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(54) Title: ANTI-STEM CELL FACTOR (SCF) AND ANTI-THYMIC STROMAL LYMPHOPOIETIN (TSLP) ANTIBODIES AND BISPECIFIC CONSTRUCTS

(57) Abstract: Provided herein are novel anti-TSLP and anti-SCF antibodies, and binding domains thereof, as well as bispecific constructs comprising such antibodies and binding domains. Also provided herein are methods of treating disorders associated with an immune response (e.g., immune cell migration, activation, and/or proliferation) via interaction (e.g., binding) of TSLP and/or SCF with its receptor (TSLPR and/or c-Kit, respectively) on immune cells (such as disorders of the immune system) by administering the antibodies (or antigen binding fragments thereof), bispecific constructs, or compositions described herein to a patient in need thereof.

ANTI-STEM CELL FACTOR (SCF) AND ANTI-THYMIC STROMAL LYMPHOPOIETIN (TSLP) ANTIBODIES AND BISPECIFIC CONSTRUCTS

This application claims the benefit of U.S. Provisional Patent Application No. 63/488,388 (filed March 3, 2023), U.S. Provisional Patent Application No. 63/452,326 (filed March 15, 2023), and U.S. Provisional Patent Application No. 63/465,970 (filed May 12, 2023), the disclosures of which are incorporated by reference herein in their entirety.

I. Background of the Invention

Inflammation plays a key role in many diseases, some of which have become more common and severe. Chronic inflammatory diseases contribute to more than half of deaths worldwide (Furman, D. *et al.*, Nature Medicine, 2019, 25(12):1822-1832). Stem cell factor (SCF) and its receptor c-Kit are involved in the perpetuation of chronic inflammation.

SCF is expressed by various structural and inflammatory cells in the airways. Binding of SCF to c-Kit (also known as Kit Ligand) leads to activation of multiple pathways, including phosphatidyl-inositol-3 (PI3)-kinase, phospholipase C (PLC)-gamma, Src kinase, Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) and mitogen activated protein (MAP) kinase pathways (Reber, L. *et al.*, Eur J Pharmacol, 2006, 533(1-3):327-40). SCF is produced in two transmembrane forms (viz SCF^{220} and SCF^{248}) as a result of alternative splicing of exon 6 (Lennartsson and Rönnstrand, Physiol Rev. 2012 Oct; 92(4):1619-49). In SCF^{248}, exon 6 is retained and encodes a proteolytic cleavage site, generating the soluble SCF^{165} when this is cleaved. SCF^{220}, which lacks the cleavage site, forms membrane-bound SCF dimers (mSCF).

c-Kit is a type III receptor tyrosine kinase encoded by the c-kit gene. c-Kit comprises five extracellular immunoglobulin (Ig)-like domains, a single transmembrane region, an inhibitory cytoplasmic juxtamembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment (see, e.g., Yarden et al., Nature, 1986, 323:226-232; Ullrich and Schlessinger, Cell, 1990, 61 :203-212; Clifford et al., J. Biol. Chem., 2003, 278:31461-31464). The human c-kit gene encoding the c-Kit receptor has been cloned as described by Yarden et al., EMBO J., 1987, 6:3341-3351. c-Kit is also known as CD117 or stem cell factor receptor ("SCFR"), because it is the receptor for the stem cell factor (also known as Kit Ligand). SCF ligand binding to the first three extracellular Ig-like domains of c-Kit induces receptor dimerization, and thereby activates intrinsic tyrosine kinase activity through the phosphorylation of specific tyrosine residues in the juxtamembrane and kinase

domains (see, e.g., Weiss and Schlessinger, Cell, 1998, 94:277-280; Clifford et al., J. Biol. Chem., 2003, 278:31461- 31464). Members of the Stat, Src, ERK, and AKT signaling pathways have been shown to be downstream signal transducers of c-Kit signaling. The fourth (D4) and fifth (D5) extracellular Ig-like domains of c-Kit are believed to mediate receptor dimerization (see, e.g., International Patent Application Publication No. WO 2008/153926; Yuzawa et al., Cell, 2007, 130:323-334).

Expression of c-Kit has been detected in various cell types, such as mast cells, stem cells, brain cells, melanoblasts, ovary cells, and cancer cells (e.g., leukemia cells) (see, e.g., Besmer, P. Curr. Opin. Cell Biol, 1991, 3:939-946; Lyman et al., Blood, 1998, 91 : 1101-1134; Ashman, L. K., Int. J. Biochem. Cell Biol, 1999, 31 : 1037-1051; Kitamura et al., Mutat. Res., 2001, 477: 165-171; Mol et al., J. Biol. Chem., 2003, 278:31461-31464). Moreover, c-Kit plays an important role in hematopoiesis, melanogenesis, and gametogenesis (see Ueda et al., Blood, 2002, 99:3342-3349).

Mast cells are long-lived innate immune sentinel cells that reside in tissues across the body, particularly at interfaces with the external environment (Alvarado D, Maurer M, Gedrich R, et al. Allergy. 2022;00:1–11). During normal homeostasis, mast cells can exert protective functions against helminth infections, venoms, and may play a role in wound healing and initiating adaptive responses. However, mast cells are better known for their role in driving or contributing to numerous allergic, inflammatory, and autoimmune disorders.

Upon stimulation, mast cells release pre-formed mediators stored in granules (proteases, histamine, serotonin, and cytokines), followed by a second wave of eicosanoids (leukotrienes and prostaglandin D2) and a wide array of inflammatory cytokines and chemokines through de novo synthesis. These events lead to a rapid inflammatory response characterized by vasodilation, extravasation, smooth muscle contraction, itch, and recruitment of additional immune cell types, which can manifest in both acute and chronic Conditions (Alvarado D, Maurer M, Gedrich R, et al. Allergy. 2022;00:1–11).

Mast cell activation underlies the etiology of allergic reactions and has been strongly implicated in chronic acute and pruritic conditions, neuroinflammatory disorders, pain, fibrosis, and autoimmune diseases. Indeed, therapies that inhibit specific mast cell triggers, such as anti-IgE (omalizumab) or mediators (antihistamines) have been approved by health authorities and recommended by guidelines as therapies, although many patients have limited benefit indicating additional mast cell triggers or mediators are likely involved. Thus, therapies that lead to comprehensive mast cell suppression may result in broader efficacy in

indications where mast cells contribute to disease pathophysiology (Alvarado D, Maurer M, Gedrich R, et al. Allergy. 2022;00:1–11).

The c-Kit (c-KIT/CD117) receptor tyrosine kinase and its only ligand stem cell factor (SCF) are master regulators of mast cell biology. c-Kit is highly expressed throughout the life of a mast cell and is also expressed in hematopoietic stem cells, melanocytes, interstitial cells of Cajal, germ cells, and a subset of taste receptor cells. Mast cells arise from multipotent hematopoietic stem cell progenitors, entering circulation as immature progenitors and influx into tissues, where they reach maturity. c-Kit phosphorylation by soluble or transmembrane SCF expressed in stromal cells (e.g., fibroblasts, keratinocytes, and endothelial cells) and mast cells themselves, regulates their differentiation, tissue migration, adhesion, maturation, survival, and modulates their activation. Similarly, exogenous SCF is required to differentiate, mature, and maintain primary mast cells grown in vitro (Alvarado D, Maurer M, Gedrich R, et al. Allergy. 2022;00:1–11).

Thymic stromal lymphopoietin (TSLP) also has been shown to play a critical role in driving inflammation (Rui He and Raif S. Geha, Ann NY Acad Sci, 2010, 1183:13-24). TSLP is expressed by epithelial cells in the thymus, lung, skin, intestine, and tonsils, as well as airway smooth muscle cells, lung fibroblasts, and stromal cells (Reche *et al.*, Journal of Immunology, 2001, 167: 336-343). These cells produce TSLP in response to proinflammatory stimuli, and TSLP drives allergic inflammatory responses through its activity on a number of innate immune cells, including dendritic cells, monocytes, and mast cells (Soumelis *et al.*, Nature Immunology, 2002, 3:673-680; Reche *et al.*, Journal of Immunology, 2001, 167:336-343; (Allakhverdi *et al.* (2007) The Journal of Experimental Medicine 204:253-258). TSLP has also been shown to play a role in the pathogenesis of diseases that include fibrosis. For example, TSLP has been shown to be upregulated in both cutaneous and lung fibrotic conditions. (Shin *et al.*, Journal of Investigative Dermatology, 2016, 136(2):360-362).

Despite therapeutic advances, there is a need in the art for new and improved agents to treat conditions or diseases associated with inflammation.

II. Summary of the Invention

Provided herein are anti-TSLP and anti-SCF antibodies (*e.g.*, fully human, humanized, and chimeric antibodies), and binding domains thereof (i.e., antigen binding fragments). Bispecific and multispecific constructs comprising an anti-TSLP and/or anti-

SCF antibody (or antigen binding fragments thereof) linked to at least one additional binding agent (*e.g.*, a ligand or an antibody or antigen binding fragment thereof) also are provided. In one embodiment, the bispecific and multispecific constructs comprise the anti-TSLP and/or anti-SCF antibodies (or antigen binding fragments thereof) described herein linked at least one additional binding agent. Compositions comprising the antibodies, bispecific and multispecific constructs also are provided.

Also provided are methods of treating an inflammatory disease or condition associated with expression and/or activity of TSLP and/or SCF, *e.g.*, a disease or condition associated with immune cell migration, activation, and/or proliferation *via* interaction of TSLP with its receptor (TSLPR) and/or SCF with its receptor (c-Kit) on immune cells. In some embodiments, the present disclosure provides methods for inhibiting or blocking the binding of TSLP to TSLPR and/or blocking the binding of SCF to c-Kit, inhibiting or preventing activation of immune cells, as well as reducing or preventing the accumulation of immune cells within organs or tissues, thereby treating or preventing various diseases and disorders that involve inflammation. Also provided herein are methods of reducing inflammation and methods of treating an inflammatory disease or disorder in a subject in need thereof (*e.g.*, autoimmune diseases, cardiovascular diseases, gastrointestinal diseases, lung diseases, metabolic diseases (such as Type 2 diabetes), neurodegenerative diseases (such as Parkinson's disease), certain types of cancer (such as colon cancer) and mental illnesses (such as depression)) by administering the bispecific or multispecific constructs, antibodies, or antigen binding fragments thereof, or compositions described herein to a patient in need thereof.

In one embodiment, the anti-TSLP antibody or binding domain thereof comprises the heavy and/or light chain CDRs or variable regions of any one of antibodies 1D10-A, 1D10-B, 1D10-C, 1D10-D, 1D10-E, 1D10-F, 1D10-G, 1D10-H, or 1D10-I (as shown in Table 6 of Example 2). In another embodiment, the anti-TSLP antibody or binding domain thereof comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 5, 9, or 13, and/or the CDR1, CDR2 and CDR3 domains of the light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17, 21, 25, or 29. In another embodiment, the anti-TSLP antibody or binding domain thereof comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 5A (of Example 2), or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino

acid sequences respectively set forth in Table 5B (of Example 2), or conservative sequence modifications thereof. In another embodiment, the anti-TSLP antibody or binding domain thereof respectively comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 2, 3, and 4, (b) SEQ ID NOs: 6, 7, and 8, (c) SEQ ID NOs: 10, 11, and 12, (d) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 18, 19, and 20, (b) SEQ ID NOs: 22, 23, and 24, (c) SEQ ID NOs: 26, 27, and 28, (d) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof, as set forth in Table 1A below. In another embodiment, the anti-TSLP antibody or binding domain respectively comprises the heavy chain CDR1, CDR2 and CDR3 sequences of SEQ ID NOs: 6, 7, and 8 (i.e., the heavy chain CDR1, CDR2 and CDR3 sequences of 1D10-H2) and light chain CDR1, CDR2 and CDR3 sequences of SEQ ID NOs: 18, 19, and 20 (i.e., the light chain CDR1, CDR2 and CDR3 sequences of 1D10-L1).

Table 1A: Anti-TSLP Heavy and Light Chain CDR Pairings

	VH1 CDRs SEQ ID NOs: 2, 3, and 4	**VH2 CDRs** SEQ ID NOs: 6, 7, and 8	**VH3 CDRs** SEQ ID NOs: 10, 11, and 12	**VH4 CDRs** SEQ ID NOs: 14, 15, and 16
VL1 CDRs SEQ ID NOs: 18, 19, and 20	SEQ ID NOs: 2, 3, and 4 and SEQ ID NOs: 18, 19, and 20	SEQ ID NOs: 6, 7, and 8 and SEQ ID NOs: 18, 19, and 20	SEQ ID NOs: 10, 11, and 12 and SEQ ID NOs: 18, 19, and 20	SEQ ID NOs: 14, 15, and 16 and SEQ ID NOs: 18, 19, and 20
VL2 CDRs SEQ ID NOs: 22, 23, and 24	SEQ ID NOs: 2, 3, and 4 and SEQ ID NOs: 22, 23, and 24	SEQ ID NOs: 6, 7, and 8 and SEQ ID NOs: 22, 23, and 24	SEQ ID NOs: 10, 11, and 12 and SEQ ID NOs: 22, 23, and 24	SEQ ID NOs: 14, 15, and 16 and SEQ ID NOs: 22, 23, and 24
VL3 CDRs SEQ ID NOs: 26, 27, and 28	SEQ ID NOs: 2, 3, and 4 and SEQ ID NOs: 26, 27, and 28	SEQ ID NOs: 6, 7, and 8 and SEQ ID NOs: 26, 27, and 28	SEQ ID NOs: 10, 11, and 12 and SEQ ID NOs: 26, 27, and 28	SEQ ID NOs: 14, 15, and 16 and SEQ ID NOs: 26, 27, and 28
VL4 CDRs SEQ ID NOs: 30, 31, and 32	SEQ ID NOs: 2, 3, and 4 and	SEQ ID NOs: 6, 7, and 8 and	SEQ ID NOs: 10, 11, and 12 and	SEQ ID NOs: 14, 15, and 16 and

	VH1 CDRs SEQ ID NOs: 2, 3, and 4	**VH2 CDRs** SEQ ID NOs: 6, 7, and 8	**VH3 CDRs** SEQ ID NOs: 10, 11, and 12	**VH4 CDRs** SEQ ID NOs: 14, 15, and 16
	SEQ ID NOs: 30, 31, and 32	SEQ ID NOs: 30, 31, and 32	SEQ ID NOs: 30, 31, and 32	SEQ ID NOs: 30, 31, and 32

In another embodiment, the anti-TSLP antibody or binding domain thereof comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 5, 9, or 13, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences). In another embodiment, the antibody or binding domain thereof comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17, 21, 25, or 29, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In another embodiment, the anti-TSLP antibody or binding domain thereof comprises a combination of heavy and light chain variable regions having the amino acid sequences as set forth in Table 1B below. In one embodiment, the anti-TSLP antibody or binding domain comprises the heavy chain variable region having the amino acid sequence of SEQ ID NO: 5 (i.e., the heavy chain variable region of 1D10-H2) and the light chain variable region having the amino acid sequence of SEQ ID NO: 17 (i.e., the light chain variable region of 1D10-L1).

Table 1B: Anti-TSLP Heavy and Light Chain VH/VL Pairings

	VH1 SEQ ID NO: 1	**VH2** SEQ ID NO: 5	**VH3** SEQ ID NO: 9	**VH4** SEQ ID NO: 13
VL1 SEQ ID NO: 17	SEQ ID NOs: 1 and 17	SEQ ID NOs: 5 and 17	SEQ ID NOs: 9 and 17	SEQ ID NOs: 13 and 17
VL2 SEQ ID NO: 21	SEQ ID NOs: 1 and 21	SEQ ID NOs: 5 and 21	SEQ ID NOs: 9 and 21	SEQ ID NOs: 13 and 21
VL3 SEQ ID NO: 25	SEQ ID NOs: 1 and 25	SEQ ID NOs: 5 and 25	SEQ ID NOs: 9 and 25	SEQ ID NOs: 13 and 25
VL4 SEQ ID NO: 29	SEQ ID NOs: 1 and 29	SEQ ID NOs: 5 and 29	SEQ ID NOs: 9 and 29	SEQ ID NOs: 13 and 29

In a particular embodiment, the anti-TSLP antibody or binding domain thereof comprises a combination of heavy and light chain variable regions having the amino acid sequences as set forth in Table 6 of Example 2.

In one embodiment, the anti-SCF antibody or binding domain thereof comprises the heavy and/or light chain CDRs or variable regions of any one of antibodies anti-SCF antibody mAb12-A, mAb12-B, mAb12-C, mAb12-D, mAb12-E, mAb12-F, mAb12-G, mAb12-H, or mAb12-I (as shown in Table 9 of Example 9). In another embodiment, the anti-SCF antibody or binding domain thereof comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 33, 37, 41, or 45, and/or the CDR1, CDR2 and CDR3 domains of the light chain variable region having the amino acid sequence set forth in SEQ ID NO: 49, 53, 57, or 61. In another embodiment, the anti-SCF antibody or binding domain thereof comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8A (of Example 9), or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8B, or conservative sequence modifications thereof. In another embodiment, the anti-SCF antibody or binding domain thereof respectively comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 34, 35, and 36, (b) SEQ ID NOs: 38, 39, and 40, (c) SEQ ID NOs: 42, 43, and 44, (d) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 50, 51, and 52, (b) SEQ ID NOs: 54, 55, and 56, (c) SEQ ID NOs: 58, 59, and 60, (d) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof, as set forth in Table 2A below. In one embodiment, the anti-SCF antibody or binding domain comprises the heavy chain CDR1, CDR2 and CDR3 sequences of SEQ ID NOs: 46, 47, and 48 (i.e., the heavy chain CDR1, CDR2 and CDR3 sequences of mAb12-H4) and the light chain CDR1, CDR2 and CDR3 sequences of SEQ ID NOs: 58, 59, and 60 (i.e., the light chain CDR1, CDR2 and CDR3 sequences of mAb12-L3).

Table 2A: Anti-SCF Heavy and Light Chain CDR Pairings

	VH1 CDRs SEQ ID NOs: 34, 35, and 36	**VH2 CDRs** SEQ ID NOs: 38, 39, and 40	**VH3 CDRs** SEQ ID NOs: 42, 43, and 44	**VH4 CDRs** SEQ ID NOs: 46, 47, and 48
VL1 CDRs	SEQ ID NOs:	SEQ ID NOs:	SEQ ID NOs:	SEQ ID NOs:

	VH1 CDRs SEQ ID NOs: 34, 35, and 36	**VH2 CDRs** SEQ ID NOs: 38, 39, and 40	**VH3 CDRs** SEQ ID NOs: 42, 43, and 44	**VH4 CDRs** SEQ ID NOs: 46, 47, and 48
SEQ ID NOs: 50, 51, and 52	34, 35, and 36 and SEQ ID NOs: 50, 51, and 52	38, 39, and 40 and SEQ ID NOs: 50, 51, and 52	42, 43, and 44 and SEQ ID NOs: 50, 51, and 52	46, 47, and 48 and SEQ ID NOs: 50, 51, and 52
VL2 CDRs SEQ ID NOs: 54, 55, and 56	SEQ ID NOs: 34, 35, and 36 and SEQ ID NOs: 54, 55, and 56	SEQ ID NOs: 38, 39, and 40 and SEQ ID NOs: 54, 55, and 56	SEQ ID NOs: 42, 43, and 44 and SEQ ID NOs: 54, 55, and 56	SEQ ID NOs: 46, 47, and 48 and SEQ ID NOs: 54, 55, and 56
VL3 CDRs SEQ ID NOs: 58, 59, and 60	SEQ ID NOs: 34, 35, and 36 and SEQ ID NOs: 58, 59, and 60	SEQ ID NOs: 38, 39, and 40 and SEQ ID NOs: 58, 59, and 60	SEQ ID NOs: 42, 43, and 44 and SEQ ID NOs: 58, 59, and 60	SEQ ID NOs: 46, 47, and 48 and SEQ ID NOs: 58, 59, and 60
VL4 CDRs SEQ ID NOs: 62, 63, and 64	SEQ ID NOs: 34, 35, and 36 and SEQ ID NOs: 62, 63, and 64	SEQ ID NOs: 38, 39, and 40 and SEQ ID NOs: 62, 63, and 64	SEQ ID NOs: 42, 43, and 44 and SEQ ID NOs: 62, 63, and 64	SEQ ID NOs: 46, 47, and 48 and SEQ ID NOs: 62, 63, and 64

In another embodiment, the antibody or binding domain thereof comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 33, 37, 41, or 45, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences). In another embodiment, the antibody or binding domain thereof comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 49, 53, 57, or 61, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In another embodiment, the anti-SCF antibody or binding domain thereof comprises a combination of heavy and light chain variable regions having the amino acid sequences as set forth in Table 2B below. In one embodiment, the anti-SCF antibody or binding domain comprises the heavy chain variable region having the amino acid sequence of SEQ ID NO: 45 (i.e., the heavy chain variable region of mAb12-H4) and the light chain variable region

having the amino acid sequence of SEQ ID NO: 57 (i.e., the light chain variable region of mAb12-L3).

