[0004] DR3 is a TNF receptor-related death-domain receptor expressed on the majority of activated T lymphocytes and NK cells (Migone *et al.*, 2002, *supra*; Screaton G.R. *et al.*, 1997, *Proc Natl Acad Sci (USA)* 94:4615-4619). TL1A engages DR3 on T cells, enhancing their responsiveness to IL-2 (Migone *et al.*, 2002, *supra*), potentiating T cell proliferation and release of IFNγ and GM-CSF under conditions of suboptimal costimulation (Migone *et al.*, 2002, *supra*; Meylan *et al.*, 2008, *supra*). TL1A has also been shown to synergize with suboptimal levels of IL-12/IL-18 to induce IFNγ production by $CD4^+$ T cells (Papadakis, K.A. *et al.*, 2004, *J Immunol* 172:7002-7007; Prehn, J.L. *et al.*, 2004, *Clin Immunol* 112:66-77; Papadakis, K.A. *et al.*, 2005, *J Immunol* 174:4985-4990; Cassatella, M.A. *et al.*, 2007, *J Immunol* 178:7325-7333).

[0005] TL1A has been implicated in various inflammatory diseases and/or auto immune diseases, including inflammatory bowel diseases [*e.g.*, ulcerative colitis (UC) and Crohn's disease (CD)], rheumatoid arthritis, multiple sclerosis (MS), atherosclerosis, and the like (*see* Bayry, J., 2010, *Nature Reviews/Rheumatology* 6:67-68; Takedatsu, H. *et al.*, 2008, *Gastroenterology* 135:552-567; Prehn *et al.*, 2004, *supra*; Bamias, G. *et al.*, 2008, *Clin Immunol* 129:249-255; Bull, M.J. *et al.*, 2008, *J Exp Med* 205:2457-2464; Pappu, B.P. *et al.*, 2008, *J Exp Med* 205:1049-1062; Bamias, G. *et al.*, 2003, *J Immunol* 171:4868-4874; Kang, Y. *et al.*, 2005, *Cytokine* 29:229-235). Although the majority of the published data are consistent with a pivotal role for TL1A in driving differentiation of T_H1 and T_H17 effector function, a recent study has proposed a role for the TL1A/DR3 interaction in development of T_H2 T cell responses in asthma models (Fang, L. *et al.*, 2008, *J Exp Med* 205:1037-1048). Thus, the use of TL1A inhibitors, such as fully human antibodies against TL1A with high affinities and neutralizing activity, alone or in combination with currently available anti-inflammatory agents, immunosuppresants (*e.g.*, TNF-α antagonists, cortisone or steroids, and the like), and/or anti-allergy agents, provides effective treatment for these diseases and disorders.

[0006] The nucleic acid and the amino acid sequences of human TL1A are shown in SEQ ID NOS: 243 and 244, respectively, and those of Fhm are shown in SEQ ID NOS:245 and 246, respectively. Antibodies to TL1A are disclosed in, for example, US 7,597,886, US 7,820,798 and US 2009/0280116.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0007] Provided herein are~~In a first aspect, the invention provides~~ fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that specifically bind and neutralize human TL1A (hTL1A) activity.

[0007a] In one aspect, there is provided an isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2 and HCDR3 sequence combination of SEQ ID NO: 20/22/24; and/or a light chain complementarity determining region 1 (LCDR1), LCDR2 and LCDR3 sequence combination of SEQ ID NO: 28/30/32.

[0007b] In one aspect, there is provided an antibody or antigen-binding fragment thereof which binds the same epitope on hTL1A as an antibody or antigen-binding fragment comprising heavy chain and light chain complementarity determining regions (CDRs) of SEQ ID NO:20/22/24/28/30/32.

[0007c] In one aspect, there is provided an isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a heavy chain variable region (HCVR) comprising an amino acid sequence of SEQ ID NO: 18 and/or a light chain variable region (LCVR) comprising an amino acid sequence of SEQ ID NO: 26.

[0008] The antibodies can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.*, to eliminate residual effector functions (Reddy *et al.*, 2000, *J. Immunol.* 164:1925-1933).

