding agent comprises a heavy chain variable region CDR1, CDR2, and CDR3 and a light chain variable region CDR1, CDR2, and CDR3 of antibody 73D1, a humanized version of antibody 73D1, or antibody Hz73D1.v1.

[00375] In some embodiments of the method described herein, an ILT2/ILT4-binding agent is an anti-ILT2/ILT4 antibody. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence GYTFTDYIN (SEQ ID NO:111), a heavy chain variable region CDR2 comprising the amino acid sequence NVNPNDDGGTTYNQKFKG (SEQ ID NO:112), and a heavy chain variable region CDR3 comprising the amino acid sequence

REIYFYGTIYYYAMDY (SEQ ID NO:107), and (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence RASESVDYYGNSFMY (SEQ ID NO:89), a light chain variable region CDR2 comprising the amino acid sequence FASNLES (SEQ ID NO:90), and a light chain variable region CDR3 comprising the amino acid sequence QQNNEDPWT (SEQ ID NO:91). In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:143 and (b) a light chain variable region of SEQ ID NO:142. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain variable region of SEQ ID NO:144 and (b) a light chain variable region of SEQ ID NO:145. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody comprises: (a) a heavy chain of SEQ ID NO:156 and (b) a light chain of SEQ ID NO:157. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody 73D1. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is a humanized version of antibody 73D1. In some embodiments of the methods described herein, the anti-ILT2/ILT4 antibody is antibody Hz73D1.v1.

[00376] In some embodiments of the methods described herein, a method comprises administering an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein in combination with at least one additional therapeutic agent or therapeutic therapy. In some embodiments of the methods described herein, a method comprises administering an ILT2/ILT4-binding agent described herein in combination with at least one additional therapeutic agent or therapeutic therapy. Treatment with two or more therapeutic agents often uses agents that work by different mechanisms of action, although this is not required. Combination therapy using agents with different mechanisms of action may result in additive or synergistic effects. Combination therapy may allow for a lower dose of each agent than is used in monotherapy, thereby reducing toxic side effects and/or increasing

the therapeutic index of the agent(s). Combination therapy may decrease the likelihood that resistance to an agent will develop.

[00377] In some embodiments of the methods described, the combination of an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein and at least one additional therapeutic agent results in additive or synergistic results. In some embodiments, the combination therapy results in an increase in the therapeutic index of the ILT-binding agent. In some embodiments, the combination therapy results in an increase in the therapeutic index of the additional therapeutic agent(s). In some embodiments, the combination therapy results in a decrease in the toxicity and/or side effects of the ILT-binding agent. In some embodiments, the combination therapy results in a decrease in the toxicity and/or side effects of the additional therapeutic agent(s). In some embodiments, combination therapy comprises a therapeutic agent that affects the immune response (*e.g.*, enhances or activates the response) and a therapeutic agent that affects (*e.g.*, inhibits or kills) the tumor/cancer cells.

[00378] In some embodiments of the methods described herein, a combination treatment comprises one additional therapeutic agent. In some embodiments of the methods described herein, a combination treatment comprises at least one additional therapeutic agent. In some embodiments of the methods described herein, a combination treatment comprises two or more additional therapeutic agents.

[00379] Useful classes of therapeutic agents include, but are not limited to, anti-tubulin agents, auristatins, DNA minor groove binders, DNA replication inhibitors, alkylating agents (*e.g.*, platinum complexes such as cisplatin, mono(platinum), bis(platinum) and tri-nuclear platinum complexes and carboplatin), anthracyclines, antibiotics, anti-folates, anti-metabolites, chemotherapy sensitizers, duocarmycins, etoposides, fluorinated pyrimidines, ionophores, lexitropsins, nitrosoureas, platinols, purine antimetabolites, puromycins, radiation sensitizers, steroids, taxanes, topoisomerase inhibitors, vinca alkaloids, or the like. In some embodiments, the second therapeutic

agent is an alkylating agent, an antimetabolite, an antimitotic, a topoisomerase inhibitor, or an angiogenesis inhibitor.

[00380] Therapeutic agents that may be administered in combination with the ILT-binding agents described herein include chemotherapeutic agents. Thus, in some embodiments, the method or treatment involves the administration of an ILT-binding agent of the present disclosure in combination with a chemotherapeutic agent or in combination with a cocktail of chemotherapeutic agents.

[00381] Chemotherapeutic agents useful in the present disclosure include, but are not limited to, alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytosine arabinoside, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanol, testolactone; anti-

adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenishers such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziqunone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK; razoxane; sizofuran; spirogermanium; tenuazonic acid; triaziqunone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); taxoids, *e.g.* paclitaxel (TAXOL) and docetaxel (TAXOTERE); chlorambucil; gemcitabine; 6- thioguanine; mercaptopurine; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; ibandronate; CPT 11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine (XELODA); and pharmaceutically acceptable salts, acids or derivatives of any of the above.

**[00382]** Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

**[00383]** In some embodiments of the methods described herein, the chemotherapeutic agent is a topoisomerase inhibitor. Topoisomerase inhibitors are chemotherapy agents that interfere with the action of a topoisomerase enzyme (*e.g.*, topoisomerase I or II). Topoisomerase inhibitors include, but are not limited to, doxorubicin HC1, daunorubicin citrate, mitoxantrone HC1, actinomycin D, etoposide, topotecan HC1, teniposide (VM-26), and irinotecan, as well as pharmaceutically acceptable salts, acids,

or derivatives of any of these. In some embodiments, the additional therapeutic agent is irinotecan.

**[00384]** In some embodiments, the chemotherapeutic agent is an anti-metabolite. An anti-metabolite is a chemical with a structure that is similar to a metabolite required for normal biochemical reactions, yet different enough to interfere with one or more normal functions of cells, such as cell division. Anti-metabolites include, but are not limited to, gemcitabine, fluorouracil, capecitabine, methotrexate sodium, ralitrexed, pemetrexed, tegafur, cytosine arabinoside, thioguanine, 5-azacytidine, 6-mercaptopurine, azathioprine, 6-thioguanine, pentostatin, fludarabine phosphate, and cladribine, as well as pharmaceutically acceptable salts, acids, or derivatives of any of these. In some embodiments, the additional therapeutic agent is gemcitabine.

**[00385]** In some embodiments of the methods described herein, the chemotherapeutic agent is an antimetabolic agent, including, but not limited to, agents that bind tubulin. In some embodiments, the agent is a taxane. In some embodiments, the agent is paclitaxel or docetaxel, or a pharmaceutically acceptable salt, acid, or derivative of paclitaxel or docetaxel. In some embodiments, the agent is paclitaxel (TAXOL), docetaxel (TAXOTERE), albumin-bound paclitaxel (nab-paclitaxel; ABRAXANE), DHA-paclitaxel, or PG-paclitaxel. In certain alternative embodiments, the antimetabolic agent comprises a vinca alkaloid, such as vincristine, vinblastine, vinorelbine, or vindesine, or pharmaceutically acceptable salts, acids, or derivatives thereof. In some embodiments, the antimetabolic agent is an inhibitor of kinesin Eg5 or an inhibitor of a mitotic kinase such as Aurora A or Plkl. In some embodiments, the additional therapeutic agent is paclitaxel. In some embodiments, the additional therapeutic agent is nab-paclitaxel.

**[00386]** In some embodiments of the methods described herein, an additional therapeutic agent comprises an agent such as a small molecule. For example, treatment can involve the combined administration of an ILT-binding agent of the present disclosure with a small molecule that acts as an inhibitor against tumor-associated antigens including, but not limited to, EGFR, HER2 (ErbB2), and/or VEGF. In some embodiments, an ILT-binding agent (*e.g.*, an anti-ILT2 antibody, an anti-ILT4 antibody,

or an anti-ILT2/ILT4 antibody) of the present disclosure is administered in combination with a protein kinase inhibitor selected from the group consisting of: gefitinib (IRESSA), erlotinib (TARCEVA), sunitinib (SUTENT), lapatanib, vandetanib (ZACTIMA), AEE788, CI-1033, cediranib (RECENTIN), sorafenib (NEXAVAR), and pazopanib (GW786034B). In some embodiments, an additional therapeutic agent comprises an mTOR inhibitor.

[00387] In some embodiments of the methods described herein, an additional therapeutic agent comprises a biological molecule, such as an antibody. For example, treatment can involve the combined administration of an ILT-binding agent of the present disclosure with antibodies against tumor-associated antigens including, but not limited to, antibodies that bind EGFR, HER2/ErbB2, and/or VEGF.

[00388] In some embodiments, the additional therapeutic agent is an antibody that is an angiogenesis inhibitor (*e.g.*, an anti-VEGF or VEGF receptor antibody). In some embodiments, the additional therapeutic agent is bevacizumab (AVASTIN), ramucirumab, trastuzumab (HERCEPTIN), pertuzumab (OMNITARG), panitumumab (VECTIBIX), nimotuzumab, zalutumumab, or cetuximab (ERBITUX).

[00389] In some embodiments of the methods described herein, the additional therapeutic agent is an immunotherapeutic agent. In some embodiments of the methods described herein the immunotherapeutic agent is selected from the group consisting of: a modulator of PD-1 activity, a modulator of PD-L1 activity, a modulator of PD-L2 activity, a modulator of CTLA-4 activity, a modulator of CD28 activity, a modulator of CD80 activity, a modulator of CD86 activity, a modulator of 4-1BB activity, an modulator of OX40 activity, a modulator of KIR activity, a modulator of Tim-3 activity, a modulator of LAG3 activity, a modulator of CD27 activity, a modulator of CD40 activity, a modulator of GITR activity, a modulator of TIGIT activity, a modulator of CD20 activity, a modulator of CD96 activity, a modulator of IDO1 activity,

[00390] In some embodiments of the methods described herein, an immunotherapeutic agent is selected from the group consisting of: a PD-1 antagonist, a PD-L1 antagonist, a PD-L2 antagonist, a CTLA-4 antagonist, a CD80 antagonist, a CD86 antagonist, a KIR

antagonist, a Tim-3 antagonist, a LAG3 antagonist, a TIGIT antagonist, a CD20 antagonist, a CD96 antagonist, and/or an IDO1 antagonist.

[00391] In some embodiments of the methods described herein, the additional therapeutic agent is a checkpoint inhibitor. In some embodiments, the additional therapeutic agent is an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-CTLA-4 antibody, or an anti-TIGIT antibody, an anti-CD28 antibody, an anti-CD80 antibody, an anti-CD86 antibody, an anti-4-1BB antibody, an anti-OX40 antibody, an anti-KIR antibody, an anti-Tim-3 antibody, an anti-LAG3 antibody, an anti-CD27 antibody, an anti-CD40 antibody, an anti-GITR antibody, an anti-TIGIT antibody, an anti-CD20 antibody, an anti-CD96 antibody, or an anti-IDO1 antibody. In some embodiments, the additional therapeutic agent is an anti-HLA-G antibody. In some embodiments, the additional therapeutic agent is B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, or an anti-CD3 antibody.

[00392] In some embodiments of the methods described herein, the PD-1 antagonist is an antibody that specifically binds PD-1. In some embodiments, the antibody that binds PD-1 is Pembrolizumab (MK-3475; KEYTRUDA), Pidilizumab (CT-011), Nivolumab (OPDIVO), Durvalumab (MEDI0680), Cemiplimab (REGN2810), Tislelizumab (BGB-A317), Spartalizumab (PDR-001), or STI-A1110. Exemplary anti-PD-1 antibodies are provided, for example, in US Patent Nos. US10316089, US9580504, US9856320, US8609089, and US8952136; the contents of all of which are incorporated by reference in their entirety herein. In some embodiments, the antibody that binds PD-1 is described in PCT Publication WO 2014/179664, for example, an antibody identified as APE2058, APE1922, APE1923, APE1924, APE 1950, or APE1963, or an antibody containing the CDR regions of any of these antibodies. In other embodiments, the PD-1 antagonist is a fusion protein that includes PD-L2, for example, AMP-224. In other embodiments, the PD-1 antagonist is a peptide inhibitor, for example, AU P-12.

[00393] In some embodiments, the PD-L1 antagonist is an antibody that specifically binds PD-L1. In some embodiments, the antibody that binds PD-L1 is Atezolizumab (TECENTRIQ), MEDI4736, BMS-936559 (MDX-1105), Avelumab (BAVENCIO),

Durvalumab (IMFINZI), KD033, the antibody portion of KD033, or STI-A1014. In some embodiments, the antibody that binds PD-L1 is described in PCT Publication WO 2014/055897, for example, Ab-14, Ab-16, Ab-30, Ab-31, Ab-42, Ab-50, Ab-52, or Ab-55, or an antibody that contains the CDR regions of any of these antibodies.

[00394] In some embodiments, the CTLA-4 antagonist is an antibody that specifically binds CTLA-4. In some embodiments, the antibody that binds CTLA-4 is Ipilimumab (YERVOY) or Tremelimumab (CP-675,206). In some embodiments, the CTLA-4 antagonist is a CTLA-4 fusion protein, for example, KAHR-102.

[00395] In some embodiments, the LAG3 antagonist is an antibody that specifically binds LAG3. In some embodiments, the antibody that binds LAG3 is IMP701, IMP731, BMS-986016, LAG525, and GSK2831781. In some embodiments, the LAG3 antagonist includes a soluble LAG3 receptor, for example, IMP321.

[00396] In some embodiments, the KIR antagonist is an antibody that specifically binds KIR. In some embodiments, the antibody that binds KIR is Lirilumab.

[00397] In some embodiments, an immunotherapeutic agent is selected from the group consisting of: a CD28 agonist, a 4-1BB agonist, an OX40 agonist, a CD27 agonist, a CD80 agonist, a CD86 agonist, a CD40 agonist, and a GITR agonist.

[00398] In some embodiments, the OX40 agonist includes OX40 ligand, or an OX40-binding portion thereof. For example, the OX40 agonist may be MEDI6383. In some embodiments, the OX40 agonist is an antibody that specifically binds OX40. In some embodiments, the antibody that binds OX40 is MEDI6469, MEDI0562, PF-8600, or MOXR0916 (RG7888). In some embodiments, the OX40 agonist is a vector (*e.g.*, an expression vector or virus, such as an adenovirus) capable of expressing OX40 ligand. In some embodiments the OX40-expressing vector is Delta -24 -RGDOX or DNX2401.

[00399] In some embodiments, the 4-1BB (CD137) agonist is a binding molecule, such as an anticalin. In some embodiments, the anticalin is PRS-343. In some embodiments, the 4-1BB agonist is an antibody that specifically binds 4-1BB. In some embodiments, antibody that binds 4-1BB is Utomilumab (PF-05082566) or Urelumab (BMS-663513).

[00400] In some embodiments, the CD27 agonist is an antibody that specifically binds CD27. In some embodiments, the antibody that binds CD27 is varlilumab (CDX-1127).

[00401] In some embodiments, the GITR agonist comprises a GITR ligand or a GITR-binding portion thereof. In some embodiments, the GITR agonist is an antibody that specifically binds GITR. In some embodiments, the antibody that binds GITR is TRX518, MK-4166, or INBRX-110.

[00402] In some embodiments of the methods described herein, the additional therapeutic agent is a biologic molecule, such as, a cytokine, a chemokine, a growth factor, an interferon, an interleukin, a lymphokine, a member of the tumor necrosis factor (TNF) family, and an immunostimulatory oligonucleotide (*e.g.*, CpG dinucleotides). In some embodiments, the biologic molecule is selected from the group consisting of: adrenomedullin (AM), angiopoietin (Ang), BMPs, BDNF, EGF, erythropoietin (EPO), FGF, GDNF, granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), GDF9, HGF, HDGF, IGF, migration-stimulating factor, myostatin (GDF-8), NGF, neurotrophins, PDGF, thrombopoietin, TGF- $\alpha$ , TGF- $\beta$ , TNF- $\alpha$ , VEGF, PIGF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-12, IL-15, and IL-18.

[00403] Furthermore, treatment with an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein can be accompanied by surgical removal of tumors, removal of cancer cells, or any other therapy deemed necessary by a treating physician.

[00404] In some embodiments, treatment with an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) can occur prior to, concurrently with, or subsequent to administration of the additional therapeutic agents. In some embodiments, combined administration includes co-administration, either in a single pharmaceutical formulation or using separate formulations, or consecutive administration in either order but generally within a time period such that all active agents can exert their biological activities. In some embodiments, preparation

of agents and/or dosing schedules for additional therapeutic agents are according to manufacturers' instructions or as determined empirically by the skilled practitioner.

[00405] In some embodiments of the methods described herein, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) is administered to a subject as part of a combination therapy.

[00406] It will be appreciated that the combination of an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) described herein and at least one additional therapeutic agent may be administered in any order or concurrently. In some embodiments, an ILT-binding agent is administered to subjects that have previously undergone treatment with a therapeutic agent. In some embodiments, an ILT-binding agent and a second therapeutic agent are administered substantially simultaneously or concurrently. For example, a subject may be given an ILT-binding agent while undergoing a course of treatment with a second therapeutic agent (*e.g.*, a chemotherapeutic agent). In some embodiments, an ILT-binding agent is administered within 1 year of the treatment with a second therapeutic agent. In some embodiments, an ILT-binding agent is administered within 10, 8, 6, 4, or 2 months of any treatment with a second therapeutic agent. In some embodiments, an ILT-binding agent is administered within 4, 3, 2, or 1 weeks of any treatment with a second therapeutic agent. In some embodiments, an ILT-binding agent is administered within 5, 4, 3, 2, or 1 days of any treatment with a second therapeutic agent. It will further be appreciated that the two (or more) agents or treatments can be administered to the subject within a matter of hours or minutes (*i.e.*, substantially simultaneously).

[00407] For the treatment of a disease, the appropriate dosage of an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) of the present disclosure depends on the disorder or disease to be treated, the severity and course of the disorder or disease, the responsiveness of the disorder or disease, whether the agent is administered for therapeutic or preventative purposes, previous therapy, the patient's clinical history, and so on. An ILT-binding agent can be administered one time

or over a series of treatments lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved.

[00408] The present disclosure provides pharmaceutical compositions comprising an ILT-binding agent described herein and a pharmaceutically acceptable vehicle. The present disclosure also provides pharmaceutical compositions comprising an ILT2-binding agent described herein and a pharmaceutically acceptable vehicle. The present disclosure also provides pharmaceutical compositions comprising an ILT4-binding agent described herein and a pharmaceutically acceptable vehicle. The present disclosure also provides pharmaceutical compositions comprising an ILT2/ILT4-binding agent described herein and a pharmaceutically acceptable vehicle.

[00409] Formulations are prepared for storage and use by combining a purified antibody or agent of the present disclosure with a pharmaceutically acceptable vehicle (*e.g.*, a carrier or excipient). Those of skill in the art generally consider pharmaceutically acceptable carriers, excipients, and/or stabilizers to be inactive ingredients of a formulation or pharmaceutical composition.

[00410] Suitable pharmaceutically acceptable vehicles include, but are not limited to, nontoxic buffers such as phosphate, citrate, and other organic acids; salts such as sodium chloride; antioxidants including ascorbic acid and methionine; preservatives such as octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol, alkyl parabens, such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol; low molecular weight polypeptides (*e.g.*, less than about 10 amino acid residues); proteins such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; carbohydrates such as monosaccharides, disaccharides, glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counterions such as sodium; metal complexes such as Zn-protein complexes; and non-ionic surfactants such as TWEEN or polyethylene glycol. (*Remington: The Science and*

*Practice of Pharmacy, 22<sup>nd</sup> Edition*, 2012, Pharmaceutical Press, London.). In some embodiments, the formulation is in the form of an aqueous solution. In some embodiments, the formulation is stored in a lyophilized or in an alternative dried form.

**[00411]** The ILT-binding agents of the present disclosure can be formulated in any suitable form for delivery to a target cell/tissue. In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) can be formulated as a liposome, microparticle, microcapsule, albumin microsphere, microemulsion, nanoparticle, nanocapsule, or macroemulsion.

**[00412]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) is formulated with liposomes. Methods to produce liposomes are known to those of skill in the art. For example, some liposomes can be generated by reverse phase evaporation with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE).

**[00413]** In some embodiments, an ILT-binding agent (*e.g.*, an ILT2-binding agent, an ILT4-binding agent, or an ILT2/ILT4-binding agent) is formulated as a sustained-release preparation. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing an agent, where the matrices are in the form of shaped articles (*e.g.*, films or microcapsules). Sustained-release matrices include but are not limited to polyesters, hydrogels such as poly(2-hydroxyethyl-methacrylate) or poly(vinyl alcohol), polylactides, copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

**[00414]** The pharmaceutical compositions or formulations of the present disclosure can be administered in any number of ways for either local or systemic treatment. Administration can be topical by epidermal or transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders; pulmonary by

inhalation or insufflation of powders or aerosols, including by nebulizer, intratracheal, and intranasal; oral; or parenteral including intravenous, intraarterial, intratumoral, subcutaneous, intraperitoneal, intramuscular (*e.g.*, injection or infusion), or intracranial (*e.g.*, intrathecal or intraventricular).

## EXAMPLES

### Example 1

Generation of antibodies and screening of antibodies

**[00415]** Anti-ILT antibodies were generated using the extracellular domain of human ILT2, the extracellular domain of human ILT4, and/or the extracellular domain of rhesus ILT2 as the immunogen. For examples, anti-ILT2 antibodies were generated using the extracellular domain of human ILT2. Similarly, anti-ILT4 antibodies were generated using the extracellular domain of human ILT4. Anti-ILT2/ILT4 antibodies were generated using a mixture of the extracellular domain of human ILT2, the extracellular domain of human ILT4, and the extracellular domain of rhesus ILT2. Single cell suspensions of lymphocytes were obtained from the spleens and lymph nodes of immunized mice after the individual animals had been determined to have suitable antibody titers. Lymphocytes were fused with murine myeloma cells by standard methods. Hybridoma fusions were plated onto semi-solid media for HAT selection. After 5-7 days, single colonies were selected using a ClonePix™ system and plated into 96-well plates.

**[00416]** ELISA assays were used to screen antibodies against human ILT2, human ILT4, and rhesus ILT2. Antibodies that bound to human ILT2 only, human ILT4 only, or human ILT2, human ILT4 and rhesus ILT2 were selected.

## Example 2

Synteny between human and cynomolgus monkey ILT2 and ILT4 genes

[00417] In rodents, paired Ig-like receptor B (PirB) and gp49B1 have been described as the potential orthologues of human LILRB family of receptors (Kang X, et al. *Cell Cycle*. (2016);15(1):25-40). However, PirB and gp49B1 show less than 50% identity to both human ILT2 and human ILT4. Further, marked differences exist in the receptor/ligand pairing among the rodent and human LILRB family members and the biological function of the rodent receptors are unclear. Thus, rodents are not considered relevant species to test the biological effects of anti-ILT antibodies.

[00418] An analysis of genomic structure (synteny) was used to identify candidate orthologs of both human ILT2 and ILT4 in cynomolgus monkey. The genomic organization of the locus that contains the LILR family members in human (hg38) and cynomolgus monkey (*Macaca fascicularis* v5.0.95, "cyno") were compared using the gene annotations provided by Ensembl. In cases where annotations were not found, manual analysis of the intervening sequence was used to confirm lack of an open reading frame. The predicted protein sequence of genes in cynomolgus monkey without pre-annotated gene symbols was compared to all human genes using blastp tools on UniProt to find the most likely human ortholog based on the identity score.

[00419] It was found that the cynomolgus monkey genomic organization is missing a gene at the same genome location as human LILRB2 (ILT4), while retaining a gene at the same location as human LILRB1 (ILT2). A similar organization was observed with rhesus macaque. The sequence identity between human ILT2, human ILT4 and cyno ILT2 ranges from 73%-80%. The sequence identity between human ILT2 and cyno ILT2 is 73%, while sequence identity between human ILT4 and cyno ILT2 is 78%. In comparison, the sequence identity between human ILT2 and human ILT4 is 80%.

## Example 3

Binding characteristics of anti-human ILT2, ILT4, and ILT2/ILT4 antibodies

[00420] The binding affinities of anti-ILT2 and anti-ILT4 antibodies were measured using a Biacore system (GE Healthcare LifeSciences). Equilibrium dissociation constant ( $K_D$ ) measurements were carried out with purified antibodies to evaluate their binding to human ILT2, human ILT4, and rhesus ILT2. Briefly, purified anti-ILT2 antibody 27F9, anti-ILT4 antibodies 47C8 and 48A5, and anti-ILT2/ILT4 antibodies 47H6, 51A1, 64A12, 73C4, and 73D1 were captured on a Sensor Chip Protein A (GE HealthCare). The surface of the Biacore Sensor Chip Protein A consists of a carboxymethylated dextran matrix with a recombinant Protein A variant covalently attached. Soluble human ILT2-ECD, human ILT4-ECD, or rhesus ILT2-ECD were injected at a flow rate of 30  $\mu$ L/min at 25°C. The ILT2 or ILT4 proteins were used at concentrations ranging from 1.6 - 200 nM in PBS-P buffer with 2 fold dilutions. Kinetic data were collected over time and fit using the simultaneous global fit equation to yield affinity constants ( $K_D$  values) for each antibody.

[00421] Binding data is shown in Tables 9A and 9B.

Table 9A

Antibody	Human ILT2			Human ILT4		
	$K_{on}$ [1/Ms]	$K_{off}$ [s <sup>-1</sup> ]	$K_D$ M	$K_{on}$ [1/Ms]	$K_{off}$ [s <sup>-1</sup> ]	$K_D$ M
27F9	$2.1 \times 10^5$	$5.4 \times 10^{-5}$	$2.6 \times 10^{-10}$	NB	NB	NB
47C8	NB	NB	NB	$3.4 \times 10^5$	$2.5 \times 10^{-5}$	$7.4 \times 10^{-11}$
48A5	NB	NB	NB	$8.1 \times 10^5$	$2.1 \times 10^{-5}$	$2.6 \times 10^{-11}$
47H6	$4.2 \times 10^4$	$8.6 \times 10^{-5}$	$2.1 \times 10^{-9}$	$3.7 \times 10^4$	$2.8 \times 10^{-5}$	$7.6 \times 10^{-10}$
51A1	$3.9 \times 10^4$	$2.2 \times 10^{-4}$	$5.8 \times 10^{-9}$	$6.8 \times 10^4$	$1.4 \times 10^{-5}$	$2.0 \times 10^{-10}$

64A12 <sup>1</sup>	$2.0 \times 10^4$	$\sim 1.0 \times 10^5$	$< 1.0 \times 10^{-10}$	$8.2 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
73C4 <sup>1</sup>	$3.1 \times 10^4$	$\sim 1.0 \times 10^5$	$< 1.0 \times 10^{-10}$	$9.7 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
73D1	$5.0 \times 10^4$	$6.0 \times 10^{-5}$	$1.2 \times 10^{-9}$	$3.0 \times 10^5$	$5.4 \times 10^{-5}$	$1.8 \times 10^{-10}$

1 - Binding assay was performed under low resolution parameters

Table 9B

	Rhesus ILT2		
Antibody	$K_{on}$ [1/Ms]	$K_{off}$ [s <sup>-1</sup> ]	$K_D$ M
27F9	NB	NB	NB
47C8	$5.9 \times 10^5$	$1.4 \times 10^{-3}$	$2.3 \times 10^{-9}$
48A5	$1.1 \times 10^6$	$2.6 \times 10^{-3}$	$2.3 \times 10^{-9}$
47H6 <sup>1</sup>	$4.7 \times 10^4$	$\sim 1 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
51A1	$1.0 \times 10^5$	$2.1 \times 10^{-5}$	$2.0 \times 10^{-10}$
64A12 <sup>1</sup>	$2.0 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
73C4 <sup>1</sup>	$3.1 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
73D1	$5.0 \times 10^4$	$6.0 \times 10^{-5}$	$1.2 \times 10^{-9}$

1 - Binding assay was performed under low resolution parameters

#### Example 4

Sequence analyses of anti-ILT2, anti-ILT4, and anti-ILT2/ILT4 antibodies

[00422] Representative anti-ILT2 antibody 27F9, anti-ILT4 antibodies 47C8 and 48A5, and anti-ILT2/ILT4 antibodies 47H6, 51A1, 64A12, 73C4, and 73D1 were

sequenced and the heavy chain variable region and light chain variable region amino acid sequences are disclosed herein and summarized in Table 10.