Table 2B: Anti-SCF Heavy and Light Chain VH/VL Pairings

	VH1 SEQ ID NO: 33	**VH2** SEQ ID NO: 37	**VH3** SEQ ID NO: 41	**VH4** SEQ ID NO: 45
VL1 SEQ ID NO: 49	SEQ ID NOs: 33 and 49	SEQ ID NOs: 37 and 49	SEQ ID NOs: 41 and 49	SEQ ID NOs: 45 and 49
VL2 SEQ ID NO: 53	SEQ ID NOs: 33 and 53	SEQ ID NOs: 37 and 53	SEQ ID NOs: 41 and 53	SEQ ID NOs: 45 and 53
VL3 SEQ ID NO: 57	SEQ ID NOs: 33 and 57	SEQ ID NOs: 37 and 57	SEQ ID NOs: 41 and 57 VH3 + VL3	SEQ ID NOs: 45 and 57
VL4 SEQ ID NO: 61	SEQ ID NOs: 33 and 61	SEQ ID NOs: 37 and 61	SEQ ID NOs: 41 and 61	SEQ ID NOs: 45 and 61

In a particular embodiment, the anti-SCF antibody or binding domain thereof comprises a combination of heavy and light chain variable regions having the amino acid sequences as set forth in Table 9 of Example 9.

In one embodiment, the CDR1, 2, and/or 3 regions of the anti-TSLP antibodies or binding domains described herein comprise the amino acid sequences of antibody 1D10 (i.e., heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 2, 3, and 4, (b) SEQ ID NOs: 6, 7, and 8, (c) SEQ ID NOs: 10, 11, and 12, (d) SEQ ID NOs: 14, 15, and 16, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 18, 19, and 20, (b) SEQ ID NOs: 22, 23, and 24, (c) SEQ ID NOs: 26, 27, and 28, (d) SEQ ID NOs: 30, 31, and 32).

In one embodiment, the CDR1, 2, and/or 3 regions of the anti-SCF antibodies or binding domains described herein comprise the amino acid sequences of antibody mAb12 (i.e., heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 34, 35, and 36, (b) SEQ ID NOs: 38, 39, and 40, (c) SEQ ID NOs: 42, 43, and 44, (d) SEQ ID NOs: 46, 47, and 48, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ

ID NOs: 50, 51, and 52, (b) SEQ ID NOs: 54, 55, and 56, (c) SEQ ID NOs: 58, 59, and 60, (d) SEQ ID NOs: 62, 63, and 64) disclosed herein.

In another embodiment, the antibody comprises a derivative of the CDR sequences of 1D10 and mAb12, yet still retain the ability of to bind either TSLP or SCF effectively. Such derivatives include CDRs that include one or more (*e.g.*, 1, 2, 3, 4, 5, or 6) amino acid additions, deletions, or substitutions, *e.g.*, conservative sequence substitutions.

In another embodiment, the anti-TSLP or anti-SCF antibodies or binding domains comprise one or more CDRs that are, for example, 90%, 95%, 98% or 99.5% identical to one or more CDRs of antibodies 1D10 and mAb12, respectively. Ranges intermediate to the above-recited values, *e.g.*, CDRs that are 90-95%, 95-98%, or 98-100% identical identity to one or more of the above sequence. The antibody or binding domain sequences can also include consensus sequences.

Sequences substantially identical to the anti-TSLP and/or anti-SCF antibody or binding domain sequences described herein (*e.g.*, at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences), are also encompassed. In one embodiment, the anti-TSLP antibody or binding domain comprises a heavy chain variable region comprising SEQ ID NO: 1, 5, 9, 13, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences). In another embodiment, the anti-TSLP binding domain comprises a light chain variable region comprising SEQ ID NO: 17, 21, 25, 29, 18, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In another embodiment, the anti-SCF antibody or binding domain comprises a heavy chain variable region comprising SEQ ID NO: 33, 37, 41, 45, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences). In another embodiment, the anti-SCF antibody or binding domain comprises a light chain variable region comprising SEQ ID NO: 49, 53, 57, 61, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

Anti-TSLP and/or anti-SCF antibodies or binding domains thereof that compete for binding with any of the antibodies or binding domains thereof described herein or that bind the same epitope as any of the antibodies or binding domains described herein also are encompassed. For example, in one embodiment, the anti-TSLP antibody or binding domain

thereof competes for binding to TSLP with antibody 1D10, as described herein. In another embodiment, the anti-TSLP antibody or binding domain binds to the same epitope on TSLP as antibody 1D10, as described herein. In another embodiment, the anti-SCF antibody or binding domain thereof competes for binding to SCF with antibody mAb12, as described herein. In another embodiment, the anti-SCF antibody or binding domain thereof binds to the same epitope on SCF as antibody mAb12, as described herein. In another embodiment, the anti-SCF antibody or binding domain binds to soluble human SCF ($hSCF^{165}$) in preference to membrane bound human SCF ($hSCF^{222}$). In another embodiment, the anti-SCF antibody or binding domain binds to an epitope comprising residue K100 of human SCF.

In one embodiment, the bispecific or multispecific constructs provided herein comprise an anti-TSLP antibody (or binding domain) or anti-SCF antibody (or binding domain), linked to a second binding agent (e.g., a ligand, a second antibody, or antigen binding domain thereof). In another embodiment, the construct comprises an anti-TSLP antibody (or binding domain) or anti-SCF antibody (or antigen binding domain) comprising the heavy and light chain CDR and/or full-length variable region sequences respectively set forth in Tables 1A, 1B, and Tables 2A, 2B. In yet another embodiment, the second antibody (or binding domain) binds to a member of the TNF superfamily (e.g., TNFα), a tumor necrosis factor (TNF) receptor (e.g., TNFRSF4), an interleukin (e.g., IL-23, IL-23A, IL-17A, IL-5, IL-11, IL-12 or IL-13), an immunoglobulin (e.g., IgE) or an integrin (e.g., integrin α4β7) or OX40L or VEGF. The term "bispecific construct," as used herein, also refer to "multispecific constructs" which include a third, fourth, or more antibody (or fragment thereof).

In one such embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a member of the TNF superfamily (e.g., TNFα; for example variable domains of adalimumab, golimumab or certolizumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a tumor necrosis factor (TNF) receptor (e.g., TNFRSF4).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-12 and/or IL-23 (for example variable domains of guselkumab, tildrakizumab or ustekinumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-23A (for example variable domains of risankizumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-17A (for example variable domains of secukinumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-13 (for example variable domains of lebrikizumab or tralokinumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IgE (for example variable domains of omalizumab or ligelizumab).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-5.

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-11.

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to CD40L (for example variable domains of oxelumab; see US Patent 7501496).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to VEGF (for example variable domains of bevacizumab; see US Patent 7060269).

In a further embodiment there is provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to an integrin (e.g., integrin $\alpha 4\beta 7$; for example variable domains of vedolizumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a member of the TNF superfamily (e.g., TNFα; for example variable domains of adalimumab, golimumab or certolizumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to

IL-12 and/or IL-23 (for example variable domains of guselkumab, tildrakizumab or ustekinumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-23A (for example variable domains of risankizumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-17A (for example variable domains of secukinumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-13 (for example variable domains of lebrikizumab or tralokinumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IgE (for example variable domains of omalizumab or ligelizumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to an integrin (e.g., integrin $\alpha 4\beta 7$; for example variable domains of vedolizumab).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to CD40L (for example variable domains of oxelumab; see US Patent 7501496).

In a further embodiment there is provided a construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to VEGF (for example variable domains of bevacizumab; see US Patent 7060269).

In another embodiment, the anti-TSLP antibody (or antigen binding domain) of the bispecific or multispecific construct comprises the heavy and/or light chain CDR and/or full-length variable region amino acid sequences as respectively set forth in Tables 1A and 1B. In another embodiment, the anti-SCF antibody (or antigen binding domain) of the bispecific or multispecific construct comprises the heavy and/or light chain CDR and/or full-length variable region amino acid sequences as set forth in Tables 2A and 2B.

In another embodiment, a bispecific or multispecific construct comprises an anti-TSLP antibody (or binding domain) and an anti-SCF antibody (or binding domain) linked to each other. Thus, there is further provided a construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to TSLP.

In particular embodiments the anti-SCF and/or anti-TSLP antibodies or binding domains are antibodies or binding domains having CDRs and/or variable domain sequences as described herein.

In one embodiment, the bispecific construct comprises:

(a) an anti-TSLP binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 5A, or conservative sequence modifications thereof, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 5B, or conservative sequence modifications thereof; and

(b) an anti-SCF binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8A, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8B, or conservative sequence modifications thereof.

In another embodiment, the bispecific construct comprises:

(a) an anti-TSLP binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 2, 3, and 4, (ii) SEQ ID NOs: 6, 7, and 8, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 18, 19, and 20, (ii) SEQ ID NOs: 22, 23, and 24, (iii) SEQ ID NOs: 26, 27, and 28, (iv) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof; and

(b) an anti-SCF binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 34, 35, and 36, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, (iv) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino

acid sequences respectively set forth in (i) SEQ ID NOs: 50, 51, and 52, (ii) SEQ ID NOs: 54, 55, and 56, (iii) SEQ ID NOs: 58, 59, and 60, (iv) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof.

In one embodiment, the bispecific construct comprises:

(a) an anti-TSLP binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 6, 7, and 8, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 18, 19, and 20, or conservative sequence modifications thereof; and

(b) an anti-SCF binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 58, 59, and 60, or conservative sequence modifications thereof.

In another embodiment, the bispecific construct comprises a combination of anti-TSLP heavy and light chain variable region sequences having the amino acid sequences set forth in Table 1B, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences), and anti-SCF heavy and light chain variable region sequences having the amino acid sequences set forth in Table 2B, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In another embodiment, the bispecific constructcomprises anti-TSLP heavy and light chain variable region sequences having the amino acid sequences set forth in Table 4, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences), and anti-SCF heavy and/or light chain variable region sequences having the amino acid sequences set forth in Table 5, or a sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In another embodiment, the bispecific construct comprises:

(a) an anti-TSLP binding domain comprising a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 1B, or sequences at least 90% identical thereto; and

(b) an anti-SCF binding domain comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 34, 35, and 36, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, (iv) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 50, 51, and 52, (ii) SEQ ID NOs: 54, 55, and 56, (iii) SEQ ID NOs: 58, 59, and 60, (iv) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof.

In another embodiment, the bispecific construct comprises:

(a) an anti-SCF binding domain comprising a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 2B, or sequences at least 90% identical thereto; and

(b) an anti-TSLP binding domain comprising heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 2, 3, and 4, (ii) SEQ ID NOs: 6, 7, and 8, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 18, 19, and 20, (ii) SEQ ID NOs: 22, 23, and 24, (iii) SEQ ID NOs: 26, 27, and 28, (iv) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof.

In another embodiment, the bispecific construct comprises an anti-TSLP binding domain and an anti-SCF binding domain comprising amino acid sequences set forth in Table 10 of Example 19, e.g., construct 5.7 (1D10 (VH1-L1) – mAb12 (VH4-L3)), also referred to herein as CDX-622.In one embodiment, the anti-TSLP binding domain and the anti-SCF binding domain are genetically fused. The bispecific construct can be, for example, a fusion protein, which can be made by genetic engineering using standard recombinant DNA techniques to operatively link nucleic acid encoding the anti-TSLP7 and anti-SCF binding

domains. In another embodiment, the anti-TSLP binding domain and the anti-SCF binding domain are chemically conjugated.

For example, the bispecific construct can be a conjugate made by chemical conjugation of the anti-TSLP and anti-SCF binding domains. In one embodiment, the anti-TSLP binding domain further comprises a human IgG1 constant domain. In another embodiment, the anti-SCF binding domain is linked to the C-terminus of the heavy chain of the anti-TSLP binding domain. In another embodiment, the anti-SCF binding domain is a scFv.

In another embodiment, the anti-TSLP binding domain further comprises a human IgG1 constant domain. In another embodiment, the anti-SCF binding domain is linked to the C-terminus of the heavy chain of the anti-TSLP binding domain. In another embodiment, the anti-SCF binding domain is a scFv.

In another embodiment, the anti-SCF binding domain further comprises a human IgG1 constant domain. In another embodiment, the anti-TSLP binding domain is linked to the C-terminus of the heavy chain of the anti-SCF binding domain. In another embodiment, the anti-TSLP binding domain is a scFv.

In a particular embodiment, the bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 2, 3, and 4, (ii) SEQ ID NOs: 6, 7, and 8, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 18, 19, and 20, (ii) SEQ ID NOs: 22, 23, and 24, (iii) SEQ ID NOs: 26, 27, and 28, (iv) SEQ ID NOs: 30, 31, and 32;

(b) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 34, 35, and 36, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, or (iv) SEQ ID NOs: 46, 47, and 48, and/or light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 50, 51, and 52, (ii) SEQ ID NOs: 54, 55, and 56, (iii) SEQ ID NOs: 58, 59, and 60, or (iv) SEQ ID NOs: 62, 63, and 64; and

and

(c) a human IgG1 constant domain.

In one embodiment, the bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 6, 7, and 8, and light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 18, 19, and 20;

(b) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 46, 47, and 48, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 58, 59, and 60; and

and

(c) a human IgG1 constant domain.

In another particular embodiment, the bispecific construct comprises an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 34, 35, and 36, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, or (iv) SEQ ID NOs: 46, 47, and 48, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 50, 51, and 52, (ii) SEQ ID NOs: 54, 55, and 56, (iii) SEQ ID NOs: 58, 59, and 60, or (iv) SEQ ID NOs: 62, 63, and 64 and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 2, 3, and 4, (ii) SEQ ID NOs: 6, 7, and 8, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, and light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 18, 19, and 20, (ii) SEQ ID NOs: 22, 23, and 24, (iii) SEQ ID NOs: 26, 27, and 28, (iv) SEQ ID NOs: 30, 31, and 32.

In one embodiment, the bispecific construct comprises an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(c) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 46, 47, and 48, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 58, 59, and 60, and a human IgG1 constant domain; and

(d) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 6, 7, and 8, and light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in SEQ ID NOs: 18, 19, and 20.

In a particular embodiment, the bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-TSLP antibody comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 1B and a human IgG1 constant domain; and

(b) the anti-SCF scFv comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 2B.

In another particular embodiment, the bispecific construct comprises an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 2B and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 1B.

In a particular embodiment, the bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-TSLP antibody comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 4 and a human IgG1 constant domain; and

(b) the anti-SCF scFv comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 5.

In another particular embodiment, the bispecific construct comprises an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 5 and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 4.

In a particular embodiment, the bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-TSLP antibody comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 6 and a human IgG1 constant domain; and

(b) the anti-SCF scFv comprises a combination of heavy and light chain variable region sequences having the amino acid sequences set forth in Table 6.

An exemplary bispecific is construct 5.2 (1D10 H2-mAb 12 VH1VL4 (ds)) having the amino acid sequence as set forth in SEQ ID NO: 65 or encoded by the nucleotide sequence as set forth in SEQ ID NO: 66.

Another exemplary bispecific is construct 5.7 (1D10 H2- mAb12 VH4VL3 (ds)), also referred to herein as "CDX-622," having the amino acid sequence as set forth in SEQ ID NO: 67 or encoded by the nucleotide sequence as set forth in SEQ ID NO: 68.

Also provided herein are compositions including any of the antibodies, antigen binding fragments, or bispecific constructs described herein and a pharmaceutically acceptable carrier. Further provided are kits or vials comprising any of the antibodies, antigen binding fragments, or bispecific constructs described herein and instructions for use.

In a further embodiment, isolated nucleic acid molecules encoding the antibodies, antigen binding fragments, or bispecific constructs described herein are also provided, as well as expression vectors comprising such nucleic acids and host cells comprising such expression vectors.

In one embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding an antibody variable region, wherein the antibody variable region comprises an amino acid sequence as set forth in SEQ ID NO: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, or an amino acid sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to one or more of the aforementioned sequences).

In another embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding heavy and light chain variable regions of an antibody, wherein the heavy and light chain variable regions comprise the amino acid sequences as shown in Table 1B or Table 2B, or amino acids sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical the aforementioned sequences).

Also provided herein are *in vitro* and *in vivo* methods for blocking or inhibiting TSLP and/or SCF binding to its receptor (i.e., TLSPR and c-Kit, respectively) comprising contacting cells expressing TSLPR or c-Kit with the antibodies, antigen binding fragments, or bispecific constructs (or compositions) described herein, in an amount effective to block TSLP and/or SCF binding to its receptor.

In another aspect, methods for inhibiting activation of immune cells, as well as reducing or preventing the accumulation of immune cells within organs or tissues, in a subject are provided comprising administering to the subject any of the antibodies, antigen binding fragments, or bispecific constructs(or compositions) described herein, in an amount effective to inhibit activation of immune cells or reduce accumulation of immune cells within organs or tissues in a subject. In one embodiment, such methods result in inhibition or blocking of (a) TSLP-induced activation and/or proliferation of mast cells, DC, and/or NKT cells, (b) TSLP-induced osteoprotegerin (OPG) secretion, (c) TSLP-induced secretion of Th2 cytokines (such as TARC, CCL22, IL-4, IL-13 or IL-5), and / or (d) SCF-induced secretion of mast cells, eosinophils, type 2 innate lymphoid (ILC2) cells, and/or type 3 innate lymphoid (ILC3) cells.

In another embodiment, methods are provided herein for reducing or inhibiting inflammation, as well as methods of treating an inflammatory disease or disorder in a subject in need thereof (*e.g.*, autoimmune diseases, cardiovascular diseases, gastrointestinal diseases, lung diseases, metabolic diseases (such as Type 2 diabetes), vasculitis (including large vessel vasculitis such as Takayasu's arteritis, polymyalgia rheumatica and temporal arteritis; medium vessel vasculitis such as Buerger's disease, Kawasaki disease, cutaneous vasculitis and polyarteritis nodosa and small vessel vasculitis such as Behcet's syndrome, Churg-Strauss syndrome, cutaneous vasculitis, Henoch-Schonlein purpura, granulomatosis with polyangiitis, microscopic polyangiitis and cryoglobulinemia), neurodegenerative diseases (such as Parkinson's disease), certain types of cancer (such as colon cancer) and mental

illnesses (such as depression)), by administering the antibodies, antigen binding fragments, or bispecific constructs (or compositions) described herein to a patient in need thereof in an amount effective to inhibit or reduce inflammation in a subject.

In another embodiment, methods of for treating a condition or disease in a subject are provided comprising administering to the subject any of the antibodies, antigen binding fragments, or bispecific constructs (or compositions) described herein, in an amount effective to treat the condition or disease. The subject can be, for example, one who suffers from a condition or disease in which reduction of inflammation is desired. In one embodiment, the condition or disease is associated with immune cell migration, activation, and/or proliferation *via* interaction (*e.g.*, binding) of TSLP and/or SCF with is receptor (TSLPR and/or c-Kit, respectively) on immune cells, such as disorders of the immune system, allergic inflammation, allergic airway inflammation, DC-mediated inflammatory Th2 responses, atopic dermatitis, atopic eczema, asthma, obstructive airways disease, chronic obstructive pulmonary disease (COPD), and food allergies, inflammatory arthritis, rheumatoid arthritis, psoriasis, IgE-mediated disorders, and rhino-conjunctivitis. Other conditions and disorders include fibrotic diseases and maladies associated with tissue remodeling, *e.g.*, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, smoking-induced lung injury, acute respiratory distress syndrome, cystic fibrosis, peribronchial fibrosis, hypersensitivity pneumonitis, asthma, sclerodoma, inflammation, liver cirrhosis, renal fibrosis, parenchymal fibrosis, endomyocardial fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, fibrous histiocytoma, fibrothorax, hepatic fibrosis, fibromyalgia, gingival fibrosis, or radiation-induced fibrosis.