[0009] In one embodiment, the ~~invention~~disclosure features an antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:2, 18, 34, 50, 66, 82, 98, 114, 118, 134, 138, 154, 158, 174, 178, 194, 198, 214, 218 and 234, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In another embodiment, the antibody or an antigen-binding fragment thereof comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO:2, 18, 34, 50, 66, 134, 174 and 234. In yet another embodiment, the antibody or fragment thereof comprises a HCVR comprising SEQ ID NO:2, 18, 174 or 234.

[0010] In one embodiment, the antibody or fragment thereof further comprises a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO:10, 26, 42, 58, 74, 90, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226 and 236, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In another embodiment, the antibody or antigen-binding portion of an antibody comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO:10, 26, 42, 58, 74, 136, 176 and 236. In yet another embodiment, the antibody or fragment thereof comprises a LCVR comprising SEQ ID NO:10, 26, 176 or 236.

[0011] In further embodiments, the antibody or fragment thereof comprises a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/116, 118/126, 134/136, 138/146, 154/156, 158/166, 174/176, 178/186, 194/196, 198/206, 214/216, 218/226 and 234/236. In one embodiment, the antibody or fragment thereof comprises a HCVR and LCVR selected from the amino acid sequence pairs of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 134/136, 174/176 and 234/236. In another embodiment, the antibody or fragment thereof comprises a HCVR/LCVR pair comprising SEQ ID NO:2/10, 18/26, 174/176 or 234/236.

[0012] In ~~a second aspect~~one embodiment, the ~~invention~~disclosure features an antibody or antigen-binding fragment of an antibody comprising a heavy chain complementarity determining region 3 (HCDR3) amino acid sequence selected from the group consisting of SEQ ID NO:8, 24, 40, 56, 72, 88, 104, 124, 144, 164, 184, 204 and 224, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) amino acid sequence selected from the group consisting of SEQ ID NO:16, 32, 48, 64, 80, 96, 112, 132, 152, 172, 192, 212 and 232, or substantially similar sequences thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the antibody or fragment thereof comprises a HCDR3/LCDR3 amino acid sequence pair comprising SEQ ID NO:8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 124/132, 144/152, 164/172, 184/192, 204/212 or 224/232. In another embodiment, the antibody or fragment thereof comprises a HCDR3/LCDR3 amino acid sequence pair comprising SEQ ID NO: 8/16, 24/32,

40/48, 56/64, 72/80, 124/132, 164/172 or 224/232. In yet another embodiment, the antibody or fragment thereof comprises a HCDR3/LCDR3 amino acid sequence pair comprising SEQ ID NO:8/16, 24/32, 164/172 or 224/232.

[0013] In a further embodiment, the ~~invention~~disclosure features an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) amino acid sequence selected from the group consisting of SEQ ID NO:4, 20, 36, 52, 68, 84, 100, 120, 140, 160, 180, 200 and 220, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) amino acid sequence selected from the group consisting of SEQ ID NO:6, 22, 38, 54, 70, 86, 102, 122, 142, 162, 182, 202 and 222, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and/or a light chain CDR1 (LCDR1) amino acid sequence selected from the group consisting of SEQ ID NO:12, 28, 44, 60, 76, 92, 108, 128, 148, 168, 188, 208 and 228, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and/or a light chain CDR2 (LCDR2) amino acid sequence selected from the group consisting of SEQ ID NO:14, 30, 46, 62, 78, 94, 110, 130, 150, 170, 190, 210 and 230, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the antibody or fragment thereof comprises a combination of HCDR1/HCDR2/HCDR3 selected from the group consisting of SEQ ID NO:4/6/8, 20/22/24, 36/38/40, 52/54/56, 68/70/72, 84/86/88, 100/102/104, 120/122/124, 140/142/144, 160/162/164, 180/182/184, 200/202/204 and 220/222/224; and/or a combination of LCDR1/LCDR2/LCDR3 selected from the group consisting of SEQ ID NO:12/14/16, 28/30/32, 44/46/48, 60/62/64, 76/78/80, 92/94/96, 108/110/112, 128/130/132, 148/150/152, 168/170/172, 188/190/192, 208/210/212 and 228/230/232. In another embodiment, the heavy and light chain CDR amino acid sequences comprise a CDR sequence combination selected from the group consisting of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 84/86/88/92/94/96, 100/102/104/108/110/112, 120/122/124/128/130/132, 140/142/144/148/150/152, 160/162/164/168/170/172, 180/182/184/188/190/192, 200/202/204/208/210/212 and 220/222/224/228/230/232. In another embodiment, the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR sequences of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 120/122/124/128/130/132, 160/162/164/168/170/172 or 220/222/224/228/230/232. In yet another embodiment, the heavy and light chain CDR amino acid sequences comprise a CDR sequence combination of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 160/162/164/168/170/172 or 220/222/224/228/230/232.