Table 10

Antibody	Target	Heavy Chain Variable Region	Light Chain Variable Region
27F9	ILT2	SEQ ID NO:125	SEQ ID NO:126
47C8	ILT4	SEQ ID NO:127	SEQ ID NO:128
48A5	ILT4	SEQ ID NO:129	SEQ ID NO:130
47H6	ILT2/ILT4	SEQ ID NO:131	SEQ ID NO:132
51A1	ILT2/ILT4	SEQ ID NO:135	SEQ ID NO:136
64A12	ILT2/ILT4	SEQ ID NO:137	SEQ ID NO:138
73C4	ILT2/ILT4	SEQ ID NO:141	SEQ ID NO:142
73D1	ILT2/ILT4	SEQ ID NO:143	SEQ ID NO:142

[00423] The heavy chain and light chain variable region CDRs for the individual antibodies are disclosed in Tables 1-8 and as SEQ ID NOs:22-124.

#### Example 5

##### Generation of Humanized Antibodies

[00424] Several of the anti-ILT2/ILT4 antibodies, *i.e.*, 47H6, 64A12, and 73D1, were humanized by methods known to those skilled in the art. These humanized antibodies are referred to herein as Hz47H6.v2, Hz64A12, and Hz73D1.v1, respectively. During the humanization process for antibody 47H6, the heavy chain variable region CDR2 was modified from DFNPNNGGTTYNQKFEG (SEQ ID NO:71) to DFNPNNAGTTYNQKFEG (SEQ ID NO:118). The heavy chain variable region sequence of Hz47H6.v2 is SEQ ID NO:133 and the light chain variable region sequence of Hz47H6.v2 is SEQ ID NO:134; the heavy chain variable region sequence of Hz64A12 is SEQ ID NO:139 and the light chain variable region sequence of Hz64A12 is SEQ ID NO:140; and the heavy chain variable region sequence of Hz73D1.v1 is SEQ

ID NO:144 and the light chain variable region sequence of Hz73D1.v1 is SEQ ID NO:145.

[00425] The binding affinities of the humanized antibodies to human ILT2 and human ILT4 were measured using a Biacore system as described herein. The binding affinities of antibodies Hz47H6.v2, Hz64A12, and Hz73D1.v1 are shown in Table 11 as compared with the parental antibodies.

Table 11

Antibody	Human ILT2			Human ILT4		
	$K_{on}$ [1/Ms]	$K_{off}$ [s <sup>-1</sup> ]	$K_D$ M	$K_{on}$ [1/Ms]	$K_{off}$ [s <sup>-1</sup> ]	$K_D$ M
47H6	$1.0 \times 10^5$	$2.1 \times 10^{-5}$	$2.0 \times 10^{-10}$	$1.0 \times 10^5$	$2.1 \times 10^{-5}$	$2.0 \times 10^{-10}$
Hz47H6.v2	$2.3 \times 10^5$	$9.0 \times 10^{-4}$	$4.0 \times 10^{-9}$	$8.7 \times 10^4$	$1.8 \times 10^{-4}$	$2.0 \times 10^{-9}$
64A12 <sup>1</sup>	$2.0 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$	$8.2 \times 10^4$	$\sim 1.0 \times 10^{-5}$	$< 1.0 \times 10^{-10}$
Hz64A12 <sup>1</sup>	$9.3 \times 10^4$	$1.4 \times 10^{-4}$	$1.6 \times 10^{-9}$	$3.0 \times 10^5$	$\sim 1.0 \times 10^{-5}$	$< 1 \times 10^{-10}$
73D1	$1.5 \times 10^5$	$2.4 \times 10^{-4}$	$1.8 \times 10^{-9}$	$4.0 \times 10^5$	$3.0 \times 10^{-5}$	$7.4 \times 10^{-10}$
Hz73D1.v1	$8.5 \times 10^4$	$2.5 \times 10^{-4}$	$3.0 \times 10^{-9}$	$3.6 \times 10^5$	$2.7 \times 10^{-4}$	$7.5 \times 10^{-10}$

1 - Binding assay was performed under low resolution parameters

[00426] These results demonstrated that the humanization process for exemplary anti-ILT2/ILT4 antibodies did not have a significant effect on the antibodies' binding capabilities to human ILT2 or human ILT4.

[00427] Cross-reactivity of humanized anti-ILT2/ILT4 antibodies with cynomolgus monkey ("cyno", *Macaca fascicularis*) ILT2 were also assayed. Similar to anti-ILT2/ILT4 antibodies, humanized anti-ILT2/ILT4 antibodies bind to cyno ILT2. Binding affinities of an exemplary clone Hz73D1.v1 measured by a Biacore system are shown in Table 12. In the Biacore system, a humanized anti-ILT2/ILT4 antibody was captured on a Protein A chip. ILT proteins were injected at different concentrations into

the flow cells to evaluate kinetic parameters at 25°C. The binding affinity ( $K_D$ ) of Hz73D1.v1 to human ILT2 and ILT4 was determined to be 1.03 and 0.205 nM, respectively. The  $K_D$  of Hz73D1.v1 to cyno ILT2 was determined to be 19.1 nM.

Table 12

Species of ILT	$K_D$ (nM)	$k_{on}$ (1/Ms)	$k_{off}$ (1/s)
Human ILT2	1.03	$4.72 \times 10^4$	$4.85 \times 10^{-5}$
Human ILT4	0.205	$2.2 \times 10^5$	$4.6 \times 10^{-5}$
Cynomolgus monkey ILT2	19.1	$3.4 \times 10^6$	0.06

### Example 6

ILT2 and ILT4 expression in subsets of immune cells

[00428] ILT2 and ILT4 expression has been described on various cells of hematopoietic origin, including myeloid cells, granulocytes, and lymphocytes (Colonna M et al. *J Exp Med.* (1997) Dec 1; 186(11): 1809–1818; Colonna M et al., *J Immunol* (1998), 160(7): 3096-3100). Anti-ILT antibodies described herein were used to further elucidate the expression of ILT2 and ILT4 on subsets of human and cyno immune cells.

[00429] Flow cytometry analysis of blood immune cells was performed on human and cyno PBMC and whole blood. PBMC were prepared from a leukopak (Allcells Inc.) by centrifugation through ficoll, washing with PBS and freezing in cryopreservation buffer in liquid nitrogen until use. Whole blood (Allcells Inc.) was obtained fresh and red blood cells (RBC) depleted using ammonium chloride RBC lysing solution (Biolegend). PBMC or whole blood samples were stained with a fluorescently labeled antibody panel to distinguish various immune subsets (monocytes, B cells, NK cells, CD4+ and CD8+ T cells, neutrophils and eosinophils). Samples were further stained with fluorescently labeled isotype, 27F9 (ILT2 specific), 48A5 (ILT4 specific), 73D1, and Hz73D1.v1. The number of ILT2 and ILT4 molecules per cell of each immune subset was estimated

by incubation with Quantum Simply Cellular microspheres followed by flow cytometry analysis.

[00430] As shown in Table 13 and Figure 1, high expression of ILT2 was observed on monocytes, B cells, a subset of NK cells (5-20% total NK cells), and a subset of CD8+ T cells (5-20% total CD8+ T cells). High expression of ILT4 was observed on monocytes, eosinophils and neutrophils. The results showed that cynomolgus monkey peripheral immune cells express ILT2 protein with a level of expression and immune cell distribution comparable with the combination of ILT2 and ILT4 in human peripheral blood.

Table 13

Antigen	Monocyte	Neutrophil	B Cell	NK Cell (Subset)	CD8 T Cell (Subset)
Human ILT2	$5.0 \times 10^4$	0	$2.0 \times 10^4$	$4.0 \times 10^3$	$5.5 \times 10^3$
Human ILT4	$5.0 \times 10^4$	$2.5 \times 10^4$	0	0	0
Cynomolgus monkey ILT2	$1.3 \times 10^5$	$5.0 \times 10^4$	$2.0 \times 10^3$	$8.0 \times 10^3$	$5.0 \times 10^3$

Example 7

Inhibition of the interaction between ILT2 or ILT4 and MHC I molecules by anti-ILT antibodies

[00431] As part of the characterization process, the ability of exemplary antibodies to inhibit or block the interaction of ILT2 or ILT4 with their natural ligands was evaluated in competition experiments using a Biacore system. As described herein, the natural ligands of ILT2 and ILT4 include, but are not limited to, HLA class I molecules, including HLA-A, HLA-B, HLA-C, HLA-E, and HLA-G. Biotinylated HLA-A\*1101 was captured in high amounts on a NeutrAvidin chip surface. Antigen-antibody complexes were prepared with (i) ILT2-ECD and anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, or anti-ILT2/ILT4 antibody Hz73D1.v1 and (ii) ILT4-ECD and anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, or anti-ILT2/ILT4 antibody

Hz73D1.v1. The antibody concentration of each antibody was titrated from 0.09 - 100 nM and the concentration of human ILT2-ECD or ILT4-ECD was kept constant at 20 nM. The complexes were mixed in a 96-well microplate and each was injected onto the HLA-A-coated chip surface. The measured signal (response unit, RU) was plotted against the antibody concentration.

[00432] The results are shown in Figure 2. A decrease in binding of ILT2 to HLA-A was observed with increasing concentrations of anti-ILT2 antibody 27F9 and anti-ILT2/ILT4 antibody Hz73D1.v1 in a dose-dependent manner. In contrast, anti-ILT4 antibody 48A5 had no effect on the binding of ILT2 to HLA-A. Similarly, a decrease in binding of ILT4 to HLA-A was observed with increasing concentrations of anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibody Hz73D1.v1, with no effect by anti-ILT2 antibody 27F9. The antibodies were observed to inhibit the interactions at IC50s in the nanomolar range. Another set of experiments was carried out using a HLA-G-coated chip surface with similar results.

[00433] These data demonstrate that anti-ILT2 and anti-ILT2/ILT4 antibodies described herein inhibit the interactions between ILT2 and its natural ligands. In addition, anti-ILT4 and anti-ILT2/ILT4 antibodies described herein inhibit the interactions between ILT4 and its natural ligands. Importantly, this experiment also showed that the anti-ILT2/ILT4 antibody not only bound to both targets, *i.e.*, ILT2 and ILT4, but was biologically functional in blocking the interactions of both targets with their ligands. These results show that anti-ILT2/ILT4 antibodies may be a potential therapeutic for blocking ILT2-induced and ILT4-induced suppression of immune responses.

### Example 8

Binding of anti-ILT2/ILT4 antibody to cells

[00434] The binding of anti-ILT2/ILT4 antibodies to monocytes was evaluated. The binding of exemplary anti-ILT2/ILT4 antibody 73D1 and the humanized version Hz73D1.v1 to the CD14<sup>+</sup> monocyte population of human and cyno PBMC were

determined by flow cytometry analysis. Briefly, human or cyno PBMCs (from 2 donors each) were thawed, washed in media (RPMI, 10% FBS, L-glutamine, pen/strep), and resuspended in fresh media. PBMCs were stained with a cocktail of labeled antibodies to differentiate between the different cell types.  $1 \times 10^6$  cells/well were stained with fluorescently-labelled 73D1 or Hz73D1.v1 antibody and incubated on ice. The cells were washed with ice-cold reagents and immediately analyzed by flow cytometry. The geometric mean fluorescence intensity for CD14<sup>+</sup> monocytes was calculated for each sample. As shown in Figure 3, an increase in fluorescence was observed at increasing concentrations of antibodies 73D1 and Hz73D1.v1 in both human cells and cyno cells. Furthermore, binding of the antibodies to human cells and cyno cells was comparable. For example, the 50% effective concentration ( $EC_{50}$ ) of Hz73D1.v1 was 8.8 nM with human monocytes and 1.8 nM with cyno monocytes. Cells stained with a control antibody showed no shift in fluorescence. These results demonstrate that anti-ILT2/ILT4 antibodies recognize ILT2 and/or ILT4 on intact cells, *i.e.*, primary monocytes. Importantly, these results show that there is comparable binding to both human and cyno monocytes, suggesting that monkeys will be a suitable model for future studies. Further, no binding of anti-ILT2/ILT4 antibodies described herein was observed to monocytes and other immune cells from rat and mouse, confirming that rodents are not an appropriate species for nonclinical testing.

[00435] In addition to binding to ILT2 and ILT4, anti-ILT2/ILT4 antibodies show cross-reactivity with LILRA1, but not with ILLRB3, ILLRB4, ILLRB5, ILLRA2, ILLRA4, ILLRA5, and ILLRA6. Binding of anti-ILT2/ILT4 antibodies to ILT family members was evaluated by fluorescent-activated cell sorting (FACS) using 293T cells expressing human and cynomolgus monkey ILT2, ILT4, LILRA1, ILLRB3, ILLRB4, ILLRB5, ILLRA2, ILLRA4, ILLRA5, and ILLRA6 respectively. The binding affinities of an exemplary anti-ILT2/ILT4 antibody Hz73D1.v1 to human ILT2, human ILT4,

human LILRA1, and cyno LILRA1 expressed on 293T cells and measured by flow cytometry are shown to be 1.2nM, 1.4nM, 2.64nM and 1.97 nM respectively.

#### Example 9

Inhibition of the interaction between ILT2 or ILT4 and MHC I molecules by anti-ILT antibodies

**[00436]** The ability of anti-ILT2/ILT4 antibodies to inhibit the interaction between ILT2 and/or ILT4 and MHC I molecules was evaluated using a reporter cell system. The Raji cell line was established over 50 years ago from a Burkitt lymphoma and has been shown to express MHC I and MHC II molecules. The lymphoblastoid cell line (LCL) 721.221 is a mutant of parent LCL 721, wherein LCL 721.221 does not express any MHC I molecules. LCL 721.221 cells were transfected with the non-classical MHC I molecule HLA-G and a stable cell line was established, referred to herein as 721.221-HLA-G. Raji cells or 721.221-HLA-G cells were co-cultured with cells expressing a stable reporter system and a cell surface receptor of interest ("reporter cells"). In this chimeric receptor system, the extracellular domain of the receptor of interest (*e.g.*, ILT2 or ILT4) is fused with the transmembrane/intracellular domain of PILR $\beta$  that associates with the adaptor protein DAP12. When the chimeric receptor (*e.g.*, ILT2 or ILT-4) is activated by binding to a ligand (*e.g.*, MHC I molecule), DAP12 becomes phosphorylated and activates an NFAT-responsive promoter which drives GFP expression (see, *e.g.*, Deng et al., 2014, *Blood*, 124:924-935).

**[00437]** ILT2 and ILT4 reporter cells (expressing human ILT2 or human ILT4) were stained with CellTracker Deep Red (ThermoFisher) to distinguish them from Raji or 721.221-HLA-G cells upon analysis. Reporter cells were washed after staining and resuspended at  $1 \times 10^6$  cells/ml in X-VIVO™ 15 media (Lonza). Raji cells or 721.221-HLA-G cells were washed and resuspended in X-VIVO™ 15 media at  $1 \times 10^6$  cell/ml. For assays with Raji cells: anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibody 73D1 and Hz73D1.v1, and a control antibody were serially diluted and 50  $\mu$ l was added to each well of a 96-well flat-bottom cell culture plate. For assays

with 721.221-HLA-G cells: anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibody Hz73D1.v1, and a control antibody were serially diluted and 50  $\mu$ l was added to each well of a 96-well flat-bottom cell culture plate. ILT2-expressing or ILT4-expressing reporter cells (100  $\mu$ l/well) were co-cultured with Raji cells or 721.221-HLA-G cells (100  $\mu$ l/well). The plates were incubated overnight at 37°C. The next day, reporter cells were assayed for GFP expression by FACS.

[00438] As shown in Figure 4A, expression of GFP was induced when ILT2 or ILT4 was expressed on the surface of the reporter cells in the presence of Raji cells. With reporter cells expressing ILT2 on their cell surface, an increasing concentration of anti-ILT2 antibody 27F9 and anti-ILT2/ILT4 antibody 73D1 or Hz73D1.v1 was observed to inhibit GFP expression in a dose-dependent manner (expressed as the % GFP-positive cells). Anti-ILT4 antibody was seen to have no inhibitory effect. Similarly, with reporter cells expressing ILT4 on their cell surface, an increasing concentration of anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibody 73D1 or Hz73D1.v1, was observed to inhibit GFP expression in a dose-dependent manner and the anti-ILT2 antibody had no effect. As shown in Figure 4B, expression of GFP was induced when ILT2 or ILT4 was expressed on the surface of the reporter cells in the presence of 721.221-HLA-G cells. With reporter cells expressing ILT2 on their cell surface, an increasing concentration of anti-ILT2/ILT4 antibody Hz73D1.v1 was observed to inhibit GFP expression in a dose-dependent manner. With reporter cells expressing ILT4 on their cell surface, an increasing concentration of anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibody Hz73D1.v1 was observed to inhibit GFP expression in a dose-dependent manner. Table 14 shows IC<sub>50</sub> of Hz73D1.v1 for blocking the interaction of human ILT2, human ILT4, and cyno ILT2 with MHC I molecules on Raji cells. Table 15 shows IC<sub>50</sub> of Hz73D1.v1 for blocking the interaction of human ILT2, human ILT4 with HLA-G expressed on 721.221 cells.

Table 14

Reporter Construct	Raji Cell IC <sub>50</sub> (nM)
Human ILT2	0.25
Human ILT4	0.066
Cyno ILT2	0.094

Table 15

Reporter Construct	721.221-HLA-G IC <sub>50</sub> (nM)
Human ILT2	0.23
Human ILT4	0.26

[00439] These results show that anti-ILT2 or anti-ILT2/ILT4 antibodies are able to inhibit and/or block the functional interaction between ILT2 and classical MHC I molecules to a high level. In parallel, these results show that anti-ILT4 or anti-ILT2/ILT4 antibodies are able to inhibit and/or block the functional interaction between ILT4 and classical and non-classical MHC I molecules (*e.g.*, HLA-G) to a high level. These results support the idea that an antibody that binds ILT2 and ILT4 would modulate pathways induced by both of these molecules. Therefore, an anti-ILT2/ILT4 antibody may be a stronger therapeutic agent than an antibody that targets only ILT2 or only ILT4.

[00440] An additional study was undertaken with reporter cells expressing cyno ILT2. As described above, cyno ILT2 reporter cells were stained with CellTracker Deep Red, washed, and resuspended at  $1 \times 10^6$  cells/ml in X-VIVO™ 15 media (Lonza). Raji cells were washed and resuspended in X-VIVO™ 15 media at  $1 \times 10^6$  cell/ml. Anti-ILT2/ILT4 antibody 73D1 and Hz73D1.v1 and a control antibody were serially diluted and 50  $\mu$ l was added to each well of a 96-well flat-bottom cell culture plate. ILT2-expressing reporter cells (100  $\mu$ l/well) were co-cultured with Raji cells (100  $\mu$ l/well). The plates were incubated overnight at 37°C. The next day, reporter cells were assayed for GFP expression by FACS.

[00441] As shown in Figure 5, expression of GFP was induced when cyno ILT2/4 was expressed on the surface of the reporter cells in the presence of Raji cells. In the

presence of an increasing concentration of anti-ILT2/ILT4 antibody 73D1 or Hz73D1.v1, the percentage of GFP-expressing cells was decreased in a dose-dependent manner. Table 14 shows IC<sub>50</sub> of Hz73D1.v1 for blocking the interaction of cyno ILT2 with MHC I molecules on Raji cells. These results are further evidence that monkeys would be a good model for testing.

[00442] In addition to the reporter cell system, the inhibitory activity of anti-ILT2/ILT4 antibodies towards the interaction between ILT2 and MHC I molecules, and the interaction between ILT4 and MHC I molecules was evaluated using the Biacore system. Human ILT2-Fc and ILT4-Fc were used as target receptors and their interaction with an exemplary MHC- I molecule (HLA-A) was assayed in the presence or absence of an exemplary anti-ILT2/ILT4 antibody Hz73D1.v1 at 25°C. Anti-human ILT2 (clone 27F9) or ILT4 (clone 48A5) antibodies were used as tool reagents to dissect ILT2- and ILT4-specific blocking activities. Anti-ILT2/ILT4 antibodies produced a dose-dependent reduction in the interaction between ILT2 and HLA-A, as well as between ILT4 and HLA-A. IC<sub>50</sub>s of the antibodies tested are shown in Table 16.

Table 16

Antibody	ILT2 IC <sub>50</sub> (nM)	ILT4 IC <sub>50</sub> (nM)
Hz73D1.v1	10 ± 0.36	9.4 ± 0.34
48A5 (ILT4 specific)	No blocking	8.4 ± 0.46
27F9 (ILT2 specific)	8.9 ± 0.37	No blocking

#### Example 10

Effect of anti-ILT antibodies on activity of NK cells

[00443] NKL is a human natural killer (NK) cell line established from the peripheral blood of a patient with large granular lymphocyte (LGL) leukemia and kindly provided by Dr. Louis Lanier. As disclosed herein, NK cells express ILT2 but generally do not express ILT4. 721.221 cells were transfected with plasmids expressing either HLA-G or HLA-A\*0201 and high-expressing pools were enriched by antibiotic selection, generating 721.221-HLA-G and 721.221-A\*0201 cell lines. 721.221-HLA-G cells

(described herein) or 721.221-HLA-A\*0201 cells are used as targets in cytolytic cell assays. The target cells were labeled with CellTracker Deep Red (ThermoFisher) to distinguish them from NKL cells (after co-culture) and then resuspended at  $5 \times 10^5$  cells/ml in assay media (RPMI with 10% FBS, penicillin/streptomycin, L-glutamine, 5% human serum and recombinant human IL-2 (rhIL-2) at 20 ng/ml). NKL cells were suspended at  $7.5 \times 10^6$  cells/ml in assay media. Serial dilutions of anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 73D1 or Hz73D1.v1, and a control isotype antibody were prepared in assay media and 50  $\mu$ l was added to wells of a V-bottom 96-well plate. NKL cells (50  $\mu$ l) were added to each well, followed by target cells (50  $\mu$ l), resulting in a target to NK ratio of 1:15. Plates were cultured for 3.5 hours at 37°C followed by centrifugation at 360 x g for 8 minutes at room temperature and removal of media. Cells were then resuspended in PBS containing a 1:1,000 dilution of Sytox Blue (ThermoFisher). Sytox Blue will stain cells with compromised cell membranes allowing live cells to be distinguished from dead or damaged cells. Cells were analyzed by FACS and the percent target cell killing was calculated based on the value of a positive control well of target cells permeabilized with detergent (100% lysis).

**[00444]** As shown in Figure 6, anti-ILT2 antibody 27F9 and anti-ILT2/ILT4 antibodies 73D1 and Hz73D1.v1 enhanced NK cytolytic activity in a dose-dependent manner. EC<sub>50</sub> values for Hz73D1.v1 were 2.4 nM for HLA-G expressing target cells and 0.13 nM for HLA-A\*0201 expressing target cells. In comparison, EC<sub>50</sub> for 27F9 was 0.064 nM for HLA-G expressing target cells. Anti-ILT4 antibody 48A5 had little to no effect on NK cell activity. These results show that anti-ILT2 antibodies and anti-ILT2/ILT4 antibodies are able to block the functional interaction between ILT2 on NK cells and MHC I molecules on the surface of target cells, leading to the enhancement of cytolytic activity. This supports the theory that anti-ILT2/ILT4 antibodies could enhance killing of tumor cells by inhibiting ILT2-induced suppression of NK cells.

**[00445]** Similar experiments were undertaken using human primary NK cells. Briefly, NK cells were isolated from PBMC by negative selection, washed in assay media

(RPMI with 10% FBS, pen/strep, 5% human serum, rhIL-2 (40 ng/ml), and IL-15 (50 ng/ml)), and resuspended at  $7.5 \times 10^6$  cells/ml in assay media. 721.221-HLA-G target cells were labeled with CellTracker Deep Red (ThermoFisher) and resuspended at  $5 \times 10^5$  cells/ml in assay media. Target cells and NK cells (50  $\mu$ l each) were combined in each well of a V-bottom plate. Anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, or anti-ILT2/ILT4 antibodies 47H6, 73D1, or 64A12 were added to wells at a final concentration of 1  $\mu$ g/ml. Plates were cultured overnight at 37°C followed by centrifugation at 360 x g for 8 minutes at room temperature and removal of media. Cells were then resuspended in PBS containing a 1:1,000 dilution of Sytox Blue (ThermoFisher). Cells were analyzed by FACS and the percent target cell killing was calculated based on the value of a positive control well of target cells permeabilized with detergent (100% lysis).

[00446] As shown in Figure 7, the presence of anti-ILT2 antibody 27F9 or anti-ILT2/ILT4 antibodies 47H6, 73D1, and 64A12, enhanced killing by primary NK cells. In agreement with other experiments described herein, these results show that ILT2 mediates suppression of primary NK cells and this suppression can be reversed with antagonist antibodies inhibiting or blocking ILT2/MHC I interactions.

[00447]

[00448] Further experiments were performed to evaluate NK cell cytolytic activity via analysis of CD137 expression, a marker that is upregulated on NK cells during cytolysis. NK cells were isolated from PBMC and cultured with a K562 cell line transfected to express the non-classical MHC-I molecule HLA-G. NK cell cytolytic activity was evaluated by FACS analysis of expression of activation marker CD137, gating on the CD3 negative, CD56 positive NK population. CD57 staining was performed to enrich for memory (adaptive) NK cells known to preferentially express ILT2 (Lopez-Vergès S et al, *Proc.Natl. Acad. Sci.* (2011), 108 (36) 14725-14732). CD137 is upregulated on NK cells during cytolysis, providing a surrogate measure of cell killing. Hz73D1.v1 or anti-ILT2 (27F9), but not anti-ILT4 (48A5), significantly increased the CD137+ population (Figure 8). This effect was most pronounced in the

CD57+ memory NK cell population. These data suggest that anti-IL2/ILT4 antibodies are able to block the interaction of ILT2 on primary NK cells with MHC-I on target cells, leading to enhanced activation and cytolytic activity.

To evaluate activity of anti-IL2/ILT4 antibodies on killing of target cells naturally expressing HLA-A/B/C (classic MHC-I), an antibody dependent cellular cytotoxicity (ADCC) assay was performed. NK cells were isolated from PBMC and cultured with the CAL-27 squamous cell carcinoma cell line which expresses high levels of HLA-A, HLA-B, HLA-C and the NKG2A ligand HLA-E (data not shown). Anti-EGFR antibody was added to induce ADCC of these EGFR+ CAL-27 cells. CD137 was upregulated on NK cells during cytolysis, providing a surrogate measure of cell killing. Hz73D1.v1 or anti-ILT2 27F9, but not anti-ILT4 48A5, significantly increased the percent CD137+ NK cells in the CD57+ population (Figure 9). By comparison, an anti-NKG2A antibody significantly increased percent CD137+ in the CD57-, but not the CD57+ population. Both antibodies induced a comparable fold increase in activation (Hz73D1.v1 increased percent CD137+ cells 1.8-fold while anti-NKG2A antibody increased percent CD137+ cells 2.1-fold). An anti-KIR2DL antibody showed no activity in this assay. These data suggest that anti-ILT2/ILT4 antibodies are able to block the interaction of ILT2 on primary NK cells with classic MHC-I on target cells, leading to enhanced activation and cytolytic activity of NK cells.