In another embodiment, methods for treating a condition or disease in a subject are provided, wherein the method comprises administering to the subject a combination of any of the anti-TSLP antibodies, or antigen binding fragments thereof, described herein, and anti-SCF antibodies, or antigen binding fragments thereof, described herein. In one embodiment:

(i) the anti-TSLP antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 2, 3, and 4, (b) SEQ ID NOs: 6, 7, and 8, (c) SEQ ID NOs: 10, 11, and 12, (d) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 18, 19, and 20, (b)

SEQ ID NOs: 22, 23, and 24, (c) SEQ ID NOs: 26, 27, and 28, (d) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof; and

(ii) the anti-SCF antibody, or antigen binding fragment thereof, comprising heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 34, 35, and 36, (b) SEQ ID NOs: 38, 39, and 40, (c) SEQ ID NOs: 42, 43, and 44, (d) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 50, 51, and 52, (b) SEQ ID NOs: 54, 55, and 56, (c) SEQ ID NOs: 58, 59, and 60, (d) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof.

In another embodiment,

(i) the anti-TSLP antibody, or antigen binding fragment thereof, comprises heavy and light chain variable region amino acid sequences as set forth in Table 1B, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences); and

(ii) the anti-SCF antibody, or antigen binding fragment thereof, comprises heavy and light chain variable region amino acid sequences as set forth in Table 2B, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

In one embodiment, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen binding fragment thereof, are administered separately. In one embodiment, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen binding fragment thereof, are administered sequentially. For example, the anti-TSLP antibody, or antigen binding fragment thereof, can be administered first followed by (*e.g.*, immediately followed by) administration of the anti-SCF antibody, or antigen binding fragment thereof, or vice versa. In another embodiment, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen binding fragment thereof, are administered together. In another embodiment, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen binding fragment thereof, are administered simultaneously. In another embodiment, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen binding fragment thereof, are simultaneously administered in a single formulation. Alternatively, the anti-TSLP antibody, or antigen binding fragment thereof, and the anti-SCF antibody, or antigen

binding fragment thereof, are formulated for separate administration and are administered concurrently or sequentially. Such concurrent or sequential administration preferably results in both antibodies being simultaneously present in treated patients.

In one embodiment, an antibody, antigen binding fragment, or bispecific construct (or composition described herein) is administered in combination with one or more additional therapeutic agent or procedure.

III. Brief Description of the Drawings

FIGs. 1-3 are graphs showing binding of anti-TSLP antibodies to human TSLP, as a function of antibody concentration.

FIGs. 4-6 are graphs showing anti-TSLP antibodies block binding of human TSLP to human TSLP receptor (TSLP-R).

FIG. 7 is a graph showing anti-TSLP antibodies inhibit BaF3 cell proliferation.

FIG. 8 is a graph showing anti-TSLP antibodies inhibit TARC induction in human dendritic cells.

FIGs. 9A and 9B are tables showing the affinity and kinetic parameters (with background subtracted) of anti-TSLP antibodies for human (FIG. 9A) and cynomolgus (FIG. 9B) TSLP.

FIGs. 10 and 11 are graphs showing binding of anti-SCF antibodies to human SCF, as a function of antibody concentration.

FIGs. 12 and 13 are graphs showing anti-SCF antibodies block binding of human SCF to human c-Kit.

FIGs. 14A and 14B are tables showing the affinity and kinetic parameters (with background subtracted) of anti-SCF antibodies for human (FIG. 14A) and cynomolgus (FIG. 14B) SCF.

FIG. 15 is a graph showing anti-SCF antibodies inhibit c-Kit phosphorylation in human CHO-KIT cells.

FIG. 16 is a graph showing anti-SCF antibodies inhibit human mast cell degranulation.

FIG. 17 is a graph showing anti-SCF antibodies inhibit M-07e cell proliferation.

FIGs. 18A and 18B are graphs showing how binding of anti-SCF to human SCF is affected by mutating amino acid residues in human SCF.

FIG. 18C is a three-dimensional drawing showing the binding of SCF to KIT-D1 including residue K100.

FIGs. 19A and 19B are graphs showing binding of anti-SCF antibodies to Sl/Sl4 mouse cells.

FIG. 20 is a graph showing anti-SCF antibodies inhibit c-Kit phosphorylation in human M-07e cells.

FIGs. 21A and 21B are schematics showing the structure of the bispecific construct having an anti-SCF antibody linked to an anti-TSLP scFV (A) and an anti-TSLP antibody linked to an anti-SCF scFV (B).

FIG. 22 is a graph showing binding of bispecific antibody constructs to human TSLP.

FIG. 23 is a graph showing binding of bispecific antibody constructs to human SCF.

FIG. 24 is a graph showing binding of bispecific antibody constructs to human TSLP and human SCF.

FIGs. 25A and 25B are graphs showing bispecific antibody constructs block binding of human TSLP to human TSLP receptor (TSLP-R).

FIG. 26 is a graph showing bispecific antibody constructs block binding of human SCF to c-Kit.

FIGs. 27A and 27Bare graphs showing bispecific antibody constructs inhibit BaF3 cell proliferation.

FIGs. 28A and 28B are graphs showing bispecific antibody constructs inhibit TARC induction in human dendritic cells.

FIGs. 29A and 29B are tables showing the affinity and kinetic parameters (with background subtracted) of bispecific antibody constructs for human TSLP and SCF and cynomolgus TSLP and SCF.

FIG. 30 is a graph showing bispecific antibody constructs inhibit c-Kit phosphorylation in human CHO-KIT cells.

FIG. 31 is a graph showing bispecific antibody constructs inhibit human mast cell degranulation.

FIG. 32 is a graph showing bispecific antibody constructs inhibit M-07e cell proliferation.

FIG. 33 is a graph showing bispecific antibody, CDX-622, blocks KIT phosphorylation in M-07e cells that have been stimulated with soluble SCF with greater potency than KIT stimulated with SCF^{220}-expressing cells.

FIGs. 34A and 34B are graphs respectively showing downregulation in the expression of mast cell and melanocyte genesassociated with mast cell function in skin biopsies of cynomolgus macaques after dosing with mAb12.

FIGs. 35A and 35B are representative images of the biopsy cross sections from animals treated with mAb12 before treatment (FIG. 35A) and at day 30 (FIG. 35B).

FIGs. 36A and 36B are tables showing the mast cell count with the average data shown in FIG. 36A and the aggregate data shown in FIG. 36B.

FIGs. 37A, 37B, and 37C are graphs analyzing Mean Corpuscular Hemoglobin (FIG. 37A), Mean Corpuscular Hemoglobin Concentration (FIG. 37B), and Mean Corpuscular Volume (FIG. 37C).

FIG. 38 is a graph showing circulating levels of mAb12 from serum samples collected from the monkeys over the course of the study.

FIG. 39 is a graph showing the presence of anti-drug antibodies (ADAs) from the monkeys over the course of the study (the red line indicates the cutpoint of the assay).

FIGs. 40A-40F are graphs showing administration of bispecific antibody, CDX-622, did not result in significant decreases in hematological parameters in a study in cynomolgus macaques.

FIGs. 41A-41F are graphs showing the decrease in the expression of several selected genes associated with mast cell function in skin biopsies of cynomolgus macaques after dosing with CDX-622.

FIG. 42 is a graph showing inhibition by the bispecific antibody, CDX-622, of TSLP-induced CD80 expression on human dendritic cells.

FIG. 43 is a graph showing inhibition by the bispecific antibody, CDX-622, of TSLP binding to TSLP-R (ELISA).

FIG. 44 is a graph showing inhibition by the bispecific antibody, CDX-622, of TSLP-mediated cell proliferation (BaF3 Cells).

FIG. 45 is a graph showing the survival rate of human eosinophils treated with bispecific antibody, CDX-622.

FIG. 46 is a graph showing SCF-induced cytokine release from human primary mast cells treated with antibodies mAb12, 1D10, or bispecific, CDX-622.

FIG. 47 is a graph showing MCP-1 induction with SCF and TSLP in LAD2 cells.

FIG. 48 is a graph showing simultaneous blockade of SCF and TSLP in LAD2 cells treated with antibodies mAb12, 1D10, or bispecific, CDX-622.

FIG. 49 is a graph showing inhibition of TSLP-induced CD80 expression on human dendritic cells treated with antibody 1D10 or bispecific CDX-622.

IV. Detailed Description of the Invention

In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

A. Definitions

As used herein, the term "subject" includes any human or non-human animal. For example, the methods and compositions of the present invention can be used to treat a subject with an immune disorder. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, *etc.*

As used herein, the terms "binding domain" and "antigen binding portion" are used interchangeably and refer to the portion of a protein or antibody which comprises the amino acid residues that interact with an antigen. Binding domains include, but are not limited to, antibodies (*e.g.*, full length antibodies), as well as antigen-binding portions thereof. The binding domain confers on the binding agent its specificity and affinity for the antigen. The term also covers any protein having a binding domain which is homologous or largely homologous to an immunoglobulin-binding domain. Such proteins may be derived from natural sources, or partly or wholly synthetically produced.

The term "antibody" as referred to herein includes whole antibodies. An "antibody" refers, in one preferred embodiment, to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds~~, or an antigen binding fragment thereof~~. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that

interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

The term "antigen-binding fragment" of an antibody (or simply "antibody fragment" or "binding domain"), as used herein, refers to one or more fragments or portions of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, human TSLP or human SCF). Such "fragments" are, for example between about 8 and about 1500 amino acids in length, suitably between about 8 and about 745 amino acids in length, suitably about 8 to about 300, for example about 8 to about 200 amino acids, or about 10 to about 50 or 100 amino acids in length. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR) or (vii) a combination of two or more isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (sFv); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

The term "monoclonal antibody," as used herein, refers to an antibody that displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to an antibody which displays a single binding specificity and which has variable and optional constant regions derived from human germline

immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma that includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody," as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art (see, *e.g.*, Lonberg (2005) Nature Biotech. 23(9):1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen may not have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

The term "human antibody" includes antibodies having variable and constant regions (if present) of human germline immunoglobulin sequences. Human antibodies of the invention can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*) (*see*, Lonberg, N. *et al.* (1994) *Nature* 368(6474): 856-859); Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764:536-546). However, the term "human antibody" does not

include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences (*i.e.*, chimeric and humanized antibodies).

An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds to human TSLP or human SCF is substantially free of antibodies that specifically bind antigens other than human TSLP or human SCF; an isolated antibody that specifically binds to human TSLP is substantially free of antibodies that specifically bind antigens other than human TSLP). An isolated antibody that specifically binds to an epitope may, however, have cross-reactivity to the same antigen from different species. In addition, an isolated antibody is typically substantially free of other cellular material and/or chemicals.

The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*, epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from the antigen (*e.g.*, TSLP or SCF) are tested for reactivity with the given antibody (*e.g.*, an anti-TSLP or anti-SCF antibody. Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, *Epitope Mapping Protocols in Methods in Molecular Biology,* Vol. 66, G. E. Morris, Ed. (1996)).

The term "antibody that binds the same epitope" as another antibody is intended to encompass antibodies that interact with, i.e., bind to, the same structural region on human TSLP or human SCF as a reference anti-TSLP antibody or reference anti-SCF antibody. The "same epitope" to which the antibodies bind may be a linear epitope or a conformational epitope formed by tertiary folding of the antigen.

The term "competing antibody" refers to an antibody that competes for binding to human TSLP with a reference anti-TSLP antibody or an antibody that competes for binding to human SCF with a reference anti-SCF antibody, i.e., competitively inhibits binding of the reference anti-TSLP antibody to TSLP or competitively inhibits binding of the reference anti-SCF antibody to SCF. A "competing antibody" may bind the same epitope on TSLP or SCF as the reference anti-TSLP antibody or reference anti-SCF antibody, may bind to an overlapping epitope or may sterically hinder the binding of the reference anti-TSLP antibody to TSLP or reference anti-SCF antibody to SCF.

Antibodies that recognize the same epitope or compete for binding can be identified using routine techniques. Such techniques include, for example, an immunoassay, which shows the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as TSLP or SCF. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

Other techniques include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope. Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue

within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest to affinity isolate specific short peptides from combinatorial phage display peptide libraries. The peptides are then regarded as leads for the definition of the epitope corresponding to the antibody used to screen the peptide library. For epitope mapping, computational algorithms have also been developed which have been shown to map conformational discontinuous epitopes.

As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to antibody binding to an epitope on a predetermined antigen. Typically, the antibody binds with an equilibrium dissociation constant (K_D) of approximately less than 10^{-7} M, such as approximately less than 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument (*e.g.*, using recombinant human TSLP or recombinant human SCF as the analyte and the antibody as the ligand) and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

The term "K_D," as used herein, is intended to refer to the dissociation equilibrium constant of a particular antibody-antigen interaction. Typically, the human antibodies of the invention bind to TSLP or SCF with a dissociation equilibrium constant (K_D) of approximately 10^{-8} M or less, such as less than 10^{-9} M or 10^{-10} M or even lower when determined by surface plasmon resonance (SPR) technology in a BIACORE 2000 instrument (*e.g.*, using recombinant human TSLP or recombinant human SCF as the analyte and the antibody as the ligand).

The term "kd" as used herein, is intended to refer to the off rate constant for the dissociation of an antibody from the antibody/antigen complex.

The term "ka" as used herein, is intended to refer to the on rate constant for the association of an antibody with the antigen.

The term "EC50," as used herein, refers to the concentration of an antibody or an antigen-binding portion thereof, which induces a response, either in an *in vitro* or an *in vivo*

assay, which is 50% of the maximal response, *i.e.*, halfway between the maximal response and the baseline.

As used herein, "isotype" refers to the antibody class (*e.g.*, IgM or IgGl) that is encoded by heavy chain constant region genes. In one embodiment, a human monoclonal antibody of the invention is of the IgG1 isotype. In another embodiment, a human monoclonal antibody of the invention is of the IgG2 isotype.

As used herein, the terms "inhibits" or "blocks" (*e.g.*, referring to inhibition/blocking of binding of TSLP to TSLP receptor (TSLP-R) and/or SCF to c-Kit) are used interchangeably and encompass both partial and complete inhibition/blocking. The inhibition/blocking preferably reduces or alters the normal level or type of activity that occurs when binding occurs without inhibition or blocking. Inhibition and blocking are also intended to include any measurable decrease in the binding affinity of TSLP-R when in contact with an anti-TSLP antibody as compared to TSLP-R not in contact with an anti-TSLP antibody, *e.g.*, inhibits binding of CD70 by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% , 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. Similarly, inhibition and blocking are also intended to include any measurable decrease in the binding affinity of c-Kit when in contact with an anti-SCF antibody as compared to c-Kit not in contact with an anti-SCF antibody, *e.g.*, inhibits binding of CD70 by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% , 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In one embodiment, the anti-TSLP antibody (or anti-SCF antibody) inhibits binding of TSLP-R (or c-Kit) by at least about 70%. In another embodiment, the anti-TSLP antibody (or anti-SCF antibody) inhibits binding of TSLP-R (or c-Kit) by at least 80%. Inhibition and blocking are also intended to include any measurable decrease in the binding affinity of TSLP or SCF when in contact with an anti-TSLP (or anti-SCF) antibody as compared to TSLP or SCF not in contact with an anti-TSLP (or anti-SCF) antibody, *e.g.*, inhibits binding of TSLP or SCF by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% , 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In one embodiment, the anti-TSLP antibody inhibits binding of TSLP by at least about 70%. In another embodiment, the anti-TSLP antibody inhibits binding of TSLP by at least 80%. In one embodiment, the anti-SCF antibody inhibits binding of SCF by at least about 70%. In another embodiment, the anti-SCF antibody inhibits binding of SCF by at least 80%.

The term "cross-reacts," as used herein, refers to the ability of an anti-TSLP binding domain or an anti-SCF binding domain of the invention to bind to TSLP or SCF, respectively, from a different species. For example, a TSLP binding domain of the invention that binds human TSLP may also bind another species of TSLP. Similarly, an anti-SCF binding domain of the invention that binds human SCF may also bind another species of SCF. As used herein, cross-reactivity is measured by detecting a specific reactivity with purified antigen in binding assays (*e.g.*, SPR, ELISA) or binding to, or otherwise functionally interacting with, cells physiologically expressing TSLP or SCF. Methods for determining cross-reactivity include standard binding assays as described herein, for example, by Biacore™ surface plasmon resonance (SPR) analysis using a Biacore™ 2000 SPR instrument (Biacore AB, Uppsala, Sweden), or flow cytometric techniques.

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The present invention also encompasses "conservative sequence modifications" of any of the sequences set forth in SEQ ID NOs: 1-349, *i.e.*, nucleotide and amino acid sequence modifications which do not abrogate the binding of the VH and VL sequences encoded by the nucleotide sequence or containing the amino acid sequence, to the antigen. Such conservative sequence modifications include conservative nucleotide and amino acid substitutions, as well as, nucleotide and amino acid additions and deletions. For example, modifications can be introduced into SEQ ID NOs:1-349 by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions include ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an anti-TSLP or anti-SCF

antibody is preferably replaced with another amino acid residue from the same side chain family. Methods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, *e.g.*, Brummell *et al.*, *Biochem.* 32:1180-1187 (1993); Kobayashi *et al. Protein Eng.* 12(10):879-884 (1999); and Burks *et al. Proc. Natl. Acad. Sci. USA* 94:412-417 (1997)).

In certain embodiments, conservative amino acid sequence modifications refer to at most 1, 2, 3, 4 or 5 conservative amino acid substitutions to the CDR sequences described herein. For example, each such CDR may contain up to 5 conservative amino acid substitutions, *e.g.*, up to (i.e., not more than) 4 conservative amino acid substitutions, *e.g.*,up to (i.e., not more than) 3 conservative amino acid substitutions, *e.g.*, up to (i.e., not more than) 2 conservative amino acid substitutions, or no more than 1 conservative amino acid substitution.

Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an anti-TSLP or anti-SCF binding domain coding sequence, such as by saturation mutagenesis, and the resulting modified anti-TSLP or anti-SCF antibodies can be screened for binding activity.

For nucleic acids, the term "substantial homology" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

For amino acids, the term "substantial homology" indicates that two amino acid sequences, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate amino acid insertions or deletions, in at least about 80% of the amino acids, usually at least about 90% to 95%, and more preferably at least about 98% to 99% or 99.5% of the amino acids.

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences identical to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences identical to the protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

In specific embodiments, an antibody os bispecific antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues.

In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG1 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six)

non-naturally occurring amino acid residues selected from the group consisting of 234A, 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235A, 235D, 235R, 235W, 235P, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 236E, 239D, 239E, 239N, 239Q, 239F, 239T, 239H, 239Y, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R.243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 252Y, 254T, 256E, 2621, 262A, 262T, 262E, 2631, 263A, 263T, 263M, 264L, 2641, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 2651, 265L, 265H, 265T, 2661, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 269G, 297S, 297D, 297E, 298H, 298I, 298T, 298F, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 322Q, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327G, 327W, 327N, 327L, 328S, 328M, 328D, 328E, 328N, 328Q, 328F, 3281, 328V, 328T, 328H, 328A, 329F, 329H, 329Q, 330K, 330G, 330T, 330C, 330L, 330Y, 330V, 3301, 330F, 330R, 330H, 332D, 332S, 332W, 332F, 332E, 332N, 332Q, 332T, 332H, 332Y, and 332A as numbered by the EU index as set forth in Kabat. Optionally, the Fc region or domain may comprise additional and/or alternative non-naturally occurring amino acid residues known to one skilled in the art (see, e.g., U.S. Patents 5,624,821; 6,277,375; 6,737,056; PCT Patent Publications WO 01/58957; WO 04/016750; WO 04/029207; WO 04/035752 and WO 05/040217). In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG2 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG3 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG4 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or

addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art.

