Figure 19 shows kinetic and affinity constants for ST2L Domain 1 binding antibody for ST2L variants as indicated in the figure.

Figure 20 shows inhibition of A) GM-CSF; B) IL-5; C) IL-8; D) IL-13 secretion from primary human lung mast cells by an anti-ST2L antibody STLM208.

Summary of the invention

The invention provides an isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I (SEQ ID NO: 9) of human ST2L.

The invention also provides human-adapted antibody antagonists specifically binding human ST2L having certain light chain and heavy chain variable region sequences, or certain heavy chain and light chain complementarity determining sequences.

The invention also provides human or human-adapted antibody antagonists specifically biding human ST2L at defined epitope regions and/or having certain characteristics as described herein.

The invention also provides an isolated polynucleotide encoding the heavy chain variable regions (VH) or the light chain variable regions (VL) of the invention.

The invention also provides a vector comprising an isolated polynucleotide of the invention.

The invention also provides a host cell comprising a vector of the invention.

The invention also provides a method of producing an antibody of the invention, comprising culturing a

host cell of the invention and recovering the antibody from the cell.

The invention also provides a pharmaceutical composition comprising an isolated antibody of the invention and a pharmaceutically accepted carrier.

The invention also provides a method of treating or preventing a ST2L-mediated condition comprising administering a therapeutically effective amount of an isolated antibody of the invention to a patient in need thereof for a time sufficient to treat or prevent the ST2L-mediated condition.

The invention also provides a method of inhibiting mast cell response in a patient comprising administering a therapeutically effective amount of an isolated antibody of the invention to a patient in need thereof for a time sufficient to inhibit the mast cell response.

The invention also provides a method of inhibiting interaction of IL-33 and ST2L in a subject, comprising administering to the subject an antibody that specifically binds domain I of ST2L in an amount sufficient to inhibit the interaction of IL-33 and ST2L.

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. Unless defined

can be selected from libraries of variants or fragments by panning with human and/or cyno ST2L and optionally by further antibody affinity maturation. Antibodies can be identified based on their inhibition of ST2L biological activity using any suitable method. Such methods may utilize reporter-gene assays or assays measuring cytokine production using well known methods and as described in the application.

One embodiment of the invention is an isolated antibody antagonist specifically binding human ST2L comprising:

a heavy chain complementarity determining region (HCDR) 1 (HCDR1) of SEQ ID NO: 160 ($X_1X_2X_3MX_4$); wherein

X_1 is S, F, D, I, G or V;

X_2 is Y or D;

X_3 is K, D or S; and

X_4 is S, F or I;

a HCDR 2 (HCDR2) of SEQ ID NO: 161 ($X_5IX_6GX_7GGX_8TX_9YADSVKG$); wherein

X_5 is A, S, T, Y or D;

X_6 is S, R, E, K, G or A;

X_7 is S, E or N;

X_8 is S, R, E, G, T, D or A; and

X_9 is Y, D, N, A or S; and

a HCDR 3 (HCDR3) of SEQ ID NO: 162 ($X_{10}X_{11}$WSTEGSFFVLDY); wherein

X_{10} is D, A, R, N, Q, P, E, I, H, S, T or Y; and

X_{11} is P, A, H, Y, E, Q, L, S, N, T, V, or I.

Another embodiment of the invention is an isolated antibody antagonist specifically binding human ST2L comprising:

a light chain complementarity determining region (LCDR) 1 (LCDR1) of SEQ ID NO: 163 (RASQSVDDX$_{12}$LA); wherein

X_{12} is A or D;

a LCDR 2 (LCDR2) of SEQ ID NO: 90 (DASNRAT); and

a LCDR 3 (LCDR3) of SEQ ID NO: 164 (QQX$_{13}$X$_{14}$X$_{15}$X$_{16}$X$_{17}$X$_{18}$T); wherein

X_{13} is F or Y;

X_{14} is Y, I or N;

X_{15} is N, G, D or T;

X_{16} is W or A;

X_{17} is P or deleted; and

X_{18} is L or I.

The antibodies of the invention comprising the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 160, 161, 162, 163, 90 and 164, respectively, can be made by well known mutagenesis methods using for example HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 78, 81, 84, 87, 90 and 92, respectively as a template. The heavy chain CDRs and the light chain CDRs of SEQ ID NOs: 160, 161, 162, 163, 90 and 164, respectively, can be grafted to human frameworks, such as frameworks described *infra*. The antibodies can be assayed for binding to ST2L and for their ability to block IL-33/ST2L interaction and for other characteristics such as

SEQ ID NOs: 24, 28, 32, 36, 40 and 44, respectively; (HFA CDRs);
SEQ ID NOs: 24, 28, 146, 36, 40 and 147, respectively; or
SEQ ID NOs: 24, 28, 146, 36, 40 and 44, respectively.

Another embodiment of the invention is an isolated human or human-adapted antibody antagonist or fragment thereof specifically binding human ST2L as described herein, (SEQ ID NO: 1) comprising a heavy chain variable region (VH) comprising a VH framework derived from human IGHV3-23 (SEQ ID NO: 158), IGHV1-24*01 (SEQ ID NO: 148) or IGHV1-f*01 (SEQ ID NO: 149) framework sequences, and a light chain variable region (VL) comprising a VL framework derived from a human IGKV3-11 (L6) (SEQ ID NO: 159), IGKV3-15*01 (L2) (SEQ ID NO: 150), IGKV1-9*01 (L8) (SEQ ID NO: 151), IGKV1-5*01 (L12) (SEQ ID NO: 152), IGKV1-12*01 (L5) (SEQ ID NO: 153), IGKV1-39*01 (O12) (SEQ ID NO: 154), IGKV1-27*01 (A20) (SEQ ID NO: 155)or IGKV1-33*01 (O18) (SEQ ID NO: 156) framework sequences.

