surface of human plasmacytoid dendrite cells (pDCs) and is not on myeloid dendritic cells or other peripheral blood leukocytes. Cao et al., *J. Exp. Medicine 6*:1399-1405 (2006). ILT7 contains four immunoglobulin-like extracellular domains and a transmembrane domain. The extracellular portion is important for interacting with the ILT7 ligand, bone marrow stromal cell antigen 2 (BST2), and the transmembrane domain of ILT7 contains a positively charged residue that allows it to complex with FcεRIγ. It has been postulated that the BST2-ILT7 interaction negatively regulates the innate immune function of pDCs, potentially as a mechanism of negative feed back. In addition, *in vitro* antibody cross-linking of ILT7 has been shown to negatively regulate the production of IFN-alpha and TNF-alpha by pDCs. Therefore, antibodies and other ILT7 binding molecules that are useful for neutralizing ILT7 and regulating pDC activity and IFN release are needed, for example, for treating and preventing diseases such as autoimmune diseases.

Field of the Invention

[0005] The invention relates to ILT7 binding molecules, *e.g.*, anti-ILT7 antibodies and antigen-binding fragments, variants, or derivatives thereof, methods of using the antibodies and fragments, and methods for treating or preventing autoimmune diseases and conditions associated with ILT7-expressing cells.

BRIEF SUMMARY OF THE INVENTION

[0006] Provided herein are ILT7 binding molecules, e.g., anti-ILT7 antibodies and antigen-binding fragments thereof.

[0007] In one instance, an isolated ILT7 binding protein is an ILT7 binding protein that can bind to the same ILT7 epitope as an antibody comprising a heavy chain variable region (VH) of SEQ ID NO:202 and a light chain variable region (VL) of SEQ ID NO:207.

[0008] In one instance, an isolated ILT7 binding protein is an ILT7 binding protein that competitively inhibits the binding to ILT7 of an antibody comprising a VH of SEQ ID NO:202 and a VL of SEQ ID NO:207

[0009] In one aspect, the present disclosure provides for an anti-Immunoglobulin-like transcript-7 (ILT7) antibody comprising Complementarity-Determining Regions (CDRs) HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs:203, 204, 205, 208, 209, and 210, respectively. In one instance, an isolated ILT7 binding protein is an ILT7 binding protein comprising Complementarity-Determining Regions (CDRs) HCDR1, HDR2, HCDR3,

[0024] In one instance, the ILT7 binding protein suppresses interferon (IFN) alpha release from peripheral blood mononuclear cells (PBMCs). In one instance, the ILT7 binding protein has ADCC activity against plasmacytoid dendritic cells (pDCs) in PMBCs.

[0025] In one instance, the ILT7 binding protein comprises a murine, human, chimeric, humanized, or resurfaced antibody or antigen-binding fragment thereof.

[0026] In one instance, the ILT7 binding protein comprises an antibody, Fab, Fab', F(ab')2, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGΔCH2, minibody, F(ab')3, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb2, (scFv)2, or scFv-Fc.

[0027] In one instance, the ILT7 binding protein comprises a monoclonal antibody or an antigen binding fragment thereof.

[0028] In one instance, the ILT7 binding protein comprises a heavy chain immunoglobulin constant domain selected from the group consisting of: (a) an IgA constant domain; (b) an IgD constant domain; (c) an IgE constant domain; (d) an IgG1 constant domain; (e) an IgG2 constant domain; (f) an IgG3 constant domain; (g) an IgG4 constant domain; and (h) an IgM constant domain.

[0029] In one instance, the ILT7 binding protein comprises a light chain immunoglobulin constant domain selected from the group consisting of: (a) an Ig kappa constant domain; and (b) an Ig lambda constant domain.

[0030] In one aspect, the present disclosure provides for an afucosylated, human, monoclonal anti-ILT7 antibody comprising: (i) Complementarity-Determining Regions (CDRs) HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3; (ii) a human IgG1 constant domain; and (iii) a human lambda constant domain, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs:203, 204, 205, 208, 209, and 210, respectively. In one instance, the ILT7 binding protein comprises a human IgG1 constant domain and a human lambda constant domain.

[0031] In one instance, provided herein is a host cell producing the ILT7 binding molecule.

[0032] In one instance, provided herein is an isolated polynucleotide comprising a nucleic acid encoding a VH, wherein the VH comprises an amino acid sequence at least 85%, 90%, 95% identical, or identical to the VH of SEQ ID NO: 202, 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 212, 222, 232, or 242. In one instance, the polynucleotide comprises a sequence at least 85%, 90%, 95% identical, or identical to SEQ ID NO:201, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 211, 221, 231, or 241.

[0033] In one instance, provided herein is an isolated polynucletide comprising a nucleic acid encoding a VL, wherein the VL comprises an amino acid sequence at least 85%, 90%, 95% identical, or identical to the VL of 207, 17, 27, 47, 57, 67, 77, 87, 97, 107, 117, 127,

137, 147, 157, 167, 177, 187, 197, 217, 227, 237, or 247. In one instance, the polynucleotide comprises a sequence at least 85%, 90%, 95% identical, or identical to SEQ ID NO: 206, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 216, 226, 236, or 246.