[0014] In a related embodiment, the ~~invention~~disclosure comprises an antibody or antigen-binding fragment of an antibody which specifically binds hTL1A, wherein the antibody or fragment

thereof comprises heavy and light chain CDR domains contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/116, 118/126, 134/136, 138/146, 154/156, 158/166, 174/176, 178/186, 194/196, 198/206, 214/216, 218/226 and 234/236. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are known in the art and can be applied to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Conventional definitions that can be applied to identify the boundaries of CDRs include the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody. In one embodiment, the antibody or fragment thereof comprises CDR sequences contained within a HCVR and LCVR pair selected from the group consisting of the amino acid sequence pairs of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 134/136, 174/176 and 234/236. In another embodiment, the antibody or fragment thereof comprises CDR sequences contained within the HCVR and LCVR sequence pair of SEQ ID NO: 2/10, 18/26, 174/176 or 234/236.

[0015] In another related embodiment, the ~~invention~~disclosure provides an antibody or antigen-binding fragment thereof that competes for specific binding to hTL1A with an antibody or antigen-binding fragment comprising heavy and light chain CDR sequences of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 120/122/124/128/130/132, 160/162/164/168/170/172 or 220/222/224/228/230/232. In one embodiment, the antibody or antigen-binding fragment thereof competes for specific binding to hTL1A with an antibody or antigen-binding fragment comprising heavy and light chain CDR sequences of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 160/162/164/168/170/172 or 220/222/224/228/230/232. In another embodiment, the antibody or antigen-binding fragment of the ~~invention~~disclosure competes for specific binding to hTL1A with an antibody or antigen-binding fragment comprising a HCVR/LCVR sequence pair of SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 134/136, 174/176 or 234/236. In yet another embodiment, the antibody or antigen-binding fragment thereof competes for specific binding to hTL1A with an antibody or antigen-binding fragment comprising a HCVR/LCVR sequence pair of SEQ ID NO:2/10, 18/26, 174/176 or 234/236.

[0016] In another related embodiment, the ~~invention~~disclosure provides an antibody or antigen-binding fragment thereof that binds the same epitope on hTL1A that is recognized by an antibody or fragment thereof comprising heavy and light chain CDR sequences of SEQ ID

NO:4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 120/122/124/128/130/132, 160/162/164/168/170/172 or 220/222/224/228/230/232. In one embodiment, the antibody or antigen-binding fragment thereof binds the same epitope on hTL1A that is recognized by an antibody or antigen-binding fragment thereof comprising heavy and light chain CDR sequences of SEQ ID NO:4/6/8/12/14/16, 20/22/24/28/30/32, 160/162/164/168/170/172 or 220/222/224/228/230/232. In another embodiment, the antibody or antigen-binding fragment of the ~~invention~~disclosure recognizes the same epitope on hTL1A that is recognized by an antibody or antigen-binding fragment thereof comprising a HCVR/LCVR sequence pair of SEQ ID NO: SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 134/136, 174/176 or 234/236. In yet another embodiment, the antibody or antigen-binding fragment thereof recognizes the same epitope on hTL1A that is recognized by *an antibody or antigen-binding fragment thereof comprising a HCVR/LCVR sequence pair of* SEQ ID NO:2/10, 18/26, 174/176 or 234/236.

[0016b] In one aspect, there is provided an isolated nucleic acid molecule encoding the antibody or antigen-binding fragment as defined above.

[0017] In ~~a third aspect~~one embodiment, the ~~invention~~disclosure provides nucleic acid molecules encoding anti-TL1A antibodies or fragments thereof described above. Recombinant expression vectors carrying the nucleic acids of the ~~invention~~disclosure, and isolated host cells, *e.g.*, bacterial cells, such as *E. coli*, or mammalian cells, such as CHO cells, into which such vectors have been introduced, are also encompassed by the ~~invention~~disclosure, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0017a] In one aspect, there is provided an expression vector comprising the nucleic acid molecule as defined above.