In another embodiment, the isolated antibody specifically binding Domain I of human ST2L as described herein comprises a VH comprising a VH framework derived from human VH 3-23 framework sequences (SEQ ID NO: 158); and a light chain variable region (VL) comprising a VL framework derived from a human Vκ L6 framework sequences (SEQ ID NO: 159). Human framework sequences are well known, and typically include human immunoglobulin germline variable region sequences joined to the joining (J) sequences. The

An exemplary human myeloma cell line is U266 (ATTC CRL-TIB-196). Other useful cell lines include those derived from Chinese Hamster Ovary (CHO) cells such as CHO-K1SV (Lonza Biologics, Walkersville, MD), CHO-K1 (ATCC CRL-61) or DG44.

Another embodiment of the invention is a method of producing an antibody that specifically binds Domain I of ST2L, comprising culturing a host cell of the invention and recovering the antibody produced by the host cell. Methods of making antibodies and purifying them are well known in the art.

Another embodiment of the invention of a method of inhibiting interaction of ST2L with IL-33 in a subject comprising administering the subject an antibody specifically binding domain I of ST2L in an amount sufficient to inhibit interaction of ST2L and IL-33.

Methods of Treatment

ST2L antagonists of the invention as described herein, for example ST2L antibody antagonists blocking IL-33/ST2L interaction and binding Domain I of ST2L, antibodies that compete for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region of SEQ ID NO: 47 and a light chain variable region of SEQ ID NO: 51, or antibodies binding human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) may be utilized to modulate the immune system. Antibodies of the invention as described herein may be more efficient in antagonizing ST2L biological activity when compared to antibodies binding other domains and/or regions on ST2L as the antibodies of the invention are able to more efficiently reduce IL-33-induced mast cell responses. Any antibodies of the invention can be used in the methods of the invention.

Exemplary antibodies that can be used in the methods of the invention are antibodies STLM62, STLM15, STLM103, STLM107, STLM108, STLM123, STLM124, STLM206, STLM207, STLM208, STLM209, STLM210, STLM211, STLM212, STLM213. Without wishing to be bound by any theory, it is suggested that antibody antagonists that bind Domain I and block IL-33/ST2L interaction may inhibit formation of the IL-1RAcP/IL-33/ST2L/cKit complex or downstream signaling on mast cells, whereas Domain III binding antibodies, while being able to inhibit recruitment of IL-1RAcP to the ST2L/IL-33 complex, may be unable to disrupt the formation of the larger IL-1RAcP/IL-33/ST2L/cKit complex specifically found on mast cells. Microarray analysis conducted supports the suggestion as it was demonstrated that anti-ST2L Domain I binding antibodies suppressed the majority of mast cell signaling pathways induced by IL-33, and that anti-ST2L Domain III binding antibodies were only able to inhibit a small subset of these signaling pathways. It is feasible that because IL-33 binds to ST2L prior to the association of the accessory protein IL-1RAcP, blockade of IL-33 binding to ST2L by Domain I-binding antibodies could prevent association of any other accessory protein, including cKit or as-yet unidentified co-receptors. Domain III-binding antibodies, which do not interfere with IL-33 binding to ST2L, could theoretically block IL-1RAcP association but not the association of other co-receptors, including as-yet unidentified co-receptors. Multiple models have been proposed for how IL-1RAcP interacts with the IL-1/IL-1R or ST2L/IL-33 complexes (Lingel *et al.*, Structure 17: 1398-1410, 2009; and reviewed by Thomas *et al.*, Nat Struct & Molec Biol 19: 455-457, 2012). These models indicate that IL-1RAcP could bind to one side of the complex, but which side has not been conclusively shown. Therefore it is feasible that the 'other side'or 'free side' of the complex is available for association with an alternate

co-receptor, that would not be blocked by a Domain III antibody, and off-target effects such as increased recruitment of another co-receptor, resulting in increased signaling, is possible.

In the methods of the invention, any antibody antagonist specifically binding Domain I of human ST2L, antibody antagonist blocking IL-33/ST2L interaction and binding Domain I of human ST2L, antibodies that competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region of SEQ ID NO: 47 and a light chain variable region of SEQ ID NO: 51, or antibodies binding human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) may be used. Additional characteristics of such antibodies include ability of the antibody to block IL-33/ST2L interaction and to inhibit human mast cell responses.

Therefore, antibodies of the invention are suitable for treating a spectrum of ST2L-mediated conditions, ST2L-mediated inflammatory conditions and conditions where inhibition of mast cell responses is desired.

The methods of the invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats and farm animals. For example, the antibodies of the invention are useful in the prophylaxis and treatment of ST2L-mediated conditions, such as inflammatory diseases including asthma, airway hyper-reactivity, sarcoidosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, inflammatory bowel disease (IBD), rheumatoid arthritis, eosinophilic esophagitis, scleroderma, atopic dermatitis, allergic rhinitis, bullous pemphigoid, chronic urticaria, diabetic nephropathy, interstitial cystitis or Graft Versus Host Disease (GVHD). The antibodies of the invention are useful

sclerosing cholangitis. The kidney fibrosis can be associated with diabetic nephropathy or lupus glomeruloschelerosis. The heart fibrosis can be associated with myocardial infarction. The vascular fibrosis can be associated with postangioplasty arterial restenosis or atherosclerosis. The skin fibrosis can be associated with burn scarring, hypertrophic scarring, keloid, or nephrogenic fibrosing dermatopathy. The eye fibrosis can be associated with retro-orbital fibrosis, postcataract surgery or proliferative vitreoretinopathy. The bone marrow fibrosis can be associated with idiopathic myelofibrosis or drug induced myelofibrosis. The systemic fibrosis can be systemic sclerosis or graft versus host disease.

Other inflammatory conditions and neuropathies, which may be prevented or treated by the methods of the invention are those caused by autoimmune diseases. These conditions and neuropathies include multiple sclerosis, systemic lupus erythematous, and neurodegenerative and central nervous system (CNS) disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, bipolar disorder and Amyotrophic Lateral Sclerosis (ALS), liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease/steatohepatitis, fibrosis, hepatitis C virus (HCV) and hepatitis B virus (HBV), diabetes and insulin resistance, cardiovascular disorders including atherosclerosis, cerebral hemorrhage, stroke and myocardial infarction, arthritis, rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis (JRA), osteoporosis, osteoarthritis, pancreatitis, fibrosis, encephalitis, psoriasis, Giant cell arteritis, ankylosing spondolytis, autoimmune hepatitis, human immunodeficiency virus (HIV), inflammatory skin conditions, transplant, cancer, allergies, endocrine diseases, wound repair, other autoimmune disorders, airway

hyperresponsiveness and cell, virus, or prion-mediated infections or disorders.