[0034] In one instance, the nucleic acid is operably linked to a control sequence. In one instance, an antibody or antigen-binding fragment thereof comprising the VH or the VL encoded by the nucleic acid can specifically bind to ILT7.

[0035] In one aspect, the present disclosure provides for a polynucleotide comprising a nucleic acid encoding the anti-ILT7 antibody as disclosed herein. In one instance, a polynucleotide encodes an ILT7 binding molecule provided herein.

[0036] In one instance, provided herein is a vector comprising the polynucleotide.

[0037] In one instance, provided herein is a polypeptide encoded by the polynucleotide.

[0038] In one instance, provided herein is a host cell transformed with a polynucleotide provided herein (e.g., a polynucleotide comprising a nucleic acid encoding a VH and a polynucleotide comprising a nucleic acid encoding a VL).

[0039] In one aspect, the present disclosure provides for an isolated host cell comprising the polynucleotide as disclosed herein. In one instance, provided herein is a host cell comprising a polynucleotide provided herein (e.g., a polynucleotide comprising a nucleic acid encoding a VH and a polynucleotide comprising a nucleic acid encoding a VL), a vector provided herein, or a polypeptide provided herein. In one instance, the host cell is a mammalian host cell. In one instance, the host cell is a NS0 murine myeloma cell, a PER.C6® human cell, or a Chinese hamster ovary (CHO) cells. In one instance, the host cell lacks the enzyme α-1,6-fucosyltransferase.

[0040] In one aspect, the present disclosure provides for a method of producing an anti-ILT7 antibody, comprising culturing the isolated host cell as disclosed herein, and recovering said antibody. In one instsance, provided herein is a method of producing an anti-ILT7 binding molecule, comprising culturing a host cell provided herein and recovering said binding molecule. In one instance, provided herein is an anti- ILT7 binding molecule, produced by the method.

[0041] In one aspect, the present disclosure provides for a method for detecting ILT7 expression in a sample comprising (a) contacting the sample with an ILT7 binding molecule provided herein and (b) detecting binding of the binding molecule in the sample.

[0042] In one instance, provided herein is a method for detecting plasmacytoid dendritic cells comprising (a) contacting a sample containing cells with an ILT7 binding molecule provided herein and (b) detecting binding of the binding molecule in the sample.

[0043] In one instance, provided herein is a pharmaceutical composition comprising (a) an ILT7 binding molecule provided herein, a polynucleotide provided herein, a vector provided herein, a polypeptide provided herein, or a host cell provided herein and (b) a carrier.

[0044] In one aspect, the present disclosure provides for an *in vitro* method for decreasing interferon (IFN)-alpha release from a plasmacytoid dendritic cell (pDC), comprising contacting a sample containing pDC with the anti-ILT7 antibody as described herein. In one instance, provided herein is a method for decreasing IFN-alpha release from a plasmacytoid dendritic cell, comprising contacting a plasmacytoid dendritic cell with an ILT7 binding molecule provided herein, a polynucleotide provided herein, a vector provided herein, a polypeptide provided herein, a host cell provided herein, or a pharmaceutical composition provided herein.

[0045] In one instance, provided herein is a method for treating a human subject with an autoimmune disease comprising administering to the subject an effective amount of an ILT7 binding molecule provided herein, a polynucleotide provided herein, a vector provided herein, a polypeptide provided herein, a host cell provided herein, or a pharmaceutical composition provided herein.

[0046] In one instance, provided herein is a method for preventing an autoimmune disease in a human subject comprising administering to the subject an effective amount of an ILT7 binding molecule provided herein, a polynucleotide provided herein, a vector provided herein, a polypeptide provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one instance, the autoimmune disease is systemic lupus erythematosus. In one instance, the autoimmune disease is chronic rheumatism.

[0046a] In one aspect, the present disclosure provides for the anti-ILT7 antibody as described herein for use in therapy. In another aspect, the present disclosure provides for a use of the anti-ILT7 antibody as described herein in the manufacture of a medicament for the treatment of an autoimmune disease, wherein the autoimmune disease is selected from the group consisting of: myositis, diabetes, Hashimoto's disease, autoimmune adrenal insufficiency, pure red cell anemia, multiple sclerosis, rheumatoid carditis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, chronic inflammation, Sjogren's syndrome, polymyositis, dermatomyositis, inclusion body myositis, juvenile myositis, and scleroderma. In yet another aspect, the present disclosure provides for an afucosylated IgG1 human monoclonal anti-ILT7 antibody comprising a heavy chain variable region

(VH) and a light chain variable region (VL), wherein the heavy chain variable region comprises the amino acid of SEQ ID NO:202 and the light chain variable region comprises the amino acid of SEQ ID NO:207. In a further aspect, the present disclosure provides for a pharmaceutical composition comprising the afucosylated IgG1 human monoclonal anti-ILT7 antibody as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0047] **Figures 1A and 1B**: show the variable heavy chain (**1A**) and variable light chain (**1B**) sequence alignments of the SBI28 (#28), 10D10, and 7C7 antibodies. Shading indicates CDR sequences. Open boxes represent mutations introduced in 10D10 to generate 7C7.