[0017b] In one aspect, there is provided an isolated host cell comprising the expression vector as defined above.

[0017c] In one aspect, there is provided a method of producing an anti-hTL1A antibody or antigen-binding fragment thereof, comprising growing the host cell as defined above under conditions permitting production of the antibody or fragment thereof, and recovering the antibody or fragment thereof so produced.

[0018] In one embodiment, the ~~invention~~disclosure provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, 17, 33, 49, 65, 81, 97, 113, 117, 133, 137, 153, 157, 173, 177, 193, 197, 213, 217 and 233, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In another embodiment, the antibody or fragment thereof comprises a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, 17, 33, 49, 65, 133, 173 and 233. In yet another embodiment, the antibody or

fragment thereof comprises a HCVR encoded by the nucleic acid sequence of SEQ ID NO:1, 17, 173 or 233.

[0019] In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, 25, 41, 57, 73, 89, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225 and 235, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In another embodiment, the antibody or fragment thereof comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, 25, 41, 57, 73, 135, 175 and 235. In yet another embodiment, the antibody or fragment thereof comprises a LCVR encoded by the nucleic acid sequence of SEQ ID NO:9, 25, 175 or 235.

[0020] In further embodiments, the antibody or fragment thereof comprises a HCVR and LCVR (HCVR/LCVR) sequence pair encoded by a nucleic acid sequence pair selected from the group consisting of SEQ ID NO:1/9, 17/25, 33/41, 49/57, 65/73, 81/89, 97/105, 113/115, 117/125, 133/135, 137/145, 153/155, 157/165, 173/175, 177/185, 193/195, 197/205, 213/215, 217/225 and 233/235. In one embodiment, the antibody or fragment thereof comprises a HCVR/LCVR sequence pair encoded by a nucleic acid sequence pair selected from the group consisting of SEQ ID NO:1/9, 17/25, 33/41, 49/57, 65/73, 133/135, 173/175 and 233/235. In yet another embodiment, the antibody or fragment thereof comprises a HCVR/LCVR pair encoded by a nucleic acid sequence pair of SEQ ID NO:1/9, 17/25, 173/175 or 233/235.

[0021] In one embodiment, the ~~invention~~disclosure features an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 23, 39, 55, 71, 87, 103, 123, 143, 163, 183, 203 and 223, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:15, 31, 47, 63, 79, 95, 111, 131, 151, 171, 191, 211 and 231, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In another embodiment, the antibody or fragment thereof comprises a HCDR3 and LCDR3 sequence pair encoded by the nucleic acid sequence pair of SEQ ID NO:7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 123/131, 143/151, 163/171, 183/191, 203/211 or 223/231. In another embodiment, the antibody or fragment thereof comprises a HCDR3 and LCDR3 sequence pair encoded by the nucleic acid sequence pair of SEQ ID NO:7/15, 23/31, 39/47, 55/63, 71/79, 123/131, 163/171 or 223/231. In yet another embodiment, the HCDR3/LCDR3 sequence pair is encoded by the nucleic acid sequence pair of SEQ ID NO:7/15, 23/31, 163/171 or 223/231.

[0022] In a further embodiment, the antibody or fragment thereof further comprises, a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:3, 19, 35, 51, 67, 83, 99, 119, 139, 159, 179, 199 and 219, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:5, 21, 37, 53, 69, 85, 101, 121, 141, 161, 181, 201 and 221, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:11, 27, 43, 59, 75, 91, 107, 127, 147, 167, 187, 207 and 227, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:13, 29, 45, 61, 77, 93, 109, 129, 149, 169, 189, 209 and 229, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology

thereof. In one embodiment, the antibody or fragment thereof comprises a combination of HCDR1/HCDR2/HCDR3 encoded by SEQ ID NO:3/5/7, 19/21/23, 35/37/39, 51/53/55, 67/69/71, 83/85/87, 99/101/103, 119/121/123, 139/141/143, 159/161/163, 179/181/183, 199/201/203 or 219/221/223; and a combination of LCDR1/LCDR2/LCDR3 encoded by SEQ ID NO:11/13/15, 27/29/31, 43/45/47, 59/61/63, 75/77/79, 91/93/95, 107/109/111, 127/129/131, 147/149/151, 167/169/171, 187/189/191, 207/209/211 or 227/229/231. In one embodiment, the antibody or fragment thereof comprises heavy and light chain CDR sequences encoded by a nucleic acid sequence combination selected from the group consisting of SEQ ID NO:3/5/7/11/13/15, 19/21/23/27/29/31, 35/37/39/43/45/47, 51/53/55/59/61/63, 67/69/71/75/77/79, 83/85/87/91/93/95, 99/101/103/107/109/111, 119/121/123/127/129/131, 139/141/143/147/149/151, 159/161/163/167/169/171, 179/181/183/187/189/191, 199/201/203/207/209/211 and 219/221/223/227/229/231. In another embodiment, the antibody or antigen-binding portion thereof comprises heavy and light chain CDR sequences encoded by a nucleic acid sequence combination of SEQ ID NO:3/5/7/11/13/15, 19/21/23/27/29/31, 35/37/39/43/45/47, 51/53/55/59/61/63, 67/69/71/75/77/79, 119/121/123/127/129/131, 159/161/163/167/169/171 or 219/221/223/227/229/231. In yet another embodiment, the antibody or antigen-binding portion thereof comprises heavy and light chain CDR sequences encoded by a nucleic acid sequence combination of SEQ ID NO: 3/5/7/11/13/15, 19/21/23/27/29/31, 159/161/163/167/169/171 or 219/221/223/227/229/231.

[0023] In ~~a fourth aspect~~one embodiment, the ~~invention~~disclosure features an isolated antibody or antigen-binding fragment of an antibody that specifically binds hTL1A, comprising a HCDR3 and a LCDR3, wherein the HCDR3 comprises an amino acid sequence of the formula X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12} - X^{13} - X^{14} - X^{15} - X^{16} (SEQ ID NO:239), wherein X^1 is Thr or Ala, X^2 is Lys, Arg or absent, X^3 is Glu, Gly or absent, X^4 is Asp, Pro or absent, X^5 is Leu or absent, X^6 is Arg, Tyr, Glu or absent, X^7 is Gly, Asp, Ala or absent, X^8 is Asp, Ser or Tyr, X^9 is Tyr or Trp, X^{10} is Tyr or Asp, X^{11} is Tyr, Lys or Ile, X^{12} is Gly, Tyr, Asn, or Ser, X^{13} is Val, Gly or Ser, X^{14} is Phe or Met, X^{15} is Asp, and X^{16} is Tyr or Val; and the LCDR3 comprises an amino acid sequence of the formula X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 (SEQ ID NO:242), wherein X^1 is Gln, X^2 is Gln, X^3 is Tyr, Leu or Phe, X^4 is His, Tyr or Asn, X^5 is Arg or Ser, X^6 is Ser, Thr or Tyr, X^7 is Trp or Pro, X^8 is Phe, Leu or absent, and X^9 is Thr.

[0024] In a further embodiment, the antibody or fragment thereof further comprises a HCDR1 sequence comprising an amino acid sequence of the formula X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 (SEQ ID NO:237), wherein X^1 is Gly, X^2 is Phe, X^3 is Thr, X^4 is Phe, X^5 is Ser, X^6 is Thr, Ser or Asn, X^7 is Tyr, and X^8 is Gly, Trp, Val or Ala; a HCDR2 sequence comprising an amino acid sequence of the formula X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 (SEQ ID NO:238), wherein X^1 is Ile or Val, X^2 is Ser or Lys, X^3 is Gly or Glu, X^4 is Thr, Asp, Ser or Arg, X^5 is Gly, X^6 is Arg, Ser or Gly, X^7 is Thr, Glu or Ser, and X^8 is Thr or Lys; a LCDR1 sequence comprising an amino acid

sequence of the formula X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12} (SEQ ID NO:240), wherein X^1 is Gln, X^2 is Thr, Ser, Ala or Gly, X^3 is Ile, X^4 is Ser or Leu, X^5 is Tyr or *absent*, X^6 *is Ser or absent*, X^7 *is Ser or absent*, X^8 *is Asn or absent*, X^9 *is Asn or absent*, X^{10} *is* Lys or absent, X^{11} is Ser, Asn or Thr, and X^{12} is Trp or Tyr; and a LCDR2 sequence comprising an amino acid sequence of the formula X^1 - X^2 - X^3 (SEQ ID NO:241) wherein X^1 is Ala, Trp or Ser, X^2 is Ala or Thr, and X^3 is Ser.