One embodiment of the invention is method of treating or preventing a ST2L-mediated condition comprising administering a therapeutically effective amount of an isolated human or human-adapted antibody antagonist that specifically binds Domain I (SEQ ID NO: 9) of human ST2L, blocks IL-33/ST2L interaction, competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51 and/or binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) to a patient in need thereof for a time sufficient to treat or prevent the ST2L-mediated condition.

Another embodiment of the invention is a method of inhibiting mast cell response in a patient comprising administering a therapeutically effective amount of an isolated human or human-adapted antibody antagonist that specifically binds Domain I (SEQ ID NO: 9) of human ST2L, blocks IL-33/ST2L interaction, competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51 and/or binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) to a patient in need thereof for a time sufficient to inhibit the mast cell response.

Another embodiment of the invention is a method of inhibiting interaction of IL-33 and ST2L in a

CLAIMS

1) An isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I (SEQ ID NO: 9) of human ST2L, comprising:

a) a heavy chain complementarity determining region (HCDR) 1 (HCDR1)of SEQ ID NO: 160 ($X_1X_2X_3MX_4$); wherein

X_1 is S, F, D, I, G or V;

X_2 is Y or D;

X_3 is A, D or S; and

X_4 is S, F or I;

b) a HCDR 2 (HCDR2) of SEQ ID NO: 161 ($X_5IX_6GX_7GGX_8TX_9YADSVKG$); wherein

X_5 is A, S, T, Y or D;

X_6 is S, R, E, K, G or A;

X_7 is S, E or N;

X_8 is S, R, E, G, T, D or A; and

X_9 is Y, D, N, A or S;

c) a HCDR 3 (HCDR3) of SEQ ID NO: 162 ($X_{10}X_{11}$WSTEGSFFVLDY); wherein

X_{10} is D, A, R, N, Q, P, E, I, H, S, T or Y; and

X_{11} is P, A, H, Y, E, Q, L, S, N, T, V, or I;

d) a light chain complementarity determining region (LCDR) 1 (LCDR1) of SEQ ID NO: 163 (RASQSVDDX_{12}LA); wherein

X_{12} is A or D;

e) a LCDR 2 (LCDR2) of SEQ ID NO: 90 (DASNRAT); and

f) a LCDR 3 (LCDR3) of SEQ ID NO: 164 (QQ$X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}$T); wherein

X_{13} is F or Y;

X_{14} is Y, I or N;

X_{15} is N, G, D or T;

X_{16} is W or A;

X_{17} is P or deleted; and

X_{18} is L or I.

2) The isolated antibody of claim 1, wherein the antibody blocks IL-33/ST2L interaction.

3) The isolated antibody of claim 2 having a dissociation constant (K_D) to human ST2L between about $5x10^{-12}$ M to about $7x10^{-10}$ M, an on rate constant (K_{on}) to human ST2L between about $2x10^6$ $M^{-1}s^{-1}$ to about $1x10^8$ $M^{-1}s^{-1}$, or an off rate constant (K_{off}) to human ST2L between about $1x10^{-6}$ s^{-1} to about $1x10^{-2}$ s^{-1}.

4) The isolated antibody of claim 3 having a dissociation constant (K_D) to *Macaca fascicularis* (cyno) ST2L (SEQ ID NO: 2) between about $3x10^{-12}$ M to about $2x10^{-9}$ M, an on rate constant (K_{on}) to cyno ST2L between about $4x10^6$ $M^{-1}s^{-1}$ to about $1x10^8$ $M^{-1}s^{-1}$, or an off rate constant (K_{off}) to cyno ST2L between about $7x10^{-5}s^{-1}$ to about $1x10^{-1}s^{-1}$.

5) The isolated antibody of claim 4, comprising:

a) the HCDR1 of SEQ ID NO: 87;

b) the HCDR2 of SEQ ID NO: 114;

c) the HCDR3 of SEQ ID NO: 84;

d) the LCDR1 of SEQ ID NO: 130;

e) the LCDR2 of SEQ ID NO: 90; and

f) the LCDR3 of SEQ ID NO: 134; or

g) the VH of SEQ ID NO: 191 and the VL of SEQ ID NO: 209.

6) The isolated antibody of claim 4 comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of:

a) SEQ ID NOs: 78, 81, 84, 87, 90 and 92, respectively;

b) SEQ ID NOs: 78, 81, 84, 130, 90 and 131, respectively;

c) SEQ ID NOs: 78, 81, 84, 130, 90 and 132, respectively;

d) SEQ ID NOs: 78, 81, 84, 130, 90 and 133, respectively;

e) SEQ ID NOs: 78, 81, 84, 130, 90 and 134, respectively;

f) SEQ ID NOs: 95, 109, 84, 130, 90 and 131, respectively;

g) SEQ ID NOs: 96, 110, 84, 130, 90 and 131, respectively;

h) SEQ ID NOs: 97, 111, 84, 130, 90 and 131, respectively;

i) SEQ ID NOs: 96, 110, 84, 130, 90 and 134, respectively;

j) SEQ ID NOs: 97, 111, 84, 130, 90 and 134, respectively;

k) SEQ ID NOs: 97, 112, 84, 130, 90 and 134, respectively;

l) SEQ ID NOs: 98, 113, 84, 130, 90 and 134, respectively;

m) SEQ ID NOs: 97, 114, 84, 130, 90 and 134, respectively;

n) SEQ ID NOs: 97, 115, 84, 130, 90 and 134, respectively;

o) SEQ ID NOs: 99, 116, 84, 130, 90 and 133, respectively;

p) SEQ ID NOs: 100, 117, 84, 130, 90 and 133, respectively;

q) SEQ ID NOs: 101, 118, 84, 130, 90 and 133, respectively;

r) SEQ ID NOs: 102, 120, 84, 130, 90 and 132, respectively;

s) SEQ ID NOs: 103, 121, 84, 130, 90 and 132, respectively;