#### Example 11

Effect of anti-ILT antibodies on MDSC activity in MLR assay

**[00449]** Myeloid-derived suppressor cells (MDSC) have been shown to be critical in regulating immune responses by suppressing antigen presenting cells (APC) and T-cells. Furthermore, they have been observed to have a negative effect on anti-tumor activity by immune cells. The effect of anti-ILT antibodies on MDSC activity was investigated using a mixed lymphocyte reaction assay (MLR). To generate MDSC-like cells, human peripheral monocytes were grown in pre-conditioned X-VIVO™ 15 media (Lonza). Pre-conditioned media is generated by culture with the OVISE cell line. The

OVISE cell line is an ovarian clear cell adenocarcinoma which secretes a large number of factors into its growth media. Monocytes were cultured in media consisting of 50% OVISE-conditioned media and 50% fresh X-VIVO™ 15 for 5 days; the resulting MDSC-like cells are referred to as ovMDSCs. These MDSC-like cells show MDSC functional characteristics, including increased Arg1 and IDO and suppression of T cell proliferation and pro-inflammatory cytokines in MLR (Mixed Lymphocyte Reaction) assays when compared to monocyte derived dendritic cells (data not shown). As a positive control for the assays, monocyte-derived dendritic cells (moDC) were generated by culture of human peripheral monocytes with GM-CSF and IL-4 for 5 days. To perform the MLR assay,  $1 \times 10^5$  allogeneic T-cells were co-cultured with  $2.5 \times 10^4$  ovMDSCs or moDCs in a 96-well round bottom cell culture plate. The cells were co-cultured in the presence of anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 47H6 or 73D1, or an isotype control antibody (each at 10 µg/ml). Controls included T-cells only, moDCs only, moDCs with T-cells (positive MLR), ovMDSCs only, and ovMDSCs with T-cells. Cells were incubated at 37°C and after 5 days 50 µl of media containing  $^3\text{H}$ -Thymidine was added to each well. After 18 hours of incubation, the cells from each well were harvested and analyzed for thymidine incorporation as a marker for proliferation, and the supernatants were analyzed for cytokine secretion by multiplex bead array.

**[00450]** As shown in Figure 10, T-cell proliferation was suppressed by co-culture with ovMDSCs. The presence of anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibodies 47H6 and 73D1 increased proliferation of T-cells cultured with ovMDSC to a level equivalent to the MLR response of T-cells with moDCs. Anti-ILT2 antibody 27F9 showed no ability to enhance T-cell proliferation.

**[00451]** Another MLR assay was set up wherein  $1 \times 10^5$  allogeneic T-cells were co-cultured with  $2.5 \times 10^4$  ovMDSCs in a 96-well round bottom cell culture plate. The cells were co-cultured in the presence of serial dilutions of anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 73D1 or Hz73D1.v1, or a control isotype antibody. Cells were incubated at 37°C and after 5 days 50 µl of supernatant

was harvested from each well for cytokine analysis using a Luminex system. Subsequently, 50  $\mu$ l of media containing  $^3\text{H}$ -Thymidine was added to each well. After 18 hours of incubation, the cells from each well were harvested and analyzed for thymidine incorporation.

**[00452]** Similar to results described above, anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibodies 73D1 and Hz73D1.v1 were shown to increase T-cell proliferation (Figure 11A). In addition, it was determined that TNF- $\alpha$  secretion and GM-CSF secretion were increased in a dose-dependent manner in the presence of anti-ILT4 and anti-ILT2/ILT4 antibodies (Figure 11B-11C). As in the previous experiment, no effect was seen with anti-ILT2 antibodies.

**[00453]** These results show that anti-ILT4 and anti-ILT2/ILT4 antibodies are able to inhibit and/or block the functional interaction between ILT4 on MDSCs and MHC I molecules on neighboring cells (*e.g.*, APCs), leading to the reversal of MDSC suppression and the enhancement of T-cell activation. The reversal of MDSC-induced suppression also appears to lead to the increased secretion of pro-inflammatory cytokines such as TNF- $\alpha$  and GM-CSF.

### Example 12

Effect of anti-ILT2/4 antibodies on LPS-mediated stimulation of cells

**[00454]** Lipopolysaccharide (LPS) stimulates innate immune responses on myeloid cells via toll-like receptors 2 and 4 (TLR2 and TLR4). To determine whether anti-ILT2 and/or anti-ILT4 antibodies can enhance LPS-mediated stimulation, a PBMC/LPS assay was performed. Briefly, frozen human PBMCs were thawed, washed in media (RPMI with 10% FBS, L-glutamine and pen/strep) and counted. Anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 73D1 and Hz73D1.v1, and a control isotype antibody were serially diluted in media and 50  $\mu$ l added to each well of a 96-well round bottom tissue culture plate. PBMCs were added at  $1 \times 10^6$  cells/ml in a volume of 100  $\mu$ l and the plate was incubated at 37°C for 30 minutes. LPS was added in 50  $\mu$ l of media (final concentration of 30 ng/ml) and the plate were incubated at 37°C

for 2 days. Cell supernatants were removed for analysis of cytokines using a Luminex® system.

**[00455]** As shown in Figure 12, the presence of anti-ILT4 and anti-ILT2/ILT4 antibodies resulted in the increased production of GM-CSF and TNF $\alpha$  in a dose-dependent manner. For example, the EC<sub>50</sub> values of Hz73D1.v1 were 0.76 nM for TNF $\alpha$  secretion and 1.5 nM for GM-CSF secretion. Anti-ILT2 antibody 27F9 and the control antibody showed little GM-CSF and TNF $\alpha$  secretion (approximately 20-40 pg/ml). These results show that the expression of ILT4 on myeloid cells in the PBMC culture can strongly suppress the production of pro-inflammatory cytokines induced by LPS, and importantly, that the suppression can be reversed by inhibiting and/or blocking ILT4/MHC I interactions.

**[00456]** A similar experiment was set up using cyno PMBCs. Briefly, cyno PMBCs were washed in media (RPMI with 10% FBS, L-glutamine and pen/strep) and counted. Anti-ILT2/ILT4 antibody Hz73D1.v1 or a control antibody was serially diluted in media and 50  $\mu$ l added to each well of a 96-well round bottom tissue culture plate. PMBCs were added at  $2 \times 10^6$  cells/ml in 100  $\mu$ l and plates were incubated at 37°C for 30 minutes. LPS was added in 50  $\mu$ l of media (final concentration of 50 ng/ml) and plates were incubated at 37°C for 2 days. Cell supernatants were removed for analysis of cytokines using a Luminex® system.

**[00457]** Similar to the results with human PBMCs, anti-ILT2/4 antibody Hz73D1.v1 enhanced GM-CSF secretion from cyno PMBCs (Figure 13). EC<sub>50</sub> was determined to be 14 nM. These results show that anti-ILT2/ILT4 antibodies had a similar biological effect on cyno immune cells and human immune cells.

**[00458]** To further evaluate the effect of anti-ILT antibodies on cells involved in suppression of immune responses to tumor cells, a LPS assay with tolerogenic dendritic cells (tolDC) was set up. Briefly, isolated human monocytes were plated onto 10 cm tissue culture dishes at  $4 \times 10^6$  cells/dish in a volume of 20 ml media (X-VIVO™ 15 media (Lonza) supplemented with 50 ng/mL each of recombinant GM-CSF and IL-4 (Peprotech)). The monocytes were incubated for 5-7 days at 37°C and then the cells

were harvested. For the assay, the *in vitro* generated DCs were suspended in fresh media containing 1:50 dilution of Fc Block (Biolegend) at a concentration of  $6 \times 10^5$  cells/ml. DCs were seeded in 96-well tissue culture plates at 50  $\mu$ l/well and anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibody Hz73D1.v1, or a control antibody were added in serial dilutions at 50  $\mu$ l/well. LPS was added (6  $\mu$ g/ml final concentration) together with one of a variety of tolerizing agents in a volume of 50  $\mu$ l media. The tolerizing agents included: vitamin D3/dexamethasone (VitD3/Dex) at 100 nM and 10 nM respectively, cyclosporin A at 750 ng/ml, rapamycin at 100 ng/ml, prostaglandin E2 (PGE2) at 1  $\mu$ g/ml, IL-6 at 20 ng/ml, IL-10 at 20 ng/ml or TGF $\alpha$  at 20 ng/ml. Plates were incubated at 37°C for 2 days and supernatants were harvested for analysis using a Luminex® system.

[00459] As shown in Figure 14, anti-ILT4 and anti-ILT2/ILT4 antibodies enhanced LPS-mediated cytokine (e.g., TNF $\alpha$ ) secretion in a dose-dependent manner. The EC<sub>50</sub> values of Hz73D1.v1 induced TNF $\alpha$  secretion in the presence of LPS and an additional tolerizing agent are shown in table 17. In contrast, there was no increase of TNF- $\alpha$  in tolDCs treated with a control antibody and anti-ILT2 antibody (data not shown). These data show that tolDCs present within a patient's tumor would be responsive to reactivation by the presence of anti-ILT4 and/or anti-ILT2/ILT4 antibodies that inhibit or block ILT4 and MHC I molecule interactions.

Table 17

Treatment	VitD3/Dex	PGE2	IL-10	Cyclosporine	Rapamycin	IL-6	TGF $\beta$
EC <sub>50</sub> (nM)	0.40	0.44	1.2	0.20	0.15	0.14	0.10

## Example 13

Effect of anti-ILT antibodies on HMGB1, STING and/or anti-CD3 stimulation of PBMCs

[00460] High mobility group protein B1 (HMGB1) is a nuclear protein that can be released from cells and binds to TLRs. HMGB1 has been shown to be present at high concentrations in necrotic tumor tissue, providing a potential source of innate stimulation of tumor infiltrating DC, monocytes, and macrophages (see, *e.g.*, Guerriero *et al.*, 2011, *J. Immunol.*, 186:3517-3526). Experiments were designed to determine whether anti-ILT antibodies could enhance pro-inflammatory cytokine secretion from PBMCs treated with HMGB1. Briefly, anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 47H6, 73D1 and 64A12, and a control isotype antibody were serially diluted in media and 50  $\mu$ l added to each well of a 96-well round bottom tissue culture plate. PBMCs were added at  $1 \times 10^6$  cells/ml in a volume of 100  $\mu$ l and the plate was incubated at 37°C for 30 minutes. Recombinant HMGB1 (Biolegend) was added at a concentration of 2.5  $\mu$ g/ml (a concentration anticipated to be present in the microenvironment of a tumor) and the plate was incubated at 37°C for 2 days. Cell supernatants were removed for analysis of cytokines using a Luminex® system.

[00461] As shown in Figure 15, anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibodies 47H6, 73D1, and 64A12 enhanced secretion of TNF- $\alpha$ . These data show that anti-ILT4 and anti-ILT2/ILT4 antibodies will enhance the pro-inflammatory function of infiltrating monocytes within a tumor.

[00462] Similarly, tumor cell necrosis and/or tumor cell death from radiotherapy results in the release of nuclear DNA. Free nuclear DNA can lead to myeloid cell stimulation via STING (stimulator of interferon genes) signaling. Experiments were designed to determine whether anti-ILT antibodies could enhance inflammatory cytokine production from PBMCs treated with a STING agonist. Briefly, PBMCs were plated in 96-well round bottom tissue culture plates and anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, and a control isotype antibody were added. After a 30-minute

incubation, STING agonist 2'3'-cGAMP (Invivogen) was added at a concentration of 10  $\mu\text{g/ml}$  (a concentration anticipated to be present in the microenvironment of a necrotic tumor). Cells were incubated for two days and supernatants were analyzed using a Luminex® system.

[00463] As shown in Figure 16, exemplary anti-ILT4 antibody 48A5 enhanced secretion of  $\text{IFN}\gamma$ ,  $\text{TNF-}\alpha$ , and  $\text{IL-1}\beta$ . These data show that anti-ILT4 and anti-ILT2/ILT4 antibodies will enhance the pro-inflammatory functions of tumor infiltrating monocytes.

[00464] In addition to suppression of innate immune activators, ILT2 or ILT4 may play a role in suppression of T-cell-mediated stimulation of myeloid cells. To evaluate T-cell stimulation of myeloid cells, PBMCs were activated with an anti-CD3 antibody and recombinant IL-2. Briefly, anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 47H6 and 64A12, and a control isotype antibody were serially diluted in media and 50  $\mu\text{l}$  added to each well of a 96-well round bottom tissue culture plate. PBMCs were added at  $1 \times 10^6$  cells/ml in a volume of 100  $\mu\text{l}$  and the plate was incubated at  $37^\circ\text{C}$  for 30 minutes. Anti-CD3 antibody clone HIT3a (eBioscience) was added at a concentration of 10  $\text{ng/ml}$  and recombinant IL-2 was added at a concentration of 100  $\text{U/ml}$  (Peprotech). Cells were incubated for two days and supernatants were analyzed using a Luminex® system.

[00465] As shown in Figure 17, anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibodies 47H6 and 64A12 enhanced  $\text{TNF-}\alpha$  secretion in a dose-dependent manner. Anti-ILT2 antibody 27F9 did not have any effect of cytokine production. These data show that ILT4 blockade enhances the immune response (*i.e.*, pro-inflammatory cytokine secretion) resulting from interaction between activated T-cells and myeloid cells.

## Example 14

## Effect of anti-ILT antibodies on macrophage phagocytosis

[00466] Phagocytosis assays were performed to further characterize the effect of anti-ILT2, anti-ILT4, and anti-ILT2/ILT4 antibodies on macrophage functions.

Macrophages were generated by culture of isolated monocytes in media (RPMI with 10% FBS, L-glutamine and pen/strep) containing 50ng/ml recombinant M-CSF (Peprotech) for 5 days at 37° C in 12-well tissue culture plates. Macrophages were removed from the plate with a cell scraper and plated at 20,000 cells/well in 100 µl media in a flat bottom 96-well tissue culture plate. Macrophages were incubated overnight at 37° C. The next day, antibody was added to the macrophages at a concentration of 2.5 µg/ml together with 2.5 µg/ml of anti-CD47 antibody to induce antibody dependent phagocytosis. Raji cells were stained for 1 hour with a 1:4,000 dilution of pH Rodo Red Dye (Essen Bioscience), washed in media and added at 50,000 cells/well to macrophages. Phagocytosis was measured by mean red fluorescence on an Incucyte machine at 45 minute intervals. Test antibody was compared to isotype control antibody at the peak response timepoint (3 hours).

[00467] As shown in Figure 18, anti-ILT2/ILT4 antibodies (e.g., Hz73D1.v1) and anti-ILT2 antibodies (e.g., 27F9) enhanced phagocytic activity of macrophages against Raji tumor cells opsonized with anti-CD47 antibody. Anti-ILT4 antibodies (e.g., 48A5) had no effect on phagocytosis by macrophages. To control for ILT2 expression by Raji cells, antibody 24E7, an ILT2 binder unable to block MHC-I interaction, was used. These data show that anti-ILT2 and anti-ILT2/ILT4 antibodies are able to enhance macrophage phagocytosis by blocking macrophage ILT2 interaction with MHC-I on tumor cells, and inhibiting ILT-2 induced suppression of macrophages, thus increasing macrophage phagocytosis of tumors. This activity of anti-ILT2 and anti-ILT2/ILT4 antibodies is specific to blocking ILT2/MHC-I interaction but not ILT4/MHC-1 interaction despite ILT4 expression on macrophages.

[00468]

## Example 15

## Effect of anti-ILT antibodies on dendritic cells

[00469] It is believed that ILT2 and/or ILT4 act as suppressors of myeloid cell activation and that inhibition or blocking of ILT2 and/or ILT4 would inhibit ILT2 and/or ILT4-induced suppression.

[00470] Activation of myeloid cells can be achieved by the crosslinking of Fc receptors (FcR) on the cell surface and the crosslinking results in cytokine production; this is used as the basis for a myeloid cell activation assay. Dendritic cells were generated as described herein. Briefly, isolated human monocytes were plated on 10 cm tissue culture dishes with  $4 \times 10^6$  cells per dish in a volume of 20 ml media (Lonza) supplemented with 50 ng/mL each of recombinant GM-CSF and IL-4 (Peprotech). The monocytes were incubated for 5 - 7 days at 37°C and the resulting dendritic cells were harvested. Maxisorp 96-well ELISA plates were coated with anti-KLH antibody (5 µg/mL) and incubated overnight at 4°C. The anti-KLH antibody contains an Fc domain capable of binding Fc receptors on the dendritic cells. The plates were washed and blocked with X-VIVO™ 15 media for one hour. Dendritic cells were added at  $7 \times 10^4$  cells/well. Anti-ILT2 antibody 27F9, anti-ILT4 antibody 48A5, a combination of antibodies 27F9 and 48A5, anti-ILT2/ILT4 antibody Hz73D1.v1 or a control antibody were added at serial dilutions and plates incubated at 37°C for 2 days. Supernatants were collected and analyzed for TNF-α secretion using a Luminex® system.

[00471] As shown in Figure 19, a combination of anti-ILT2 antibody 27F9 and anti-ILT4 antibody 48A5 and anti-ILT2/ILT4 antibody 73D1 enhanced TNF-α secretion from dendritic cells in a dose-dependent manner. Anti-ILT2 antibody 27F9 as a single agent and anti-ILT4 antibody 48H6 as a single agent had only a small effect on increasing cytokine production. Thus the strong increase in cytokine secretion by the combination of anti-ILT2 antibody 27F9 with anti-ILT4 antibody 48A5 was surprising. This response was mirrored with the dual binding anti-ILT2/ILT4 antibody Hz73D1.v1. These data show that both ILT2 and ILT4 inhibit Fc-receptor-mediated activation of dendritic cells and that these effects are non-redundant. These data show that inhibiting

the suppression of dendritic cells with agents that target both ILT2 and ILT4 (*i.e.*, a dual binding anti-ILT2/ILT4 antibody) may result in a much better therapeutic effect than therapy with mono-specific antibodies.

#### Example 16

Effect of anti-ILT antibodies on cytokine secretion from human and cyno blood cells

**[00472]** To investigate the potential for toxicity related to cytokine release (*i.e.*, a “cytokine storm”), a variety of antibodies were cultured with human or cyno blood cells and cytokine production was analyzed. Briefly, antibodies were added at 10 µg/ml to 96-well flat-bottom plates and shaken at room temperature for 1 hour. The antibodies tested included anti-ILT4 antibody 48A5, anti-ILT2/ILT4 antibodies 47H6, 73D1, and Hz73D1.v1, superagonist anti-CD28 antibody clone 5D10 (Ancell), polyclonal anti-ILT2 antibody (R&D Systems), polyclonal anti-ILT4 antibody (R&D Systems), anti-LILRA1 antibody (R&D Systems), anti-CD3 antibody, and a control antibody. Plates were washed and blocked with culture media (RPMI with 10% FBS, L-glutamine and pen/strep) for 1 hour with shaking. Blood was obtained from healthy human donors and cyno monkeys. Red blood cells were removed from blood by lysis in RBC lysis buffer (eBioscience), followed by centrifugation, and the remaining cells were washed with culture media.  $5 \times 10^5$  cells were added per well, with LPS added to replicate wells as a positive control, and plates incubated at 37°C for 24 hours. Supernatants were collected and assayed for cytokine secretion using a Luminex® system.

**[00473]** As shown in Figure 20, incubation of human blood cells with soluble LPS or plate-coated anti-CD28 antibody induced a significant increase in many cytokines including TNF- $\alpha$ , GM-CSF, MIP-1 $\alpha$ , IL-6, IL-1 $\beta$ , and IL-10. In contrast, polyclonal anti-ILT2 antibody, polyclonal anti-ILT4 antibody, anti-LILRA1 antibody, anti-ILT4 antibody 48A5, and anti-ILT2/ILT4 antibodies 73D1 and Hz73D1.v1 failed to induce cytokine levels above isotype control antibody from the human blood cells. As shown in Figure 21, incubation of cyno blood cells with soluble LPS induced a significant increase in cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , MIP-1 $\alpha$ , IL-6 and MIP-1 $\beta$ . Similar to the

human blood cell assay, polyclonal anti-ILT2 antibody, polyclonal anti-ILT4 antibody, anti-LILRA1 antibody, anti-CD3 antibody, and anti-ILT2/ILT4 antibodies 47H6, 73D1, and Hz73D1.v1 failed to induce cytokine levels above the level seen with the isotype control antibody from the cyno blood cells. These data show that the potential of anti-ILT2 antibodies, ILT-4 antibodies, and anti-ILT2/ILT4 antibodies to produce a toxic immune response, such as a cytokine storm, is low.

**[00474]** A further in vitro cytokine release assay was performed to evaluate the capacity of anti-ILT2/ILT4 antibodies to induce pro-inflammatory cytokines IL-2, TNF- $\alpha$ , IL-6 and IFN- $\gamma$ . Whole blood samples for 10 healthy donors were used. Anti-ILT2/ILT4 antibodies were compared with a number of positive and negative controls. An anti-KLH isotype control antibody was used as a negative control. A super-agonist anti-CD28 antibody (clone ANC28.1) was used as a positive control (Walker 2011). In addition, Staphylococcus enterotoxin B (SEB) was used as a positive control for soluble antibody cultures. Two assay formats were used. In the first format, cells were cultured with an antibody (Hz73D1.v1, an isotype control antibody or anti-CD28 antibody) or SEB at increasing concentrations. Antibodies were tested at 0.1, 1, 10 and 100  $\mu\text{g/ml}$ . SEB was tested at 0.01, 0.1 and 1  $\mu\text{g/ml}$ . In the second format, 96-well tissue culture plates were pre-incubated with an antibody overnight at 4° C, washed and then cells were added and cultured. Cell culture supernatant was then collected and tested for cytokine levels by cytometric bead array assay.

**[00475]** In the first assay format, SEB at 1  $\mu\text{g/mL}$  induced high levels of all cytokines evaluated (IL-2, IL-6, TNF $\alpha$  and IFN $\gamma$ ), with cytokine levels above isotype control for all 10 donors. Soluble anti-CD28 antibody at 100  $\mu\text{g/mL}$  induced cytokine levels above isotype control for IL-6, TNF $\alpha$  and IFN $\gamma$ . Median values with Hz73D1.v1 were comparable with the isotype control (Table 18). In the second assay format, the positive control of plate-coated anti-CD28 (100  $\mu\text{g/ml}$ ) induced IL-6 in 5 of 10 donors. In contrast, plate-coated Hz73D1.v1 did not induce any of the 4 cytokines to a level above that of isotype control (Table 19).

Table 18

	Anti-CD28 (µg/mL)	SEB (µg/mL)	Isotype (µg/mL)	Hz73D1.v1 (µg/mL)
	10	0.1	1	10
	100	0.1	10	100
IL-6	1115	571	7	3
	8934	1422	5	6
IL-2	44	1309	19	17
	48	3418	21	20
TNFα	52	614	4	6
	605	1452	7	10
IFNγ	35	208	5	5
	343	704	6	5

Table 19

	Anti-CD28 (µg/mL)	Isotype (µg/mL)	Hz73D1.v1 (µg/mL)
	10	10	10
	100	100	100
IL-6	17	9	7
	93	10	9
IL-2	33	38	32
	45	40	28
TNFα	18	19	12
	26	17	16
IFNγ	12	13	12
	21	13	14

## Example 17

## Effect of anti-ILT antibodies on T cell activity

[00476] ILT2 expression is known to be enriched on a population of effector memory CD45RA<sup>+</sup> CD8<sup>+</sup> T cells (CD8<sup>+</sup> T<sub>EMRA</sub> cells) (Gustafson 2017). This population is only a small proportion of CD8<sup>+</sup> T cells in healthy donors, making bulk CD8<sup>+</sup> T cell cell-killing assays challenging. Therefore, to characterize the cytolytic activity of ILT2<sup>+</sup> CD8<sup>+</sup> T cells, primary CD8<sup>+</sup> T cells were transduced with ILT2 and expanded in vitro to generate sufficient numbers of ILT2<sup>+</sup> CD8<sup>+</sup> T cells. Cytolytic activity was then evaluated in a CD8<sup>+</sup> T cell killing assay using fluorescently labeled 721.221-HLA-G target cells. Briefly, frozen PBMC were thawed, washed in media (RPMI with 10% FBS, L-glutamine and pen/strep) and CD8<sup>+</sup> T cells were isolated using a CD8<sup>+</sup> T cell positive selection kit. Isolated CD8<sup>+</sup> T cells were cultured in basic media (Xvivo15 media with 10mM HEPES, 2mM Glutamine, pen/strep and 5% normal human serum) and stimulated for 24 hours at 37° C with CD3/28 beads adding 5µl beads per million cells. Activated T cells ( $2 \times 10^5$ ) were then harvested and resuspended in 1 ml of Lentivirus expressing human ILT2 at a viral concentration of  $1 \times 10^7$  PFU/ml in the presence of polybrene to infect cells. Infected cells were then resuspended in T cell media (basic media supplemented with 5 ng/ml IL-7, 5 ng/ml IL-15 and 25 ng/ml IL-2) and allowed to expand for two weeks. Cells were then FACS sorted for the ILT2<sup>+</sup> population and expanded for an additional 6 weeks to generate sufficient cells for the study. For evaluation of cytolytic activity,  $2.5 \times 10^4$  CellTracker deep red-labelled 721.221-HLAG cells were mixed with  $2.5 \times 10^5$  ILT2-transduced CD8<sup>+</sup> T cells at a 10:1 T cell:Target ratio and 0.1 µg/ml anti-CD3/CD19 bispecific antibody in RPMI-10% FBS media. Anti-ILT antibodies or control antibodies were added to the cells at a concentration of 10µg/ml and incubated for 18 hours. Target cells were analyzed by FACS and percent target cell killing was calculated as the number of dead target cells divided by the total number of target cells.

[00477] As shown in Figure 22, anti-ILT2/ILT4 antibodies (e.g., Hz73D1.v1) and anti-ILT2 antibodies (e.g., 27F9), but not anti-ILT4 antibodies (e.g., 48A5), enhanced cytolytic activity of CD8<sup>+</sup> T cells against 721.221-HLA-G target cells. These data show that anti-ILT2 and anti-ILT2/ILT4 antibodies enhance CD8<sup>+</sup> T cell cytolytic activity by blocking CD8<sup>+</sup> T cell ILT2 interaction with MHC-I on target cells. As such, anti-ILT2 and anti-ILT2/ILT4 antibodies disrupt the immune suppressive activity of ILT2 on cytolytic lymphocytes, in particular effector memory T cells known to be involved in anti-tumor cell killing.