[0025] In ~~a fifth aspect~~one embodiment, the ~~invention~~disclosure features a human anti-TL1A antibody or antigen-binding fragment thereof comprising a heavy chain variable region (HCVR) encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a light chain variable region (LCVR) encoded by nucleotide sequence segments derived from V_K and J_K germline sequences. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the HCVR and the LCVR encoded by nucleotide sequence segments derived from a germline gene combination selected from the group consisting of: (i) V_H3-23, D_H2-21, J_H4, V_K1-5 and J_K1; (ii) V_H3-7, D_H1-7, J_H6, V_K4-1 and J_K3; (iii) V_H3-23, D_H2-2, J_H6, V_K1-9 and J_K2; (iv) V_H3-23, D_H6-6, J_H4, V_K1-9 and J_K4; (v) V_H1-2, D_H2-15, J_H3, V_K1-12 and J_K4; (vi) V_H4-34, D_H3-9, J_H4, V_K3-20 *and* J_K4; *(vii)* V_H4-34, D_H1-1, J_H4, V_K3-20 *and* J_K4; *and (viii)* V_H4-34, D_H3-3, J_H4, V_K2-24 and J_K4.

[0026] In ~~a sixth aspect~~one embodiment, the ~~invention~~disclosure features an antibody or antigen-binding fragment thereof that specifically binds to hTL1A or Fhm with an equilibrium dissociation constant (K_D) of about 1 nM or less, as measured by surface plasmon resonance assay (for example, BIACORE™). In certain embodiments, the antibody of the ~~invention~~disclosure exhibits a K_D of about 800 pM or less; about 700 pM or less; about 600 pM or less; about 500 pM or less; about 400 pM or less; about 300 pM or less; about 200 pM or less; about 150 pM or less; about 100 pM or less; about 90 pM or less; about 80 pM or less; about 50 pM or less; or 30 pM or less.

[0027] In ~~a seventh aspect~~one embodiment, the present ~~invention~~disclosure provides an anti-hTL1A antibody or antigen-binding fragment thereof that binds hTL1A protein of SEQ ID NO:244, but does not cross-react with a variant thereof, such as Fhm of SEQ ID NO:246, as determined by, for example, ELISA, surface plasmon resonance assay, or Luminex® xMAP® Technology, as described herein. Fhm contains a single amino acid substitution at position 167, corresponding to Gln in hTL1A, with Arg (*see* U.S. Patent No. 6,521,422). In related embodiments, the ~~invention~~disclosure also provides an anti-hTL1A antibody or antigen-binding fragment thereof that binds a hTL1A protein and cross-reacts with an Fhm. In another related embodiment, the ~~invention~~disclosure provides an anti-hTL1A antibody or antigen binding fragment thereof that does not cross-react with mouse TL1A (mTL1A: SEQ ID NO:250, encoded by the nucleotide sequence of SEQ ID NO:249) but does cross-react with TL1A of cynomolgus monkey (*Macaca fascicularis*, or MfTL1A: SEQ ID NO:248, encoded by the nucleotide sequence of SEQ ID NO:247) or rhesus monkey (*Macaca mulatta*: the same amino acid sequence as MfTL1A). In further related embodiments, the

~~invention~~disclosure provides an anti-hTL1A antibody or antigen-binding fragment thereof that cross-reacts with both mTL1A and MfTL1A.

[0028] The ~~invention~~disclosure encompasses anti-hTL1A antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or *e.g.*, removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* (2002) JBC 277:26733). In other applications, removal of N-glycosylation site may reduce undesirable immune reactions against the therapeutic antibodies, or increase affinities of the antibodies. In yet other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0028a] In one aspect, there is provided a pharmaceutical composition comprising the antibody or antigen-binding fragment as defined above, wherein the antibody or antigen-binding fragment thereof further neutralizes hTL1A, and a pharmaceutically acceptable carrier.