In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG1 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one non-naturally occurring amino acid residue (e.g., one, two, three, four, five or six) selected from the group consisting of 234A, 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235A, 235D, 235R, 235W, 235P, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235F, 236E, 239D, 239E, 239N, 239Q, 239F, 239T, 239H, 239Y, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R.243W, 243L 243Y, 243R, 243Q, 244H, 245A, 247V, 247G, 252Y, 254T, 256E, 2621, 262A, 262T, 262E, 2631, 263A, 263T, 263M, 264L, 2641, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265G, 265N, 265Q, 265Y, 265F, 265V, 2651, 265L, 265H, 265T, 2661, 266A, 266T, 266M, 267Q, 267L, 269H, 269Y, 269F, 269R, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 269G, 297S, 297D, 297E, 298H, 298I, 298T, 298F, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 313F, 322Q, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 327G, 327W, 327N, 327L, 328S, 328M, 328D, 328E, 328N, 328Q, 328F, 3281, 328V, 328T, 328H, 328A, 329F, 329H, 329Q, 330K, 330G, 330T, 330C, 330L, 330Y, 330V, 3301, 330F, 330R, 330H, 332D, 332S, 332W, 332F, 332E, 332N, 332Q, 332T, 332H, 332Y, and 332A as numbered by the EU index as set forth in Kabat. Optionally, the Fc region or domain may comprise additional and/or alternative non-naturally occurring amino acid residues known to one skilled in the art (see, e.g., U.S. Patents 5,624,821; 6,277,375; 6,737,056; PCT Patent Publications WO 01/58957; WO 04/016750; WO 04/029207; WO 04/035752 and WO 05/040217). In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG2 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG3 and comprises at least one (e.g., one, two, three, four, five or six) amino acid

modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In a specific embodiment, an antibody described herein comprises a modified Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG4 and comprises at least one (e.g., one, two, three, four, five or six) amino acid modifications (e.g. substitution, deletion or addition) or at least one (e.g., one, two, three, four, five or six) non-naturally occurring amino acid residues, which are equivalents to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art.

In a certain aspect, provided herein is an antibody comprising an Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG1 and comprises at least a non-naturally occurring amino acid at one or more positions selected from the group consisting of 239, 330 and 332, as numbered by the EU index as set forth in Kabat. In a specific embodiment, provided herein is an antibody comprising an Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG1 and comprises at least one non-naturally occurring amino acid selected from the group consisting of 239D, 330L and 332E, as numbered by the EU index as set forth in Kabat. Optionally, the Fc region or domain may further comprise additional non-naturally occurring amino acid at one or more positions selected from the group consisting of 252, 254, and 256, as numbered by the EU index as set forth in Kabat. In a specific embodiment, provided herein is an antibody comprising an Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG1 and comprises at least one non-naturally occurring amino acid selected from the group consisting of 239D, 330L and 332E, as numbered by the EU index as set forth in Kabat and at least one non-naturally occurring amino acid at one or more positions are selected from the group consisting of 252Y, 254T and 256E, as numbered by the EU index as set forth in Kabat. In a specific embodiment, provided herein is an antibody comprising an Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG2, IgG3, or IgG4, and comprises at least one non-naturally occurring amino acid residue that is an equivalent(s) to the amino acid residue(s) described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In a specific embodiment, provided herein is an antibody comprising an Fc region or domain, wherein the Fc region or domain is an Fc region or domain of human IgG2, IgG3, or IgG4, and comprises

at least one non-naturally occurring amino acid residue at one or more positions that are equivalent(s) to the positions described herein for a human IgG1 Fc region or domain, as can be determined by one of skill in the art. In one embodiment, an Fc region or domain comprising such sequence exhibits one or more Fc activity, for example, binding affinity to an Fc receptor or effector function, such as ADCC or CDC. In a specific embodiment, an Fc region or domain comprising such sequence exhibits reduced Fc activity, for example, reduced binding affinity to an Fc receptor or reduced effector function, such as ADCC or CDC. In a particular embodiment, an Fc region or domain comprising such sequence exhibits enhanced FcRn activity, for example, enhanced half-life.

Additional non- limiting examples of Fc region or domain modifications are provided in Ghetie et al., 1997, Nat Biotech.15:637-40; Duncan et al., 1988, Nature 332:563-564; Lund et al., 1991, J. Immunol 147:2657-2662; Lund et al., 1992, Mol Immunol 29:53-59; Alegre et al., 1994, Transplantation 57: 1537-1543; Hutchins et al., 1995, Proc Natl. Acad Sci U S A 92: 11980-11984; Jefferis et al., 1995, Immunol Lett.44: 111-117; Lund et al., 1995, Faseb J 9: 115-119; Jefferis et al., 1996, Immunol Lett 54: 101-104; Lund et al., 1996, J Immunol 157:4963-4969; Armour et al., 1999, Eur J Immunol 29:2613-2624; Idusogie et al., 2000, J Immunol 164:4178-4184; Reddy et al., 2000, J Immunol 164: 1925-1933; Xu et al., 2000, Cell Immunol 200: 16-26; Idusogie et al., 2001, J Immunol 166:2571-2575; Shields et al., 2001, J Biol Chem 276:6591-6604; Jefferis et al., 2002, Immunol Lett 82:57-65; Presta et al., 2002, Biochem Soc Trans 30:487-490); U.S. Patent Nos.5,624,821; 5,885,573; 5,677,425; 6,165,745; 6,277,375; 5,869,046; 6,121,022; 5,624,821; 5,648,260; 6,528,624; 6,194,551; 6,737,056; 6,821,505; 6,277,375; 8,163,882; 7,355,008; 7,960,512; 8,039,592; 8,039,359; 8,101,720; 7,214,775; 7,682,610; 7,741,442; U.S. Patent Publication Nos.2004/0002587 and PCT Publications WO 94/29351; WO 99/58572; WO 00/42072; WO 04/029207; WO 04/099249; WO 04/063351.

In specific embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG1 Fc region or domain, which comprises non-naturally occurring amino acids 234A, 235Q and 322Q as numbered by the EU index as set forth in Kabat. In a particular embodiment, the modified (e.g., mutated) human IgG1 Fc region or domain further comprises non-naturally occurring amino acids 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat.

In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG2 Fc region or domain, which comprises non-naturally occurring amino

acids that are equivalents to 234A, 235Q and 322Q as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art. In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG2 Fc region or domain, which comprises non-naturally occurring amino acids that are equivalents to 234A, 235Q, 322Q, 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art.

In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG3 Fc region or domain, which comprises non-naturally occurring amino acids that are equivalents to 234A, 235Q and 322Q as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art. In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG3 Fc region or domain, which comprises non-naturally occurring amino acids that are equivalents to 234A, 235Q, 322Q, 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art.

In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG4 Fc region or domain, which comprises non-naturally occurring amino acids that are equivalents to 234A, 235Q and 322Q as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art. In certain embodiments, the antibody described herein comprises a modified (e.g., mutated) human IgG4 Fc region or domain, which comprises non-naturally occurring amino acids that are equivalents to 234A, 235Q, 322Q, 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat for human IgG1 Fc region or domain, as can be determined by one of skill in the art.

In a specific embodiment, the antibody described herein comprises VL and VH CDR sequences set herein and a modified (e.g., mutated) human IgG1 Fc region or domain, wherein the modified (e.g., mutated) human IgG1 Fc region or domain comprises non-naturally occurring amino acids 234A, 235Q, and 322Q as numbered by the EU index as set forth in Kabat.

In a preferred embodiment, the antibody described herein comprises VL and VH CDR sequences set forth herein and a modified (e.g., mutated) human IgG1 Fc region or domain, wherein the modified (e.g., mutated) human IgG1 Fc region or domain comprises non-

naturally occurring amino acids 234A, 235Q, 322Q, 252Y, 254T and 256E as numbered by the EU index as set forth in Kabat.

B. Anti-TSLP Antibodies

Provided herein are novel anti-TSLP antibodies and binding domains thereof. The term "TSLP" (also referred to as "thymic stromal lymphopoietin") refers to a cytokine that is involved in the maturation of T cell populations through activation of antigen-presenting cells. TSLP is produced by non-hematopoietic cells, such as fibroblasts, epithelial cells, and different types of stromal or stromal-like cells. TSLP signals *via* a TSLP receptor (TSLPR, (also referred to as "CRFL2). TSLPR forms a functional complex with TSLP and IL7R and stimulates cell proliferation by activating STAT3 and STAT5, as well as JAK2. The TSLPR chain is closely related to the common receptor gamma chain that is expressed on a wide range of cell types in the adaptive and innate immune system and is implicated in the development of the haematopoietic system.

TSLP also affects the polarization of dendritic cells to drive T helper (Th) 2 cytokine production, directly promotes T-cell proliferation in response to T-cell receptor activation and Th2 cytokine production, and supports B-cell expansion and differentiation. TSLP further amplifies Th2 cytokine production by mast cells and natural killer T cells. These properties confer on TSLP a critical role in driving Th2-mediated inflammation. Accordingly, TSLP expression is linked to many disease states including asthma, inflammatory arthritis, atopic dermatitis, eczema, eosinophilic esophagitis, and others.

The term "TSLP" includes any variants or isoforms of TSLP which are naturally expressed by cells (*e.g.*, human TSLP deposited with the UniProt® consortium having accession no. Q969D9-1 as set forth in SEQ ID NO: 70).

Accordingly, TSLP antibodies (or binding domains) of the invention may cross-react with TSLP from species other than human. Alternatively, the TSLP antibodies (or binding domains) may be specific for human TSLP and may not exhibit any cross-reactivity with other species. TSLP or any variants and isoforms thereof, may either be isolated from cells or tissues that naturally express them or be recombinantly produced using well-known techniques in the art and/or those described herein. Preferably the TSLP antibodies (or binding domains) are targeted to human TSLP, which has a normal glycosylation pattern.

In another embodiment, the anti-TSLP antibody (or binding domain) comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable region of any one of

antibodies 1D10-A, 1D10-B, 1D10-C, 1D10-D, 1D10-E, 1D10-F, 1D10-G, 1D10-H, or 1D10-I (as shown in Tale 5 of Example 2). For example, the anti-TSLP antibody or binding domain thereof comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 5, 9, or 13, and/or the CDR1, CDR2 and CDR3 domains of the light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17, 21, 25, or 29. In another embodiment, the anti-TSLP antibody (or binding domain) comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 5A, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 5B, or conservative sequence modifications thereof. In another embodiment, the anti-TSLP antibody or (binding domain) comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 2, 3, and 4, (b) SEQ ID NOs: 6, 7, and 8, (c) SEQ ID NOs: 10, 11, and 12, (d) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the sequences respectively set forth in (a) SEQ ID NOs: 18, 19, and 20, (b) SEQ ID NOs: 22, 23, and 24, (c) SEQ ID NOs: 26, 27, and 28, (d) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof, as set forth in Table 1A. In one embodiment, the anti-TSLP antibody (or binding domain) respectively comprises the heavy chain CDR1, CDR2, and CDR3 sequences set forth in SEQ ID NOs: 6, 7, and 8, and the light chain CDR1, CDR3, and CDR3 sequences set forth in SEQ ID NOs: 18, 19, and 20.

In another embodiment, the anti-TSLP antibody (or binding domain) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 5, 9, or 13. In another embodiment, the antibody or binding domain thereof comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17, 21, 25, or 29. In another embodiment, the antibody (or binding domain) comprises a combination of heavy and/or light chain variable regions having the amino acid sequences set forth in Table 1B. In yet another embodiment, the anti-TSLP antibody (or binding domain) comprises a combination of heavy and light chain variable regions having the amino acid sequences set forth in Table 4. In one embodiment, the anti-TSLP antibody (or binding domain) respectively comprises the heavy and light chain variable region sequences set forth in SEQ ID NOs: 5 and 17.

Sequences substantially identical to the anti-TSLP antibodies (or binding domains) described herein (*e.g.*, at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical (identical) to the aforementioned sequences), are also provided. In one embodiment, the anti-TSLP antibody (or binding domain) comprises a heavy chain variable region comprising the combinations set forth in Table 1B or Table 4, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

Anti-TSLP antibodies (and binding domains thereof) that compete for binding with any of the anti-TSLP antibodies (or binding domains) described herein or that bind the same epitope as any of the anti-TSLP antibodies (or binding domains) described herein, are also suitable for use and provided herein. For example, in one embodiment, the anti-TSLP antibody (or binding domain), competes for binding to TSLP with antibody 1D10, as described herein (or an antibody having the heavy and/or light chain CDRs and/or heavy and light chain variable region sequences corresponding to antibody 1D10, as described herein). In another embodiment, the antibody or anti-TSLP binding domain thereof binds to the same epitope on TSLP as antibody 1D10,as described herein (or an antibody having the heavy and light chain CDRs and/or heavy and light chain variable region sequences corresponding to antibody 1D10, as described herein).

C. Anti-SCF Antibodies / Binding Domains

As used herein, the terms "stem cell factor," "SCF," "Mast cell growth factor," "MGF," "KIT-ligand," "KL," and "steel factor") are used interchangeably, and include variants, isoforms, species homologs of human SCF, and analogs having at least one common epitope with SCF. The complete SCF sequence can be found under UniProt accession no. P21583 as set forth in SEQ ID NO: 71).

SCF is a ligand for the receptor-type protein-tyrosine kinase KIT ("c-Kit") and is involved in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration, survival, activation, and in melanogenesis. Upon binding to cKit, SCF activates several signaling pathways, thus promoting phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, and subsequent activates the kinase AKT1. Binding of SCF to c-Kit also transmits signals *via* GRB2 and activates RAS, RAF1 and the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK1. SCF binding also promotes activation of STAT family members STAT1,

STAT3 and STAT5, as well as PLCG1, leading to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. SCF / c-Kit binding also acts synergistically with other cytokines, such as interleukins.

In one embodiment, the anti-SCF antibody (or binding domain thereof) comprises the heavy and light chain CDRs or variable regions of any one of anti-SCF antibodies mAb12-A, mAb12-B, mAb12-C, mAb12-D, mAb12-E, mAb12-F, mAb12-G, mAb12-H, or mAb12-I (as shown in Table 9 of Example 9). In another embodiment, the anti-SCF antibody (or binding domain) comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO: 33, 37, 41, or 45, and/or the CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO: 49, 53, 57, or 61. In another embodiment, the anti-SCF antibody (or binding domain) comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8A, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in Table 8B, or conservative sequence modifications thereof. In another embodiment, the anti-SCF antibody (or binding domain) comprises heavy chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 34, 35, and 36, (b) SEQ ID NOs: 38, 39, and 40, (c) SEQ ID NOs: 42, 43, and 44, (d) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and/or light chain CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (a) SEQ ID NOs: 50, 51, and 52, (b) SEQ ID NOs: 54, 55, and 56, (c) SEQ ID NOs: 58, 59, and 60, (d) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof, as set forth in Table 2A. In one embodiment, the anti-SCF antibody (or binding domain) respectively comprises the heavy chain CDR1, CDR2, and CDR3 sequences set forth in SEQ ID NOs: 46, 47, and 48, and the light chain CDR1, CDR3, and CDR3 sequences set forth in SEQ ID NOs: 58, 59, and 60.

In another embodiment, the anti-SCF antibody (or binding domain) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 33, 37, 41, or 45. In another embodiment, the anti-SCF antibody (or binding domain) comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 49, 53, 57, or 61. In another embodiment, the anti-SCF antibody (or binding domain) comprises a combination of heavy and light chain variable regions having the amino acid sequences set forth in Table 2B. In yet another embodiment, the antibody (or binding domain) comprises a

combination of heavy and light chain variable regions having the amino acid sequences set forth in Table 5 of Example 9. In one embodiment, the anti-SCF antibody (or binding domain) respectively comprises the heavy and light chain variable region sequences set forth in SEQ ID NOs: 45 and 57.

Sequences substantially identical to the anti-SCF antibodies (or binding domains) described herein (*e.g.*, at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical (identical) to the aforementioned sequences), are also provided. In one embodiment, the anti-SCF antibody (or binding domain) comprises a heavy chain variable region comprising the combinations set forth in Table 2B or Table 5, or sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the aforementioned sequences).

Anti-SCF antibodies and binding domains thereof that that compete for binding with any of the anti-SCF antibodies (or binding domains thereof) described herein or that bind the same epitope as any of the anti-SCF antibodies (or binding domains thereof) described herein, are also suitable for use and provided herein. For example, in one embodiment, the anti-SCF antibody, or binding domain thereof, competes for binding to SCF with antibody mAb12, as described herein (or an antibody having the heavy and light chain CDRs and/or heavy and light chain variable region sequences corresponding to antibody mAb12, as described herein). In another embodiment, the anti-SCF antibody (or binding domain) binds to the same epitope on SCF as antibody mAb12, as described herein (or an antibody having the heavy and light chain CDRs and/or heavy and light chain variable region sequences corresponding to antibody mAb12).

D. Bispecific Constructs and Multispecific Constructs

Provided herein are bispecific constructs comprising an anti-TSLP antibody (or binding domain) or an anti-SCF antibody (or binding domain) linked to a second binding agent(s) (e.g., a ligand, an antibody, or antigen binding portion thereof). Bispecific constructs comprising an anti-TSLP antibody (or binding domain) linked to an anti-SCF antibody (or binding domain) also are provided. The term "bispecific construct," as used herein, also refers to bispecific constructs linked to one or more additional binding agents (i.e., a third, fourth, or fifth binding agent) to form a "multispecific construct."

A "bispecific" or "bifunctional" construct is an artificial hybrid having two different binding domain (*e.g.*, heavy/light chain) pairs and two different binding sites. Bispecific

constructs can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny *et al.*, *J. Immunol.* 148, 1547-1553 (1992). A bispecific construct having more than two different binding domains (e.g., three, four, or more) is a multispecific construct.

As used herein, the term "linked" refers to the association of two or more molecules. The linkage can be covalent or non-covalent. The linkage also can be genetic (*i.e.*, recombinantly fused). Such linkages can be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

For chemical conjugation, suitable reagents and methods are known in the art for coupling two or more moieties, in particular two or more antibodies, or fragments thereof, together. A variety of coupling or crosslinking agents are commercially available and can be used to conjugate the anti-TSLP binding domain and anti-SCF binding domain. Non-limiting examples include Sulfo-SMCC, protein A, carboiimide, dimaleimide, dithio-bis-nitrobenzoic acid (DTNB), and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP). Sulfo-SMCC, SPDP and DTNB are preferred agents, with Sulfo-SMCC being particularly preferred. Other suitable procedures for crosslinking components (*e.g.*, binding domains) with cross-linking agents are known in the art. See *e.g.*, Karpovsky, B. *et al.*, (1984) *J. Exp. Med.* 160:1686; Liu, M. A. *et al.*, (1985) *Proc. Natl. Acad. Sci USA* 82:8648; Segal, D. M. and Perez, P., U.S. Pat. No. 4,676,980; and Brennan, M. (1986) Biotechniques 4:424.

For genetic engineering, nucleic acid molecules encoding the anti-TSLP antibody (or binding domain) or anti-SCF antibody (or binding domain) can be inserted into an appropriate expression vector using standard recombinant DNA techniques. A nucleic acid molecule(s) encoding the second binding agent (e.g., a ligand, antibody, or binding domain thereof) also can be inserted into the same expression vector, such that it is operatively linked (*e.g.*, in-frame cloning) to the anti-TSLP antibody (or binding domain) or anti-SCF-binding antibody (or binding domain), thereby resulting in an expression vector that encodes a fusion protein that is the bispecific construct.

Exemplary bispecific constructs include a combination of binding agents that bind to the targets listed in Table 3A and comprise, e.g., an anti-TSLP antibody (or binding domain) or anti-SCF antibody (or binding domain) linked to a second binding agent that binds to a member of the TNF superfamily (e.g., TNFα), a tumor necrosis factor (TNF) receptor (e.g., TNFRSF4), an interleukin (e.g., IL-23, IL-17A, or IL-13), an immunoglobulin (e.g., IgE), or

an integrin (e.g., integrin α 4beta7). In one embodiment, the bispecific construct comprises the anti-TSLP and anti-SCF antibodies (or antigen binding domains) described herein having the heavy and light chain CDR and/or full-length variable regions sequences respectively set forth in Tables 1A, 1B, and Tables 2A, 2B.

Other exemplary bispecific constructs comprise an anti-TSLP antibody (or binding domain) linked to an anti-SCF antibody (or binding domain), e.g., the anti-TSLP antibody (or binding domain) 1D10-D linked to the anti-SCF antibody (or binding domain) mAb12-G. Preferably, the anti-SCF binding portion is operatively linked to the C-terminal region of the heavy chain of the anti-TSLP binding portion. Other suitable expression vectors and cloning strategies for preparing the bispecific constructs described herein are known in the art.