#### Example 18

Synergistic Effect of anti-ILT2/ILT4 antibodies and anti-PD1 antibodies on T cell activity

[00478] A mixed leukocyte reaction assay was developed to evaluate potential synergistic or additive effects of anti-ILT2/ILT4 antibodies in combination with an anti-PD1 antibody (Pembrolizumab). Monocyte derived macrophages were generated and cultured with allogeneic CD4<sup>+</sup> T cells from 11 different donors, together with either isotype control, Hz73D1.v1, Pembrolizumab, or the combination of Hz73D1.v1 and Pembrolizumab. Briefly, monocyte derived macrophages were generated by culturing 100,000 monocytes per well for 6 days with 50ng/ml recombinant M-CSF. On day 6, allogeneic purified CD4<sup>+</sup> T cells (200,000/well) were added together with either 1 µg/ml anti-KLH isotype control, 1 µg/ml Pembrolizumab, 1 µg/ml Hz73D1.v1, or the combination of anti-PD1 and Hz73D1.v1 at 1µg/ml each. Cells were cultured for an additional 6 days and supernatant collected for multiplex bead array analysis on secreted cytokines (IFN-γ, TNF-α, and GM-CSF).

[00479] As shown in Figure 23A-23C, the anti-ILT2/ILT4 antibody or Pembrolizumab alone typically induced <2ng/ml of interferon gamma in cultures, with 3 out of 11 donors inducing >2 ng/ml interferon gamma. In contrast, the combination of the anti-ILT2/ILT4 antibody and Pembrolizumab induced >2 ng/ml interferon gamma in 7 out of 11 CD4<sup>+</sup> T cell donor pairs, with a greater-than-additive response compared to each

reagent alone in these 7 donor pairs. Similar responses were observed with GM-CSF and TNF- $\alpha$  secretion. These data shows that the anti-ILT2/ILT4 antibody and pembrolizumab together have a synergistic effect on allogeneic CD4+ T cell induced cytokine secretion, possibly through a combination of anti-ILT2/ILT4 antibody-mediated stimulation of macrophage APC activity and the release of CD4+ T cell checkpoint inhibition by Pembrolizumab. Altogether, an anti-ILT2/ILT4 antibody or anti-PD-1 antibody alone modestly enhance T cell activation and increase in cytokine secretion. Combination of an anti-ILT2/ILT4 antibody or anti-PD-1 antibody leads to synergetic increase in T cell activation and cytokine secretion.

#### Example 19

Anti-ILT2/ILT4 antibodies induce M2-like to M1-like polarization of monocyte-derived macrophages

**[00480]** Macrophages are traditionally characterized as either pro-inflammatory (M1) or immune suppressive (M2) based on surface expression markers CD80, CD86 (M1), CD163, CD204, and CD206 (M2). Anti-IL2/ILT4 antibodies as well as anti-IL2 and anti-ILT4 antibodies were evaluated for their ability to polarize macrophages toward an M1-like or M2-like phenotype.

**[00481]** Macrophages were generated by culture of monocytes in media (RPMI with 10% FBS, L-glutamine and pen/strep) containing Hz73D1.v1, 27F9, 48A5 or isotype control antibody (1 ug/ml) and 50 ng/ml recombinant M-CSF (Peprotech) for 5 days at 37° C in 48-well tissue culture plates. On day 5 samples were analyzed by flow cytometry for various surface markers indicative of an M1-like or M2-like phenotype.

**[00482]** As shown in Figure 24, Hz73D1.v1 induced a decrease in M2-like macrophage phenotypic markers CD163, CD204, and CD206 and additional M2-like markers CD14 and CD209, consistent with an M2-like to M1-like polarization of the monocytes during differentiation. Anti-ILT4 specific antibody 48A5, but not anti-ILT2 specific antibody 27F9, induced an increase in M1-like marker CD86 and a decrease in M2-like markers CD163, CD204, and CD206, and additional M2-like markers CD14, CD209, and CCR5, consistent with an M2-like to M1-like polarization with ILT4

blockade. Overall, these data demonstrate that anti-ILT2/ILT4 antibodies induce a more pro-inflammatory M1-like phenotype during macrophage differentiation, and this response is mediated by inhibition of ILT4 interaction with MHC-I.

[00483] Although the foregoing present disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the present disclosure. The embodiments of the present disclosure described herein are intended to be merely exemplary, and those skilled in the art will recognize numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present disclosure and are covered by the embodiments.

[00484] All publications, patents, patent applications, internet sites, and accession numbers/database sequences including both polynucleotide and polypeptide sequences cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, internet site, or accession number/database sequence were specifically and individually indicated to be so incorporated by reference.

[00485] Following are sequences disclosed in the application. CDR sequences are listed in Tables 1-8.

Human ILT2 amino acid sequence with predicted signal sequence underlined (SEQ ID NO:1)

MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVITQGSPVTLRCQGGQETQEYR  
 L  
 YREKKTALWITRIPQELVKKGQFPIPSITWEHAGRYRCYYGSDTAGRSESSDPLELVVT  
 G  
 AYIKPTLSAQSPVVNSGGNVILQCDSQVAFDGFSLCKEGEDHPQCLNSQPHARGSSR  
 A  
 IFSVGPVSPSRRWWYRCYAYDSNSPYEWSLPSDLLELLVLGVSKKPSLSVQPGPIVAPEE  
 TLTLCGSDAGYNRFVLYKDGERDFLQLAGAQPQAGLSQANFTLGPVSRSYGGQYRC  
 YGA  
 HNLSSEWSAPSDPLDILIAGQFYDRVLSVQPGPTVASGENVTLLCQSQGWMQTFLLTK  
 E  
 GAADDPWRLRSTYQSQKYQAEFPMGPV TSAHAGTYRCYGSQSSKPYLLTHPSDPLELV  
 VS  
 GPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLLLLLF

LILRHRRQGKHWSTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVK  
 HTQ  
 PEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ  
 MD  
 TEAAASEAPQDVITYAQLHSLTLRREATEPPPSQEGPSPA VPSIYATLAIH

Human ILT2 amino acid sequence without predicted signal sequence (SEQ ID NO:2)  
 GHLPKPTLWAEPGSVITQGSPVTLRCQGGQETQEYRLYREKKTALWITRIPQELVKKGQ  
 F  
 PIPSITWEHAGRYRCYYGSDTAGRSESSDPLELVVTGAYIKPTLSAQSPVVNSGGNVIL  
 QCDSQVAFDGFSLCKEGEDHPQLNSQPHARGSSRAIFSVGPVSPSRRWWYRCYAYD  
 SN  
 SPYEWSLPSDLELLVVLGVSKKPSLSVQPGPIVAPEETLTLQCGSDAGYNRFVLYKDGE  
 R  
 DFLQLAGAQPQAGLSQANFTLGPVSRSYGGQYRCYGAHNLSSEWSAPSDPLDILIAGQF  
 Y  
 DRVLSVQPGPTVASGENVTLLCQSQGWMTFLLTKEGAADDPWRLRSTYQSQKYQA  
 EFP  
 MGPV TSAHAGTYRCYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQP  
 LTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLLLLLFLILRHRRQGKHWSTSTQRKADFQ  
 H  
 PAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDEDPQAV  
 TYA  
 EVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVITYAQLHSLT  
 LRREA  
 TEPSPS QEGPSPA VPSIYATLAIH

Human ILT2 extracellular domain (aa 24-461) (SEQ ID NO:3)  
 GHLPKPTLWAEPGSVITQGSPVTLRCQGGQETQEYRLYREKKTALWITRIPQELVKKGQ  
 F  
 PIPSITWEHAGRYRCYYGSDTAGRSESSDPLELVVTGAYIKPTLSAQSPVVNSGGNVIL  
 QCDSQVAFDGFSLCKEGEDHPQLNSQPHARGSSRAIFSVGPVSPSRRWWYRCYAYD  
 SN  
 SPYEWSLPSDLELLVVLGVSKKPSLSVQPGPIVAPEETLTLQCGSDAGYNRFVLYKDGE  
 R  
 DFLQLAGAQPQAGLSQANFTLGPVSRSYGGQYRCYGAHNLSSEWSAPSDPLDILIAGQF  
 Y  
 DRVLSVQPGPTVASGENVTLLCQSQGWMTFLLTKEGAADDPWRLRSTYQSQKYQA  
 EFP  
 MGPV TSAHAGTYRCYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQP  
 LTPTGSDPQSGLGRHLGV

Human ILT2 Ig-like C2-type domain 1 amino acid sequence (aa 27-115) (SEQ ID  
 NO:4)  
 PKPTLWAEPGSVITQGSPVTLRCQGGQETQEYRLYREKKTALWITRIPQELVKKGQFP  
 SITWEHAGRYRCYYGSDTAGRSESSDPLE

Human ILT2 Ig-like C2-type domain 2 amino acid sequence (aa 116-221) (SEQ ID NO:5)

LVVTGAYIKPTLSAQSPVVNSGGNVILQCDSQVAFDGFSLCKEGEDHPQCLNSQPHAR  
GSSRAIFSVGPVSPSRRWWYRCYAYDSNSPYEWSLPSDLELLVLG

Human ILT2 Ig-like C2-type domain 3 amino acid sequence (aa 222-312) (SEQ ID NO:6)

VSKKPSLSVQPGPIVAPEETLTLQCGSDAGYNRFVLYKDGERDFLQLAGAQPQAGLSQAN  
FTLGPVSRSYGGQYRCYGAHNLSSEWSAPSD

Human ILT2 Ig-like C2-type domain 4 amino acid sequence (aa 313-409) (SEQ ID NO:7)

PLDILIAGQFYDRVLSVQPGPTVASGENVTLLCQSQGWMTFLLTKEGAADDPWRLRST  
YQSQKYQAEFPMGPV TSAHAGTYRCYGSQSSKPYLLT

Human ILT4 amino acid sequence with predicted signal sequence underlined (SEQ ID NO:8)

MTPIVTVLICLGLSLGPRTHVQTGTIPKPTLWAEPDSVITQGSPVTLSCQGSLEAQEYRL  
YREKKSASWITRIRPELVKNGQFHIPSITWEHTGRYGCQYYSRARWSELSDPLVLMVTGA  
A  
YPKPTLSAQSPVVTSGGRVTLQCESQVAFGGFILCKEKEEHPQCLNSQPHARGSSRAIFSVGPVSPNRRWSHRCYGYDLNSPYVWSSPSDLELLVPGVSKKPSLSVQPGPVVAPGES  
LTLQCVSDVGYDRFVLYKEGERDLRQLPGRQPQAGLSQANFTLGPVSRSYGGQYRCYGAH  
NLSSECSAPSDPLDILITGQIRGTPFISVQPGPTVASGENVTLLCQSWRQFHTFLLTKAG  
AADAPLRLRSIHEYPKYQAEFPMSPV TSAHAGTYRCYGSLNSDPYLLSHPSEPLELVVSG  
PSMGSSPPPTGP ISTPAGPEDQPLTPTGSDPQSGLGRHLGVVIGILVAVVLLLLLLLLLFL  
LILRHRQKHWSTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVKDTQ  
PEDGVEMDTRAAASEAPQDVTYAQLHSLTLRRKATEPPPSQEREPPEPSIYATLAIH

Human ILT4 amino acid sequence without predicted signal sequence (SEQ ID NO:9)

QTGTIPKPTLWAEPDSVITQGSPVTLSCQGSLEAQEYRLYREKKSASWITRIRPELVKNGQFHIPSITWEHTGRYGCQYYSRARWSELSDPLVLMVTGAYPKPTLSAQSPVVTSGGRVT  
LQCESQVAFGGFILCKEKEEHPQCLNSQPHARGSSRAIFSVGPVSPNRRWSHRCYGYDL  
NSPYVWSSPSDLELLVPGVSKKPSLSVQPGPVVAPGESLTLQCVSDVGYDRFVLYKEGE  
RDLRQLPGRQPQAGLSQANFTLGPVSRSYGGQYRCYGAHNLSSECSAPSDPLDILITGQI

RGTPFISVQPGPTVASGENVTLLCQSWRQFHTFLLTKAGAADAPLRLRSIHEYPKYQAE  
 F  
 PMSPV TSAHAGTYRCYGSLNSDPYLLSHPSEPLELVVSGPSMGSSPPPTGPISTPAGPED  
 QPLTPTGSDPQSG LGRHLGVVIGILVAVVLLLLLLLLLFLILRHRRQ GKHWSTQRKAD  
 F  
 QHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVKDTQPEDGVEMDTRAAASEAP  
 QDVT  
 YAQLHSLTLRRKATEPPPSQEREPPAEPSIYATLAIH

Human ILT4 extracellular domain (aa 22-461) (SEQ ID NO:10)

QTGTIPKPTLWAEPDSVITQGSPVTLSCQGSLEAQEYRLYREKKSASWITRIRPELVKNG  
 QFHIPSITWEHTGRYGCQYYSRARWSELS DPLVLMVTGAYPKPTLSAQSPVVTSGGRV  
 T  
 LQCESQVAFGGFILCKEGEEHPQCLNSQPHARGSSRAIFSVGPVSPNRRWSHRCYGYD  
 L  
 NSPYVWSSPSDLELLVPGVSKKPSLSVQPGPVVAPGESLTLQCVSDVGYDRFVLYKEG  
 E  
 RDLRQLPGRQPQAGLSQANFTLGPVSRSYGGQYRCYGAHNLSSECSAPSDPLDILITGQI  
 RGTPFISVQPGPTVASGENVTLLCQSWRQFHTFLLTKAGAADAPLRLRSIHEYPKYQAE  
 F  
 PMSPV TSAHAGTYRCYGSLNSDPYLLSHPSEPLELVVSGPSMGSSPPPTGPISTPAGPED  
 QPLTPTGSDPQSG LGRHLGV

Human ILT4 Ig-like C2-type domain 1 amino acid sequence (aa 27-110) (SEQ ID NO:11)

PKPTLWAEPDSVITQGSPVTLSCQGSLEAQEYRLYREKKSASWITRIRPELVKNGQFHIP  
 SITWEHTGRYGCQYYSRARWSELS

Human ILT4 Ig-like C2-type domain 2 amino acid sequence (aa 111-229) (SEQ ID NO:12)

DPLVLMVTGAYPKPTLSAQSPVVTSGGRVTLQCESQVAFGGFILCKEGEEHPQCLNS  
 Q  
 PHARGSSRAIFSVGPVSPNRRWSHRCYGYDLNSPYVWSSPSDLELLVPGVSKKPSLSV

Human ILT4 Ig-like C2-type domain 3 amino acid sequence (aa 230-318) (SEQ ID NO:13)

QPGPVVAPGESLTLQCVSDVGYDRFVLYKEGERDLRQLPGRQPQAGLSQANFTLGPVS  
 RS  
 YGGQYRCYGAHNLSSECSAPSDPLDILIT

Human ILT4 Ig-like C2-type domain 4 amino acid sequence (aa 330-419) (SEQ ID NO:14)

QPGPTVASGENVTLLCQSWRQFHTFLLTKAGAADAPLRLRSIHEYPKYQAEFPMSPVTS  
 A  
 HAGTYRCYGSLNSDPYLLSHPSEPLELVVS

Rhesus ILT2 amino acid sequence with predicted signal sequence underlined (SEQ ID NO:15)

MTPILMVLICLGLSLGSRTRVQAGTFPKPTLWAEPGSMISKGSPVTLRCQGSLPVQDYR  
 L  
 QREKKTASWVRRIQQELVKKGYFPIASITSEHAGQYRCQYYSHSWWSEPSDPLELVVT  
 GA  
 YSKPTLSALPSPVVASGGNVTLQCDSQVAXGGFVLCKEGEDEHPQCLNSQPHTRGSSR  
 AV  
 FSVGVPSPRRWSYRCYGYDSRSPYVWVSLPSDLELLVPGVSKKPSLSVQPGPVVAPGD  
 K  
 LTLQCGSDAGYNRFALYKEGERDFLQRPGRQPQAGLSQANFLLDPVRRSHGGQYRCSG  
 AH  
 NLSSEWSAPSDPLDILIAGQIRGRPSLLVQPGPTVVSGENVTLQCSSWQFHVFLLTQAG  
 ADAHLHLRSMYKYPKYQAEFPMSPVTSAHAGTYRCYGSHTSDSYLLSIPSDPLELVVS  
 G  
 PSGGPSSPTTGPTSTCGPEDQPLTPTGSDPQSGLGRHLGVVTGVLVAFVLLLFLLLLFL  
 VLRHRRQGKRWTSARQKADFQHPAGAVEPEPRDRGLQRRSSPAANTQEENLYAAVKD  
 TQP  
 EDGVELDSRPHDEDPQAVTYARVKHSRPRREMASPPSPLSEEFLDTKDTQAAASEDPQ  
 D  
 VTYAQLQSLTLRRETTEPPPSQEREPPVESSYATLTIH

Rhesus ILT2 amino acid sequence without predicted signal sequence (SEQ ID NO:16)

GTFPKPTLWAEPGSMISKGSPVTLRCQGSLPVQDYRLQREKKTASWVRRIQQELVKKG  
 YF  
 PIASITSEHAGQYRCQYYSHSWWSEPSDPLELVVTGAYSKPTLSALPSPVVASGGNVTL  
 Q  
 CDSQVAXGGFVLCKEGEDEHPQCLNSQPHTRGSSRAVFSVGVPSPRRWSYRCYGYDS  
 RS  
 PYVWVSLPSDLELLVPGVSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYNRFALYKEGE  
 RD  
 FLQRPGRQPQAGLSQANFLLDPVRRSHGGQYRCSGAHNLSSEWSAPSDPLDILIAGQIR  
 G  
 RPSLLVQPGPTVVSGENVTLQCSSWQFHVFLLTQAGAADAHLHLRSMYKYPKYQAE  
 FPM  
 SPVTSAHAGTYRCYGSHTSDSYLLSIPSDPLELVVSGPSGGPSSPTTGPTSTCGPEDQPL  
 TPTGSDPQSGLGRHLGVVTGVLVAFVLLLFLLLLFLVLRHRRQGKRWTSARQKADFQ  
 HP  
 AGAVEPEPRDRGLQRRSSPAANTQEENLYAAVKDTQPEDGVELDSRPHDEDPQAVTY  
 AR  
 VKHSRPRREMASPPSPLSEEFLDTKDTQAAASEDPQDVTYAQLQSLTLRRETTEPPPSQ  
 REPPVESSYATLTIH

Rhesus ILT2 extracellular domain (aa 24-460) (SEQ ID NO:17)

GTFPKPTLWAEPGSMISKGSPVTLRCQGSLPVQDYRLQREKKTASWVRRIQQELVKKG  
 YF

PIASITSEHAGQYRCQYYSHSWWSEPSDPLELVVTGAYSKPTLSALPSPVVASGGNVTL  
 Q  
 CDSQVAXGGFVLCKEGEDEHPQCLNSQPHTRGSSRAVFSVGPVSPSRRWSYRCYGYDS  
 RS  
 PYVWSLPSDLELLVPGVSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYNRFALYKEGE  
 RD  
 FLQRPGRQPQAGLSQANFLLDPVRRSHGGQYRCGSAHNLSSEWSAPSDPLDILIAGQIR  
 G  
 RPSLLVQPGPTVVSGENVTLQCSSWQFHVFLLTQAGAADAHLHLRSMYKYPKYQAE  
 FPM  
 SPV TSAHAGTYRCY GSHSSDSYLLSIPSDPLELVVSGPSGGPSSPTTGPTSTCGPEDQPL  
 TPTGSDPQSGLGRHLGV

Rhesus ILT2 Ig-like C2-type domain 1 amino acid sequence (aa 27-114) (SEQ ID  
 NO:18)

PKPTLWAEPGSMISKGSPVTLRCQGSPLVQDYRLQREKKTASWVRRIQQELVKKGYFPI  
 A  
 SITSEHAGQYRCQYYSHSWWSEPSDPLE

Rhesus ILT2 Ig-like C2-type domain 2 amino acid sequence n (aa 115-220) (SEQ ID  
 NO:19)

LVVTGAYSKPTLSALPSPVVASGGNVTLQCDSQVAXGGFVLCKEGEDEHPQCLNSQPH  
 TR  
 GSSRAVFSVGPVSPSRRWSYRCYGYDSRSPYVWSLPSDLELLVPG

Rhesus ILT2 Ig-like C2-type domain 3 amino acid sequence n (aa 221-311) (SEQ ID  
 NO:20)

VSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYNRFALYKEGERDFLQRPGRQPQAGLSQ  
 AN  
 FLLDPVRRSHGGQYRCGSAHNLSSEWSAPSD

Rhesus ILT2 Ig-like C2-type domain 4 amino acid sequence n (aa 312-408) (SEQ ID  
 NO:21)

PLDILIAGQIRGRPSLLVQPGPTVVSGENVTLQCSSWQFHVFLLTQAGAADAHLHLRS  
 M  
 YKYPKYQAEFPMSPV TSAHAGTYRCY GSHSSDSYLLS

27F9 Heavy chain variable region amino acid sequence (SEQ ID NO:125)

QVQLKESGPGLVAPSQSLITCTVSGFSLTNYGVSQVVRQPPGKGLEWLGIIWGDGSTNY  
 H  
 SALISRLSISKDNSKSQVFLKLNLSLQADDTATYYCAKPNWDTYAMDFWGQGTSTVTVSS

27F9 Light chain variable region amino acid sequence (SEQ ID NO:126)

DIQMTQTSSLSASLGDRVTISCRASQDISNFLNYYQQKPDGTVKLLIYCTSKLHSGVPS  
 RFSGSGSETDYSLTISNLEQEDIATYFCQQGNTLPPTFGGGTKLEII

47C8 Heavy chain variable region amino acid sequence (SEQ ID NO:127)  
 EVQLQQSGPDLVKPGASVKISCKASGYSTGYMHWVKQSHGKSLEWIGRVYPNNGD  
 TSY  
 NQKFKVKAILTVDKSSSTAYMELRSLTSEDSAVYYCARGATVVESLFAYWGQGLVT  
 VSA

47C8 Light chain variable region amino acid sequence (SEQ ID NO:128)  
 DIVLTQSPASLAVSLGQRATISCRASESVDNYGNNFLHWYQQKPGQPPKLLIYRTSNLE  
 S  
 GIPARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGKLEIK

48A5 Heavy chain variable region amino acid sequence (SEQ ID NO:129)  
 QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNWVKQAPGKGLKWMGWINTYIGE  
 PIY  
 ADDFKGRFAFSLETSASTAYLQINNKNEDMATYFCARRSDYDGYAMDYWGQGTSVT  
 VSS

48A5 Light chain variable region amino acid sequence (SEQ ID NO:130)  
 DIVMSQSPSSLAVSVGERVTMSCKSSQSLLYSGNQKNYLAWYQQKPGQSPKLLIYWAS  
 TR  
 ESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQHDSYPTFGGGSRLK

47H6 Heavy chain variable region amino acid sequence (SEQ ID NO:131)  
 EVQLQQSGPELVKPGASVKISCKASGYTFTDYMNWVKQSHGKSLEWIGDFNPNGG  
 TTY  
 NQKFEKGATLTVDKSSNTAYMDLRSLTSEDSAVYYCARGRFYYGSLYSFDYWGQGT  
 LTVSS

47H6 Light chain variable region amino acid sequence (SEQ ID NO:132)  
 DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQKSPHLLVYNAKTLADGV  
 PS  
 RFSGSGSGTQYSLKINNLQPEDFGSYQCQHFWTSITFGAGTKLDLK

Hz47H6.v2 Heavy chain variable region amino acid sequence (SEQ ID NO:133)  
 QVQLVQSGAEVKKPGASVKVSKASGYTFTDYMNWVRQAPGQRLEWIGDFNPNA  
 GTTYN  
 QKFEGRVTITVDKSASTAYMELSSLRSEDVAVYYCARGRFYYGSLYSFDYWGQGLVT  
 VSS

Hz47H6.v2 Light chain variable region amino acid sequence (SEQ ID NO:134)  
 DIQMTQSPSSLASVGDRTITCRASGNIHNYLAWYQQKPGKAPKLLIYNAKTLADGV  
 SR  
 FSGSGSGTDFTLTISLQPEDFATYYCQHFWTSITFGPGTKVDIK

51A1 Heavy chain variable region amino acid sequence (SEQ ID NO:135)

EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMHWVRQAPGKGLEWVARIRSKSSN  
YAT  
YYADSVKDRFTISRDDSQSMLYLQMNNLKTEDTAMYYCVRDGIYYYYGTMYYYAMDY  
WGQG  
TSVTVSS

51A1 Light chain variable region amino acid sequence (SEQ ID NO:136)  
NIVLTQSPASLAVSLGQRATISCRASESVDYYGNSFMYWYQQKPGQPPKLLIYFASNLE  
S  
GVPARFSGSGSRTDFTLTIDPVEAADAASYCQQNNEPWTFFGGGTKLEIK

64A12 Heavy chain variable region amino acid sequence (SEQ ID NO:137)  
EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMHWVRQAPGKGLEWVARIRSKSSN  
YAT  
YYADSVKDRFTISRDDSQSMLYLQMNNLKTEDTAMYYCVRDGIYYDDTMYYAMDY  
WGQG  
TSVTVSS

64A12 Light chain variable region amino acid sequence (SEQ ID NO:138)  
NIVLTQSPASLAVSLGQRATISCRASESVDYYGNSFIYWYQQKPGQPPKLLIYFASNLES  
GVPARFSGSGSRTDFTLTIDPVEAADAASYCQQNNEPWTFFGGGTKLEIK

H264A12 Heavy chain variable region amino acid sequence (SEQ ID NO:139)  
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMHWVRQAPGKGLEWVARIRSKSSN  
YAT  
YYADSVKDRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARDGIYYDDTMYYAMDY  
WGQG  
TLVTVSS

H264A12 Light chain variable region amino acid sequence (SEQ ID NO:140)  
NIVLTQSPDSLAVSLGERATINCRASESVDYYGNSFIYWYQQKPGQPPKLLIYFASNLES  
GVPDFRSGSGSGTDFTLTISLQAEDVAVYYCQQNNEPWTFFGGGTKVEIK

73C4 Heavy chain variable region amino acid sequence (SEQ ID NO:141)  
AVQLQQSGPELVKPGASVKISKASGYTFTDYMNWVKQSHGKSLEWIGNVNPNGG  
TSY  
NQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARREIYFYGTIYYAMDYWGQ  
GTS  
VTVSS

73C4 and 73D1 Light chain variable region amino acid sequence (SEQ ID NO:142)  
DIVLTQSPASLAVSLGQRATISCRASESVDYYGNSFMYWYQQKGRPPNLLIYFASNLE  
S  
GVPARFSGSGSRTDFTLTIDPVEADDAATYYCQQNNEPWTFFGGGTKLEIK

73D1 Heavy chain variable region amino acid sequence (SEQ ID NO:143)

AVQLQQSGPELVKPGASVKISCKASGYTFTDYYINWVKQSHGKSLQWIGNVNPNDGG  
TTY  
NQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVVYCARREIFYGTIYYYAMDYWGQ  
GTS  
VTVSS

Hz73D1.v1 Heavy chain variable region amino acid sequence (SEQ ID NO:144)  
QVQLVQSGAEVKKPGASVKVSKASGYTFTDYYINWVRQAPGQGLEWMGNVNPNDG  
GTTY  
NQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVVYCARREIFYGTIYYYAMDYWGQ  
GTL  
VTVSS

Hz73D1.v1 Light chain variable region amino acid sequence (SEQ ID NO:145)  
DIQLTQSPSFLSASVGDRVTITCRASESVDYYGNSFMWYQQKPGKAPKLLIYFASNLE  
S  
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQNNEDPWTFGGGGTKVEIK

Hz47H6.v2 Heavy chain amino acid sequence with signal sequence underlined (SEQ ID NO:146)  
MDMRVPAQLLGLLLLWLRGARCQVQLVQSGAEVKKPGASVKVSKASGYTFTDYYM  
NWVR  
QAPGQRLEWIGDFNPNNAGTTYNQKFEGRVTITVDKSASTAYMELSSLRSEDTAVYYC  
AR  
GRFYYGSLYSFDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE  
P  
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD  
K  
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV  
KFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP  
APIE  
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK  
T  
TPPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

Hz47H6.v2 Light chain amino acid sequence with signal sequence underlined (SEQ ID NO:147)  
MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWY  
QQ  
KPGKAPKLLIYNAKTLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQHFWTSITFG  
PGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG  
NS  
QESVTEQDSKDYSLSTLTLKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

Hz47H6.v2 Heavy chain amino acid sequence without signal sequence (SEQ ID NO:148)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMNWVRQAPGQRLEWIGDFNPNA  
 GTTY  
 NQKFEGRVTITVDKSASTAYMELSSLRSEDVAVYYCARGRFYYGSLYSFDYWGQGLV  
 TV  
 SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL  
 Q  
 SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL  
 GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE  
 EQ  
 YGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP  
 SR  
 EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVD  
 KS  
 RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Hz47H6.v2 Light chain amino acid sequence without signal sequence (SEQ ID  
 NO:149)

DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAPKLLIYNAKTLADGVP  
 S  
 RFSGSGSGTDFTLTISLQPEDFATYYCQHFVTSITFGPGTKVDIKRTVAAPSVFIFPPS  
 DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTL  
 TL  
 SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Hz64A12 Heavy chain amino acid sequence with signal sequence underlined (SEQ ID  
 NO:150)

MDMRVPAQLLGLLLLWLRGARCEVQLVESGGGLVQPGGSLRLSCAASGFTFTNYAMH  
 WVR  
 QAPGKGLEWVARIRSKSSNYATYYADSVKDRFTISRDDAKNSLYLQMNSLRAEDTAV  
 YYC  
 ARDGIYYDYMYYAMDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL  
 VKD  
 YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN  
 TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV  
 S  
 H  
 EDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV  
 SNKAL  
 PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE  
 NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG  
 K

Hz64A12 Light chain amino acid sequence with signal sequence underlined (SEQ ID  
 NO:151)

MDMRVPAQLLGLLLLWLRGARCNIVL TQSPDSLAVSLGERATINCRASESDVYYGNSFI  
 Y  
 WYQQKPGQPPELLIYFASNLESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQNNE  
 D

PWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN  
AL  
QSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVTKSFNRGE  
C

Hz64A12 Heavy chain amino acid sequence without signal sequence (SEQ ID  
NO:152)

EVQLVESGGGLVQPGGSLRLSCAASGFTFTNYAMHWVRQAPGKGLEWVARIRSKSSN  
YAT  
YYADSVKDRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARDGIYYDYDTMYYYAMDY  
WGQG  
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT  
F  
PAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC  
P  
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK  
TK  
PREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YT  
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK  
L  
TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Hz64A12 Light chain amino acid sequence without signal sequence (SEQ ID NO:153)

NIVLTQSPDSLAVSLGERATINCRASESVDYYGNSFIYWYQQKPGQPPKLLIYFASNLES  
GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQNNEDPWTFGGGTKVEIKRTVAAPS  
VF  
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL  
LS  
STLTLTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Hz73D1.v1 Heavy chain amino acid sequence with signal sequence underlined (SEQ  
ID NO:154)

MDMRVPAQLLGLLLWLRGARCQQLVQSGAEVKKPGASVKVSKASGYTFTDYYI  
NWVR  
QAPGQGLEWMGNVNPNDGGTTYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVY  
YCAR  
REIFYFGTIYYAMDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD  
YF  
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT  
K  
VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH  
D  
PEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNK  
ALPA  
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN  
N

YKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Hz73D1.v1 Light chain amino acid sequence with signal sequence underlined (SEQ ID NO:155)

MDMRVPAQLLGLLLWLRGARCDIQLTQSPSFLSASVGDRVTITCRASESVDYYGNSFMY  
WYQQKPGKAPKLLIYFASNLESGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQNNED  
PWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN  
AL  
QSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Hz73D1.v1 Heavy chain amino acid sequence without signal sequence (SEQ ID NO:156)

QVQLVQSGAEVKKPGASVKVSCKASGYFTDYYINWVRQAPGQGLEWMGNVNPNDG  
GTTY  
NQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARREIYFYGTIYYYAMDYWGQ  
GTL  
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA  
A  
VLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA  
P  
ELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK  
PR  
EEQYGGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY  
LP  
PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT  
V  
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Hz73D1.v1 Light chain amino acid sequence without signal sequence (SEQ ID NO:157)

DIQLTQSPSFLSASVGDRVTITCRASESVDYYGNSFMYWYQQKPGKAPKLLIYFASNLE  
S  
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQNNEDPWTFGGGTKVEIKRTVAAPSVF  
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL  
LS  
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Human IgG1 constant region (SEQ ID NO:158)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ  
S  
GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL  
LG  
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ  
YN  
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE  
E

MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSGDSFFLYSKLTVDKS  
RW  
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG1 constant region E233A/L235A (SEQ ID NO:159)  
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS  
S  
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPALAG  
G  
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ  
YN  
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE  
E  
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSGDSFFLYSKLTVDKS  
RW  
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG1 constant region L234A/L235A (SEQ ID NO:160)  
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA  
VLQSS  
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA  
PEAAGG  
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK  
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE  
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV  
LDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG1 constant region L234A/L235A/P329G (SEQ ID NO:161)  
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA  
VLQSS  
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA  
PEAAGG  
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK  
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE  
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV  
LDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG1 constant region N297G (SEQ ID NO:162)  
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS  
S  
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPPELLG  
G  
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ  
YG  
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE  
E

MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKS  
RW  
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG1 constant region N297G/H310A (SEQ ID NO:163)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS  
S  
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG  
G  
PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ  
YG  
STYRVVSVLTVLAQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE  
E  
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKS  
RW  
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human Kappa light chain constant region (SEQ ID NO:164)

RTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE  
QD  
SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Human Lambda light chain constant region (SEQ ID NO:165)

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPS  
K  
QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Cyno ILT2 amino acid sequence with predicted signal sequence underlined (SEQ ID NO:166)

MTPILMVLICLGLSLGPRTHVQAGILPKPTLWAEPGSMISEGSPVTLRCQGSLQVQEYRL  
YREKKPASWVRRIQELVKKGYFAIGFITWEHTGQYRCQYYSHSWWSEPSDPLELVV  
GA  
YSKPTLSALPSPVVASGGNVTLQCDSQVAFDSFTLCKEGEDEHPQRLNCQSHARGWSW  
AV  
FSVGPVSPSRRWSYRCYGYISSAPNVWSLPSDLELLVPGVSKKPSLSVQPGPVVAPGD  
K  
LTLQCGSDAGYDRFALYKEGEGDFLQRPVRQPQAGLSQANFLLGPVSRSHGGQYRCSG  
AH  
NLSSEWSAPSDPLDILIAGQIRGRPFLSVQPGPKVVSGENVTLQCSSWQFHAFLLTQAG  
AADAHLHLRSMYKYPKYQAEFPMPVTSAHAGTYRCYGSRSSNPYLLSVPDPLELVV  
SG  
PSGGPSSPTTGPTSTCAGPEDQPLTPTGSDPQSGLGRHLGVVTGILVAFVLLLFLLLLF  
LVLRHQRQGKHWTSAQRKADFQHPAGAVEPEPRDRGLQRRSSPAADTQEENLYAAVK  
DTQ  
PEDGVELDSRQRPHDEDPQAVTYARVKHSRPRREMASPPSPLSEEFLDTKDTQAEEDR  
QM  
DTEAAASEDPQDVTYAQLQSLTLRRETTEPPPSQERAPPVSESIYATLTIH

Cyno ILT2 amino acid sequence without predicted signal sequence (SEQ ID NO:167)  
 GILPKPTLWAEPGSMISEGSPVTLRCQGS LQVQEYRLYREKKPASWVRRIQQELVKKGY  
 F  
 AIGFITWEHTGQYRCQYYSHSWWSEPSDPLELVVTGAYSKPTLSALPSPVVASGGNVTL  
 Q  
 CDSQVAFDSFTLCKEGEDEHPQRLNCQSHARGWSWAVFSVGPVSPSRRWSYRCYGYIS  
 SA  
 PNVWSLPSDLELLVPGVSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYDRFALYKEGE  
 GD  
 FLQRPVRQPQAGLSQANFLLGPVSRSHGGQYRCSGAHNLSSEWSAPSDPLDILIAGQIR  
 G  
 RPFLSVQPGPKVVSGENVTLQCSSWQFHAFLLTQAGAADAHLHLRSMYKYPKYQAE  
 FPM  
 SPV TSAHAGTYRCYGSRSSNPYLLSVPSDPLELVVSGPSGGPSSPTTGPTSTCAGPEDQP  
 LTPTGSDPQSG LGRHLGVVTGILVAFVLLLFLLLLFLVLRHQ RQGHWTSAQRKADF  
 QH  
 PAGAVEPEPRDRGLQRRSSPAADTQEENLYAAVKDTQPEDGVELDSRQRPHDEDPQAV  
 TY  
 ARVKHSRPREMASPPSPLSEEF LDTKDTQAEEDRQMDTEAAASEDPQDV TYAQLQSL  
 TL  
 RRETTEPPPSQERAPPVESS IYATLTIH

Cyno ILT2 extracellular domain (aa 24-461) (SEQ ID NO:168)  
 GILPKPTLWAEPGSMISEGSPVTLRCQGS LQVQEYRLYREKKPASWVRRIQQELVKKGY  
 F  
 AIGFITWEHTGQYRCQYYSHSWWSEPSDPLELVVTGAYSKPTLSALPSPVVASGGNVTL  
 Q  
 CDSQVAFDSFTLCKEGEDEHPQRLNCQSHARGWSWAVFSVGPVSPSRRWSYRCYGYIS  
 SA  
 PNVWSLPSDLELLVPGVSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYDRFALYKEGE  
 GD  
 FLQRPVRQPQAGLSQANFLLGPVSRSHGGQYRCSGAHNLSSEWSAPSDPLDILIAGQIR  
 G  
 RPFLSVQPGPKVVSGENVTLQCSSWQFHAFLLTQAGAADAHLHLRSMYKYPKYQAE  
 FPM  
 SPV TSAHAGTYRCYGSRSSNPYLLSVPSDPLELVVSGPSGGPSSPTTGPTSTCAGPEDQP  
 LTPTGSDPQSG LGRHLGV

Cyno ILT2 Ig-like C2-type domain 1 amino acid sequence (aa 27-114) (SEQ ID  
 NO:169)  
 PKPTLWAEPGSMISEGSPVTLRCQGS LQVQEYRLYREKKPASWVRRIQQELVKKGYFAI  
 G  
 FITWEHTGQYRCQYYSHSWWSEPSDPLE

Cyno ILT2 Ig-like C2-type domain 2 amino acid sequence n (aa 115-220) (SEQ ID  
 NO:170)

LVVTGAYSKPTLSALPSPVVASGGNVTLCDSQVAFDSFTLCKEGEDEHPQRLNCQSH  
AR  
GWSWAVFSVGPVSPSRRWSYRCYGYISSAPNVWSLPSDLELLVPG

Cyno ILT2 Ig-like C2-type domain 3 amino acid sequence n (aa 221-311) (SEQ ID  
NO:171)

VSKKPSLSVQPGPVVAPGDKLTLQCGSDAGYDRFALYKEGEGDFLQRPVRQPQAGLSQ  
AN  
FLGPPVSRSHGGQYRCSGAHNLSSEWSAPSD

Cyno ILT2 Ig-like C2-type domain 4 amino acid sequence n (aa 312-408) (SEQ ID  
NO:172)

PLDILIAGQIRGRPFLSVQPGPKVVSGENVTLQCSSWQFHAFLLTQAGAADAHLHLRS  
MY  
KYPKYQAEFPMSPV TSAHAGTYRCYGSRSSNPYLLS

Hexahistidine peptide tag (SEQ ID NO:173)

HHHHHH

## WHAT IS CLAIMED:

1. A binding agent comprising an antigen-binding domain, wherein the antigen binding domain binds specifically to both human immunoglobulin-like transcript 2 (ILT2) and human immunoglobulin-like transcript 4 (ILT4).
2. The binding agent of claim 1, wherein the antigen-binding domain comprises:
  - (1) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:144; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:145;
  - (2) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:139; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:140;
  - (3) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:133; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:134;

- (4) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:143; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:142;
- (5) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:131; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:132;
- (6) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:137; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:138;
- (7) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:135; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:136; or

- (8) a heavy chain variable region comprising a heavy chain variable region CDR1 (VH-CDR1), a heavy chain variable region CDR2 (VH-CDR2), and a heavy chain variable region CDR3 (VH-CDR3) from the amino acid sequence of SEQ ID NO:141; and a light chain variable region comprising a light chain variable region CDR1 (VL-CDR1), a light chain variable region CDR2 (VL-CDR2), and a light chain variable region CDR3 (VL-CDR3) from the amino acid sequence of SEQ ID NO:142.
3. The binding agent of claim 2, wherein:
- (1) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:115, the VH-CDR2 having the amino acid sequence of SEQ ID NO:112, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:107; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:89, the VL-CDR2 having the amino acid sequence of SEQ ID NO:90, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:91;
  - (2) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:111, the VH-CDR2 having the amino acid sequence of SEQ ID NO:112, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:107; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:89, the VL-CDR2 having the amino acid sequence of SEQ ID NO:90, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:91;
  - (3) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:76, the VH-CDR2 having the amino acid sequence of SEQ ID NO:113, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:107; and the light chain variable

region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:89, the VL-CDR2 having the amino acid sequence of SEQ ID NO:90, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:91;

(4) a heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:111, the VH-CDR2 having the amino acid sequence of SEQ ID NO:114, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:107; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:89, the VL-CDR2 having the amino acid sequence of SEQ ID NO:90, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:91; or

(5) a heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:116, the VH-CDR2 having the amino acid sequence of SEQ ID NO:124, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:110; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:99, the VL-CDR2 having the amino acid sequence of SEQ ID NO:100, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:101.

4. The binding agent of claim 2, wherein:

(1) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 6B;

(2) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR

- definitions set forth in Table 4B;(3) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 8A;
- (4) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 4A;
- (5) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 6A;
- (6) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 5; or
- (7) the heavy chain variable region comprises the VH-CDR1, the VH-CDR2, the VH-CDR3, the VL-CDR1, the VL-CDR2, and the VL-CDR3 comprising amino acid sequences of any one of the five CDR definitions set forth in Table 7.
5. The binding agent of claim 2 or 3, wherein:
- (a) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:144;
- (b) the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:145; or

- (c) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:144 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:145.
- 6. The binding agent of claim 5, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:144.
- 7. The binding agent of claim 5 or claim 6, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:145.
- 8. The binding agent of claim 4, wherein:
  - (a) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to any one of the sequences set forth in SEQ ID NOs:139, 133, 143, 131, 137, 135, or 141;
  - (b) the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to any one of the sequences set forth in SEQ ID NOs:140, 134, 142, 132, 138, 136, or 142; or
  - (c) the variable region comprises any one of the following amino acid sequences:
    - (i) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:139 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:140;
    - (ii) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:133 and the light chain variable region comprises an amino acid

sequence having at least 80% sequence identity to the sequence of SEQ ID NO:134;

(iii) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:143 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:142;

(iv) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:131 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:132;

(v) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:137 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:138;

(vi) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:135 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:136; or

(vii) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:141 and the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:142.

9. The binding agent of claim 8, wherein the heavy chain variable region comprises the amino acid sequence of any one of SEQ ID NOs:139, 133, 143, 131, 137, 135, or 141.
10. The binding agent of claim 8, wherein the light chain variable region comprises the amino acid sequence of any one of SEQ ID NOs:140, 134, 142, 132, 138, 136, or 142.
11. The binding agent of claim 8, wherein:
- (i) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:139 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:140;
  - (ii) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:133 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:134;
  - (iii) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:143 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:142;
  - (iv) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:131 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:132;
  - (v) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:137 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:138;
  - (vi) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:135 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:136; or

(vii) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:141 and the light chain variable region comprises the amino acid sequence of SEQ ID NO:142.

12. A binding agent that specifically binds human ILT2 comprising an antigen-binding domain comprising a heavy chain variable region comprising a VH-CDR1, a VH-CDR2, and a VH-CDR3 from the amino acid sequence of SEQ ID NO:125; and a light chain variable region comprising a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the amino acid sequence of SEQ ID NO:126.

13. The binding agent of claim 12, wherein:

- (1) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:31, the VH-CDR2 having the amino acid sequence of SEQ ID NO:23, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:24; and the light chain variable region comprises the VL-CDR1 having amino acid sequence of SEQ ID NO:25, the VL-CDR2 having amino acid sequence of SEQ ID NO:26, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:27;
- (2) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:22, the VH-CDR2 having the amino acid sequence of SEQ ID NO:23, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:24; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:25, the VL-CDR2 having the amino acid sequence of SEQ ID NO:26, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:27;
- (3) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:28, the VH-CDR2 having the amino acid sequence of SEQ ID NO:29, and the VH-CDR3 having the amino

- acid sequence of SEQ ID NO:24; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:25, the VL-CDR2 having the amino acid sequence of SEQ ID NO:26, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:27;
- (4) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:22, the VH-CDR2 having the amino acid sequence of SEQ ID NO:30, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:24; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:25, the VL-CDR2 having the amino acid sequence of SEQ ID NO:26, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:27; or
- (5) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:32, the VH-CDR2 having the amino acid sequence of SEQ ID NO:33, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:34; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:35, the VL-CDR2 having the amino acid sequence of SEQ ID NO:36, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:37.
14. The binding agent of claim 12, wherein:
- (a) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:125;
- (b) the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:126; or

- (c) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:125 and /or the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:126.
15. The binding agent of claim 12, wherein:
- (a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:125;
  - (b) the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:126; or
  - (c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:125 and /or the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:126.
16. A binding agent that specifically binds human ILT4 comprising an antigen-binding domain comprising:
- (a) a heavy chain variable region comprising a VH-CDR1, a VH-CDR2, and a VH-CDR3 from the amino acid sequence of SEQ ID NO:129; and a light chain variable region comprising a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the amino acid sequence of SEQ ID NO:130; or
  - (b) a heavy chain variable region comprising a VH-CDR1, a VH-CDR2, and a VH-CDR3 from the amino acid sequence of SEQ ID NO:127; and a light chain variable region comprising a VL-CDR1, a VL-CDR2, and a VL-CDR3 from the amino acid sequence of SEQ ID NO:128.
17. The binding agent of claim 16, wherein for (a):
- (1) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:63, the VH-CDR2 having the amino acid

sequence of SEQ ID NO:55, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:56; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:57, the VL-CDR2 having the amino acid sequence of SEQ ID NO:58, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:59;

(2) the heavy chain variable region comprises VH-CDR1 having the amino acid sequence of SEQ ID NO:54, the VH-CDR2 having the amino acid sequence of SEQ ID NO:55, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:56; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:57, the VL-CDR2 having the amino acid sequence of SEQ ID NO:58, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:59;

(3) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:60, the VH-CDR2 having the amino acid sequence of SEQ ID NO:61, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:56; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:57, the VL-CDR2 having the amino acid sequence of SEQ ID NO:58, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:59;

(4) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:54, the VH-CDR2 having the amino acid sequence of SEQ ID NO:62, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:56; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:57, the VL-CDR2 having the amino acid sequence of SEQ ID NO:58, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:59; or

(5) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:64, the VH-CDR2 having the amino acid sequence of SEQ ID NO:65, and the VH-CDR3 having the amino acid sequence

of SEQ ID NO:66; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:67, the VL-CDR2 having the amino acid sequence of SEQ ID NO:68, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:69; or

wherein for (b):

- (1) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:47, the VH-CDR2 having the amino acid sequence of SEQ ID NO:39, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:40; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:41, the VL-CDR2 having the amino acid sequence of SEQ ID NO:42, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:43;
- (2) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:38, the VH-CDR2 having the amino acid sequence of SEQ ID NO:39, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:40; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:41, the VL-CDR2 having the amino acid sequence of SEQ ID NO:42, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:43;
- (3) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:44, the VH-CDR2 having the amino acid sequence of SEQ ID NO:45, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:40; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:41, the VL-CDR2 having the amino acid sequence of SEQ ID NO:42, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:43;
- (4) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:38, the VH-CDR2 having the amino acid sequence of SEQ ID NO:46, and the VH-CDR3 having the amino acid sequence

of SEQ ID NO:40; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:41, the VL-CDR2 having the amino acid sequence of SEQ ID NO:42, and the VL-CDR3 having the amino acid sequence of SEQ ID NO:43; or

(5) the heavy chain variable region comprises the VH-CDR1 having the amino acid sequence of SEQ ID NO:48, the VH-CDR2 having the amino acid sequence of SEQ ID NO:49, and the VH-CDR3 having the amino acid sequence of SEQ ID NO:50; and the light chain variable region comprises the VL-CDR1 having the amino acid sequence of SEQ ID NO:51, the VL-CDR2 having the amino acid sequence of SEQ ID NO:52, and the VL-CDR3 having an amino acid sequence of SEQ ID NO:53.

18. The binding agent of claim 16, wherein:

(a) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:129; (b) the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:130; or (c) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:129 and /or the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:130.

19. The binding agent of claim 16, wherein:

(a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:129; (b) the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:130; or (c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:129

and /or the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:130.

20. The binding agent of claim 16, wherein:
  - (a) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:127;
  - (b) the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:128; or
  - (c) the heavy chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:127 and /or the light chain variable region comprises an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:128.
  
21. The binding agent of claim 16, wherein:
  - (a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:127;
  - (b) the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:128; or
  - (c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:127 and /or the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:128.
  
22. The binding agent of any one of claims 1-21, which is an antibody.
  
23. The binding agent of any one of claims 1-22, which is a recombinant antibody.
  
24. The binding agent of any one of claims 1-23, which is a chimeric antibody.

25. The binding agent of any one of claims 1-23, which is a humanized antibody.
26. The binding agent of any one of claims 1-25, which is a bispecific antibody or a multispecific antibody.
27. The binding agent of any one of claims 22-26, wherein the antibody is an antibody fragment comprising at least one antigen-binding site.
28. The binding agent of claim 27, wherein the antibody fragment is a Fab, Fab', F(ab')<sub>2</sub>, Fv, scFv, (scFv)<sub>2</sub>, single chain antibody, dual variable region antibody, diabody, or nanobody.
29. The binding agent of any one of claims 1-25, which is an IgG1 antibody, optionally a human IgG1 antibody, and further optionally a human IgG1 antibody having reduced or no effector function.
30. The binding agent of any one of claims 1-25, which is an IgG2 antibody, optionally a human IgG2 antibody.
31. The binding agent of any one of claims 1-25, which is an IgG4 antibody, optionally a human IgG4 antibody.
32. The binding agent of any one of claims 1-25 or 29-31, which comprises a kappa light chain constant region, optionally a human kappa light chain constant region.

33. The binding agent of any one of claims 1-25 or 29-31, which comprises a lambda light chain constant region, optionally a human lambda light chain constant region.
34. The binding agent of any one of claims 1-11, comprising:
- (a) a heavy chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:148 and a light chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:149;
  - (b) a heavy chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:152 and a light chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:153; or
  - (c) a heavy chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:156 and a light chain comprising an amino acid sequence with 80% identity to the sequence of SEQ ID NO:157.
35. An antibody that specifically binds human ILT2 and ILT4, which comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO:148 and a light chain comprising the amino acid sequence of SEQ ID NO:149;
  - (b) a heavy chain comprising the amino acid sequence of SEQ ID NO:152 and a light chain comprising the amino acid sequence of SEQ ID NO:153; or
  - (c) a heavy chain comprising the amino acid sequence of SEQ ID NO:156 and a light chain comprising the amino acid sequence of SEQ ID NO:157.
36. The binding agent or antibody of any one of claims 1-35, which has one or more of the following properties:
- (1) binds rhesus ILT2;

- (2) binds cyno ILT2;
  - (3) does not bind ILT3, ILT5, and LILRB5;
  - (4) does not bind LILRA2, LILRA4, LILRA5, and LILRA6;
  - (5) is an ILT2 antagonist;
  - (6) is an ILT4 antagonist;
  - (7) inhibits ILT2 activity;
  - (8) inhibits ILT4 activity;
  - (9) inhibits ILT2 signaling in cells that express ILT2;
  - (10) inhibits ILT4 signaling in cells that express ILT4;
  - (11) inhibits binding of ILT2 to MHC I molecules;
  - (12) inhibits binding of ILT4 to MHC I molecules;
  - (13) inhibits ILT2-induced suppression of myeloid cells;
  - (14) inhibits ILT4-induced suppression of myeloid cells;
  - (15) inhibits ILT2-induced suppression of myeloid cell activity;
  - (16) inhibits ILT4-induced suppression of myeloid cell activity;
  - (17) restores FcR activation in myeloid cells;
  - (18) enhances NK cell activity;
  - (19) enhances CTL activity;
  - (20) enhances macrophage phagocytosis; and
  - (21) inhibits MDSC mediated suppression of immune cells.
37. The binding agent or antibody of any one of claims 1-36, wherein the binding agent or antibody is attached to a half-life extending moiety.
38. An antibody that competes with the binding agent or antibody of any one of claims 1-36 for binding to human ILT2 and/or ILT4.
39. A pharmaceutical composition that comprises the binding agent or antibody of any one of claims 1-38 and a pharmaceutically acceptable carrier.

40. An isolated polynucleotide or polynucleotides encoding the binding agent or antibody of any one of claims 1-39.
41. A vector or vectors comprising the polynucleotide or polynucleotides of claim 40.
42. An isolated cell comprising the polynucleotide or polynucleotides of claim 40.
43. An isolated cell comprising the vector or vectors of claim 41.
44. An isolated cell producing the binding agent or antibody of any one of claims 1-36.
45. A method of disrupting, inhibiting, or blocking the binding of ILT2 and/or ILT4 to a MHC I molecule in a mixture of cells, the method comprising contacting the cells with the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
46. A method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity in a mixture of cells, the method comprising contacting the cells with the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
47. The method of claim 45 or 46, wherein the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.

48. A method of disrupting, inhibiting, or blocking ILT2-induced suppression of myeloid cells, the method comprising contacting the myeloid cells with the binding agent or antibody of any one of claims 1-15 and 22-38.
49. A method of disrupting, inhibiting, or blocking ILT4-induced suppression of myeloid cells, comprising contacting cells the myeloid cells with the binding agent or antibody of any one of claims 1-11 and 16-38.
50. A method of disrupting, inhibiting, or blocking ILT2 and/or ILT4-induced suppression of myeloid cells, comprising contacting cells the myeloid cells with the binding agent or antibody of any one of claims 1-38.
51. A method of inhibiting or decreasing myeloid-derived suppressor cell (MDSC) activity, the method comprising contacting the MDSCs with the binding agent or antibody of any one of claims 1-38.
52. A method of enhancing or increasing natural killer (NK) cell activity, the method comprising contacting the NK cells with the binding agent or antibody of any one of claims 1-38.
53. A method of enhancing or increasing cytolytic T lymphocyte (CTL) activity, the method comprising contacting CTLs with the binding agent or antibody of any one of claims 1-38.
54. A method of disrupting, inhibiting, or blocking the binding of ILT2 or ILT4 to a MHC I molecule in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.