t) SEQ ID NOs: 103, 122, 84, 130, 90 and 131, respectively;

u) SEQ ID NOs: 103, 123, 84, 130, 90 and 131, respectively;

v) SEQ ID NOs: 104, 124, 84, 130, 90 and 131, respectively;

w) SEQ ID NOs: 105, 125, 84, 130, 90 and 131, respectively;

x) SEQ ID NOs: 106, 126, 84, 130, 90 and 131, respectively;

y) SEQ ID NOs: 95, 127, 84, 130, 90 and 131, respectively;

z) SEQ ID NOs: 107, 128, 84, 130, 90 and 131, respectively;

aa) SEQ ID NOs: 108, 129, 84, 130, 90 and 131, respectively;

bb) SEQ ID NOs: 97, 114, 165, 130, 90 and 134, respectively;

cc) SEQ ID NOs: 97, 114, 166, 130, 90 and 134, respectively;

dd) SEQ ID NOs: 97, 114, 167, 130, 90 and 134, respectively;

ee) SEQ ID NOs: 97, 114, 168, 130, 90 and 134, respectively;

ff) SEQ ID NOs: 97, 114, 169, 130, 90 and 134, respectively;

gg) SEQ ID NOs: 97, 114, 170, 130, 90 and 134, respectively;

hh) SEQ ID NOs: 97, 114, 171, 130, 90 and 134, respectively;

ii) SEQ ID NOs: 97, 114, 172, 130, 90 and 134, respectively;

jj) SEQ ID NOs: 97, 114, 173, 130, 90 and 134, respectively;

kk) SEQ ID NOs: 97, 114, 174, 130, 90 and 134, respectively;

ll) SEQ ID NOs: 97, 114, 175, 130, 90 and 134, respectively;

mm) SEQ ID NOs: 97, 114, 176, 130, 90 and 134, respectively;

nn) SEQ ID NOs: 97, 114, 177, 130, 90 and 134, respectively;

oo) SEQ ID NOs: 97, 114, 178, 130, 90 and 134, respectively;

pp) SEQ ID NOs: 97, 114, 179, 130, 90 and 134, respectively;

qq) SEQ ID NOs: 97, 114, 180, 130, 90 and 134, respectively;

rr) SEQ ID NOs: 97, 114, 181, 130, 90 and 134, respectively;

ss) SEQ ID NOs: 97, 114, 182, 130, 90 and 134, respectively;

tt) SEQ ID NOs: 97, 114, 183, 130, 90 and 134, respectively;

uu) SEQ ID NOs: 97, 114, 184, 130, 90 and 134, respectively; or

vv) SEQ ID NOs: 97, 114, 185, 130, 90 and 134, respectively.

7) The isolated antibody of claim 4, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of:
a) SEQ ID NOs: 23, 27, 31, 35, 39 and 43, respectively;
b) SEQ ID NOs: 24, 28, 32, 36, 40 and 44, respectively;
c) SEQ ID NOs: 24, 28, 146, 36, 40 and 147, respectively; or
d) SEQ ID NOs: 24, 28, 146, 36, 40 and 44, respectively.

8) The isolated antibody of claim 4, wherein the antibody competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51.

9) The isolated antibody of claim 8, wherein the antibody binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210).

10) The isolated antibody of claim 9, wherein the antibody further binds human ST2L at amino acid residues T93 and F94 of SEQ ID NO: 1.

11) The isolated antibody of claim 1, comprising a heavy chain variable region (VH) comprising a VH framework derived from human IGHV3-23 (SEQ ID NO: 158), IGHV1-24*01 (SEQ ID NO: 148) or IGHV1-f*01 (SEQ ID NO: 149) framework sequences, and a light chain variable region (VL) comprising a VL framework derived from a human IGKV3-11 (L6) (SEQ ID NO: 159), IGKV3-15*01 (L2) (SEQ ID NO: 150), IGKV1-9*01 (L8) (SEQ ID NO: 151), IGKV1-5*01 (L12) (SEQ ID NO: 152), IGKV1-12*01 (L5) (SEQ ID NO: 153), IGKV1-39*01 (O12) (SEQ ID NO: 154), IGKV1-27*01 (A20) (SEQ ID NO: 155)or IGKV1-33*01 (O18) (SEQ ID NO: 156) framework sequences.

12) The isolated antibody of claim 1 which is of IgG1, IgG2, IgG3, or IgG4 type.

13) The isolated antibody of claim 12 having a substitution in an Fc region.

14) The isolated antibody of claim 13, wherein the substitution comprises a substitution M252Y/S254T/T256E, V234A/G237A/P238S/H28A/V309L/A330S/P331S or P238S/L234A/L235A, wherein residue numbering is according to the EU numbering.

15) The isolated antibody of claim 11 comprising the VH at least 90% identical to the VH of SEQ ID NO: 191 and the VL at least 94% identical to the VL of SEQ ID NO: 209.

16) The isolated antibody of claim 15 comprising the VH of SEQ ID NOs: 143, 144, 145, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 and the VL of SEQ ID NOs: 135, 136, 137, 138, 139, 140, 141, 142, 206, 207, 208 or 209.

17) The isolated antibody of claim 16, comprising the VH and the VL of:

a) SEQ ID NO: 186 and SEQ ID NO: 206, respectively;

b) SEQ ID NO: 187 and SEQ ID NO: 206, respectively;

c) SEQ ID NO: 197 and SEQ ID NO: 206, respectively;

d) SEQ ID NO: 198 and SEQ ID NO: 206, respectively;

e) SEQ ID NO: 199 and SEQ ID NO: 206, respectively;

f) SEQ ID NO: 200 and SEQ ID NO: 206, respectively;

g) SEQ ID NO: 201 and SEQ ID NO: 206, respectively;

h) SEQ ID NO: 202 and SEQ ID NO: 206, respectively;

i) SEQ ID NO: 203 and SEQ ID NO: 206, respectively;

j) SEQ ID NO: 204 and SEQ ID NO: 206, respectively;

k) SEQ ID NO: 205 and SEQ ID NO: 206, respectively;

l) SEQ ID NO: 195 and SEQ ID NO: 207, respectively;

m) SEQ ID NO: 196 and SEQ ID NO: 207, respectively;

n) SEQ ID NO: 188 and SEQ ID NO: 208, respectively;

o) SEQ ID NO: 189 and SEQ ID NO: 208, respectively;

p) SEQ ID NO: 190 and SEQ ID NO: 208, respectively;

q) SEQ ID NO: 187 and SEQ ID NO: 209, respectively;

r) SEQ ID NO: 191 and SEQ ID NO: 209, respectively;

s) SEQ ID NO: 192 and SEQ ID NO: 209, respectively;

t) SEQ ID NO: 193 and SEQ ID NO: 209, respectively; or

u) SEQ ID NO: 194 and SEQ ID NO: 209, respectively.