[0048] **Figure 2**: shows the binding of ILT7 antibodies and negative control antibody (R437) to CT-550 cells expressing human ILT7 as determined by flow cytometry. SBI33 refers to the anti-ILT7 antibody ILT7#33 as provided in U.S. Published Application No. 2009/0280128.

[0049] **Figure 3**: shows the binding of ILT7 antibodies and negative control antibody (R437) to CT-125 cells expressing cynomolgus ILT7 as determined by flow cytometry.

WHAT IS CLAIMED IS:

1. An anti-Immunoglobulin-like transcript-7 (ILT7) antibody comprising Complementarity-Determining Regions (CDRs) HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs:203, 204, 205, 208, 209, and 210, respectively.

2. The anti-ILT7 antibody of claim 1, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL regions comprise an amino acid sequence at least 95% identical to SEQ ID NO:202 and SEQ ID NO:207, respectively.

3. The anti-ILT7 antibody of claim 2, wherein the VH and VL regions comprise the amino acid sequence of SEQ ID NO:202 and SEQ ID NO:207, respectively.

4. The anti-ILT7 antibody according to claim 1, wherein the antibody comprises a heavy chain immunoglobulin constant domain selected from the group consisting of an IgA constant domain, an IgD constant domain, an IgE constant domain, an IgG1 constant domain, an IgG2 constant domain, an IgG3 constant domain, an IgG4 constant domain, and an IgM constant domain.

5. The anti-ILT7 antibody of claim 4, wherein the antibody comprises an IgG1 constant domain.

6. The anti-ILT7 antibody according to claim 1, wherein the antibody comprises a light chain immunoglobulin constant domain selected from the group consisting of an Ig kappa constant domain and an Ig lambda constant domain.

7. The anti-ILT7 antibody of claim 6, wherein the antibody comprises a lambda constant domain.

8. The anti-ILT7 antibody according to claim 1, wherein the antibody is a monoclonal antibody.

9. The anti-ILT7 antibody according to claim 1, wherein the antibody is a human, chimeric, or resurfaced antibody.

10. The anti-ILT7 antibody of claim 9, wherein the antibody is a human antibody.

11. The anti-ILT7 antibody according to claim 1, wherein the antibody is afucosylated.

12. The anti-ILT7 antibody according to claim 1, wherein the antibody specifically binds to human and cynomolgus ILT7.

13. An afucosylated, human, monoclonal anti-ILT7 antibody comprising:

i. Complementarity-Determining Regions (CDRs) HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3;

ii. a human IgG1 constant domain; and

iii. a human lambda constant domain,

wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs:203, 204, 205, 208, 209, and 210, respectively.

14. A polynucleotide comprising a nucleic acid encoding the anti-ILT7 antibody of claim 1.

15. An isolated host cell comprising the polynucleotide of claim 14.

16. A method of producing an anti-ILT7 antibody, comprising culturing the isolated host cell of claim 15, and recovering said antibody.

17. A method for detecting ILT7 expression in a sample comprising (a) contacting said sample with the anti-ILT7 antibody of claim 1 and (b) detecting binding of said antibody in said sample.

18. An *in vitro* method for decreasing interferon (IFN)-alpha release from a plasmacytoid dendritic cell (pDC), comprising contacting a sample containing pDC with the anti-ILT7 antibody of claim 1.

19. The anti-ILT7 antibody of claim 1 for use in therapy.

20. Use of the anti-ILT7 antibody of claim 1 in the manufacture of a medicament for the treatment of an autoimmune disease, wherein the autoimmune disease is selected from the group consisting of: myositis, diabetes, Hashimoto's disease, autoimmune adrenal insufficiency, pure red cell anemia, multiple sclerosis, rheumatoid carditis, systemic lupus erythematosus, psoriasis,

rheumatoid arthritis, chronic inflammation, Sjogren's syndrome, polymyositis, dermatomyositis, inclusion body myositis, juvenile myositis, and scleroderma.

21. The use of claim 20, wherein the autoimmune disease is systemic lupus erythematosus.

22. An afucosylated IgG1 human monoclonal anti-ILT7 antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the heavy chain variable region comprises the amino acid of SEQ ID NO:202 and the light chain variable region comprises the amino acid of SEQ ID NO:207.

23. The anti-ILT7 antibody of claim 22, wherein the antibody comprises a human IgG1 constant domain; and a human lambda constant domain.

24. A pharmaceutical composition comprising the afucosylated IgG1 human monoclonal anti-ILT7 antibody of claim 22.