55. A method of disrupting, inhibiting, or blocking MHC I-induced ILT2 and/or ILT4 activity in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
56. The method of claim 49 or claim 50, wherein the MHC I molecule is HLA-A, HLA-B, HLA-C, HLA-E, and/or HLA-G.
57. A method of disrupting, inhibiting, or blocking ILT2 or ILT4-induced suppression of myeloid cells in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
58. A method of inhibiting or decreasing MDSC activity in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
59. A method of enhancing or increasing NK cell activity in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
60. A method of enhancing or increasing CTL activity in a subject, the method comprising administering to the subject an effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.

61. A method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
62. The method of claim 61, wherein the cancer is mesothelioma, glioblastoma, renal cell carcinoma, non-small cell lung cancer, melanoma, pancreatic ductal adenocarcinoma, gastric cancer, squamous cell carcinoma of the head and neck, biliary duct cancer, breast cancer, ovarian cancer, cervical cancer, endocervical cancer, colorectal cancer, or esophageal cancer.
63. A method of inhibiting tumor growth in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
64. A method of increasing or enhancing an immune response to a tumor or tumor cells in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
65. A method of activating or enhancing a persistent or long-term immune response to a tumor or tumor cells in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
66. A method of inhibiting tumor relapse or tumor regrowth in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.

67. A method of inducing a persistent or long-term immunity that inhibits tumor relapse or tumor regrowth in a subject, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
68. The method of any one of claims 63-67, wherein the tumor is a pancreatic tumor, a breast tumor, a lung tumor, a non-small cell lung tumor, a head and neck tumor, a colorectal tumor, a prostate tumor, a skin tumor, a melanoma, a gastric tumor, a colorectal tumor, an ovarian tumor, a cervical tumor, a uterine tumor, an endometrial tumor, an endocervical tumor, a bladder tumor, a brain tumor, an esophageal tumor, a liver tumor, a kidney tumor, a renal tumor, mesothelioma, glioblastoma, a biliary duct tumor, or a testicular tumor.
69. A method of activating myeloid cells in the tumor microenvironment in a subject with a tumor, the method comprising administering to the subject a therapeutically effective amount of the binding agent or antibody of any one of claims 1-38 or the pharmaceutical composition of claim 39.
70. The method of any one of claims 36, 48-51, 57, and 69, wherein the myeloid cells are dendritic cells.
71. The method of any one of claims 36, 48-51, 57, and 69, wherein the myeloid cells are monocytes or macrophages.
72. The method of any one of claims 54-71, wherein the binding agent or antibody is administered as part of a combination therapy comprising an additional therapeutic agent.

73. The method of claim 72, wherein the combination therapy comprises an anti-PD-1 antibody or anti-PD-L1 antibody.
74. The method of claim 73, wherein the combination therapy comprises at least one additional therapeutic agent.
75. The method of any one of claims 54-74, wherein the subject is a human.
76. Use of the binding agent or antibody of any one of claims 1-39 for treatment of cancer.
77. Use of the binding agent or antibody of any one of claims 1-39 in the manufacture of a medicament for treatment of cancer.
78. A pharmaceutical composition, comprising:  
(a) a means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I (e.g., on tumor cells); and  
(b) a pharmaceutically acceptable carrier.
79. The pharmaceutical composition of claim 78, wherein the means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I comprises an antibody comprising a heavy chain variable region comprising VH-CDR1, VH-CDR-2, and VH-CDR-3 and a light chain variable region comprising VL-CDR1, VL-CDR2, and VL-CDR3 from any one of 27F9, 47C8, 48A5, 47H6, Hz47H6.v2, 51A1, 64A12, Hz64A12, 73C4, 73D1, and Hz73D1.v1.
80. A combination comprising a means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I (e.g., on tumor cells), and a modulator of PD-1 or PD-L1 activity.

81. The method of claim 73, wherein the anti-PD-1 antibody is Pembrolizumab (MK-3475; KEYTRUDA), Pidilizumab (CT-011), Nivolumab (OPDIVO), Durvalumab (MEDI0680), Cemiplimab (REGN2810), Tislelizumab (BGB-A317), Spartalizumab (PDR-001), or STI-A1110.