Table 3A

Target Combinations	**TSLP**	**SCF**
TNFα	TNFα x TSLP	TNFα x SCF
TNFR	TNFR x TSLP	TNFR x SCF
TNFRSF4	TNFRSF4 x TSLP	TNFRSF4 x SCF
IL-23	IL-23 x TSLP	IL-23 x SCF
IL-17A	IL-17A x TSLP	IL-17A x SCF
IL-13	IL-13 x TSLP	IL-13 x SCF
IgE	IgE x TSLP	IgE x SCF
Integrin α4β7	Integrin α4β7 x TSLP	Integrin α4β7 x SCF
TSLP	-	SCF x TSLP
SCF	TSLP x SCF	

Binding agents for use with the bispecific constructs include, for example, the antibodies (or binding domains thereof) listed in Table 3B.

Table: 3B – Representative Binding Antibodies and Antigen Binding portions Thereof

Antibody	**US Patent Number**	**VH SEQ ID NO**	**VL SEQ ID NO**
Omalizumab XOLAIR™ Anti-IgE	US 6267958	351	352

Adalimumab HUMIRA™ Anti-TNF	US 6090382	353	354
Oxelumab Anti-OX40L	US 7501496	355	356
Lebrikizumab EBGLYSS™ Anti-IL-13	US 8088618	357	358
Vedolizumab ENTYVIO™ Anti-integrin α4β7	US 7147851	359	360
Ustekinumab STELARA™ Anti-IL-12 and IL-23	US 6902734	361	362
Secukinumab COSENTYX™ Anti-IL-17A	US 7807155	363	364
Guselkumab TREMFYA™ Anti-IL-23	US 7935344	365	366
Tildrakizumab ILUMYA™ Anti-IL-23	US 8404813	367	368
Tralokinumab ADTRALZA™ Anti-IL-13	US 7935343	369	370
Risankizumab SKYRIZI™ Anti-IL-23A	US 8778346	371	372
Tezepelumab TEZSPIRE™ Anti-TSLP	US 7982016	373	374

For expression of the bispecific constructs in host cells, the coding regions of the binding portions (e.g., antibodies or binding domains thereof) are combined with cloned promoter, leader sequence, translation initiation, leader sequence, constant region, 3' untranslated, polyadenylation, and transcription termination, sequences to form expression vector constructs. These constructs can be used to express, for example, full length human $IgG_1\kappa$ or $IgG_4\kappa$ antibodies. Fully human, humanized and chimeric antibodies used in the bispecific constructs described herein also include IgG2, IgG3, IgE, IgA, IgM, and IgD antibodies. Similar plasmids can be constructed for expression of other heavy chain isotypes, or for expression of antibodies comprising lambda light chains.

Following preparation of an expression vector encoding the bispecific construct, the bispecific construct can be expressed recombinantly in a host cell using standard transfection methods. For example, in one embodiment, nucleic acid encoding the bispecific construct can be ligated into an expression vector, such as a eukaryotic expression plasmid, such as used by GS gene expression system disclosed in WO 87/04462, WO 89/01036 and EP 338 841 or other expression systems well known in the art. The purified plasmid with the cloned bispecific construct gene can be introduced in eukaryotic host cells, such as CHO-cells or NSO-cells or alternatively other eukaryotic cells like a plant derived cells, fungi or yeast cells. The method used to introduce these genes could be methods described in the art, such as electroporation, lipofectin, lipofectamine or other. After introducing the expression vector in the host cells, cells expressing the bispecific construct can be identified and selected. These cells represent the transfectomas that can then be amplified for their expression level and upscaled to produce bispecific constructs. Alternatively these cloned bispecific constructs can be expressed in other expression systems, such as *E. coli* or in complete organisms or can be synthetically expressed. Recombinant bispecific constructs can be isolated and purified from these culture supernatants and/or cells.

A bispecific construct of the invention, whether prepared by chemical conjugation or by genetic engineering, can be isolated and purified using one or more methodologies for protein purification well established in the art. Preferred methods for isolation and purification include, but are not limited to, gel filtration chromatography, affinity chromatography, anion-exchange chromatography and the like. A particularly preferred method is gel filtration chromatography, *e.g.*, using a Superdex 200 column. Isolated and purified bispecific constructs can be evaluated using standard methods such as SDS-PAGE analysis.

Accordingly, in one embodiment, the anti-TSLP antibody (or binding domain) or the anti-SCF antibody (or binding domain) are genetically fused to the additional binding agent. Alternatively, the anti-TSLP antibody (or binding domain) and the anti-SCF antibody (or binding domain) are genetically fused to each other. In another embodiment, the anti-TSLP antibody (or binding domain) or the anti-SCF antibody (or binding domain) are chemically conjugated. Alternatively, the anti-TSLP antibody (or binding domain) and the anti-SCF antibody (or binding domain) are chemically conjugated to each other. In one embodiment, either one of the binding portions further comprises a human IgG1 constant domain.

Bispecific constructs comprising an anti-TSLP antibody (or binding domain) linked to an anti-SCF antibody (or binding domain) include the following embodiments: (a) the anti-SCF binding portion is linked to the C-terminus of the heavy chain of the anti-TSLP binding portion; (b) the anti-SCF binding portion is a scFv; (c) the anti-SCF binding portion further comprises a human IgG1 constant domain; (d) the anti-TSLP binding portion is linked to the C-terminus of the heavy chain of the anti-SCF binding portion; or (e) the anti-TSLP binding portion is a scFv.

Exemplary bispecific constructs include any one of the anti-TSLP antibodies (or binding domain) described herein having the CDR or full-length heavy and light chain variable region sequences set forth in Tables 1A and 1B or any one of the anti-SCF antibodies (or binding domain) described herein having the CDR or full-length heavy and light chain variable region sequences set forth in Tables 2A and 2B linked to a second binding domain (e.g., a ligand, antibody, or antigen binding portion thereof). Exemplary bispecific constructs also include any one of the anti-TSLP antibodies (or binding domain) described herein having the CDR or full-length heavy and light chain variable region sequences set forth in Tables 1A and 1B linked to any one of the anti-SCF antibodies (or binding domain) described herein having the CDR or full-length heavy and light chain variable region sequences set forth in Tables 2A and 2B.

Other exemplary bispecific constructs include a combination of any one of the anti-TSLP antibodies (or antigen binding fragments thereof) of Table 1A or 1B with any one of the anti-SCF antibodies (or antigen binding fragments thereof) of Table 2A or 2B, wherein bispecific construct comprises an anti-TSLP antibody linked to an anti-SCF scFv, and wherein the anti-TSLP antibody further comprises a human IgG1 constant domain. Alternatively, the bispecific construct includes a combination of an anti-TSLP antibody (or antigen binding fragment thereof) of Table 1A or 1B combined with an anti-SCF antibody (or

antigen binding fragment thereof) of Table 2A or 2B, wherein bispecific construct comprises an anti-SCF antibody linked to an anti-TSLP scFv, and wherein the anti-SCF antibody further comprises a human IgG1 constant domain.

Other exemplary bispecific constructs include an anti-TSLP binding domain and an anti-SCF binding domain comprising amino acid sequences set forth in Table 10 of Example 19.

E. Compositions

Also provided herein are compositions, *e.g.*, a composition comprising one or a combination of any of the antibodies (or binding domains), or bispecific constructs described herein, formulated together with a carrier (*e.g.*, a pharmaceutically acceptable carrier).

As used herein, the terms "carrier" and "pharmaceutically acceptable carrier" includes any and all solvents, salts, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound (*i.e.*, any of the antibodies (or binding domains), or bispecific constructs described herein), may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

Examples of adjuvants which may be used with the antibodies (or binding domains), bispecific constructs described here include, but are not limited to : Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, Mich.); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.); AS-2 (SmithKline Beecham, Philadelphia, Pa.); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatised polysaccharides; polyphosphazenes; biodegradable microspheres; cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like factors; 3D-MPL; CpG oligonucleotide; and monophosphoryl lipid A, for example 3-de-O-acylated monophosphoryl lipid A.

MPL adjuvants are available from Corixa Corporation (Seattle, Wash; see, for example, U.S. Pat. Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Pat. Nos. 6,008,200 and

5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996.

Further alternative adjuvants include, for example, saponins, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, Mass.); Escin; Digitonin; or Gypsophila or Chenopodium quinoa saponins; Montanide ISA 720 (Seppic, France); SAF (Chiron, California, United States); ISCOMS (CSL), MF-59 (Chiron); the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium); Detox (Enhanzyn™) (Corixa, Hamilton, Mont.); RC-529 (Corixa, Hamilton, Mont.) and other aminoalkyl glucosaminide 4-phosphates (AGPs); polyoxyethylene ether adjuvants such as those described in WO 99/52549A1; synthetic imidazoquinolines such as imiquimod [S-26308, R-837], (Harrison, et al., Vaccine 19: 1820-1826, 2001; and resiquimod [S-28463, R-848] (Vasilakos, et al., Cellular immunology 204: 64-74, 2000; Schiff bases of carbonyls and amines that are constitutively expressed on antigen presenting cell and T-cell surfaces, such as tucaresol (Rhodes, J. et al., Nature 377: 71-75, 1995); cytokine, chemokine and co-stimulatory molecules as either protein or peptide, including for example pro-inflammatory cytokines such as Interferon, GM-CSF, IL-1 α, IL-1 beta, TGF-α and TGF-β, Th1 inducers such as interferon gamma, IL-2, IL-12, IL-15, IL-18 and IL-21, Th2 inducers such as IL-4, IL-5, IL-6, IL-10 and IL-13 and other chemokine and co-stimulatory genes such as MCP-1, MIP-1 α, MIP-1 beta, RANTES, TCA-3, CD80, CD86 and CD40L; immunostimulatory agents targeting ligands such as CTLA-4 and L-selectin, apoptosis stimulating proteins and peptides such as Fas; synthetic lipid based adjuvants, such as vaxfectin, (Reyes et al., Vaccine 19: 3778-3786, 2001) squalene, α-tocopherol, polysorbate 80, DOPC and cholesterol; endotoxin, [LPS], (Beutler, B., Current Opinion in Microbiology 3: 23-30, 2000); ligands that trigger Toll receptors to produce Th1-inducing cytokines, such as synthetic Mycobacterial lipoproteins, Mycobacterial protein p19, peptidoglycan, teichoic acid and lipid A; and CT (cholera toxin, subunits A and B) and LT (heat labile enterotoxin from E. coli, subunits A and B), heat shock protein family (HSPs), and LLO (listeriolysin O; WO 01/72329). These and various further Toll-like Receptor (TLR) agonists are described for example in Kanzler et al, *Nature Medicine*, May 2007, Vol 13, No 5.

A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see *e.g.*, Berge, S.M., *et al.* (1977) J. Pharm. Sci. 66:1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic

inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. *See, e.g., Sustained and Controlled Release Drug Delivery Systems*, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

To administer a compound of the invention by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.* (1984) *J. Neuroimmunol.* 7:27).

Carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a

solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. For example, the antibodies of the invention may be administered once or twice weekly by subcutaneous or intramuscular injection or once or twice monthly by subcutaneous or intramuscular injection.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

For the therapeutic compositions, formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.001 per cent to about ninety percent of active ingredient, preferably from about 0.005 per cent to about 70 per cent, most preferably from about 0.01 per cent to about 30 per cent.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate. Dosage forms for the topical or transdermal administration of compositions of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as

glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given alone or as a pharmaceutical composition containing, for example, 0.001 to 90% (more preferably, 0.005 to 70%, such as 0.01 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition

required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, preferably administered proximal to the site of the target. If desired, the effective daily dose of a therapeutic composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

Therapeutic compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic composition of the invention can be administered with a needleless hypodermic injection device, such as the devices disclosed in U.S. Patent Nos. 5,399,163, 5,383,851, 5,312,335, 5,064,413, 4,941,880, 4,790,824, or 4,596,556. Examples of well-known implants and modules useful in the present invention include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,486,194, which discloses a therapeutic device for administering medicants through the skin; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Patent No. 4,475,196, which discloses an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

In certain embodiments, the antibodies (or binding domains) or bispecific constructs of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.*, U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties

that are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.*, V.V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.*, U.S. Patent 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P.G. Bloeman *et al.* (1995) *FEBS Lett.* 357:140; M. Owais *et al.* (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe *et al.* (1995) *Am. J. Physiol.* 1233:134), different species of which may comprise the formulations of the inventions, as well as components of the invented molecules; p120 (Schreier *et al.* (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M.L. Laukkanen (1994) *FEBS Lett.* 346:123; J.J. Killion; I.J. Fidler (1994) *Immunomethods* 4:273. In one embodiment of the invention, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety. In a most preferred embodiment, the therapeutic compounds in the liposomes are delivered by bolus injection to a site proximal to the tumor or infection. The composition must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

The ability of a compound to inhibit inflammation can be evaluated in an animal model system predictive of efficacy in human asthma patients. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner. A therapeutically effective amount of a therapeutic compound can decrease tumor size, or otherwise ameliorate symptoms in a subject. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

The composition must be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier can be an isotonic buffered saline solution, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be

brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

When the active compound is suitably protected, as described above, the compound may be orally administered, for example, with an inert diluent or an assimilable edible carrier.

F. Nucleic Acids

The term "nucleic acid molecule," as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated nucleic acid molecule," as used herein in reference to nucleic acids encoding antibodies (or binding domains, *e.g.*, V_H, V_L, CDR3) that bind to TSLP and/or SCF, as well as bispecific constructs comprising such antibodies. The term is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibodies (or binding domain) or bispecific are free of other nucleotide sequences encoding the antibodies (or binding domain) or bispecific , e.g., other sequences which may naturally flank the nucleic acid in human genomic DNA. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. *See*, F. Ausubel, *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

The nucleic acid molecules of the present invention, while often in a native sequence (except for modified restriction sites and the like), from either cDNA, genomic or mixtures thereof may be mutated, in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, DNA sequences substantially identical to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

A nucleic acid is "operably linked" or "operatively linked" when it is placed into a functional relationship with another nucleic acid sequence. For instance, a promoter or

enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. With respect to transcription regulatory sequences, operably linked means that the DNA sequences being linked are contiguous and, where necessary to join two protein coding regions, contiguous and in reading frame. For switch sequences, operably linked indicates that the sequences are capable of effecting switch recombination.

Isolated nucleic acid molecules encoding the antibodies (or binding domains) or bispecific constructs described herein are also provided, as well as expression vectors comprising such nucleic acids and host cells comprising such expression vectors. In another embodiment, a nucleic acid molecule coding for any of the antibodies (or binding domains) or bispecific constructs described herein is provided. In another embodiment, the nucleic acid molecule is in the form of an expression vector. In another embodiment, the nucleic acid molecule is in the form of an expression vector which expresses the antibody (or binding domain) or bispecific construct when administered to a subject *in vivo*.

In one embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding an antibody variable region, wherein the antibody variable region comprises the amino acid sequence depicted in SEQ ID NO: 1, 5, 9, 13, 17, 21, 25, 29, or an amino acid sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to one or more of the aforementioned sequences). In another embodiment, the nucleic acid molecule comprises a nucleotide sequence as set forth in Table 11, or a nucleotide sequence at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to one or more of the aforementioned sequences).

In another embodiment, the nucleic acid molecule comprises a nucleotide sequence encoding heavy and light chain variable regions of an antibody, wherein the heavy and light chain variable regions comprise a combination of the amino acid sequences depicted in Table 1B or Table 2B, or amino acids sequences at least 90% identical thereto (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical the aforementioned sequences).

The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of

autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors"(or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

G. Combination Therapies

Any of the antibodies (or binding domains) and/or bispecific constructs described herein, can be administered in combination with an additional therapy, *i.e.*, combined with other agents. The term "coadministered" as used herein includes any or all of simultaneous, separate, or sequential administration of the antibodies (or binding domains) and/or bispecific constructs described herein with one or more additional therapeutic agent, including administration as part of a dosing regimen. For example, the combination therapy can include administering any of the antibodies (or binding domains) or bispecific constructs constructs described herein with at least one or more additional therapeutic agents selected from, but not limited to: immunosuppressants (for example, corticosteroids, non-steroidal glucocorticoid receptor agonists, leukotriene D4 antagonists, leukotriene B4 antagonists, A2A agonists, A2B antagonists, dopamine receptor agonists, pirfenidone, nintedanib, or avB6 antagonists), anti-IL-6?, cyclophosphamide, methotrexate, mycophenolate mofetil,

autologous hematopoietic stem cell transplantation?, B cell depleting agents (rituximab, inebilizumab, belimumab), abatacept, anti-TGFb, anti-IL33, anti-IL25, DMARDs (disease-modifying anti-rheumatic drugs), bronchodilators (for example, β-2 adrenergic receptor agonists, muscarinic antagonists, short-acting β2 receptor agonists, long-acting β2 receptor agonists, short-acting anticholinergic drugs, methyl xanthine drugs, long-acting anticholinergic drugs), other cytokine or cytokine receptor antagonists or antibodies (for example, IL-13 antagonists, IL-6 antagonists, antagonists of IL-1, IL-33, IL-25 or TNF-α, anti-IgE antibodies, anti-IL31 antibodies, anti-IL31R antibodies, anti-IL13 antibodies, anti-endoglin antibodies, anti-ILlb antibodies, another anti-TSLP antibody or anti-hTSLPR antibodies, IL-5, anti-IgE, anti-IL4Ra), antibiotics, radiotherapy, leukotriene antagonists (for example, montelukast, zafirlukast or pranlukast), PDE4 inhibitors (for example, roflumilast, xanthene), antihistamines or antitussive drugs; optionally, the antibody or antigen-binding fragment thereof is administered sequentially or simultaneously with an additional therapeutic.

Additional agents that delete or inhibit immunosuppressive activities, for example, by immune cells (for example regulatory T-cells, NKT cells, macrophages, myeloid-derived suppressor cells, immature or suppressive dendritic cells), that may also be administered with the antibodies (or binding domains) or bispecific constructs described herein include, *e.g.*, antibodies and small molecule drugs such as IDO inhibitors such as 1 methyl tryptophan or derivatives, as well as immunosuppressive agents such as rapamycin, cyclosporin and FK506; anti-TNF agents such as etanercept, adalimumab and infliximab; and steroids. Examples of specific natural and synthetic steroids include, for example: aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisone, tixocortol and triamcinolone.

H. Uses and Methods of the Invention

Provided herein are methods of treating a disease or condition associated with the expression and/or activity of TSLP and/or SCF by administering the antibodies (or binding domains) or bispecific constructs , or compositions described herein, to a patient in need

thereof. For example, the methods provided herein are used to treat a disease or condition associated with an immune response (*e.g.*, immune cell migration, activation, and/or proliferation) *via* interaction (*e.g.*, binding) of TSLP and/or SCF with its receptor (TSLPR and/or c-Kit, respectively) on immune cells.

The terms "treat," "treating," and "treatment," as used herein, refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration to a subject, in need of such treatment, an antibody (or binding domain), bispecific construct, , or composition as described herein, for example, a subject in need of an enhanced immune response against a particular antigen or a subject who ultimately may acquire such a disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the disorder being treated and the general state of the patient's own immune system.

The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

As used herein, the term "immune cell" includes cells that have hematopoietic origins and play a role in an immune response, for example, lymphocytes, such as B cells and T cells; natural killer cells; myeloid cells, such as monocytes, macrophages, eosinophils, mast cells, basophils, and granulocytes.

As used herein, the term "immune response" means the action of immune cells (such as lymphocytes, antigen presenting cells, phagocytes or granulocytes) and soluble macromolecules (including antibodies, cytokines and complements) produced by immune cells or liver, which leads to selective damage, destruction or removal from human body of invasive pathogens, pathogen-infected cells or tissues, cancer cells, or normal human cells or tissues in the case of an autoimmune or pathological inflammation. Herein, the term "antigen-specific T cell response" refers to an immune response produced by T cells when the T cells are stimulated by an antigen specific to the T cells. Non-limiting examples of responses

produced by T cells in response to antigen-specific stimulation include proliferation of T cells and production of cytokines (*e.g.*, IL-2).