18) An isolated polynucleotide encoding the VH of SEQ ID NOs: 143, 144, 145, 186, 187, 197, 198, 199, 200, 201, 202, 203, 204 or 205, or the VL of SEQ ID NOs: 135, 136, 137, 138, 139, 140, 141, 142, 206, 207, 208 or 209.

19) A vector comprising an isolated polynucleotide of claim 18.

20) A host cell comprising a vector of claim 19.

21) A method of producing an antibody of claim 17, comprising culturing a host cell of claim 20 and recovering the antibody from the cell.

22) A pharmaceutical composition comprising an isolated antibody of claim 1 or claim 5 and a pharmaceutically accepted carrier.

23) The use of the isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I of human ST2L of any one of claims 1-17 in the manufacture of a medicament for the treatment of a ST2L-mediated condition.

24) The use according to claim 23, wherein the ST2L-mediated condition is asthma, airway hyper-reactivity, sarcoidosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, inflammatory bowel disease, (IBD), eosinophilic esophagitis, scleroderma, atopic dermatitis, allergic rhinitis, bullous pemphigoid, chronic urticaria, diabetic nephropathy, rheumatoid arthritis, interstitial cystitis or Graft Versus Host Disease (GVHD), or

is is associated with inflammatory cell recruitment in lung, goblet cell hyperplasia, increased mucous secretion or mast cell response.

25) The use according to claim 23 or 24, wherein the antibody antagonist comprises:

a) the HCDR1 of SEQ ID NO: 97;

b) the HCDR2 of SEQ ID NO: 114;

c) the HCDR3 of SEQ ID NO: 84;

d) the LCDR1 of SEQ ID NO: 130;

e) the LCDR2 of SEQ ID NO: 90; and

f) the LCDR3 of SEQ ID NO: 134; or

g) the VH of SEQ ID NO: 191 and the VL of SEQ ID NO: 209.

Figure 19 shows kinetic and affinity constants for ST2L Domain I binding antibody for ST2L variants as indicated in the figure.

Figure 20 shows inhibition of A) GM-CSF; B) IL-5; C) IL-8; D) IL-13 secretion from primary human lung mast cells by an anti-ST2L antibody STLM208.

Summary of the invention

The invention provides an isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I (SEQ ID NO: 9) of human ST2L and blocks interleukin-33 (IL-33)/ST2L interaction, comprising: a heavy chain variable region (VH), a light chain variable region (VL), a heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2), 3 (HCDR3), a light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2), and 3 (LCDR3), wherein

a) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 97;

b) the HCDR2 comprises the amino acid sequence of SEQ ID NO: 114;

c) the HCDR3 comprises the amino acid sequence of SEQ ID NO: 84;

d) the LCDR1 comprises the amino acid sequence of SEQ ID NO: 130;

e) the LCDR2 comprises the amino acid sequence of SEQ ID NO: 90; and

f) the LCDR3 comprises the amino acid sequence of SEQ ID NO: 134.

Disclosed are human-adapted antibody antagonists specifically binding human ST2L having certain light

chain and heavy chain variable region sequences, or certain heavy chain and light chain complementarity determining sequences.

Disclosed are human or human-adapted antibody antagonists specifically biding human ST2L at defined epitope regions and/or having certain characteristics as described herein.

The invention also provides an isolated polynucleotide encoding the antibody antagonist or fragment thereof of the invention.

The invention also provides a vector comprising an isolated polynucleotide of the invention.

The invention also provides a host cell comprising a vector of the invention.

The invention also provides a method of producing an antibody of the invention, comprising culturing a host cell of the invention and recovering the antibody from the cell.

The invention also provides a pharmaceutical composition comprising an isolated antibody of the invention and a pharmaceutically accepted carrier.

Disclosed is a method of treating or preventing a ST2L-mediated condition comprising administering a therapeutically effective amount of an isolated antibody to a patient in need thereof for a time sufficient to treat or prevent the ST2L-mediated condition.

Disclosed is a method of inhibiting mast cell response in a patient comprising administering a therapeutically effective amount of an isolated

antibody to a patient in need thereof for a time sufficient to inhibit the mast cell response.

Disclosed is a method of inhibiting interaction of IL-33 and ST2L in a subject, comprising administering to the subject an antibody that specifically binds domain I of ST2L in an amount sufficient to inhibit the interaction of IL-33 and ST2L.

The invention also provides use of the isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I of human ST2L of the invention in the manufacture of a medicament for the treatment of a ST2L-mediated condition, wherein the ST2L-mediated condition is asthma, airway hyper-reactivity, sarcoidosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, inflammatory bowel disease, (IBD), eosinophilic esophagitis, scleroderma, atopic dermatitis, allergic rhinitis, bullous pemphigoid, chronic urticaria, diabetic nephropathy, rheumatoid arthritis, interstitial cystitis or Graft Versus Host Disease (GVHD), or is is associated with inflammatory cell recruitment in lung, goblet cell hyperplasia, increased mucous secretion or mast cell response.

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. Unless defined

can be selected from libraries of variants or fragments by panning with human and/or cyno ST2L and optionally by further antibody affinity maturation. Antibodies can be identified based on their inhibition of ST2L biological activity using any suitable method. Such methods may utilize reporter-gene assays or assays measuring cytokine production using well known methods and as described in the application.