[0029] In ~~an eighth aspect~~one embodiment, the ~~invention~~disclosure features a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds hTL1A and a pharmaceutically acceptable carrier. In one embodiment, the ~~invention~~disclosure features a composition which is a combination of an antibody or antigen-binding fragment thereof of the ~~invention~~disclosure, and a second therapeutic agent. The second therapeutic agent may be one or more of any agent such as immunosuppressants, anti-inflammatory agents, analgesic agents, anti-allergy agents, and the like, many of which may have overlapping therapeutic effects of one another. Suitable immunosuppressants to be used in combination with the anti-hTL1A antibodies of the ~~invention~~disclosure include, but are not limited to, glucocorticoids, cyclosporin, methotrexate, interferon β (IFN-β), tacrolimus, sirolimus, azathioprine, mercaptopurine, opioids, mycophenolate, TNF-binding proteins, such as infliximab, eternacept, adalimumab, and the like, cytotoxic antibiotics, such as dactinomycin, anthracyclines, mitomycin C, bleomycin, mithramycin, and the like, antibodies targeting immune cells, such as anti-CD20 antibodies, anti-CD3 antibodies, and the like. Suitable anti-inflammatory agents and/or analgesics for combination therapies with anti-hTL1A antibodies include, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, naproxen, Cox-2 inhibitors, and the like, TNF-α antagonists, IL-1 antagonists, IL-6 antagonists, acetaminophen, morphinomimetics, and the like. Suitable anti-allergy agents include antihistamines, glucocorticoids, epinephrine (adrenaline), theophylline, cromolyn sodium and anti-leukotrienes, as well as anti-cholinergics, decongestants, mast cell stabilizers, and the like.

[0030] In ~~a ninth aspect~~one embodiment, the ~~invention~~disclosure features methods for inhibiting hTL1A activity using the anti-hTL1A antibody or antigen-binding portion of the antibody of the ~~invention~~disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the ~~invention~~disclosure and, optionally, one or more additional therapeutic agents described above.

The disease or disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented, or its occurrence rate reduced compared to that without anti-hTL1A antibody treatment, by removal, inhibition or reduction of TL1A activity. Examples of diseases

or disorders treatable by the methods of the ~~invention~~disclosure include, but are not limited to, inflammatory diseases and/or autoimmune diseases, such as inflammatory bowel diseases (IBD) including UC and CD, RA, MS, type 1 and type 2 diabetes, psoriasis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, and the like; allergic reactions or conditions, including asthma, allergic lung inflammation, and the like; cancers atherosclerosis, infections, neurodegenerative diseases, graft rejection, graft vs. host diseases (GVHD), cardiovascular disorders/diseases, and the like.

[0031] Other embodiments will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0032] Before the present invention is described in detail, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, *since the scope of the present invention will be limited only by the appended claims.*

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Definitions

[0034] The term "human TNF-like ligand 1A" or "hTL1A", as used herein, refers to hTL1A having the nucleic acid sequence shown in SEQ ID NO:243 and the amino acid sequence of SEQ ID NO:244, or a biologically active fragment thereof, as well as hTL1A variants, including Fhm having the nucleic acid sequence shown in SEQ ID NO:245 and the amino acid sequence of SEQ ID NO:246, or a biologically active fragment thereof, unless specifically indicated otherwise.

[0035] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (HCVR) and a heavy chain constant region (C_H; comprised of domains C_H1, C_H2 and C_H3). *Each light chain is comprised of a light chain variable region* (LCVR) *and a light chain constant* region (C_L). The HCVR and LCVR can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more

CLAIMS

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds and neutralizes human TNF-like ligand 1A (hTL1A) activity.

2. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof binds to hTL1A having the amino acid sequence of SEQ ID NO:244 with an equilibrium dissociation constant (K_D) of about 700 pM or less, about 300 pM or less, about 80 pM or less, or 50 pM or less.

3. An isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a heavy chain variable region (HCVR) comprising an amino acid sequence selected from SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 118, 134, 138, 154, 158, 174, 178, 194, 198, 214, 218 and 234.

4. An isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a light chain variable region (LCVR) comprising an amino acid sequence selected from SEQ ID NO:10, 26, 42, 58, 74, 90, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226 and 236

5. The antibody or antigen-binding fragment of claim 3 or 4, comprising a HCVR/LCVR sequence pair selected from SEQ ID NO:2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/116, 118/126, 134/136, 138/146, 154/156, 158/166, 174/176, 178/186, 194/196, 198/206, 214/216, 218/226 and 234/236.