Thus, in some embodiments, the present disclosure provides methods for blocking TSLP and/or SCF binding to its receptor (i.e., TLSPR and c-Kit, respectively) in a subject comprising administering to the subject any one of the antibodies (or binding domains), bispecific constructs, , or compositions described herein, in an amount effective to block TSLP and/or SCF binding to its receptor.

As used herein, the terms "blocking TSLP and/or SCF binding" and "inhibiting binding of TSLP and/or SCF" (*e.g.*, referring to TLP binding to TLSPR and/or SCF binding to c-Kit) are used interchangeably and are intended to include any measurable decrease in the binding between the ligand (TSLP or SCF) and its receptor (TSLPR or c-Kit), *e.g.*, the blocking of TSLP and/or SCF binding to TSLPR and/or c-Kit by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%.

Also provided herein are methods for inhibiting activation of immune cells in a subject, as well as reducing or preventing the accumulation of immune cells within organs or tissues, in a subject comprising administering to the subject any one of the antibodies (or binding domains), bispecific constructs, , or compositions described herein, in an amount effective to inhibit activation of immune cells or reduce the accumulation of immune cells within organs or tissues in a subject.

As used herein, the terms "inhibiting activation of immune cells" and "reducing the accumulation of immune cells" (*e.g.*, referring to cells associated with immune functions, such as cytokines) are used interchangeably and are intended to include any measurable decrease in the amount of immune cells and/or signaling between immune cells within tissue or organs, *e.g.*, the reduction of immune cell activation and/or accumulation by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%. In one aspect, the reduction of immune cell activation and/or accumulation results in the inhibition or blocking of (a) TSLP-induced activation and/or proliferation of mast cells, DC, and/or NKT cells, (b) TSLP-induced osteoprotegerin (OPG) secretion, (c) TSLP-induced secretion of Th2 cytokines (such as TARC, CCL22, IL-4, IL-13 or IL-5), and / or (d) SCF-induced secretion of mast cells, eosinophils, type 2 innate lymphoid (ILC2) cells, and/or type 3 innate lymphoid (ILC3) cells. Overall, inhibiting or preventing activation of immune cells, as well as reducing or preventing the accumulation of immune cells within organs or tissues, thereby treats or prevents various diseases and disorders that involve inflammation, *e.g.*, autoimmune

diseases, cardiovascular diseases, gastrointestinal diseases, lung diseases, metabolic diseases (such as Type 2 diabetes), neurodegenerative diseases (such as Parkinson's disease), certain types of cancer (such as colon cancer) and mental illnesses (such as depression), as well as allergic inflammation, allergic airway inflammation, DC-mediated inflammatory Th2 responses, atopic dermatitis, atopic eczema, asthma, obstructive airways disease, chronic obstructive pulmonary disease, and food allergies, inflammatory arthritis, rheumatoid arthritis, psoriasis, IgE-mediated disorders, and rhino-conjunctivitis. Other conditions and disorders include fibrotic diseases and maladies associated with tissue remodeling, e.g., idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, cystic fibrosis, peribronchial fibrosis, hypersensitivity pneumonitis, asthma, sclerodoma, inflammation, liver cirrhosis, renal fibrosis, parenchymal fibrosis, endomyocardial fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, fibrous histiocytoma, fibrothorax, hepatic fibrosis, fibromyalgia, gingival fibrosis, or radiation-induced fibrosis.

Also provided herein are methods of reducing or inhibiting inflammation and methods of treating an inflammatory disease or disorder in a subject in need thereof (*e.g.*, autoimmune diseases, cardiovascular diseases, gastrointestinal diseases, lung diseases, metabolic diseases (such as Type 2 diabetes), neurodegenerative diseases (such as Parkinson's disease), certain types of cancer (such as colon cancer) and mental illnesses (such as depression)) by administering the constructs, antibodies, or antigen binding fragments thereof, bispecific constructs, or compositions described herein to a patient in need thereof in an amount effective to inhibit or reduce inflammation in a subject.

As used herein, the terms "inhibits inflammation" and "reduces inflammation" (*e.g.*, referring to body tissues, i.e., muscle tissue, epithelial tissue, connective tissue, and nervous tissue) are used interchangeably and are intended to include any measurable decrease in the response of body tissues to harmful stimuli (such as pathogens, damaged cells, or irritants) involving immune cells, blood vessels, and molecular mediators, *e.g.*, the reduction of inflammation of a body tissue by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%.

In one aspect, methods of reducing inflammation are provided, which comprise contacting body tissue with any one of the antibodies (or binding domains), bispecific constructs, , or the compositions of described herein. Reducing inflammation can comprise, for example, inhibiting binding of human TSLP to human TSLP receptor (TSLP-R),

inhibiting binding of SCF Binding to c-Kit, inhibiting BaF3 Cell Proliferation, inhibiting TARC induction in Human Dendritic cells, inhibiting c-Kit phosphorylation in human CHO-KIT cells, inhibiting human mast cell degranulation, and/or inhibiting M-07e cell proliferation.

In another aspect, methods of for treating a condition or disease in a subject are provided, the method comprising administering to the subject any one of the antibodies (or binding domains), bispecific constructs, , or the compositions described herein, in an amount effective to treat the condition or disease.

The subject can be, for example, one who suffers from a condition or disease in which reduction of inflammation is desired. In one embodiment, the condition or disease is associated with immune cell migration, activation, and/or proliferation *via* interaction (e.g., binding) of TSLP and/or SCF with is receptor (TSLPR and/or c-Kit, respectively) on immune cells, such as disorders of the immune system, allergic inflammation, allergic airway inflammation, DC-mediated inflammatory Th2 responses, atopic dermatitis, atopic eczema, asthma, obstructive airways disease, chronic obstructive pulmonary disease, and food allergies, inflammatory arthritis, rheumatoid arthritis, psoriasis, IgE-mediated disorders, and rhino-conjunctivitis. Other conditions and disorders include fibrotic diseases and maladies associated with tissue remodeling, *e.g.*, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, cystic fibrosis, peribronchial fibrosis, hypersensitivity pneumonitis, asthma, sclerodoma, inflammation, liver cirrhosis, renal fibrosis, parenchymal fibrosis, endomyocardial fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, fibrous histiocytoma, fibrothorax, hepatic fibrosis, fibromyalgia, gingival fibrosis, or radiation-induced fibrosis.

In another aspect, methods for treating a condition or disease in a subject are provided, wherein the method comprises administering to the subject any one of the anti-TSLP antibodies, or antigen binding fragments thereof, described herein in combination with any one of the anti-SCF antibodies, or antigen binding fragments thereof, described herein. For example, any one of the anti-TSLP antibodies, or antigen binding fragments thereof, according to those listing Tables 1A or 1B can be combined with any one of the anti-SCF antibodies, or antigen binding fragments thereof, according to those listing Tables 2A or 2B for treating a condition or disease in a subject.

In one embodiment, an antibody (or binding domain), bispecific construct, , or composition described herein is administered in combination with one or more additional

therapeutics selected from, but not limited to: immunosuppressants (for example, corticosteroids, non-steroidal glucocorticoid receptor agonists, leukotriene D4 antagonists, leukotriene B4 antagonists, A2A agonists, A2B antagonists, dopamine receptor agonists, pirfenidone, nintedanib, or avB6 antagonists), bronchodilators (for example, β-2 adrenergic receptor agonists, muscarinic antagonists, short-acting β2 receptor agonists, long-acting β2 receptor agonists, short-acting anticholinergic drugs, methyl xanthine drugs, long-acting anticholinergic drugs), other cytokine or cytokine receptor antagonists or antibodies (for example, IL-13 antagonists, IL-6 antagonists, antagonists of IL-1, IL-33, IL-25 or TNF-α, anti-IgE antibodies, anti-IL31 antibodies, anti-IL31R antibodies, anti-IL13 antibodies, anti-endoglin antibodies, anti-ILlb antibodies, another anti-TSLP antibody or anti-hTSLPR antibodies), antibiotics, radiotherapy, leukotriene antagonists (for example, montelukast, zafirlukast or pranlukast), PDE4 inhibitors (for example, roflumilast, xanthene), antihistamines or antitussive drugs;
optionally, the antibody(or binding domain), bispecific construct, , or composition is administered sequentially or simultaneously with an additional therapeutic.

I. Kits

Also provided are kits (*e.g.*, diagnostic kits) comprising one or more anti-TSLP antibody (or binding domain), anti-SCF antibody (or binding domain), bispecific construct, or composition as described herein, optionally with instructions for use. Kits may also include informative pamphlets, for example, pamphlets informing one how to use reagents to practice a method disclosed herein. The term "pamphlet" includes any writing, marketing materials or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

The present invention is further illustrated by the following examples, which should not be construed as further limiting. The contents of figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

V. Examples

Example 1: Generation of TSLP-Specific Monoclonal Antibodies

Immunizations: Mouse anti-TSLP monoclonal antibodies were generated by immunizing BALB/c mice with a soluble human TSLP antigen.

Antigen and Immunization: The antigen (was a soluble fusion protein comprising a TSLP protein with a HIS tag (AcroBiosystems®)) was mixed with MPL plus TDM adjuvant system (Sigma®). 5-20 micrograms soluble recombinant TSLP antigen in PBS were mixed 1:1 with the adjuvant. Mice were injected with 200 microliters of the prepared antigen into the peritoneal cavity approximately every 14-30 days. Animals that developed anti-TSLP titers were given an iv injection of 1-10 micrograms soluble recombinant TSLP antigen three to four days prior to fusion. Mouse spleens were harvested, and the isolated splenocytes used for hybridoma preparation.

Fusions

The P3x63Ag8.653 murine myeloma cell line (ATCC® CRL 1580) was used for the fusions. RPMI 1640 (Invitrogen®) containing 10% FBS was used to culture the myeloma cells. Additional media supplements were added to the Hybridoma growth media, which included: up to 10% Hybridoma Cloning Supplement (Sigma®), 10% FBS (Sigma), L-glutamine (Gibco®) 0.1% gentamycin (Gibco), 2-mercaptoethanol (Gibco), with HAT (Sigma; 1.0×10^{4} M hypoxanthine, 4.0×10^{-7} M aminopterin, 1.6×10^{-5} M thymidine media.

Spleen cells were mixed with the P3x63Ag8.653 myeloma cells in a 6:1 ratio and pelleted by centrifugation. Polyethylene glycol was added dropwise with careful mixing to facilitate fusion. Hybridomas were cultured for two to three weeks until visible colonies become established. Supernatant was harvested and used for initial screening for mouse IgG *via* ELISA using a human soluble TSLP fusion protein and a mouse Fc specific detection. IgG positive supernatants were then assayed for TSLP blocking by ELISA. The hybridomas were also screened for cross-reactivity with cynomolgus macaque TSLP.

Hybridoma cells were expanded and cell pellets were frozen for RNA isolation and sequencing. The V_H and V_L coding regions of human mAbs were identified using RNA from the corresponding hybridomas. RNA was reverse transcribed to cDNA, the V coding regions were amplified by PCR and the PCR product was sequenced, inserted into human IgG1

vector, transiently expressed as chimeric antibodies, and purified by protein A column chromatography. Antibody 1D10 was isolated.

Example 2: Generation of Humanized TSLP Antibodies

A computer model of the parental heavy and light chain variable region domains (*i.e.*, VH and VL domains) of antibody 1D10 from Example 1 was produced and used to guide the humanization process. Parental VH and VL sequences were aligned with a panel of human germline sequences which had been filtered to select germline sequences that do not contain unwanted sequence liabilities, particularly N-linked glycosylation sites and free Cysteines. The closest matching germlines from two different VH and VL families were selected. A humanization algorithm was then used to select CDR and framework amino acids to graft from the donor parental sequences onto the human acceptor germline sequence (Table 4). Complementarity determining regions (CDRs) from the parent antibody were grafted onto the appropriate human frameworks and back mutations were introduced (Tables 4A and 4B; underlined amino acids are different from parental amino acids).

Table 4: Clone 1D10

	Name	**Human Framework**	**Protein Sequence**	**Identity to Human**	**Genewiz Synthesized DNA Sequence**
Parental	VH		SEQ ID NO:264	66.3%	SEQ ID NO:268
Humanized	hu-VH1	IGHV1-46*01	SEQ ID NO:1	78.6%	SEQ ID NO:269
Humanized	hu-VH2	IGHV1-46*01	SEQ ID NO:5	83.7%	SEQ ID NO:270
Humanized	hu-VH3	IGHV4-4*02	SEQ ID NO:265	71.0%	SEQ ID NO:271
Humanized	hu-VH4	IGHV4-4*02	SEQ ID NO:266	79.6%	SEQ ID NO:272
Parental	VL		SEQ ID NO:267	68.5%	SEQ ID NO:273
Humanized	hu-VL1	IGKV3-11*01	SEQ ID NO:17	89.9%	SEQ ID NO:274
Humanized	hu-VL2	IGKV3-11*01	SEQ ID NO:21	93.3%	SEQ ID NO:275
Humanized	hu-VL3	IGKV4-1*01	SEQ ID NO:25	81.0%	SEQ ID NO:276
Humanized	hu-VL4	IGKV4-1*01	SEQ ID NO:29	85.1%	SEQ ID NO:277

Table 5A: VH CDR Sequences

1D10 VH		**CDR-H1**	**CDR-H2**	**CDR-H3**
Parental	Chothia	TNAFTNY--- (SEQ ID NO:293)	-----NPGGGG--------- (SEQ ID NO:294)	--EDSAGYGFAY (SEQ ID NO:295)
	AbM	TNAFTNYLIE (SEQ ID NO:296)	---VINPGGGGTN------- (SEQ ID NO:297)	--EDSAGYGFAY (SEQ ID NO:298)
	Kabat	-----NYLIE (SEQ ID NO:290)	---VINPGGGGTNYNEKFKD (SEQ ID NO:291)	--EDSAGYGFAY (SEQ ID NO:292)

	Contact	----TNYLIE (SEQ ID NO:299)	WIGVINPGGGGTN------- (SEQ ID NO:300)	AREDSAGYGFA- (SEQ ID NO:301)
	IMGT	TNAFTNYL— (SEQ ID NO:302)	----INPGGGGT-------- (SEQ ID NO:303)	AREDSAGYGFAY (SEQ ID NO:304)
hu-VH1	Chothia	TNAFTNY--- (SEQ ID NO:72)	-----NPGGGG--------- (SEQ ID NO:73)	--EDSAGYGFAY (SEQ ID NO:74)
	AbM	TNAFTNYLIE (SEQ ID NO:84)	---VINPGGGGTN------- (SEQ ID NO:85)	--EDSAGYGFAY (SEQ ID NO:86)
	Kabat	-----NYLIE (SEQ ID NO:2)	---VINPGGGGTNYNEKF**QG** (SEQ ID NO:3)	--EDSAGYGFAY (SEQ ID NO:4)
	Contact	----TNYLIE (SEQ ID NO:96)	WIGVINPGGGGTN------- (SEQ ID NO:97)	AREDSAGYGFA- (SEQ ID NO:98)
	IMGT	TNAFTNYL-- (SEQ ID NO:108)	----INPGGGGT-------- (SEQ ID NO:109)	AREDSAGYGFAY (SEQ ID NO:110)
hu-VH2	Chothia	TNAFTNY--- (SEQ ID NO:75)	-----NPGGGG--------- (SEQ ID NO:76)	--EDSAGYGFAY (SEQ ID NO:77)
	AbM	TNAFTNYLIE (SEQ ID NO:87)	---VINPGGGGTN------- (SEQ ID NO:88)	--EDSAGYGFAY (SEQ ID NO:89)
	Kabat	-----NYLIE (SEQ ID NO:6)	---VINPGGGGTNYNEKF**QG** (SEQ ID NO:7)	--EDSAGYGFAY (SEQ ID NO:8)
	Contact	----TNYLIE (SEQ ID NO:99)	WMGVINPGGGGTN------- (SEQ ID NO:100)	AREDSAGYGFA- (SEQ ID NO:101)
	IMGT	TNAFTNYL-- (SEQ ID NO:111)	----INPGGGGT-------- (SEQ ID NO:112)	AREDSAGYGFAY (SEQ ID NO:113)
hu-VH3	Chothia	TNAFTNY--- (SEQ ID NO:78)	-----NPGGGG--------- (SEQ ID NO:79)	--EDSAGYGFAY (SEQ ID NO:80)
	AbM	TNAFTNYLIE (SEQ ID NO:90)	---VINPGGGGTN------- (SEQ ID NO:91)	--EDSAGYGFAY (SEQ ID NO: 92)
	Kabat	-----NYLIE (SEQ ID NO:10)	---VINPGGGGTNYNEK**LKS** (SEQ ID NO:11)	--EDSAGYGFAY (SEQ ID NO:12)
	Contact	----TNYLIE(SEQ ID NO:102)	WIGVINPGGGGTN------- (SEQ ID NO:103)	AREDSAGYGFA- (SEQ ID NO:104)
	IMGT	TNAFTNYL-- (SEQ ID NO:114)	----INPGGGGT-------- (SEQ ID NO:115)	AREDSAGYGFAY (SEQ ID NO:116)
hu-VH4	Chothia	TNAFTNY--- (SEQ ID NO:81)	-----NPGGGG--------- (SEQ ID NO:82)	--EDSAGYGFAY (SEQ ID NO:83)
	AbM	TNAFTNYLIE (SEQ ID NO:93)	---VINPGGGGTN------- (SEQ ID NO:94)	--EDSAGYGFAY (SEQ ID NO:95)
	Kabat	-----NYLIE (SEQ ID NO:14)	---VINPGGGGTNYNEK**LKS** (SEQ ID NO:15)	--EDSAGYGFAY (SEQ ID NO:16)
	Contact	----TNYLIE (SEQ ID NO:105)	WIGVINPGGGGTN------- (SEQ ID NO:106)	AREDSAGYGFA- (SEQ ID NO:107)
	IMGT	TNAFTNYL-- (SEQ ID NO:117)	----INPGGGGT-------- (SEQ ID NO:118)	AREDSAGYGFAY (SEQ ID NO:119)

Table 5B: VL CDR Sequences

1D10 VL		CDR-L1	CDR-L2	CDR-L3
Parental	Chothia	KASQSVSSDVA-- (SEQ ID NO:308)	----YASNRYT (SEQ ID NO:309)	QQDYAFPYT (SEQ ID NO:310)
	AbM	KASQSVSSDVA-- (SEQ ID NO:311)	----YASNRYT (SEQ ID NO:312)	QQDYAFPYT (SEQ ID NO:313)
	Kabat	KASQSVSSDVA-- (SEQ ID NO:305)	----YASNRYT (SEQ ID NO:306)	QQDYAFPYT (SEQ ID NO:307)
	Contact	------SSDVAWY (SEQ ID NO:314)	LLIYYASNRY- (SEQ ID NO:315)	QQDYAFPY- (SEQ ID NO:316)
	IMGT	---QSVSSD---- (SEQ ID NO:317)	----YA----- (SEQ ID NO:318)	QQDYAFPYT (SEQ ID NO:319)
hu-VL1	Chothia	**R**ASQSVSSDVA-- (SEQ ID NO:120)	----YASNRYT (SEQ ID NO:121)	QQDYAFPYT (SEQ ID NO:122)
	AbM	**R**ASQSVSSDVA-- (SEQ ID NO:132)	----YASNRYT (SEQ ID NO:133)	QQDYAFPYT (SEQ ID NO:134)
	Kabat	**R**ASQSVSSDVA-- (SEQ ID NO:18)	----YASNRYT (SEQ ID NO:19)	QQDYAFPYT (SEQ ID NO:20)
	Contact	------SSDVAWY (SEQ ID NO:144)	LLIYYASNRY- (SEQ ID NO:145)	QQDYAFPY- (SEQ ID NO:146)
	IMGT	---QSVSSD---- (SEQ ID NO:156)	----YA----- (SEQ ID NO:157)	QQDYAFPYT (SEQ ID NO:158)
hu-VL2	Chothia	**R**ASQSVSSDVA-- (SEQ ID NO:123)	----YASNRYT (SEQ ID NO:124)	QQDYAFPYT (SEQ ID NO:125)
	AbM	**R**ASQSVSSDVA-- (SEQ ID NO:135)	----YASNRYT (SEQ ID NO:136)	QQDYAFPYT (SEQ ID NO:137)
	Kabat	**R**ASQSVSSDVA-- (SEQ ID NO:22)	----YASNRYT (SEQ ID NO:23)	QQDYAFPYT (SEQ ID NO:24)
	Contact	------SSDVAWY (SEQ ID NO:147)	LLIYYASNRY- (SEQ ID NO:148)	QQDYAFPY- (SEQ ID NO:149)
	IMGT	---QSVSSD---- (SEQ ID NO:159)	----YA----- (SEQ ID NO:160)	QQDYAFPYT (SEQ ID NO:161)
hu-VL3	Chothia	KASQSVSSDVA-- (SEQ ID NO:126)	----YASNRYT (SEQ ID NO:127)	QQDYAFPYT (SEQ ID NO:128)
	AbM	KASQSVSSDVA-- (SEQ ID NO:138)	----YASNRYT (SEQ ID NO:139)	QQDYAFPYT (SEQ ID NO:140)
	Kabat	KASQSVSSDVA-- (SEQ ID NO:26)	----YASNRYT (SEQ ID NO:27)	QQDYAFPYT (SEQ ID NO:28)
	Contact	------SSDVAWY (SEQ ID NO:150)	LLIYYASNRY- (SEQ ID NO:151)	QQDYAFPY- (SEQ ID NO:152)
	IMGT	---QSVSSD---- (SEQ ID NO:162)	----YA----- (SEQ ID NO:163)	QQDYAFPYT (SEQ ID NO:164)
hu-VL4	Chothia	KASQSVSSDVA-- (SEQ ID NO:129)	----YASNRY**S** (SEQ ID NO:130)	QQDYAFPYT (SEQ ID NO:131)
	AbM	KASQSVSSDVA-- (SEQ ID NO:141)	----YASNRY**S** (SEQ ID NO:142)	QQDYAFPYT (SEQ ID NO:143)

	Kabat	KASQSVSSDVA-- (SEQ ID NO:30)	----YASNRYS (SEQ ID NO:31)	QQDYAFPYT (SEQ ID NO:32)
	Contact	------SSDVAWY (SEQ ID NO:153)	LLIYYASNRY- (SEQ ID NO:154)	QQDYAFPY- (SEQ ID NO:155)
	IMGT	---QSVSSD---- (SEQ ID NO:165)	----YA----- (SEQ ID NO:166)	QQDYAFPYT (SEQ ID NO:167)

Four heavy chain and four light chain humanized variants were designed for antibody 1D10. The 1D10 heavy chain variants were designated: 1D10-H1 (SEQ ID NO: 1), 1D10-H2 (SEQ ID NO: 5), 1D10-H3 (SEQ ID NO: 9) and 1D10-H4 (SEQ ID NO: 13). The 1D10 light chain variants were designated: 1D10-L1 (SEQ ID NO: 17), 1D10-L2 (SEQ ID NO: 21), 1D10-L3 (SEQ ID NO: 25) and 1D10-L4 (SEQ ID NO: 29). Pairing of these variable domain sequences is shown in Table 4. The activities of these antibodies and sequences were investigated further as described below.