Described is an isolated antibody antagonist specifically binding human ST2L comprising:

a heavy chain complementarity determining region (HCDR) 1 (HCDR1)of SEQ ID NO: 160 ($X_1X_2X_3MX_4$); wherein

X_1 is S, F, D, I, G or V;

X_2 is Y or D;

X_3 is A, D or S; and

X_4 is S, F or I;

a HCDR 2 (HCDR2) of SEQ ID NO: 161 ($X_5IX_6GX_7GGX_8TX_9YADSVKG$); wherein

X_5 is A, S, T, Y or D;

X_6 is S, R, E, K, G or A;

X_7 is S, E or N;

X_8 is S, R, E, G, T, D or A; and

X_9 is Y, D, N, A or S; and

a HCDR 3 (HCDR3) of SEQ ID NO: 162 ($X_{10}X_{11}$WSTEGSFFVLDY); wherein

X_{10} is D, A, R, N, Q, P, E, I, H, S, T or Y; and

X_{11} is P, A, H, Y, E, Q, L, S, N, T, V, or I.

Described is an isolated antibody antagonist specifically binding human ST2L comprising:

a light chain complementarity determining region (LCDR) 1 (LCDR1) of SEQ ID NO: 163 ($RASQSVDDX_{12}LA$); wherein

X_{12} is A or D;

a LCDR 2 (LCDR2) of SEQ ID NO: 90 (DASNRAT); and

a LCDR 3 (LCDR3) of SEQ ID NO: 164 ($QQX_{13}X_{14}X_{15}X_{16}X_{17}X_{18}T$); wherein

X_{13} is F or Y;

X_{14} is Y, I or N;

X_{15} is N, G, D or T;

X_{16} is W or A;

X_{17} is P or deleted; and

X_{18} is L or I.

The described antibodies comprising the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 160, 161, 162, 163, 90 and 164, respectively, can be made by well known mutagenesis methods using for example HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 78, 81, 84, 87, 90 and 92, respectively as a template. The heavy chain CDRs and the light chain CDRs of SEQ ID NOs: 160, 161, 162, 163, 90 and 164, respectively, can be grafted to human frameworks, such as frameworks described *infra*. The antibodies can be assayed for binding to ST2L and for their ability to block IL-33/ST2L interaction and for other characteristics such as

SEQ ID NOs: 24, 28, 32, 36, 40 and 44, respectively; (HFA CDRs);
SEQ ID NOs: 24, 28, 146, 36, 40 and 147, respectively; or
SEQ ID NOs: 24, 28, 146, 36, 40 and 44, respectively.

Described is an isolated human or human-adapted antibody antagonist or fragment thereof specifically binding human ST2L as described herein, (SEQ ID NO: 1) comprising a heavy chain variable region (VH) comprising a VH framework derived from human IGHV3-23 (SEQ ID NO: 158), IGHV1-24*01 (SEQ ID NO: 148) or IGHV1-f*01 (SEQ ID NO: 149) framework sequences, and a light chain variable region (VL) comprising a VL framework derived from a human IGKV3-11 (L6) (SEQ ID NO: 159), IGKV3-15*01 (L2) (SEQ ID NO: 150), IGKV1-9*01 (L8) (SEQ ID NO: 151), IGKV1-5*01 (L12) (SEQ ID NO: 152), IGKV1-12*01 (L5) (SEQ ID NO: 153), IGKV1-39*01 (O12) (SEQ ID NO: 154), IGKV1-27*01 (A20) (SEQ ID NO: 155)or IGKV1-33*01 (O18) (SEQ ID NO: 156) framework sequences.

In another embodiment, the isolated antibody specifically binding Domain I of human ST2L as described herein comprises a VH comprising a VH framework derived from human VH 3-23 framework sequences (SEQ ID NO: 158); and a light chain variable region (VL) comprising a VL framework derived from a human Vκ L6 framework sequences (SEQ ID NO: 159). Human framework sequences are well known, and typically include human immunoglobulin germline variable region sequences joined to the joining (J) sequences. The

An exemplary human myeloma cell line is U266 (ATTC CRL-TIB-196). Other useful cell lines include those derived from Chinese Hamster Ovary (CHO) cells such as CHO-K1SV (Lonza Biologics, Walkersville, MD), CHO-K1 (ATCC CRL-61) or DG44.

Another embodiment of the invention is a method of producing an antibody that specifically binds Domain I of ST2L, comprising culturing a host cell of the invention and recovering the antibody produced by the host cell. Methods of making antibodies and purifying them are well known in the art.

Described is a method of inhibiting interaction of ST2L with IL-33 in a subject comprising administering the subject an antibody specifically binding domain I of ST2L in an amount sufficient to inhibit interaction of ST2L and IL-33.

Methods of Treatment

ST2L antagonists of the invention as described herein, for example ST2L antibody antagonists blocking IL-33/ST2L interaction and binding Domain I of ST2L, antibodies that compete for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region of SEQ ID NO: 47 and a light chain variable region of SEQ ID NO: 51, or antibodies binding human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) may be utilized to modulate the immune system. Antibodies of the invention as described herein may be more efficient in antagonizing ST2L biological activity when compared to antibodies binding other domains and/or regions on ST2L as the antibodies of the invention are able to more efficiently reduce IL-33-induced mast cell responses. Any antibodies of the invention can be used in the described methods.