Figure 1

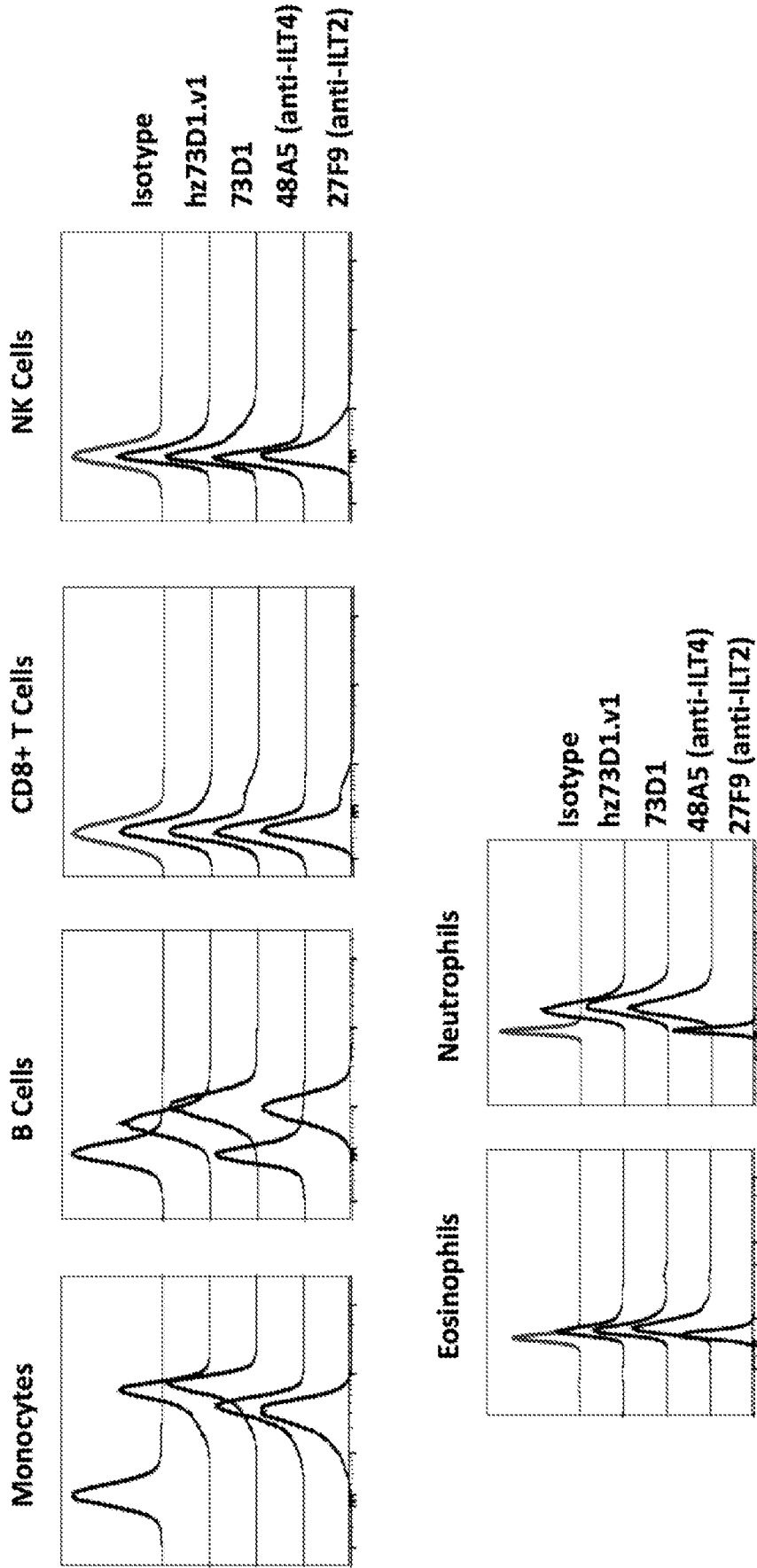


Figure 2

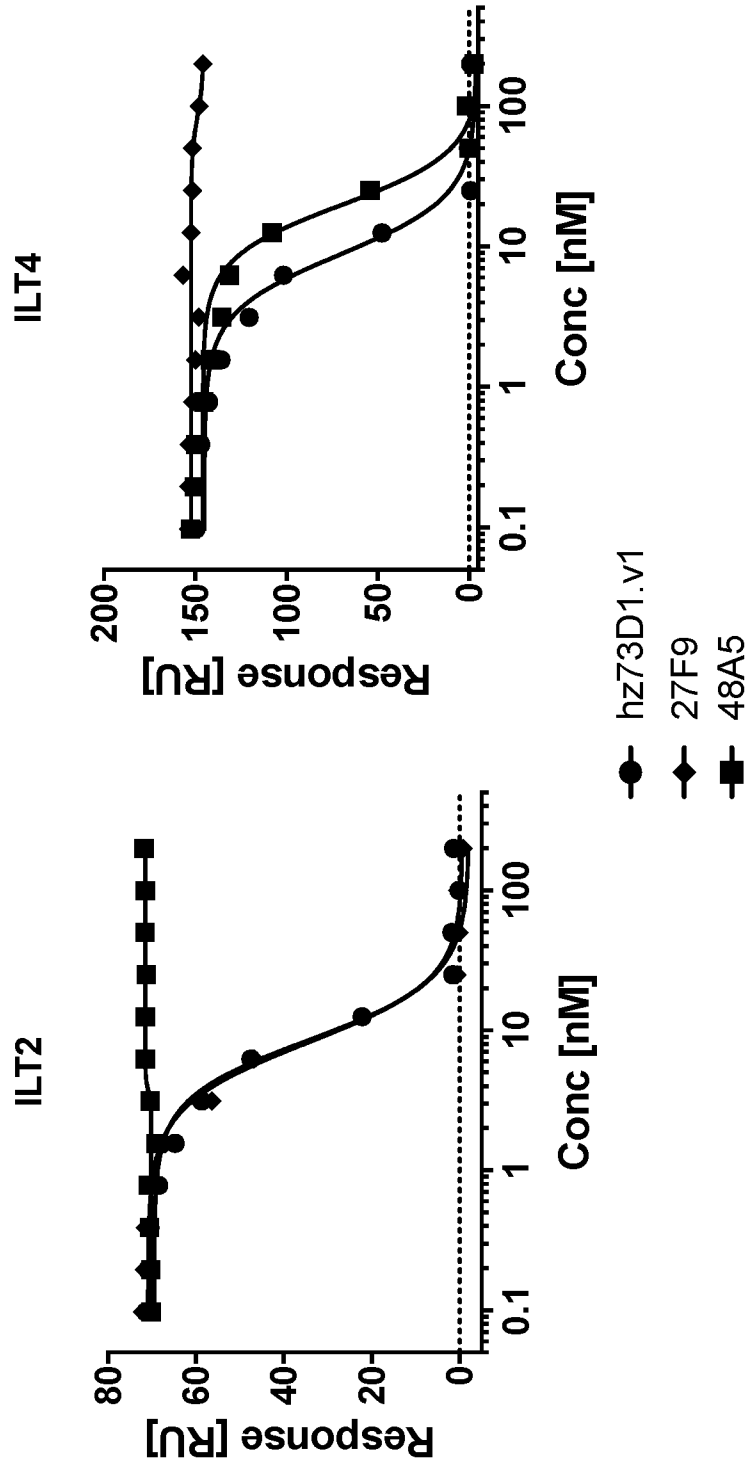


Figure 3

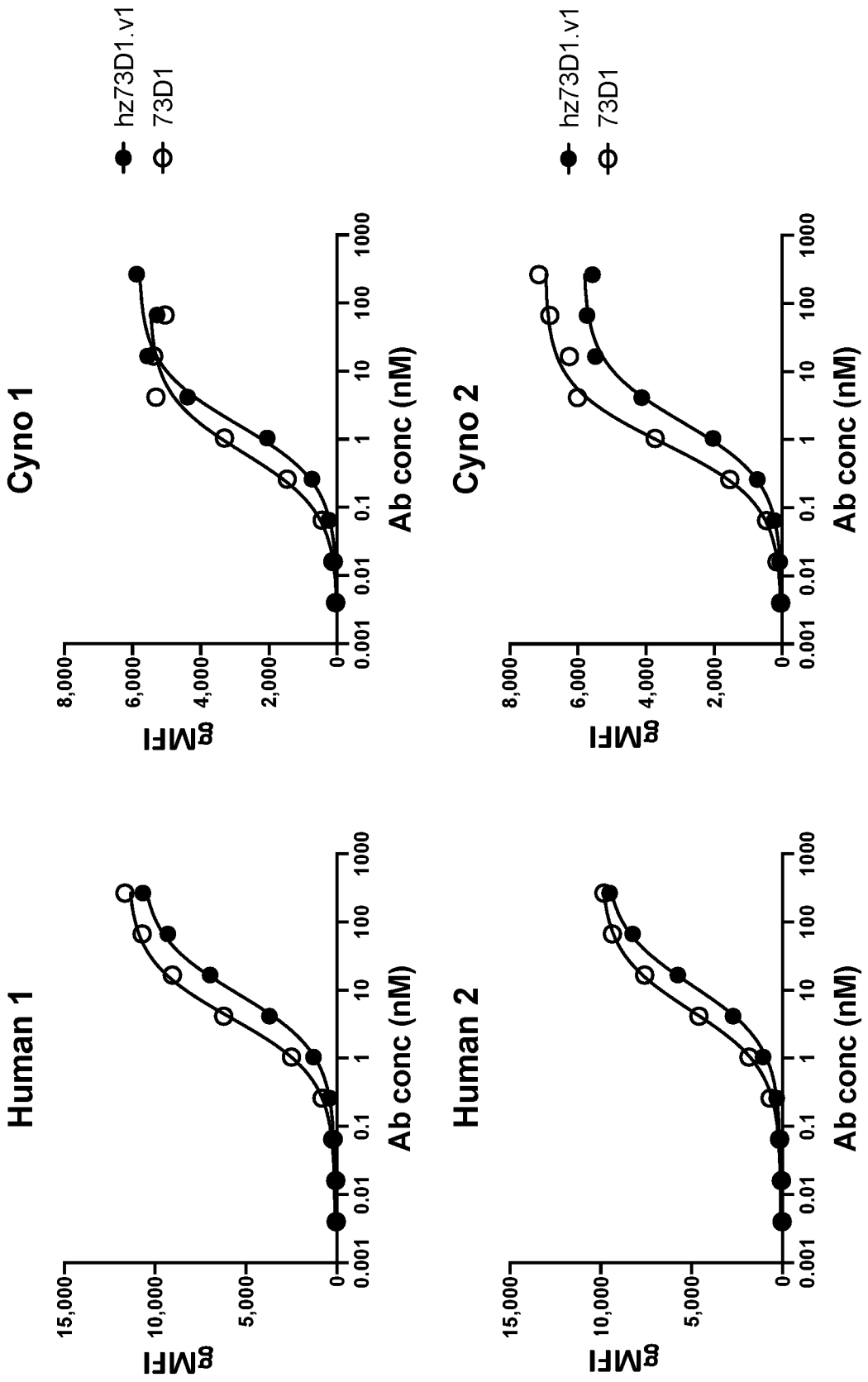


Figure 4A

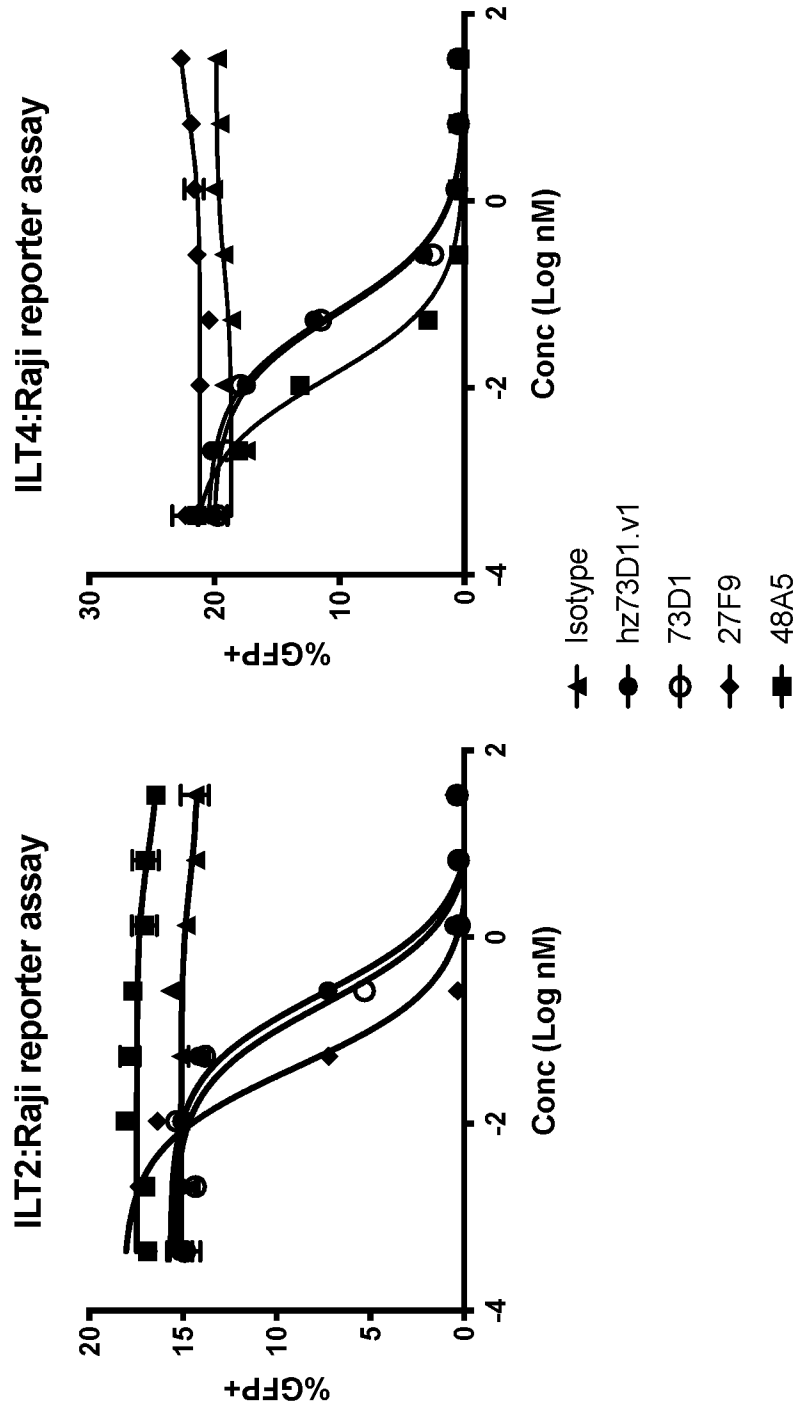


Figure 4B

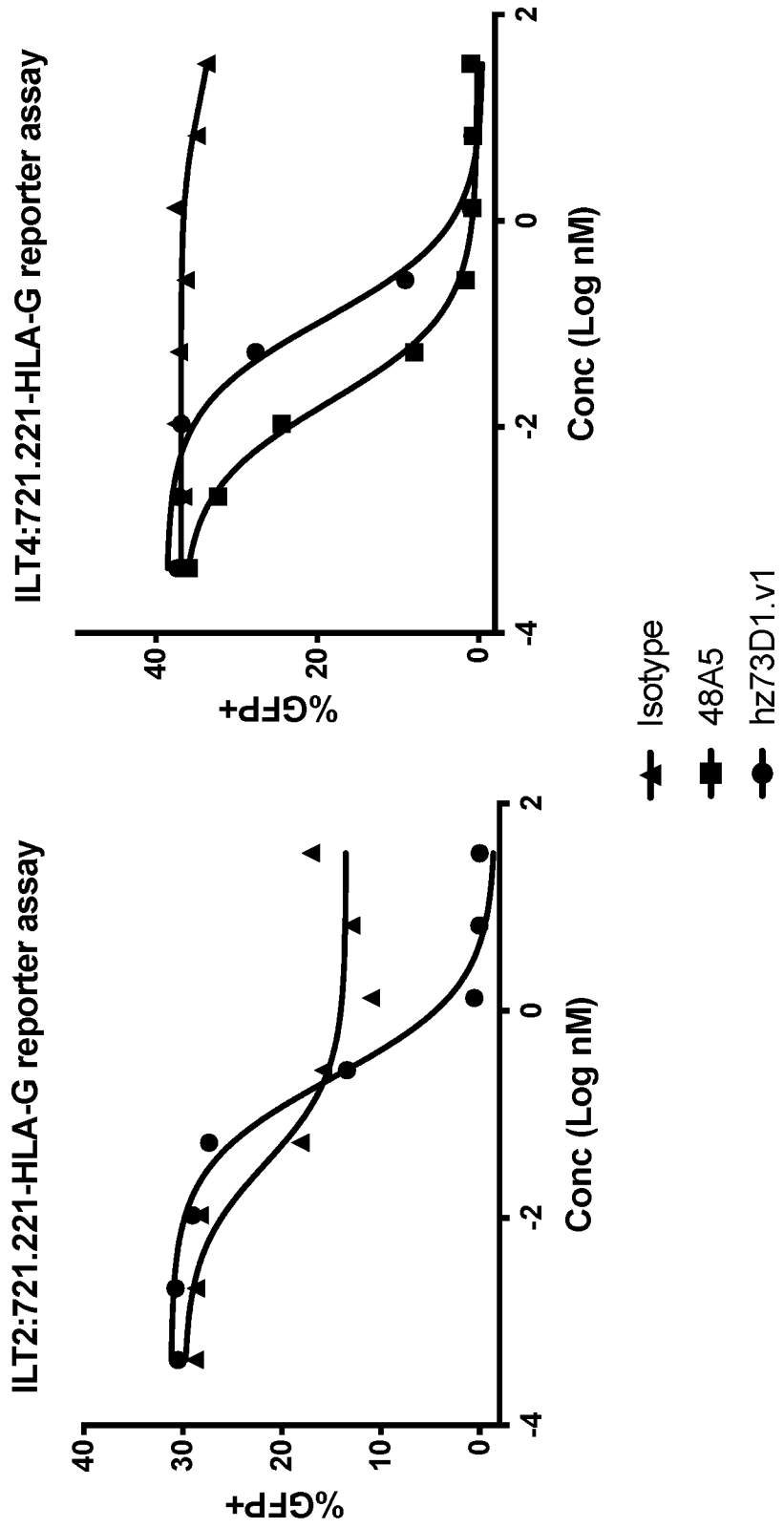


Figure 5

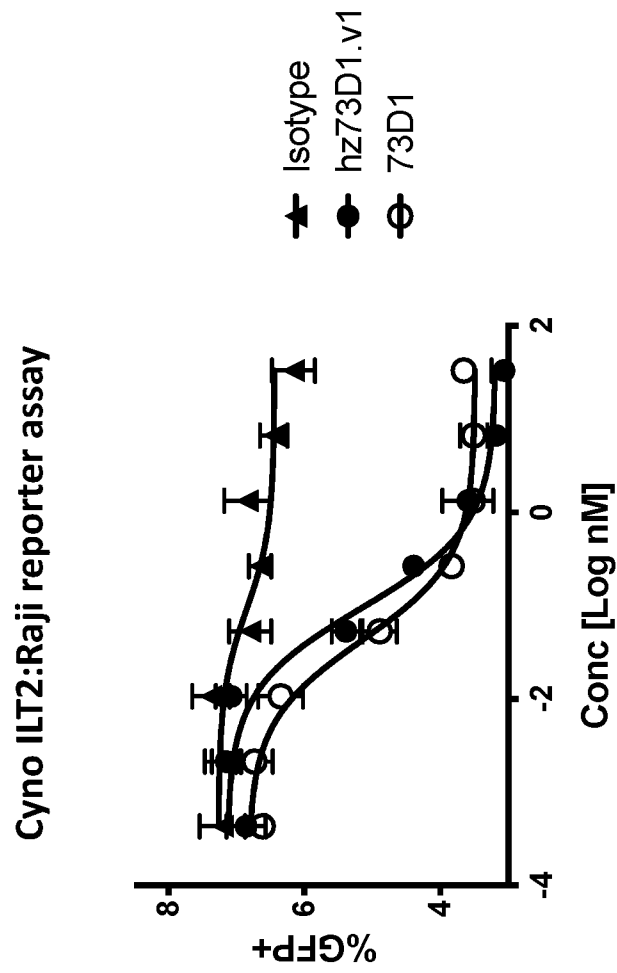


Figure 6

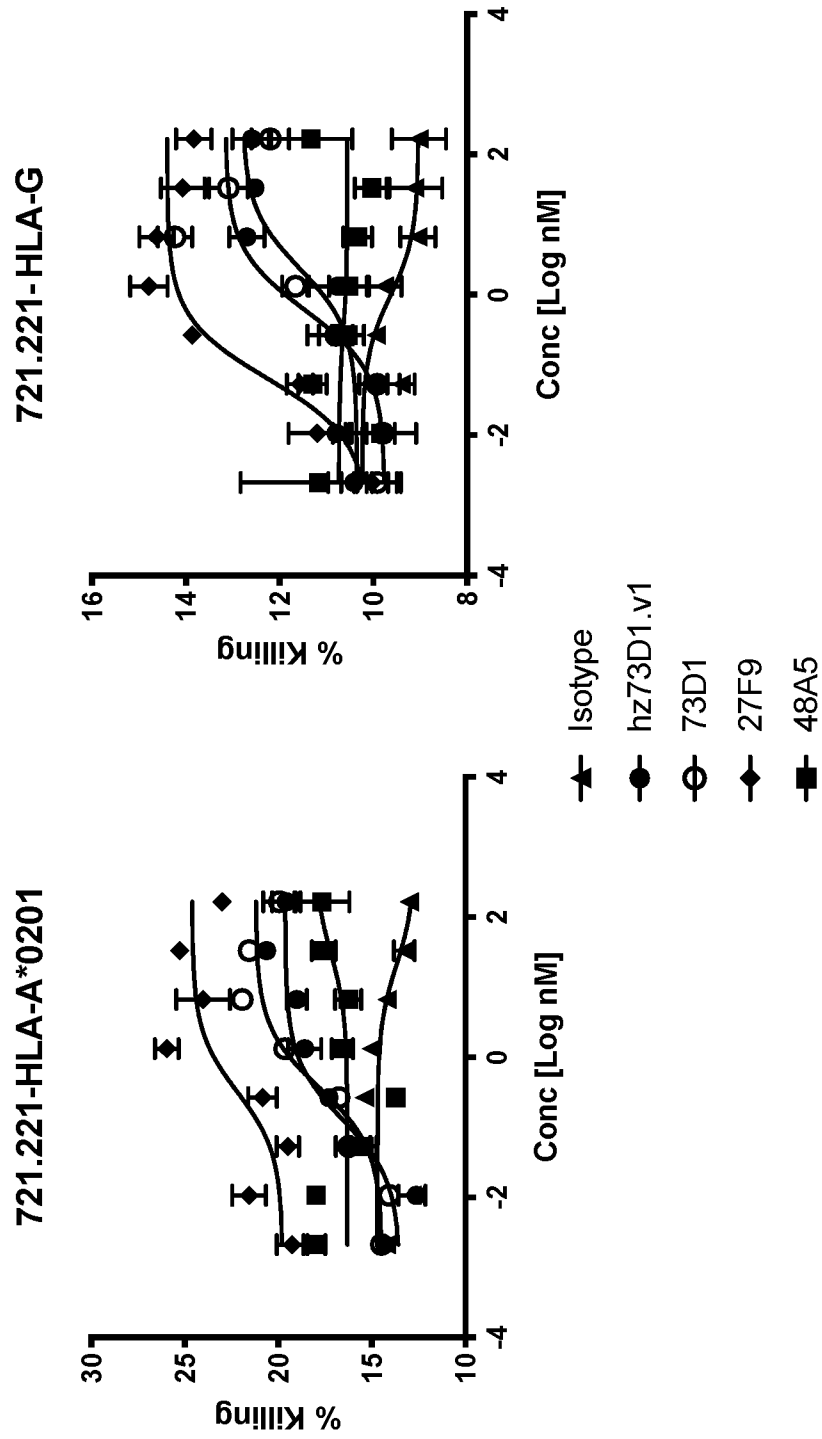


Figure 7

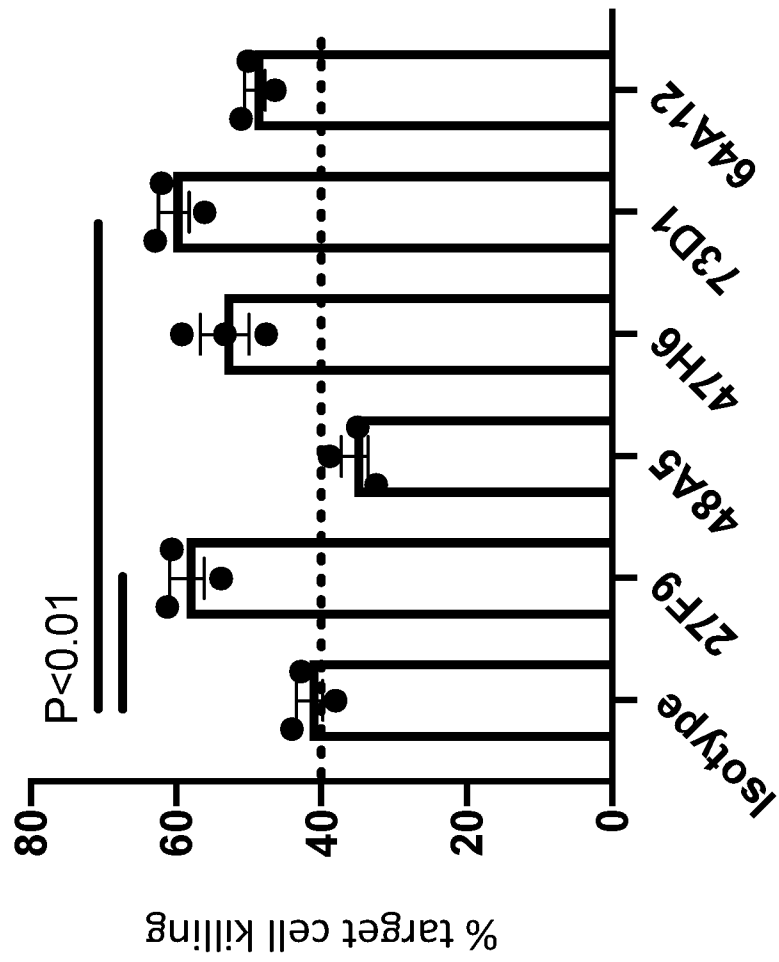


Figure 8

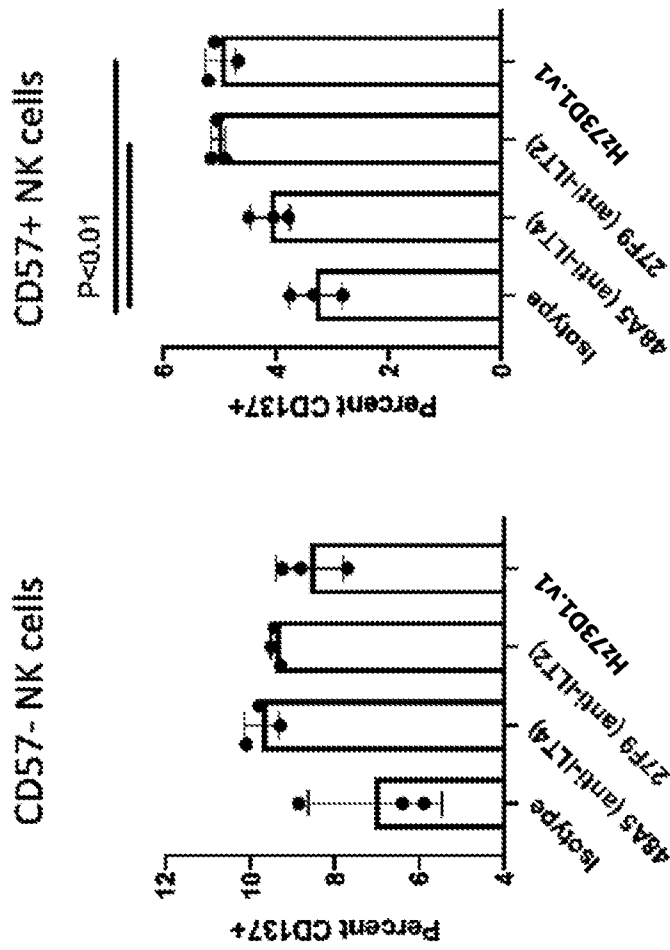


Figure 9

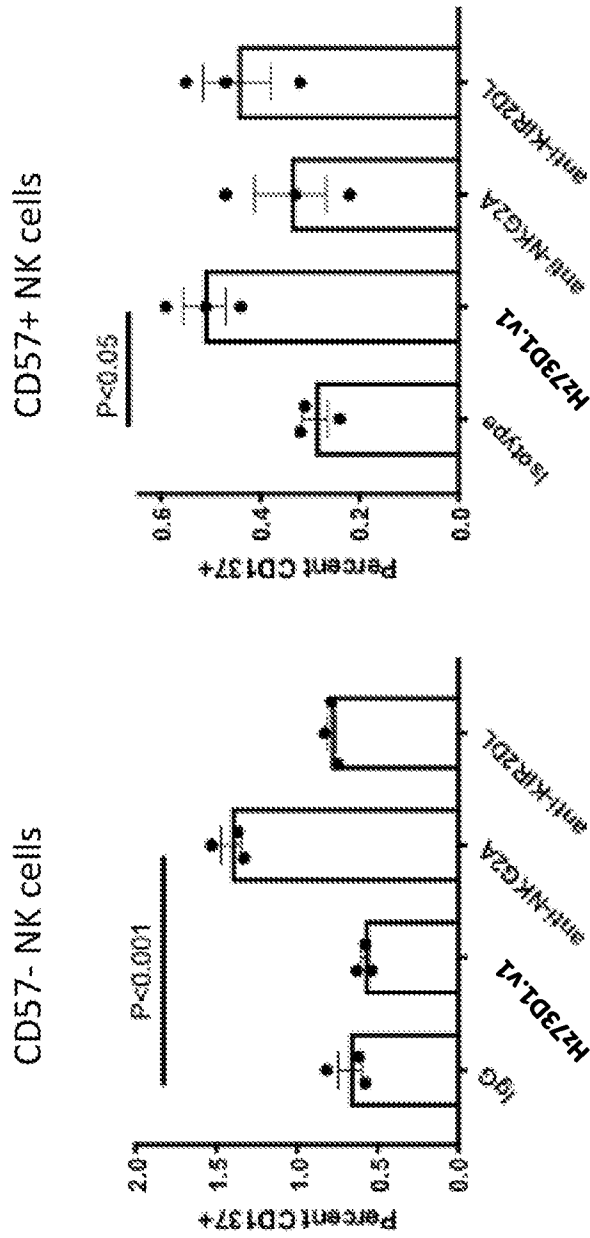


Figure 10

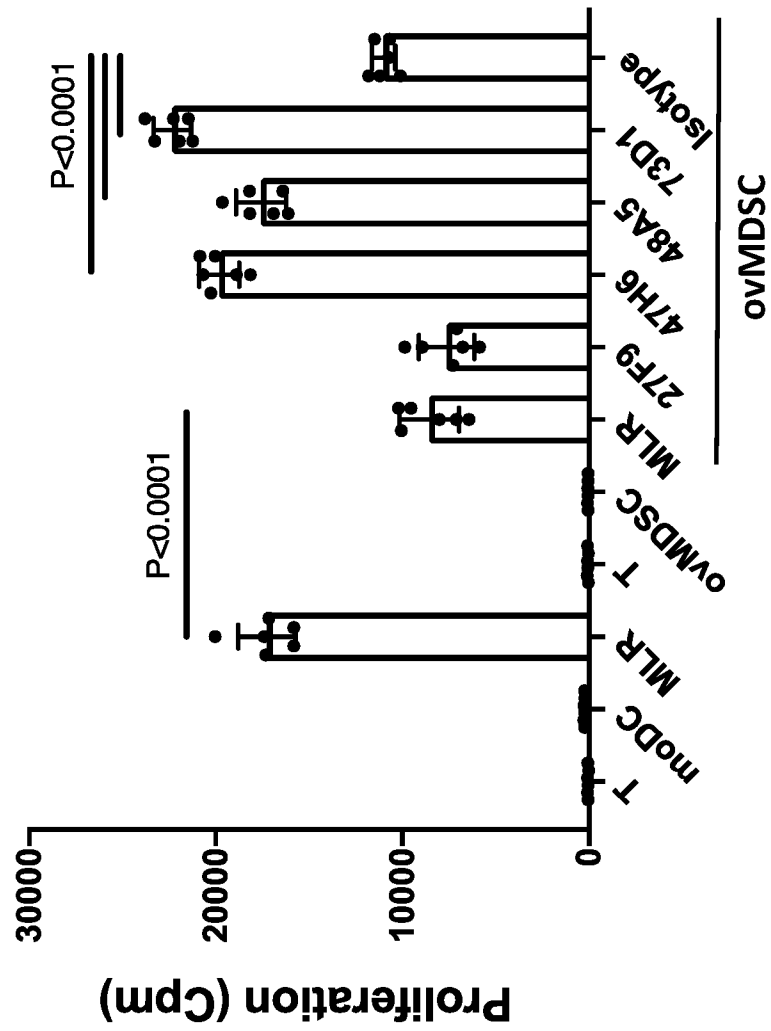
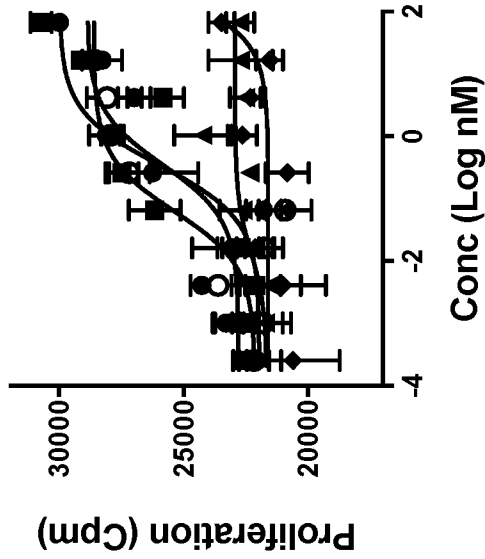


Figure 11A



- ▲ Isotype
- hz73D1.v1
- 73D1
- ◆ 27F9
- 48A5

Figure 11B

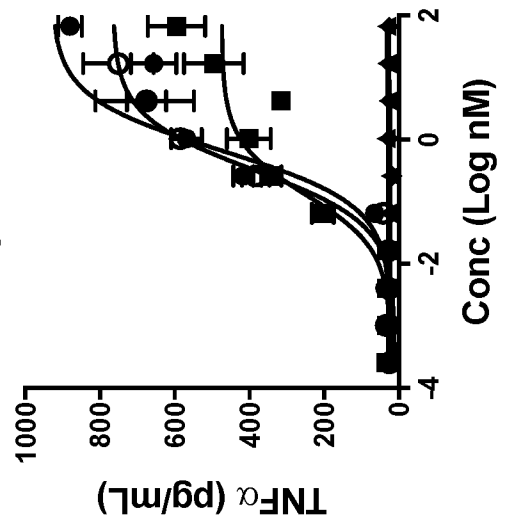


Figure 11C

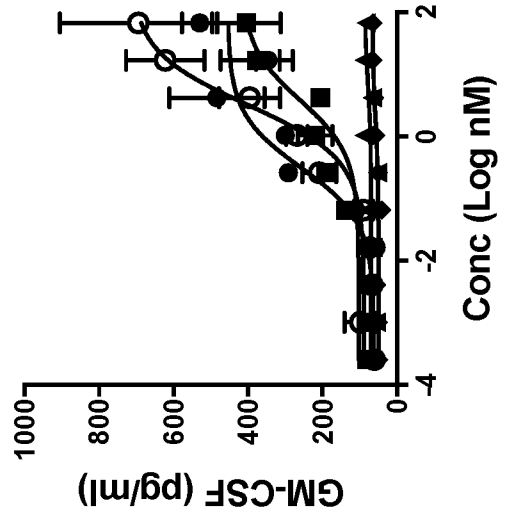


Figure 12

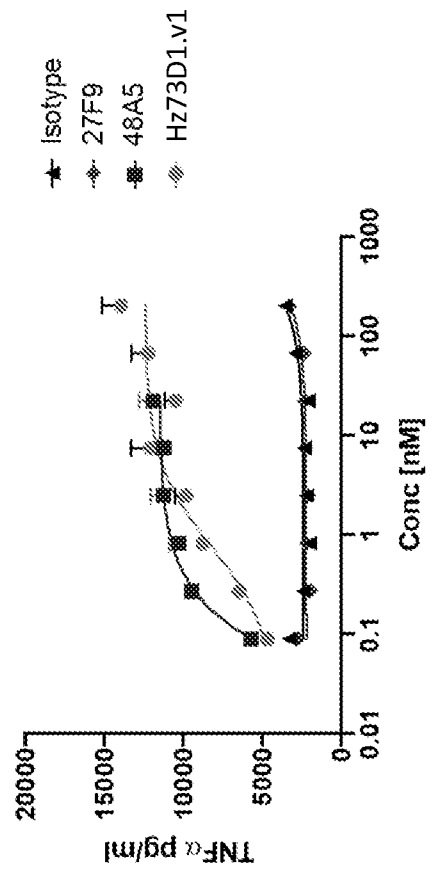
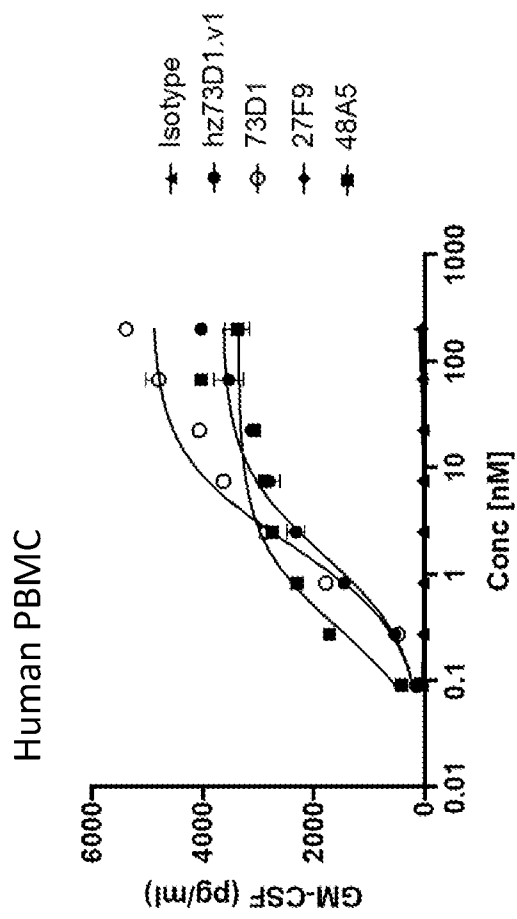
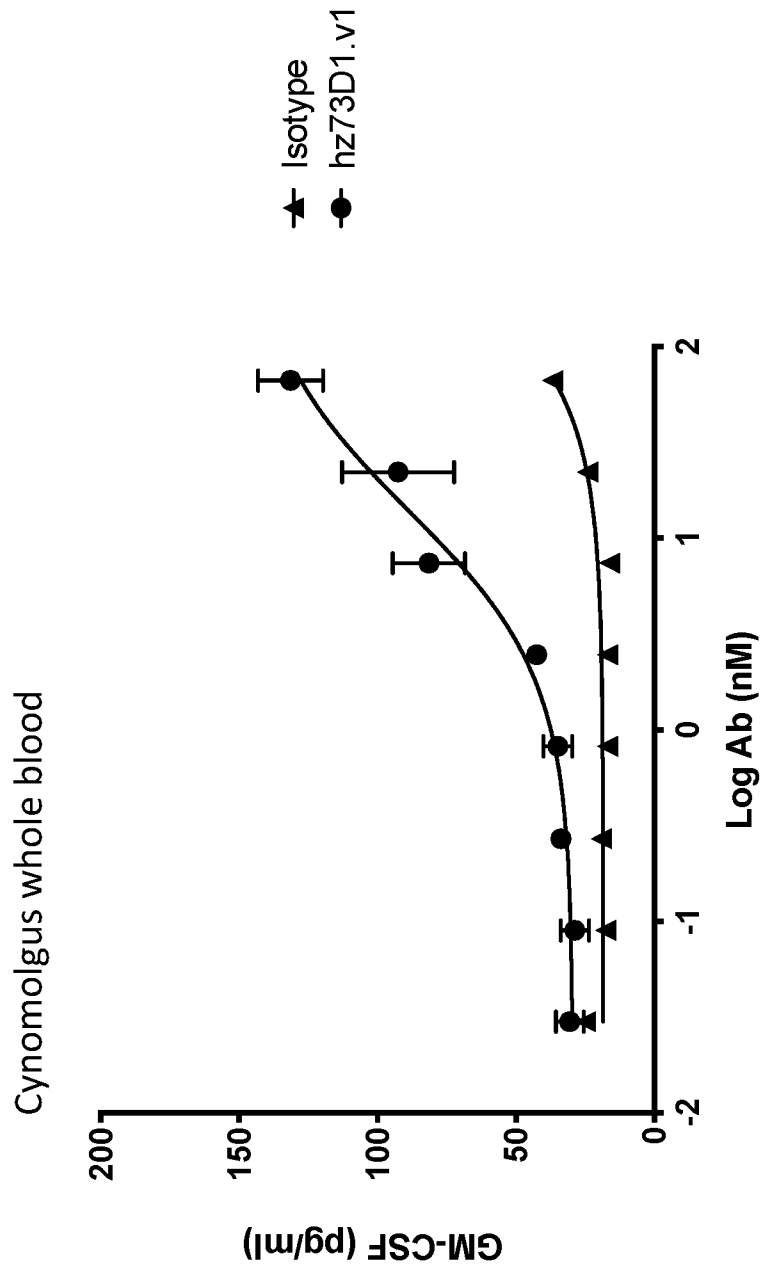