Table 6: Heavy and Light Chain Pairings

Heavy Chain	Light Chain	Resulting Antibody
1D10-H1	1D10-L1	1D10 VH1-L1 (mAb 1D10-A)
1D10-H1	1D10-L2	1D10 VH1-L2 (mAb 1D10-B)
1D10-H1	1D10-L3	1D10 VH1-L3 (mAb 1D10-C)
1D10-H2	1D10-L1	1D10 VH2-L1 (mAb 1D10-D)
1D10-H2	1D10-L2	1D10 VH2-L2 (mAb 1D10-E)
1D10-H2	1D10-L3	1D10 VH2-L3 (mAb 1D10-F)
1D10-H3	1D10-L1	1D10 VH3-L1 (mAb 1D10-G)
1D10-H3	1D10-L2	1D10 VH3-L2 (mAb 1D10-H)
1D10-H3	1D10-L3	1D10 VH3-L3 (mAb 1D10-I)

Example 3: Binding to Human TSLP

Microtiter plates were coated with recombinant human TSLP-kappa (Celldex Therapeutics, Inc.®) in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified chimeric mAb 1D10, its humanized versions and an isotype control were added at various concentrations and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with

HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative binding curves are shown in FIGs. 1-3.

Example 4: Blocking of TSLP Binding to TSLP-R

The ability of anti-TSLP human mAbs to block binding of human TSLP to human TSLP receptor (TSLP-R) was investigated by ELISA as follows:

Microtiter plates were coated with recombinant human TSLP-R (AcroBiosystems) in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified chimeric mAb 1D10, its humanized versions and an isotype control at various concentrations were pre-incubated for 20 minutes at room temperature with biotinylated recombinant human TSLP (AcroBiosystems), then added to the plate and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with strepavidin conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIGs. 4-6 showing the ability of anti-TSLP human mAbs to block binding of human TSLP to human TSLP receptor (TSLP-R).

Example 5: Inhibition of BaF3 Cell Proliferation

BaF3 cells were transfected to express human TSLP and human IL-7Ra on their surface. The cells were incubated with recombinant human TSLP (R&D Systems®) in the presence of either media, Protein A purified chimeric mAb 1D10, select humanized versions or an isotype control at 37°C, 6%CO_2. After 3 days, CellTiter Glo (Promega®) was added according to the kit instructions and luminescence as a result of cell proliferation was detected and quantitated on a Perkin Elmer Victor X4 luminometer. Representative curves are shown in FIG. 7 showing the ability of anti-TSLP human mAbs to inhibit BaF3 proliferation.

Example 6: Inhibition of TARC Induction in Human Dendritic Cells

Human dendritic cells (DCs) were isolated from previously frozen peripheral blood mononuclear cell leukopaks (BioIVT®) using a MACS Cell separation Pan DC Enrichment Kit from Miltenyi Biotec®. The cells were incubated overnight with recombinant human TSLP (R&D Systems®) in the presence of either media, Protein A purified chimeric mAb 1D10, select humanized versions or an isotype control at 37°C, 6%CO_2. Supernatants were

harvested and TARC production was quantitated by ELISA (R&D Systems). Representative curves are shown in FIG. 8 showing the ability of anti-TSLP human mAbs to inhibit TARC induction in human DCs.

Example 7: Affinity and Rate Constants of Humanized mAbs

Binding affinity and binding kinetics of various human anti-TSLP antibodies were examined by bio-layer interferometry (BLI®) using an Octet® QK_e instrument (Sartorius®) according to the manufacturer's guidelines.

To assess affinity to human TSLP, purified antibodies were captured on Anti-Human Fc Capture (AHC) biosensors (Sartorius). Sensors were preconditioned by running two association and regeneration cycles with an irrelevant HuIgG1 antibody. Each anti-TSLP antibody was prepared in dilution buffer (10mM PO_4 + 150mM NaCl + 1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 0.5 to 1.0µg/mL and loaded on freshly hydrated and preconditioned AHC biosensors for 300sec at 30°C and 1000rpm plate shake speed. For one assay, eight biosensors were loaded with the same antibody.

Binding was determined by exposing seven of the antibody loaded biosensors to analyte: either soluble human TSLP-HIS or soluble cynomolgus TSLP (AcroBiosciences). Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 25 to 0.4nM in dilution buffer at 30°C and 1000rpm plate shake speed. Association of the antibody loaded biosensors in analyte wells was carried out for 300 seconds, the biosensors were then moved to dilution buffer wells for 900sec for dissociation measurements. Both association and dissociation steps were carried out at 30°C and 1000rpm plate shake speed.

For cynomolgus TSLP experiments, soluble cynomolgus TSLP-HIS (ACROBiosystems) was prepared in dilution buffer (10mM PO_4 + 150mM NaCl + 1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 2.0 µg/mL and loaded on freshly hydrated and regenerated Anti-Penta-HIS (HIS1K) biosensors (Sartorius) for 300sec at 30°C and 1000rpm plate shake speed. For one assay, eight biosensors were loaded with the same ligand.

Binding of cynomolgus TSLP was determined by exposing seven of the ligand loaded biosensors to analyte: purified Anti-TSLP antibodies. Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 50 to 3.1nM in dilution buffer. Association of the ligand loaded biosensors in analyte wells was carried out for 180 seconds, the biosensors were then moved to dilution buffer wells for 300 sec for dissociation

measurements. Both association and dissociation steps were carried out at 30°C and 1000rpm plate shake speed.

Corresponding controls were conducted in each case by keeping one biosensor with captured ligand in a dilution buffer well for association and dissociation steps. The data for the control biosensor was used to subtract background and account for biosensor drift and ligand dissociation from the biosensors.

Octet BLI Analysis Software (Sartorius) was used in each case to derive kinetic parameters from the concentration series of analyte in dilution buffer binding to captured ligand. The association and dissociation curves were fitted to a 1:1 binding model using the data analysis software according to the manufacturer's guidelines.

The affinity and kinetic parameters (with background subtracted) for human and cynomolgus TSLP as determined are shown in FIGs. 9A and 9B, where k_{on} = rate of association, k_{dis} = rate of dissociation, and KD = affinity constant, determined by the ratio k_{dis}/k_{on}.

Example 8: Generation of SCF-Specific Monoclonal Antibodies

Mice were immunized and boosted with human SCF protein. Immune responses were tested by ELISA against human SCF protein. Plasma cells from mice with high antibody titer were isolated using a CD138 B cell enrichment kit, loaded onto a Beacon 14K chip, and cloned using a Beacon instrument from Berkeley Lights®. Bead-based screening on the Beacon chip was performed for human, cyno and mouse SCF specific IgG secreting B cells, and to identify single B cells with blocking activity to the ECD of the human KIT receptor. Single B cells were selected and exported into lysis buffer for single cell sequencing in 96 well plates. This was done by RNA purification, reverse transcription and cDNA amplification, VH and VL amplification, and VH and VL sequencing and analysis. Human IgG1 chimeric antibody mAb12 (SCF-12) was selected after expression and purified.

Example 9: Generation of Humanized SCF Antibodies

A computer model of the parental heavy and light chain variable region domains (*i.e.*, VH and VL domains) of antibody mAb12 from Example 8 was produced and used to guide the humanization process. Parental VH and VL sequences were aligned with a panel of human germline sequences which had been filtered to select germline sequences that do not contain unwanted sequence liabilities, particularly N-linked glycosylation sites and free

Cysteines. The closest matching germlines from two different VH and VL families were selected. A humanization algorithm was then used to select CDR and framework amino acids to graft from the donor parental sequences onto the human acceptor germline sequence (Table 7). Complementarity determining regions (CDRs) from the parent antibody were grafted onto the appropriate human frameworks and back mutations were introduced as necessary (Tables 7A and 7B; underlined amino acids are different from parental amino acids).

Table 7: Clone mAb12

	Name	**Human Framework**	**Protein Sequence**	**Identity to Human**	**Genewiz Synthesized DNA Sequence**
Parental	mouse VH		SEQ ID NO:278	68.4%	SEQ ID NO:280
Humanized	hu-VH1	IGHV3-7*01	SEQ ID NO:33	81.6%	SEQ ID NO:281
Humanized	hu-VH2	IGHV3-7*01	SEQ ID NO:37	85.7%	SEQ ID NO:282
Humanized	hu-VH3	IGHV4-4*02	SEQ ID NO:41	77.8%	SEQ ID NO:283
Humanized	hu-VH4	IGHV4-4*02	SEQ ID NO:45	81.8%	SEQ ID NO:284
Parental	mouse VL		SEQ ID NO:279	74.7%	SEQ ID NO:285
Humanized	hu-VL1	IGKV1-NL1*01	SEQ ID NO:49	86.3%	SEQ ID NO:286
Humanized	hu-VL2	IGKV1-NL1*01	SEQ ID NO:53	87.4%	SEQ ID NO:287
Humanized	hu-VL3	IGKV4-1*01	SEQ ID NO:57	76.2%	SEQ ID NO:288
Humanized	hu-VL4	IGKV4-1*01	SEQ ID NO:61	79.2%	SEQ ID NO:289

Table: 8A: VH CDR Sequences

mAb12 VH		**CDR-H1**	**CDR-H2**	**CDR-H3**
Parental	Chothia	GIDFSRY--- (SEQ ID NO:323)	-----NPDSNT--------- (SEQ ID NO:324)	--PGGGYYSYALDY (SEQ ID NO:325)
	AbM	GIDFSRYWMS (SEQ ID NO:326)	---EINPDSNTLN------- (SEQ ID NO:327)	--PGGGYYSYALDY (SEQ ID NO:328)
	Kabat	-----RYWMS (SEQ ID NO:320)	---EINPDSNTLNYAPSLED (SEQ ID NO:321)	--PGGGYYSYALDY (SEQ ID NO:322)
	Contact	----SRYWMS (SEQ ID NO:329)	WIGEINPDSNTLN------- (SEQ ID NO:330)	ARPGGGYYSYALD- (SEQ ID NO:331)
	IMGT	GIDFSRYW--	----INPDSNTL-------- (SEQ ID NO:333)	ARPGGGYYSYALDY (SEQ ID NO:334)

		(SEQ ID NO:332)		
hu-VH1	Chothia	GIDFSRY--- (SEQ ID NO:168)	-----NPDSNT--------- (SEQ ID NO:169)	--PGGGYYSYALDY (SEQ ID NO:170)
	AbM	GIDFSRYWMS (SEQ ID NO:180)	---EINPDSNTLN------- (SEQ ID NO:181)	--PGGGYYSYALDY (SEQ ID NO:182)
	Kabat	-----RYWMS (SEQ ID NO:34)	---EINPDSNTLNYAPS**VKG** (SEQ ID NO:35)	--PGGGYYSYALDY (SEQ ID NO:36)
	Contact	----SRYWMS (SEQ ID NO:192)	WIGEINPDSNTLN------- (SEQ ID NO:193)	ARPGGGYYSYALD- (SEQ ID NO:194)
	IMGT	GIDFSRYW-- (SEQ ID NO:204)	----INPDSNTL-------- (SEQ ID NO:205)	ARPGGGYYSYALDY (SEQ ID NO:206)
hu-VH2	Chothia	GIDFSRY--- (SEQ ID NO:171)	-----NPDSNT--------- (SEQ ID NO:172)	--PGGGYYSYALDY (SEQ ID NO:173)
	AbM	GIDFSRYWMS (SEQ ID NO:183)	---EINPDSNTLN------- (SEQ ID NO:184)	--PGGGYYSYALDY (SEQ ID NO:185)
	Kabat	-----RYWMS (SEQ ID NO:38)	---EINPDSNTLNYAPS**VKG** (SEQ ID NO:39)	--PGGGYYSYALDY (SEQ ID NO:40)
	Contact	----SRYWMS (SEQ ID NO:195)	W**V**GEINPDSNTLN------- (SEQ ID NO:196)	ARPGGGYYSYALD- (SEQ ID NO:197)
	IMGT	GIDFSRYW-- (SEQ ID NO:207)	----INPDSNTL-------- (SEQ ID NO:208)	ARPGGGYYSYALDY (SEQ ID NO:209)
hu-VH3	Chothia	GIDFSRY--- (SEQ ID NO:174)	-----NPDSNT--------- (SEQ ID NO:175)	--PGGGYYSYALDY (SEQ ID NO:176)
	AbM	GIDFSRYWMS (SEQ ID NO:186)	---EINPDSNTLN------- (SEQ ID NO:187)	--PGGGYYSYALDY (SEQ ID NO:188)
	Kabat	-----RYWMS (SEQ ID NO:42)	---EINPDSNTLNYAPSL**KS** (SEQ ID NO:43)	--PGGGYYSYALDY (SEQ ID NO:44)
	Contact	----SRYWMS (SEQ ID NO:198)	WIGEINPDSNTLN------- (SEQ ID NO:199)	ARPGGGYYSYALD- (SEQ ID NO:200)
	IMGT	GIDFSRYW--	----INPDSNTL-------- (SEQ ID NO:211)	ARPGGGYYSYALDY (SEQ ID NO:212)

		(SEQ ID NO:210)		
hu-VH4	Chothia	GIDFSRY--- (SEQ ID NO:177)	-----NPDSNT--------- (SEQ ID NO:178)	--PGGGYYSYALDY (SEQ ID NO:179)
	AbM	GIDFSRYWMS (SEQ ID NO:189)	---EINPDSNTLN------- (SEQ ID NO:190)	--PGGGYYSYALDY (SEQ ID NO:191)
	Kabat	-----RYWMS (SEQ ID NO:46)	---EINPDSNTLNYAPSL**KS** (SEQ ID NO:47)	--PGGGYYSYALDY (SEQ ID NO:48)
	Contact	----SRYWMS (SEQ ID NO:201)	WIGEINPDSNTLN------- (SEQ ID NO:202)	ARPGGGYYSYALD- (SEQ ID NO:203)
	IMGT	GIDFSRYW— (SEQ ID NO:213)	----INPDSNTL-------- (SEQ ID NO:214)	ARPGGGYYSYALDY (SEQ ID NO:215)

Table 8B: VL CDR Sequences

mAb12 VL		**CDR-L1**	**CDR-L2**	**CDR-L3**
Parental	Chothia	KASEDIYNRLA-- (SEQ ID NO:338)	----GTTILET (SEQ ID NO:339)	QQYWSTPYT (SEQ ID NO:340)
	AbM	KASEDIYNRLA-- (SEQ ID NO:341)	----GTTILET (SEQ ID NO:342)	QQYWSTPYT (SEQ ID NO:343)
	Kabat	KASEDIYNRLA-- (SEQ ID NO:335)	----GTTILET (SEQ ID NO:336)	QQYWSTPYT (SEQ ID NO:337)
	Contact	------YNRLAWY (SEQ ID NO:329)	LLMSGTTILE- (SEQ ID NO:330)	QQYWSTPY- (SEQ ID NO:331)
	IMGT	---EDIYNR---- (SEQ ID NO:347)	----GT----- (SEQ ID NO:348)	QQYWSTPYT (SEQ ID NO:349)
hu-VL1	Chothia	**R**ASEDIYNRLA-- (SEQ ID NO:216)	----GTTILET (SEQ ID NO:217)	QQYWSTPYT (SEQ ID NO:218)
	AbM	**R**ASEDIYNRLA-- (SEQ ID NO:228)	----GTTILET (SEQ ID NO:229)	QQYWSTPYT (SEQ ID NO:230)
	Kabat	**R**ASEDIYNRLA-- (SEQ ID NO:50)	----GTTILET (SEQ ID NO:51)	QQYWSTPYT (SEQ ID NO:52)
	Contact	------YNRLAWY (SEQ ID NO:240)	LLMSGTTILE- (SEQ ID NO:241)	QQYWSTPY- (SEQ ID NO:242)
	IMGT	---EDIYNR---- (SEQ ID NO:252)	----GT----- (SEQ ID NO:253)	QQYWSTPYT (SEQ ID NO:254)
hu-VL2	Chothia	**R**ASEDIYNRLA-- (SEQ ID NO:219)	----GTTILE**S** (SEQ ID NO:220)	QQYWSTPYT (SEQ ID NO:221)
	AbM	**R**ASEDIYNRLA-- (SEQ ID NO:231)	----GTTILE**S** (SEQ ID NO:232)	QQYWSTPYT (SEQ ID NO:233)

	Kabat	**R**ASEDIYNRLA-- (SEQ ID NO:54)	----GTTILE**S** (SEQ ID NO:55)	QQYWSTPYT (SEQ ID NO:56)
	Contact	------YNRLAWY (SEQ ID NO:243)	LLMSGTTILE- (SEQ ID NO:244)	QQYWSTPY- (SEQ ID NO:245)
	IMGT	---EDIYNR---- (SEQ ID NO:255)	----GT----- (SEQ ID NO:256)	QQYWSTPYT (SEQ ID NO:257)
hu-VL3	Chothia	KASEDIYNRLA-- (SEQ ID NO:222)	----GTTI**R**E**S** (SEQ ID NO:223)	QQYWSTPYT (SEQ ID NO:224)
	AbM	KASEDIYNRLA-- (SEQ ID NO:234)	----GTTI**R**ES (SEQ ID NO:235)	QQYWSTPYT (SEQ ID NO:236)
	Kabat	KASEDIYNRLA-- (SEQ ID NO:58)	----GTTI**R**E**S** (SEQ ID NO:59)	QQYWSTPYT (SEQ ID NO:60)
	Contact	------YNRLAWY (SEQ ID NO:246)	LLMSGTTI**R**E- (SEQ ID NO:247)	QQYWSTPY- (SEQ ID NO: 248)
	IMGT	---EDIYNR---- (SEQ ID NO:258)	----GT----- (SEQ ID NO:259)	QQYWSTPYT (SEQ ID NO:260)
hu-VL4	Chothia	KASEDIYNRLA-- (SEQ ID NO:225)	----GTTI**R**E**S** (SEQ ID NO:226)	QQYWSTPYT (SEQ ID NO:227)
	AbM	KASEDIYNRLA-- (SEQ ID NO:237)	----GTTI**R**E**S** (SEQ ID NO:238)	QQYWSTPYT (SEQ ID NO:239)
	Kabat	KASEDIYNRLA-- (SEQ ID NO:62)	----GTTI**R**ES (SEQ ID NO:63)	QQYWSTPYT (SEQ ID NO:64)
	Contact	------YNRLAWY (SEQ ID NO:249)	LLMSGTTI**R**E- (SEQ ID NO:250)	QQYWSTPY- (SEQ ID NO:251)
	IMGT	---EDIYNR---- (SEQ ID NO:261)	----GT----- (SEQ ID NO:262)	QQYWSTPYT (SEQ ID NO:263)

Four heavy chain and four light chain humanized variants were designed for antibody mAb12. The mAb12 heavy chain variants were designated: mAb12-H1 (SEQ ID NO: 33), mAb12-H2 (SEQ ID NO: 37), mAb12-H3 (SEQ ID NO: 41) and mAb12-H4 (SEQ ID NO: 45). The mAb12 light chain variants were designated: mAb12-L1 (SEQ ID NO: 49), mAb12-L2 (SEQ ID NO: 53), mAb12-L3 (SEQ ID NO: 57) and mAb12-L4 (SEQ ID NO: 61). Pairing of these variable domain sequences is shown in Table 9. The activities of these antibodies and sequences were investigated further as described below.