Exemplary antibodies that can be used in the described methods are antibodies STLM62, STLM15, STLM103, STLM107, STLM108, STLM123, STLM124, STLM206, STLM207, STLM208, STLM209, STLM210, STLM211, STLM212, STLM213. Without wishing to be bound by any theory, it is suggested that antibody antagonists that bind Domain I and block IL-33/ST2L interaction may inhibit formation of the IL-1RAcP/IL-33/ST2L/cKit complex or downstream signaling on mast cells, whereas Domain III binding antibodies, while being able to inhibit recruitment of IL-1RAcP to the ST2L/IL-33 complex, may be unable to disrupt the formation of the larger IL-1RAcP/IL-33/ST2L/cKit complex specifically found on mast cells. Microarray analysis conducted supports the suggestion as it was demonstrated that anti-ST2L Domain I binding antibodies suppressed the majority of mast cell signaling pathways induced by IL-33, and that anti-ST2L Domain III binding antibodies were only able to inhibit a small subset of these signaling pathways. It is feasible that because IL-33 binds to ST2L prior to the association of the accessory protein IL-1RAcP, blockade of IL-33 binding to ST2L by Domain I-binding antibodies could prevent association of any other accessory protein, including cKit or as-yet unidentified co-receptors. Domain III-binding antibodies, which do not interfere with IL-33 binding to ST2L, could theoretically block IL-1RAcP association but not the association of other co-receptors, including as-yet unidentified co-receptors. Multiple models have been proposed for how IL-1RAcP interacts with the IL-1/IL-1R or ST2L/IL-33 complexes (Lingel *et al.*, Structure 17: 1398-1410, 2009; and reviewed by Thomas *et al.*, Nat Struct & Molec Biol 19: 455-457, 2012). These models indicate that IL-1RAcP could bind to one side of the complex, but which side has not been conclusively shown. Therefore it is feasible that the 'other side'or 'free side' of the complex is available for association with an alternate

co-receptor, that would not be blocked by a Domain III antibody, and off-target effects such as increased recruitment of another co-receptor, resulting in increased signaling, is possible.

In the described methods, any antibody antagonist specifically binding Domain I of human ST2L, antibody antagonist blocking IL-33/ST2L interaction and binding Domain I of human ST2L, antibodies that competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region of SEQ ID NO: 47 and a light chain variable region of SEQ ID NO: 51, or antibodies binding human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) may be used. Additional characteristics of such antibodies include ability of the antibody to block IL-33/ST2L interaction and to inhibit human mast cell responses.

Therefore, antibodies of the invention are suitable for treating a spectrum of ST2L-mediated conditions, ST2L-mediated inflammatory conditions and conditions where inhibition of mast cell responses is desired.

The described methods may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats and farm animals. For example, the antibodies of the invention are useful in the prophylaxis and treatment of ST2L-mediated conditions, such as inflammatory diseases including asthma, airway hyper-reactivity, sarcoidosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, inflammatory bowel disease (IBD), rheumatoid arthritis, eosinophilic esophagitis, scleroderma, atopic dermatitis, allergic rhinitis, bullous pemphigoid, chronic urticaria, diabetic nephropathy, interstitial cystitis or Graft Versus Host Disease (GVHD). The antibodies of the invention are useful

sclerosing cholangitis. The kidney fibrosis can be associated with diabetic nephropathy or lupus glomeruloschelerosis. The heart fibrosis can be associated with myocardial infarction. The vascular fibrosis can be associated with postangioplasty arterial restenosis or atherosclerosis. The skin fibrosis can be associated with burn scarring, hypertrophic scarring, keloid, or nephrogenic fibrosing dermatopathy. The eye fibrosis can be associated with retro-orbital fibrosis, postcataract surgery or proliferative vitreoretinopathy. The bone marrow fibrosis can be associated with idiopathic myelofibrosis or drug induced myelofibrosis. The systemic fibrosis can be systemic sclerosis or graft versus host disease.

Other inflammatory conditions and neuropathies, which may be prevented or treated by the described methods are those caused by autoimmune diseases. These conditions and neuropathies include multiple sclerosis, systemic lupus erythematous, and neurodegenerative and central nervous system (CNS) disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, bipolar disorder and Amyotrophic Lateral Sclerosis (ALS), liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease/steatohepatitis, fibrosis, hepatitis C virus (HCV) and hepatitis B virus (HBV), diabetes and insulin resistance, cardiovascular disorders including atherosclerosis, cerebral hemorrhage, stroke and myocardial infarction, arthritis, rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis (JRA), osteoporosis, osteoarthritis, pancreatitis, fibrosis, encephalitis, psoriasis, Giant cell arteritis, ankylosing spondolytis, autoimmune hepatitis, human immunodeficiency virus (HIV), inflammatory skin conditions, transplant, cancer, allergies, endocrine diseases, wound repair, other autoimmune disorders, airway

hyperresponsiveness and cell, virus, or prion-mediated infections or disorders.

Described is a method of treating or preventing a ST2L-mediated condition comprising administering a therapeutically effective amount of an isolated human or human-adapted antibody antagonist that specifically binds Domain I (SEQ ID NO: 9) of human ST2L, blocks IL-33/ST2L interaction, competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51 and/or binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) to a patient in need thereof for a time sufficient to treat or prevent the ST2L-mediated condition.

Described is a method of inhibiting mast cell response in a patient comprising administering a therapeutically effective amount of an isolated human or human-adapted antibody antagonist that specifically binds Domain I (SEQ ID NO: 9) of human ST2L, blocks IL-33/ST2L interaction, competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51 and/or binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210) to a patient in need thereof for a time sufficient to inhibit the mast cell response.

Described is a method of inhibiting interaction of IL-33 and ST2L in a

CLAIMS

1. An isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I (SEQ ID NO: 9) of human ST2L and blocks interleukin-33 (IL-33)/ST2L interaction, comprising a heavy chain variable region (VH), a light chain variable region (VL), a heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2), 3 (HCDR3), a light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2), and 3 (LCDR3), wherein
   a) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 97;
   b) the HCDR2 comprises the amino acid sequence of SEQ ID NO: 114;
   c) the HCDR3 comprises the amino acid sequence of SEQ ID NO: 84;
   d) the LCDR1 comprises the amino acid sequence of SEQ ID NO: 130;
   e) the LCDR2 comprises the amino acid sequence of SEQ ID NO: 90; and
   f) the LCDR3 comprises the amino acid sequence of SEQ ID NO: 134.
2. The isolated antibody of claim 1 having a dissociation constant (K_D) to human ST2L between about $5x10^{-12}$ M to about $7x10^{-10}$ M, an on rate constant (K_{on}) to human ST2L between about $2x10^{6}$ $M^{-1}s^{-1}$ to about $1x10^{8}$ $M^{-1}s^{-1}$, or an off rate constant (K_{off}) to human ST2L between about $1x10^{-6}$ s^{-1} to about $1x10^{-2}$ s^{-1}.
3. The isolated antibody of claim 2 having a dissociation constant (K_D) to *Macaca fascicularis* (cyno) ST2L (SEQ ID NO: 2) between about $3x10^{-12}$ M to about $2x10^{-9}$ M, an on rate constant (K_{on}) to cyno ST2L between about $4x10^{6}$ $M^{-1}s^{-1}$ to about

$1x10^{8}$ $M^{-1}s^{-1}$, or an off rate constant (K_{off}) to cyno ST2L between about $7x10^{-5}s^{-1}$ to about $1x10^{-1}s^{-1}$.