6. The antibody or antigen-binding fragment of any one of claims 3 to 5, comprising a HCVR/LCVR sequence pair of SEQ ID NO: 2/10, 18/26, 174/176 or 234/236.

7. An isolated human antibody or antigen-binding fragment thereof that specifically binds hTL1A, comprising heavy and light chain complementarity determining region (CDR) sequences contained in the HCVR/LCVR sequence pair of the antibody or antigen-binding fragment of claim 5 or 6.

8. An antibody or antigen-binding fragment thereof which competes for binding to hTL1A with the antibody or antigen-binding fragment of claim 6.

9. An antibody or antigen-binding fragment thereof which binds the same epitope on hTL1A that is recognized by the antibody or antigen-binding fragment of claim 6.

10. The antibody or antigen-binding fragment of any one of claims 3 to 9, wherein the antibody or antigen-binding fragment cross-reacts with cynomolgus monkey TL1A (MfTL1A).

11. The antibody or antigen-binding fragment of any one of claims 3 to 10, wherein the antibody or fragment cross-reacts with Fhm having the amino acid sequence of SEQ ID NO:246.

~~12. The antibody or antigen-binding fragment of any one of claims 3 to 10, wherein the antibody~~ or fragment does not cross-reacts with Fhm having the amino acid sequence of SEQ ID NO:246.

13. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of any one of claims 1 to 12.

14. An expression vector comprising the nucleic acid molecule of claim 13.

15. A method of producing an anti-hTL1A antibody or antigen-binding fragment thereof, comprising growing a host cell comprising the expression vector of claim 14 under conditions permitting production of the antibody or fragment thereof, and recovering the antibody or fragment thereof so produced.

16. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, further comprising one or more additional therapeutic agents selected from an immunosuppressant, an anti-inflammatory agent, an analgesic, and an anti-allergy agent.

18. Use of the antibody or antigen-binding fragment thereof according to any one of claims 1 to 12 in the manufacture of a medicament for treating a disease or disorder which is prevented, ameliorated, improved or inhibited by removal, inhibition or reduction of TL1A activity.

19. Use of the pharmaceutical composition of claim 16 in the manufacture of a medicament for treating a disease or disorder which is prevented, ameliorated, improved or inhibited by removal, inhibition or reduction of TL1A activity.

20. The use according to claim 18 or claim 19, wherein said disease or disorder is selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma and allergic lung inflammation.

What is claimed:

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2 and HCDR3 sequence combination of SEQ ID NO: 20/22/24; and/or a light chain complementarity determining region 1 (LCDR1), LCDR2 and LCDR3 sequence combination of SEQ ID NO: 28/30/32.

2. The antibody or antigen-binding fragment according to claim 1, wherein heavy and light chain CDR sequences, HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3, comprise a CDR sequence combination of SEQ ID NO: 20/22/24/28/30/32.

3. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 18.

4. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 26.

5. The antibody or antigen-binding fragment of claim 2, wherein the antibody or fragment does not cross-react with Fhm comprising the amino acid sequence of SEQ ID NO:246.

6. An antibody or antigen-binding fragment thereof which binds the same epitope on hTL1A as an antibody or antigen-binding fragment comprising heavy chain and light chain complementarity determining regions (CDRs) of SEQ ID NO:20/22/24/28/30/32.

7. An isolated human antibody or antigen-binding fragment thereof that specifically binds human TNF-like ligand 1A (hTL1A), comprising a heavy chain variable region (HCVR) comprising an amino acid sequence of SEQ ID NO: 18 and/or a light chain variable region (LCVR) comprising an amino acid sequence of SEQ ID NO: 26.

8. The antibody or antigen-binding fragment of claim 7, comprising a HCVR/LCVR sequence pair of SEQ ID NO: 18/26.

9. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of claim 1.

10. An expression vector comprising the nucleic acid molecule of claim 9.

11. An isolated host cell comprising the expression vector of claim 10.

12. A method of producing an anti-hTL1A antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 11 under conditions permitting production of the antibody or fragment thereof, and recovering the antibody or fragment thereof so produced.

13. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof further neutralizes hTL1A, and a pharmaceutically acceptable carrier.