Figure 13



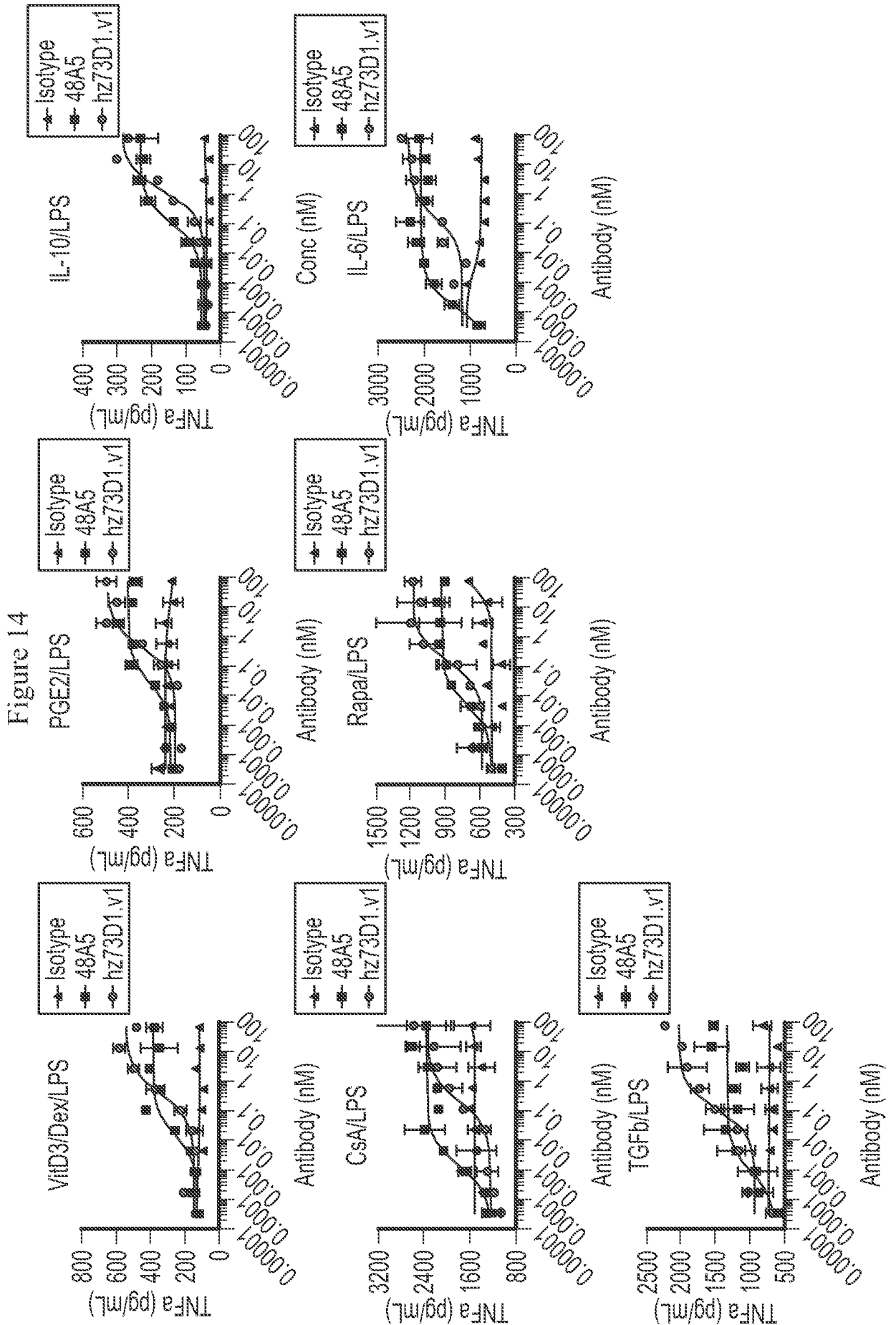


Figure 15

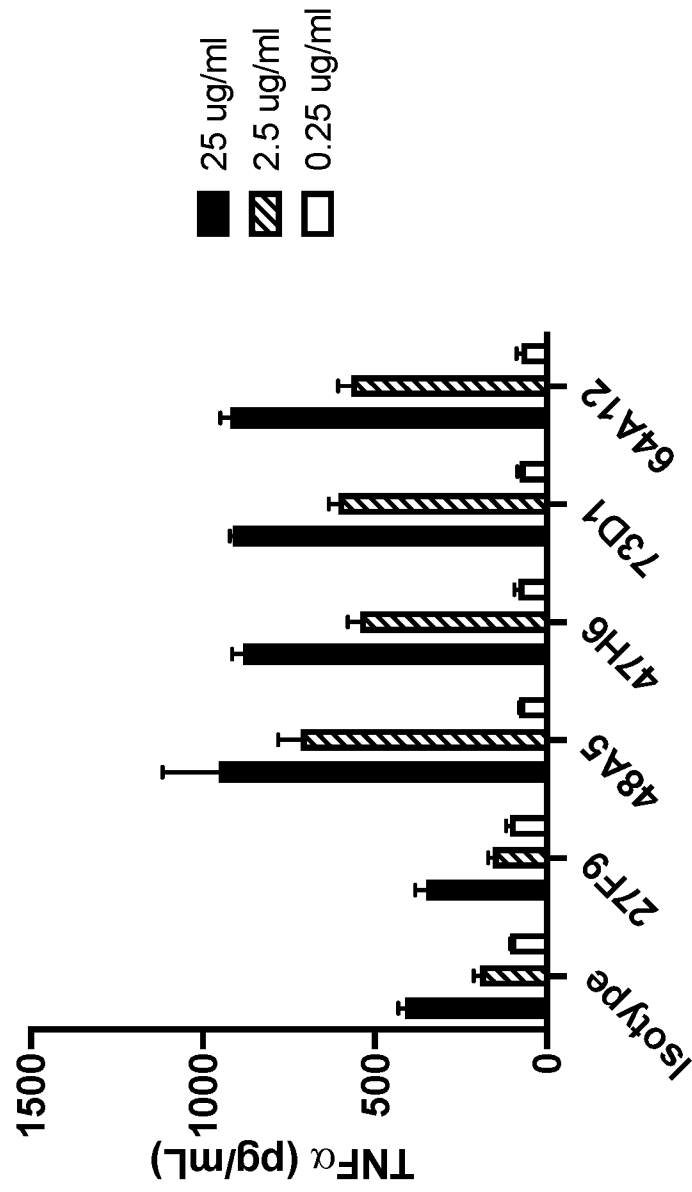


Figure 16

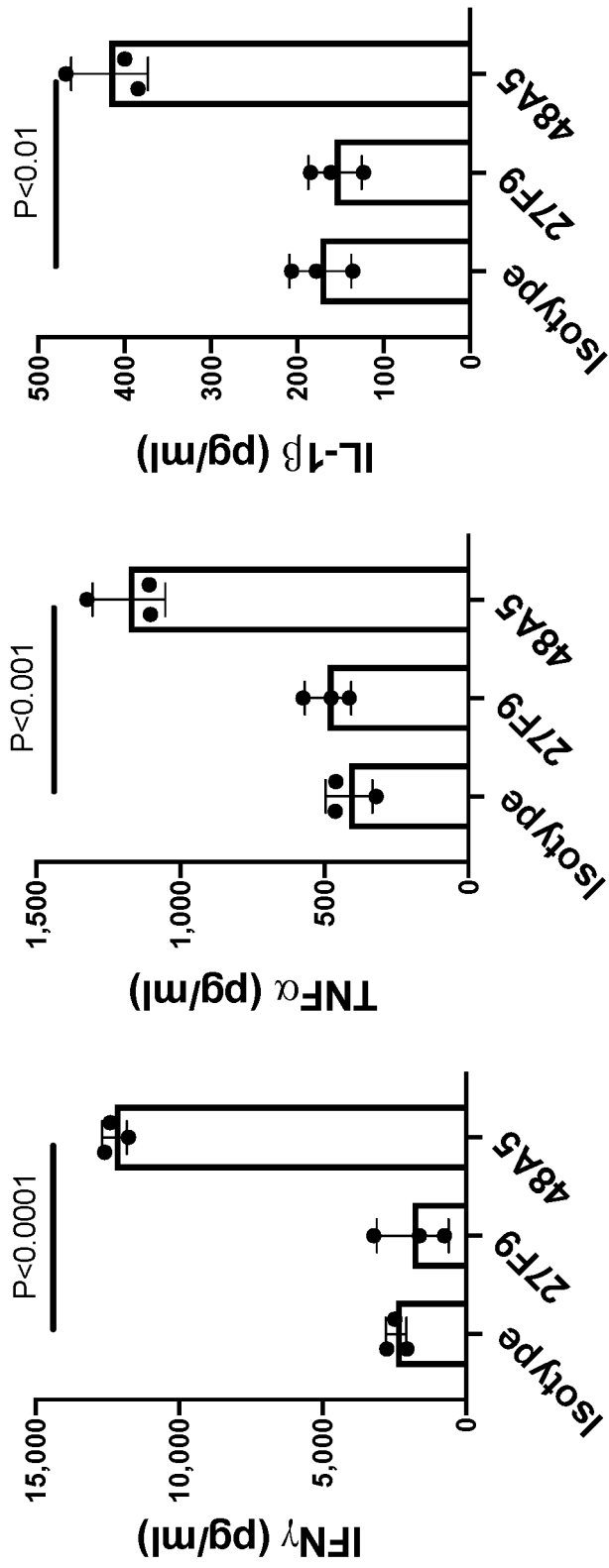


Figure 17

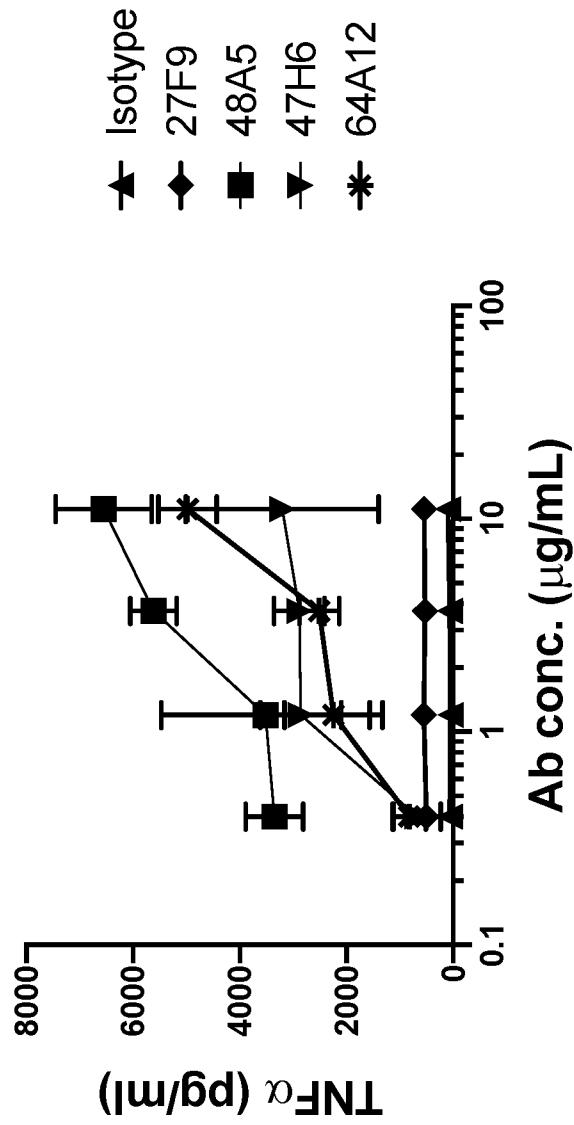


Figure 18

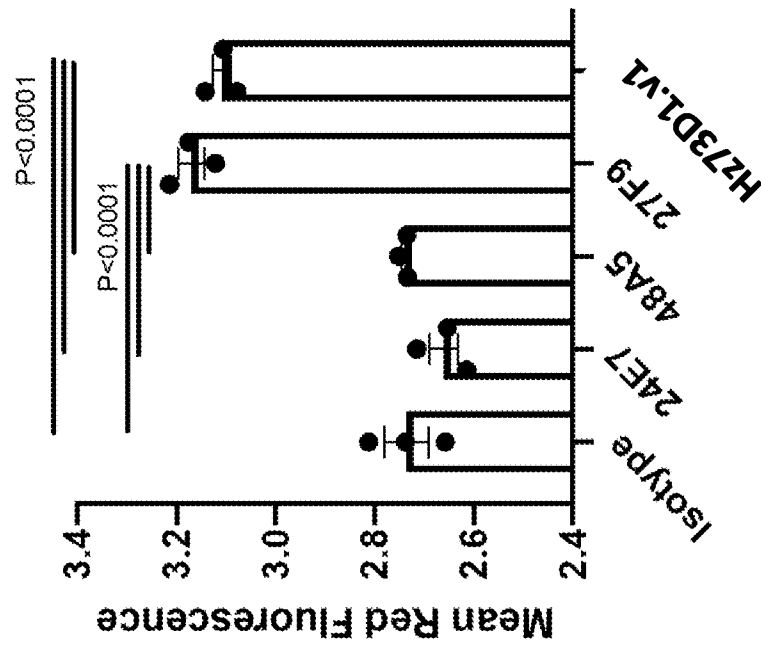
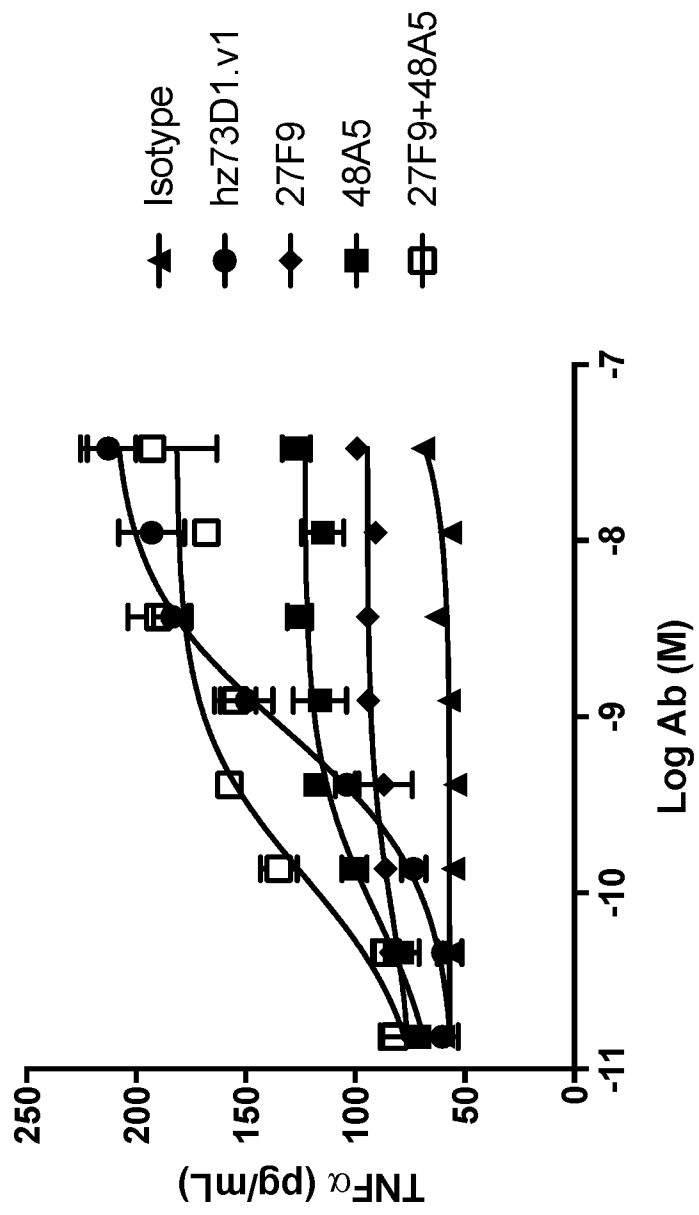


Figure 19



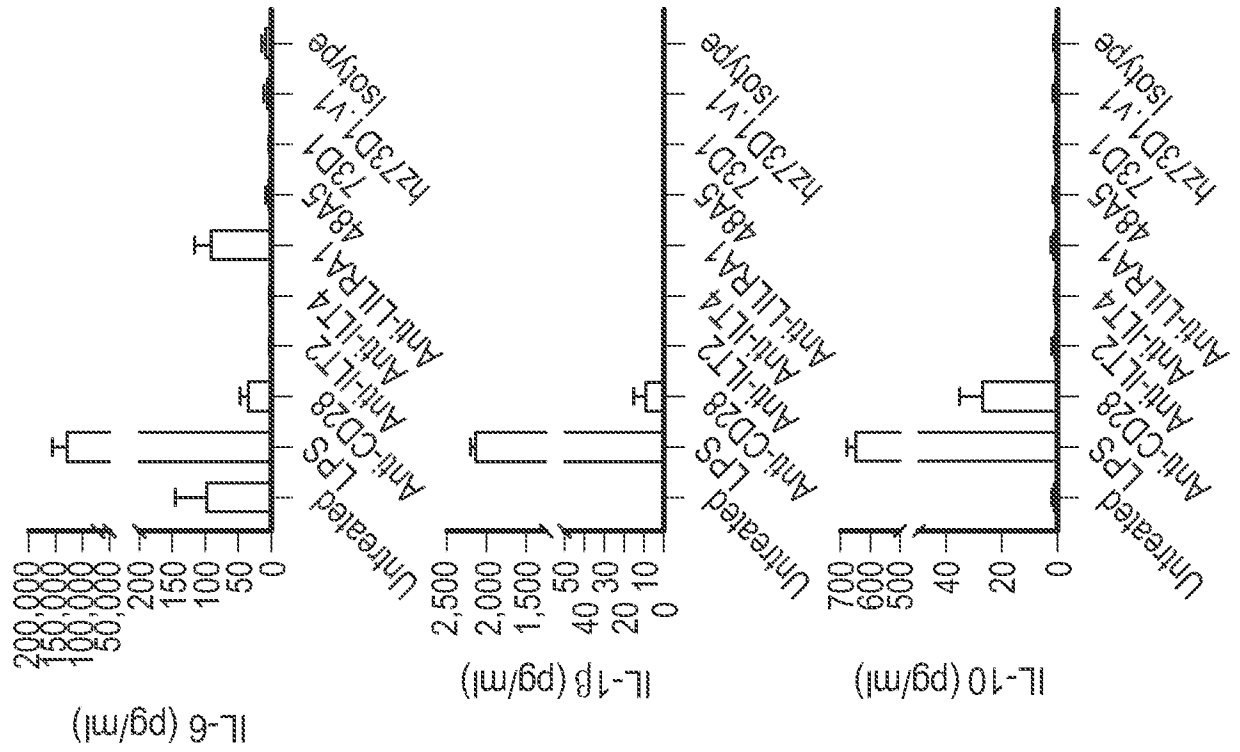
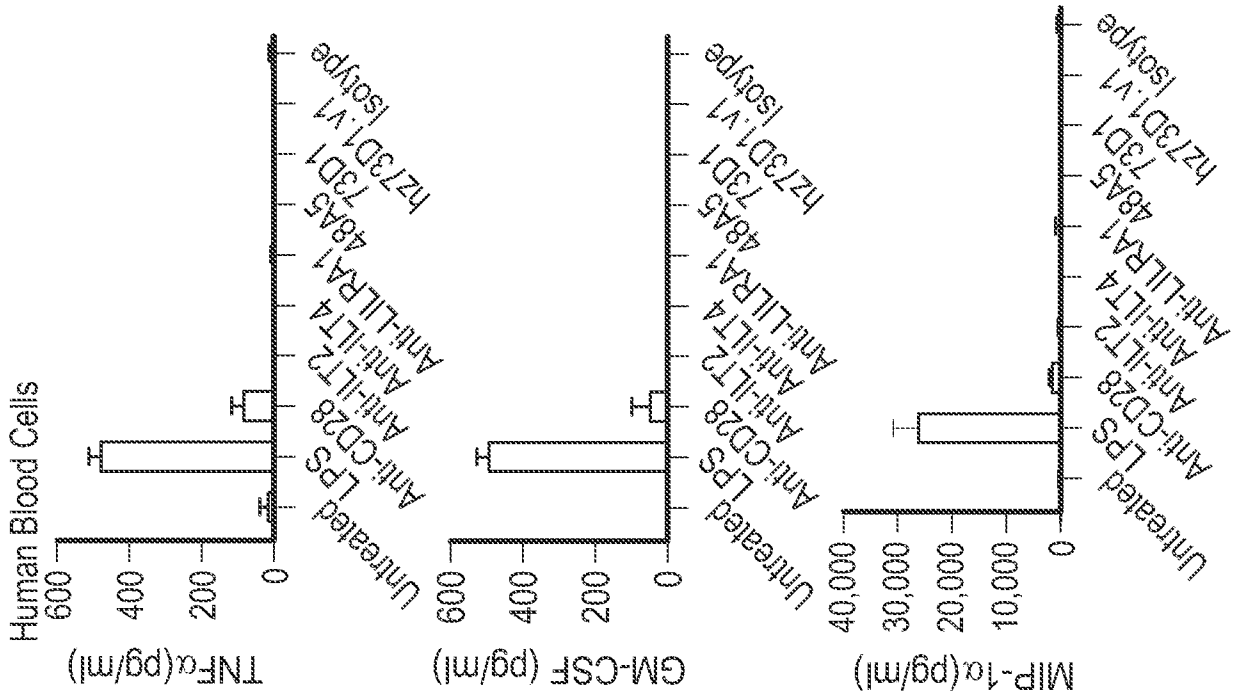


Figure 20



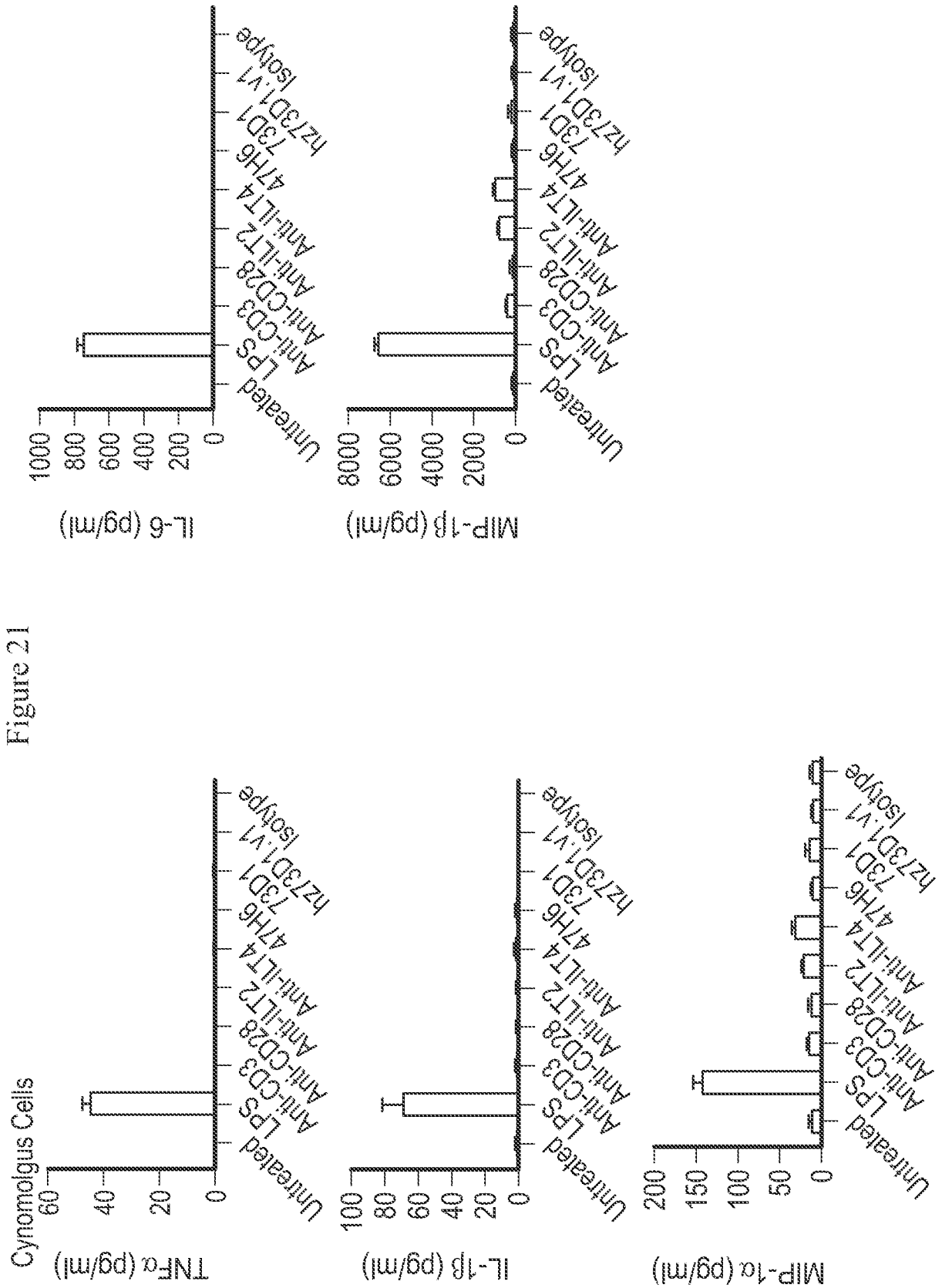


Figure 21

Figure 22

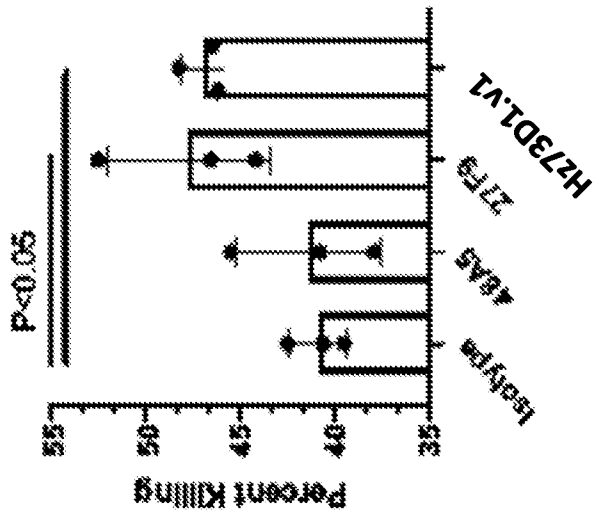


Figure 23A

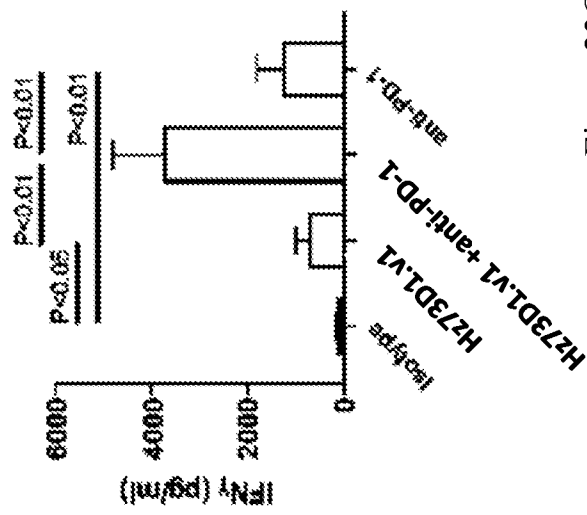


Figure 23B

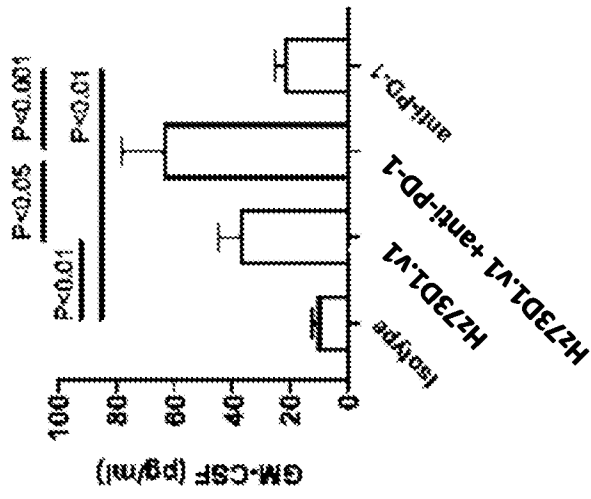


Figure 23C

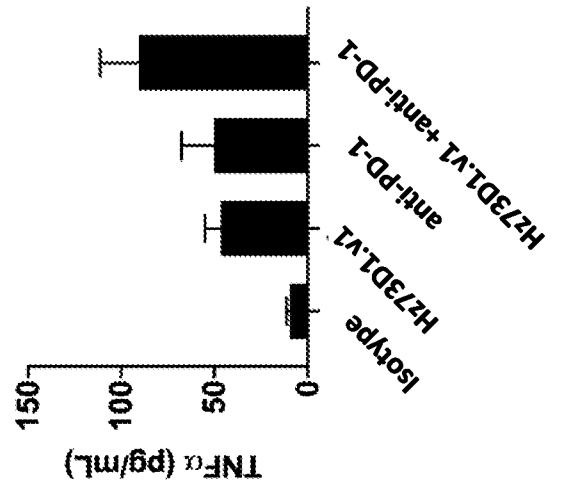
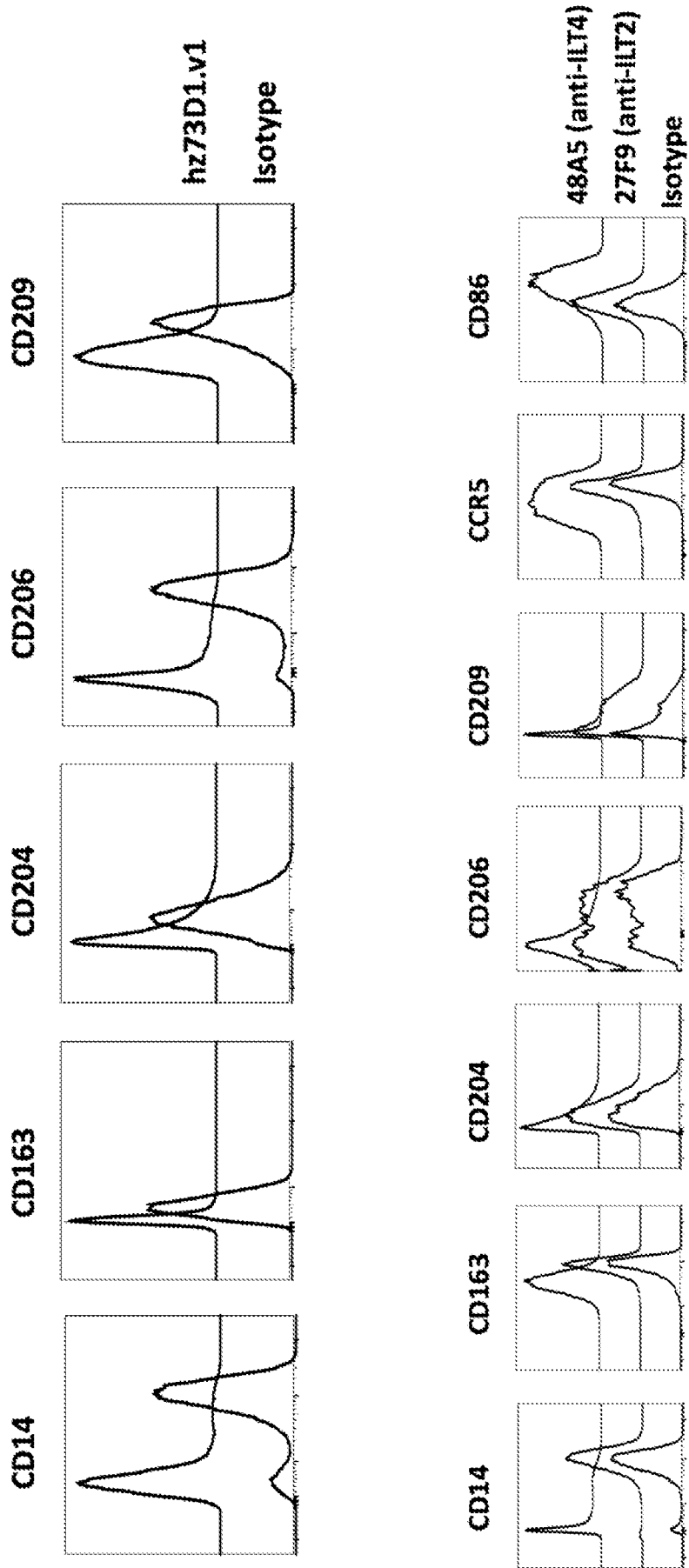


Figure 24



**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2021/029866

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C07K16/28 A61P35/00  
 ADD.  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 C07K A61P  
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 EPO-Internal, BIOSIS, Sequence Search, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/144052 A1 (ADANATE INC [US]) 25 July 2019 (2019-07-25) table 1	1-11, 34-77
X	US 2019/194327 A1 (COHEN HEATHER B [US] ET AL) 27 June 2019 (2019-06-27) paragraph [0431]; claim 4	1-11, 34-77

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search  
 19 July 2021

Date of mailing of the international search report  
 22/09/2021

Name and mailing address of the ISA/  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040,  
 Fax: (+31-70) 340-3016

Authorized officer  
 Scheffzyk, Irmgard

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/029866

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a.  forming part of the international application as filed:

in the form of an Annex C/ST.25 text file.

on paper or in the form of an image file.

b.  furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c.  furnished subsequent to the international filing date for the purposes of international search only:

in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2021/029866

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

5-7(completely); 1-4, 8-11, 22-77(partially)

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2021/029866

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019144052	A1	25-07-2019	CN 111867614 A 30-10-2020
			EP 3740224 A1 25-11-2020
			US 2021122819 A1 29-04-2021
			WO 2019144052 A1 25-07-2019
-----			
US 2019194327	A1	27-06-2019	AR 114002 A1 08-07-2020
			AU 2018389111 A1 18-06-2020
			BR 112020012650 A2 01-12-2020
			CA 3087166 A1 27-06-2019
			CL 2020001637 A1 19-02-2021
			CN 111699196 A 22-09-2020
			EA 202091540 A1 22-03-2021
			EP 3728318 A2 28-10-2020
			JP 2021506344 A 22-02-2021
			KR 20200103706 A 02-09-2020
			SG 11202004806S A 29-06-2020
			TW 201930357 A 01-08-2019
			US 2019194327 A1 27-06-2019
			US 2020207856 A1 02-07-2020
US 2020339690 A1 29-10-2020			
WO 2019126514 A2 27-06-2019			
-----			

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 5-7(completely); 1-4, 8-11, 22-77(partially)

Subject-matter relating to so-called clone 73D1, i.e. relating to SEQ.ID.NOs. 142,143, 144 and 145

---

2. claims: 1-4, 8-11, 22-77(all partially)

Subject-matter relating to so-called clone 64A12, i.e. relating to SEQ.ID.NOs. 139,140,137 and 138

---

3. claims: 1-4, 8-11, 22-77(all partially)

Subject-matter relating to so-called clone 47H6, i.e. relating to SEQ. ID.NOs. 131,132,133 and 134

---

4. claims: 1-4, 8-11, 22-34, 36-77(all partially)

Subject-matter relating to so-called clone 51A1, i.e. relating to SEQ.ID.NOs. 135 and 136

---

5. claims: 1-4, 8-11, 22-34, 36-77(all partially)

Subject-matter relating to so-called clone 73C4, i.e. relating to SEQ.ID.NOs. 141 and 142

---

6. claims: 12-15(completely); 22-33(partially)

Binding agent specifically binding ILT2 as defined in claim 12

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7. claims: 18, 19(completely); 16, 17, 22-33(partially)

Binding agent specifically binding human ILT4 as defined in claim 16 relating to SEQ.ID.NOs. 129 and 130

---

8. claims: 20, 21(completely); 16, 17, 22-33(partially)

Binding agent binding to human ILT4 relating to SEQ.ID.NOs. 127 and 128

---

9. claims: 78, 79

Composition comprising means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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10. claims: 80, 81

Composition comprising means for inhibiting the interaction between ILT2 and/or ILT4 and MHC Class I and a modulator of PD-1 or PD-L1.

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