4. The isolated antibody of any one of claims 1 to 3, comprising the VH of SEQ ID NO: 191.
5. The isolated antibody of any one of claims 1 to 4, comprising the VL of SEQ ID NO: 209.
6. The isolated antibody of any one of claims 1 to 3, comprising the VH of SEQ ID NO: 191 and the VL of SEQ ID NO: 209.
7. The isolated antibody of any one of claims 1 to 6, wherein the antibody competes for binding to human ST2L (SEQ ID NO: 1) with an isolated antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 47 and a light chain variable region (VL) of SEQ ID NO: 51.
8. The isolated antibody of claim 7, wherein the antibody binds human ST2L at amino acid residues 35-48 of SEQ ID NO: 1 (RCPRQGKPSYTVDW; SEQ ID NO: 210).
9. The isolated antibody of claim 8, wherein the antibody further binds human ST2L at amino acid residues T93 and F94 of SEQ ID NO: 1.
10. The isolated antibody of any one of claims 1 to 3, comprising a heavy chain variable region (VH) comprising a VH framework derived from human IGHV3-23 (SEQ ID NO: 158), IGHV1-24*01 (SEQ ID NO: 148) or IGHV1-f*01 (SEQ ID NO: 149) framework sequences, and a light chain variable region (VL) comprising a VL framework derived from a human IGKV3-11 (L6) (SEQ ID NO: 159), IGKV3-15*01 (L2) (SEQ ID NO: 150), IGKV1-9*01 (L8) (SEQ ID NO: 151), IGKV1-5*01 (L12) (SEQ ID NO: 152), IGKV1-12*01 (L5) (SEQ ID NO: 153), IGKV1-39*01 (O12) (SEQ ID NO: 154), IGKV1-27*01 (A20) (SEQ ID NO: 155)or IGKV1-33*01 (O18) (SEQ ID NO: 156) framework sequences.
11. The isolated antibody of any one of claims 1 to 10 which is of IgG1, IgG2, IgG3, or IgG4 type.

12. The isolated antibody of claim 11having a substitution in an Fc region.

13. The isolated antibody of claim 12, wherein the substitution comprises a substitution M252Y/S254T/T256E, V234A/G237A/P238S/H28A/V309L/A330S/P331S or P238S/L234A/L235A, wherein residue numbering is according to the EU numbering.

14. The isolated antibody of claim 10 comprising the VH at least 90% identical to the VH of SEQ ID NO: 191 and the VL at least 94% identical to the VL of SEQ ID NO: 209.

15. The isolated antibody of claim 14 comprising the VH of SEQ ID NOs: 143, 144, 145, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 and the VL of SEQ ID NOs: 135, 136, 137, 138, 139, 140, 141, 142, 206, 207, 208 or 209.

16. The isolated antibody of claim 15, comprising the VH and the VL of:

a) SEQ ID NO: 186 and SEQ ID NO: 206, respectively;

b) SEQ ID NO: 187 and SEQ ID NO: 206, respectively;

c) SEQ ID NO: 197 and SEQ ID NO: 206, respectively;

d) SEQ ID NO: 198 and SEQ ID NO: 206, respectively;

e) SEQ ID NO: 199 and SEQ ID NO: 206, respectively;

f) SEQ ID NO: 200 and SEQ ID NO: 206, respectively;

g) SEQ ID NO: 201 and SEQ ID NO: 206, respectively;

h) SEQ ID NO: 202 and SEQ ID NO: 206, respectively;

i) SEQ ID NO: 203 and SEQ ID NO: 206, respectively;

j) SEQ ID NO: 204 and SEQ ID NO: 206, respectively;

k) SEQ ID NO: 205 and SEQ ID NO: 206, respectively;

l) SEQ ID NO: 195 and SEQ ID NO: 207, respectively;

m) SEQ ID NO: 196 and SEQ ID NO: 207, respectively;

n) SEQ ID NO: 188 and SEQ ID NO: 208, respectively;

o) SEQ ID NO: 189 and SEQ ID NO: 208, respectively;

p) SEQ ID NO: 190 and SEQ ID NO: 208, respectively;

q) SEQ ID NO: 187 and SEQ ID NO: 209, respectively;

r) SEQ ID NO: 191 and SEQ ID NO: 209, respectively;

s) SEQ ID NO: 192 and SEQ ID NO: 209, respectively;

t) SEQ ID NO: 193 and SEQ ID NO: 209, respectively; or

u) SEQ ID NO: 194 and SEQ ID NO: 209, respectively.

17. An isolated polynucleotide encoding the antibody antagonist or fragment thereof of any one of the preceding claims.

18. A vector comprising an isolated polynucleotide of claim 17.

19. A host cell comprising a vector of claim 18.

20. A method of producing an antibody of any one of claims 1 to 16, comprising culturing a host cell of claim 19 and recovering the antibody from the cell.

21. A pharmaceutical composition comprising an isolated antibody of any one of claims 1 to 16 and a pharmaceutically accepted carrier.

22. The use of the isolated human or human-adapted antibody antagonist or fragment thereof that specifically binds Domain I of human ST2L of any one of claims 1-16 in the manufacture of a medicament for the treatment of a ST2L-mediated condition , wherein the ST2L-mediated condition is asthma, airway hyper-reactivity, sarcoidosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, inflammatory bowel disease, (IBD), eosinophilic esophagitis, scleroderma, atopic dermatitis, allergic rhinitis, bullous pemphigoid, chronic urticaria, diabetic nephropathy, rheumatoid arthritis, interstitial cystitis or Graft Versus Host Disease (GVHD), or is is associated with inflammatory cell recruitment in lung, goblet cell hyperplasia, increased mucous secretion or mast cell response.