Table 9: Heavy and Light Chain Pairings

Heavy Chain	Light Chain	Resulting Antibody
mAb12-H1	mAb12-L3	mAb12 VH1-L3 (mAb12-A)
mAb12-H1	mAb12-L4	mAb12 VH1-L4 (mAb12-B)
mAb12-H2	mAb12-L3	mAb12 VH2-L3 (mAb12-C)

mAb12-H2	mAb12-L4	mAb12 VH2-L4 (mAb12-D)
mAb12-H3	mAb12-L3	mAb12 VH3-L3 (mAb12-E)
mAb12-H3	mAb12-L4	mAb12 VH3-L4 (mAb12-F)
mAb12-H4	mAb12-L3	mAb12 VH4-L3 (mAb12-G)
mAb12-H4	mAb12-L4	mAb12 VH4-L4 (mAb12-H)

Example 10: Binding to Human SCF

Microtiter plates were coated with recombinant human SCF-HIS (Celldex) in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified chimeric mAb, designated as mAb12, its humanized versions and an isotype control were added at various concentrations and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative binding curves are shown in FIGs. 10 and 11.

Example 11: Blocking of SCF Binding to c-Kit

The ability of anti-SCF human mAbs to block binding of human SCF to human c-Kit was investigated by ELISA as follows:

Microtiter plates were coated with recombinant human c-Kit-Fc (Celldex) in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified chimeric mAb12, its humanized versions and an isotype control at various concentrations were pre-incubated for 20 minutes at room temperature with biotinylated recombinant human SCF (AcroBiosystems), then added to the plate and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with strepavidin conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIGs. 12 and 13 showing the ability of anti-SCF human mAbs to block SCF binding to its receptor, c-KIT.

Example 12: Affinity and Rate Constants of Humanized mAbs

Binding affinity and binding kinetics of human anti-SCF antibodies were examined by bio-layer interferometry (BLI) using an Octet® QK_e instrument (Sartorius) according to the manufacturer's guidelines.

Purified antibodies were captured on Anti-Human Fc Capture (AHC) biosensors (Sartorius). Sensors were preconditioned by running two association and regeneration cycles with an irrelevant HuIgG1 antibody. Each anti-SCF antibody was prepared in dilution buffer (10mM PO_4 + 150mM NaCl + 1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 0.5µg/mL and loaded on freshly hydrated and preconditioned AHC biosensors for 300sec at 30°C and 1000rpm plate shake speed to achieve a target response of 0.7nm. For one assay, eight biosensors were loaded with the same antibody.

Binding was determined by exposing seven of the antibody loaded biosensors to analyte: soluble human SCF-HIS or soluble cynomolgus SCF. Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 800 to 6.25nM in dilution buffer at 30°C and 1000rpm plate shake speed. Association of the antibody loaded biosensors in analyte wells was carried out for 300 seconds, the biosensors were then moved to dilution buffer wells for 900 seconds for dissociation measurements.

Corresponding controls were conducted in each case by keeping the remaining biosensor with captured antibody in a dilution buffer well for association and dissociation steps. The data for the control biosensor was used to subtract background and account for biosensor drift and antibody dissociation from the biosensors.

Octet BLI Analysis Software system (Sartorius) was used in each case to derive kinetic parameters from the concentration series of analyte in dilution buffer binding to captured antibody. The association and dissociation curves were fitted to a 1:1 binding model using the data analysis software according to the manufacturer's guidelines.

The affinity and kinetic parameters (with background subtracted) for human SCF and cynomolgus SCF are shown in FIGs. 14A and 14B, where k_{on} = rate of association, k_{dis} = rate of dissociation, and K_D = affinity constant, determined by the ratio k_{dis}/k_{on}.

Example 13: Inhibition of c-Kit phosphorylation in human CHO-KIT cells

A standard MSD plate was coated with purified anti-human CD117 (c-Kit) antibody. The plate was sealed and shaken at 500 rpm for 10 minutes, then incubated at 4°C overnight. A 96-well tissue culture treated plate was seeded with 100,000 CHO cells overexpressing human c-Kit/well and incubated at 37°C/5% CO_2 overnight. Diluted anti-SCF antibodies were added to appropriate wells and incubated for 2 hours at 37°C/5% CO_2. The antibody coating was removed from the MSD plate, washed, then blocked with TBST/5% BSA for 1 hour at room temperature with shaking at 500 RPM. Diluted recombinant human SCF was

added to all wells, then incubated for 10 minutes at 37°C/5% CO_2. Following incubation, cells were lysed in ice cold PBS/0.1% Triton X-100 plus phosphatase and protease inhibitors and shaken at 4°C for 5 minutes. The blocked MSD plate was washed with TBST and the cell lysates were applied to the MSD plate and shaken at 500 rpm for 1 hour at room temperature. SulfoTag-pY20 detection antibody was added to all wells and shaken at 500 rpm for 1 hour at room temperature. Results were read in 1x Read Buffer using MSD Sector Plate Reader. Representative curves are shown in FIG. 15 showing the ability of anti-SCF human mAbs to inhibit c-KIT phosphorylation in human CHO-KIT cells.

Example 14: Inhibition of human mast cell degranulation

Mature human mast cells were cytokine starved overnight at 37°C/5% CO_2. The following day mast cells were washed, resuspended in warm HEPES buffer and transferred to 96-well tissue culture plate. Anti-SCF antibodies were diluted and incubated with human mast cells at 37°C in air for 1 hour. Next, human IgE was added to human mast cell/antibody mixture for 30 minutes at 37°C in air. Following IgE treatment, human SCF and goat anti-human IgE were diluted and added to appropriate wells to induce crosslinking and incubated with human mast cells for 30 minutes at 37°C in air. Following incubations β-hexosaminidase was read by diluting samples in PNAG solution and incubating for 90 minutes at 37°C in air, followed by addition of glycine buffer, and analyzed at OD 405nm using a microtiter plate reader. Representative curves are shown in FIG. 16 showing the ability of anti-SCF human mAbs to inhibit human mast cell degranulation.

Example 15: Inhibition of M-07e cell proliferation

M-07e cells were incubated with dilutions of anti-SCF antibodies or an isotype control at 37°C, 5%CO_2 for 1 hour. Following incubation, recombinant human SCF (R&D Systems) were added to all wells and incubated at 37°C, 6%CO_2 for 6 days. After 6 days, CellTiter Glo (Promega) was added according to the kit instructions and luminescence as a result of cell proliferation was detected and quantitated using a microtiter plate reader. Representative curves are shown in FIG. 17 showing the ability of anti-SCF human mAbs to inhibit M-07e cell proliferation.

Example 16: Epitope mapping

Microtiter plates were coated with recombinant human wild-type SCF-HIS (Celldex), or mutated versions of SCF in PBS, and then blocked with 5% bovine serum albumin in PBS. Protein A purified humanized mAb12 were added at various concentrations and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative binding curves are shown in FIGs. 18A and 18B. A three-dimensional drawing showing the binding of SCF to KIT-D1 including residue K100 is provided in FIG. 18C.

Example 17: Sl/Sl4 SCF cell binding

Mouse Sl/Sl4 cells made to overexpress the membrane bound form of SCF, known as SCF^{220} (ATCC) were incubated with diluted humanized mAb12 or human KIT-ECD for 1 hour at 4°C. Cells were washed and incubated with goat-anti-human IgG Fc-specific polyclonal reagent conjugated to R-Phycoerythrin fluorophore for 1 hour at 4°C. Following incubation, cells were washed and fixed. Mean fluorescence intensity was read using the Bectin Dickonson® (BD) Accuri C6 Plus Personal Flow Cytometer instrument..

Mouse Sl/Sl4 cells made to overexpress the soluble SCF isoform, known as SCF-248 (ATCC) were incubated with diluted humanized mAb12 or human KIT-ECD for 1 hour at 4°C. Cells were washed and incubated with goat-anti-human IgG Fc-specific polyclonal reagent conjugated to R-Phycoerythrin fluorophore for 1 hour at 4°C. Following incubation, cells were washed and fixed. Mean fluorescence intensity was read using the BD Accuri C6 Plus Personal Flow Cytometer.

Representative binding curves are shown in FIGs. 19A and 19 B showing humanized mAb12 preferentially binds and blocks soluble SCF.

Example 18: Inhibition of c-Kit phosphorylation in human M-07e cells

Soluble and SCF^{220} induced phosphorylation were assessed by ELISA. Parental Sl/Sl4 or Sl/Sl4-SCF^{220} cells were treated with mitomycin C for 2 hours, washed, and allowed to recover overnight at 37°C, 5%CO_2. M-07e cells were washed and serum starved overnight at 37°C, 5%CO_2. Diluted mAb12 was preincubated with the source of SCF used to stimulate M-07e cells; either soluble SCF and parental Sl/Sl4 cells or Sl/Sl4-SCF^{220} cells for 1 hour at

37°C, 5%CO_2. Following preincubation, M-07e cells were added to Sl/Sl4 cells and spun down at 1200 rpm for 5 minutes, followed by incubation at 37°C, 5%CO_2 for 20 minutes. Following incubation, media was removed, and cells lysed in 2x lysis buffer at 4°C for 10 minutes. Recombinant human c-Kit was used to coat a 96-well high binding plate, followed by blocking with 5% BSA. Cell lysates were added to c-Kit coated plate and incubated at room temperature. The plates were washed with PBS/Tween and then incubated with a HRP conjugated pY20 detection antibody. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIG. 20 showing the ability of anti-SCF human mAbs to inhibit c-KIT phosphorylation in human M-07e cells.

Example 19: Construction and production of bispecific antibodies (CDX-622)

Tetravalent bispecific antibody constructs were developed using a mutated fully human IgG1 backbone for a TSLP monoclonal antibody sequence (1D10 VH1-L1 and 1D10 VH2-L1) and the scFv of the SCF monoclonal antibody genetically linked to the C-terminus of the 1D10 heavy chain through a linker (FIGs. 21A and 21B). The humanized antibody scFv sequences used in the bispecifics were taken from mAb12 VH1-L4, mAb12 VH2-L4, and mAb12 VH4-L3. The Fc domain was mutated (234A, 235Q, 322Q, 252Y, 254T and 256E).

The constant domain sequence was as follows (mutations shown in bold):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPE**AQ**GGPSVFLFPPKPKDTL**YITRE**PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC**Q**VSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:350)

Bispecific constructs were expressed in CHO cell lines. Table 10 defines the constructs.

Table 10: IgG and scFv Pairings

IgG	scFv	Resulting Bispecific Antibody	ID
1D10 VH1-L1	mAb12 VH1-L4	1D10(VH1-L1) - mAb12(VH1-L4)	1.2

1D10 VH1-L1	mAb12 VH2-L4	1D10(VH1-L1) - mAb12(VH2-L4)	1.4
1D10 VH1-L1	mAb12 VH4-L3	1D10(VH1-L1) - mAb12(VH4-L3)	1.7
1D10 VH2-L1	mAb12 VH1-L4	1D10(VH2-L1) - mAb12(VH1-L4)	5.2
1D10 VH2-L1	mAb12 VH2-L4	1D10(VH2-L1) - mAb12(VH2-L4)	5.4
1D10 VH2-L1	mAb12 VH4-L3	1D10(VH2-L1) - mAb12(VH4-L3)	5.7

The 5.7 construct ((1D10(VH2-L1) - mAb12(VH4-L3)) was designated "CDX-622" and further analyzed as described in the following examples.

Example 20: Binding to Human TSLP

Microtiter plates were coated with recombinant human TSLP-kappa (Celldex) in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of the bispecific antibodies and an isotype control were added and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIG. 22 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to bind to human TSLP.

Example 21: Binding to Human SCF

Microtiter plates were coated with recombinant human SCF-HIS (Celldex) in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of the bispecific antibodies and an isotype control were added and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG Fc-specific polyclonal reagent conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIG. 23 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to bind to human SCF.

Example 22: Bifunctional Binding to Human TSLP and Human SCF

Microtiter plates were coated with recombinant human TSLP-kappa in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of the bispecific antibodies and an isotype control were allowed to bind to the TSLP before adding biotinylated human SCF (AcroBiosystems) that was detected with HRP labeled strepavidin. After washing, the plates

were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIG. 24 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to simultaneously bind to human TSLP and human SCF.

Example 23: Blocking of TSLP Binding to TSLP-R

The ability of the bispecific antibodies to block binding of human TSLP to human TSLP receptor (TSLP-R) was investigated by ELISA as follows:

Microtiter plates were coated with recombinant human TSLP-R (AcroBiosystems) in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of the bispecific antibodies and an isotype control were pre-incubated for 20 minutes at room temperature with biotinylated recombinant human TSLP (AcroBiosystems), then added to the plate and incubated at 37°C. The plates were washed with PBS/Tween and then incubated with strepavidin conjugated to horseradish peroxidase at 37°C. After washing, the plates were developed with HRP substrate, and analyzed at OD 450nm using a microtiter plate reader. Representative curves are shown in FIGs. 25A and 25B showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to block TSLP binding to its receptor, TSLP-R.

Example 24: Blocking of SCF Binding to c-Kit

The ability of anti-SCF human mAbs to block binding of human SCF to human c-Kit expressed on the surface of MO7e cells was investigated as follows:

Dilutions of the bispecific antibodies and an isotype control were pre-incubated for 20 minutes at room temperature with biotinylated recombinant human SCF (AcroBiosystems), then added to the cells and incubated at room temperature on a plate shaker. The cells were washed and incubated with strepavidin conjugated to phycoerythrin at room temperature on a plate shaker. After washing, the cell associated fluorescence was determined by analysis using a FACSCanto II™ instrument (BD Biosciences) according to manufacturer's directions. A representative curve is shown in FIG. 26 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to block SCF binding to its receptor, c-KIT.

Example 25: Inhibition of BaF3 Cell Proliferation

BaF3 cells were transfected to express human TSLP and human IL-7Ra on their surface. The cells were incubated with recombinant human TSLP (R&D Systems) in the presence of either media, dilutions of the bispecific antibodies or an isotype control at 37°C, 6%CO_2. After 3 days, CellTiter Glo (Promega) was added according to the kit instructions and luminescence as a result of cell proliferation was detected and quantitated on a Perkin Elmer Victor X4® luminometer. Representative curves are shown in FIGs. 27A and 27B showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to inhibit BaF3 cell proliferation.

Example 26: Inhibition of TARC Induction in Human Dendritic Cells

Human dendritic cells (DCs) were isolated from previously frozen peripheral blood mononuclear cell leukopaks (BioIVT) using a MACS Cell separation Pan DC Enrichment Kit from Miltenyi Biotec®. The cells were incubated overnight with recombinant human TSLP (R&D Systems) in the presence of either media, dilutions of the bispecific antibodies or an isotype control at 37°C, 6%CO_2. Supernatants were harvested and thymus- and activation-regulated chemokine (TARC) production was quantitated by ELISA (R&D Systems). Representative curves are shown in FIGs. 28A and 28B showing the ability of constructs 5.2 and 5.7 (CDX-622) to inhibit TARC release.

Example 27: Affinity and Rate Constants of Humanized BsAbs

Binding affinity and binding kinetics of the purified bispecific antibodies were examined by bio-layer interferometry (BLI) using an Octet® QK_e instrument (Sartorius) according to the manufacturer's guidelines.

To assess affinity to human TSLP, purified bispecific antibodies were captured on Anti-Human Fc Capture (AHC) (Sartorius). Each bispecific antibody was prepared in dilution buffer (10mM PO_4 + 150mM NaCl+1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 1.0µg/mL and loaded on freshly hydrated biosensors for 300sec at 30°C and 1000rpm plate shake speed. For one assay, eight biosensors were loaded with the same antibody.

Binding of human TSLP was determined by exposing seven of the antibody loaded biosensors to analyte: soluble human TSLP-HIS (ACROBiosystems). Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 12.5 to 0.8nM in dilution buffer. Association of the antibody loaded biosensors in analyte wells was carried out for 300 seconds, the biosensors were then moved to dilution buffer wells for 1200

seconds for dissociation measurements. Both association and dissociation steps were carried out at 30°C and 1000rpm plate shake speed.

For cynomolgus TSLP experiments, soluble cynomolgus TSLP-HIS (ACROBiosystems) was prepared in dilution buffer (10mM PO_4 + 150mM NaCl + 1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 2.0µg/mL and loaded on freshly hydrated Anti-Penta-HIS (HIS1K) biosensors (Sartorius) for 300 seconds at 30°C and 1000rpm plate shake speed. For one assay, eight biosensors were loaded with the same antigen.

Binding of cynomolgus TSLP was determined by exposing seven of the ligand loaded biosensors to analyte, purified bispecific antibodies. Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 200 to 3.1nM in dilution buffer. Association of the ligand loaded biosensors in analyte wells was carried out for 180 seconds, the biosensors were then moved to dilution buffer wells for 300 seconds for dissociation measurements. Both association and dissociation steps were carried out at 30°C and 1000rpm plate shake speed.

To assess affinity to human and cynomolgus SCF, purified bispecific antibodies were captured on Anti-Human Fab-CH1 2nd Generation (FAB2G) biosensors (Sartorius). Each bispecific antibody was prepared in dilution buffer (10mM PO_4 + 150mM NaCl + 1mg/mL BSA + 0.05% Tween 20, pH 7.2) to 1.0µg/mL and loaded on freshly hydrated biosensors for 300 seconds at 30°C and 1000rpm plate shake speed. For one assay, eight biosensors were loaded with the same antibody.

Binding of human and cynomolgus SCF was determined by exposing seven of the antibody loaded biosensors to analyte: soluble human SCF-HIS or soluble cynomolgus SCF-HIS. Affinity measurements were determined using 2-fold serial dilutions of analyte ranging from 800 to 12.5 nM in dilution buffer. Association of the antibody loaded biosensors in analyte wells was carried out for 300 seconds, the biosensors were then moved to dilution buffer wells for 900 to 1200 seconds for dissociation measurements. Both association and dissociation steps were carried out at 30°C and 1000rpm plate shake speed.

Corresponding controls were conducted in each case by keeping one biosensor with captured ligand in a dilution buffer well for association and dissociation steps. The data for the control biosensor was used to subtract background and account for biosensor drift and ligand dissociation from the biosensors.

Octet BLI Analysis Software (Sartorius) was used in each case to derive kinetic parameters from the concentration series of analyte in dilution buffer binding to captured

ligand. The association and dissociation curves were fitted to a 1:1 binding model using the data analysis software according to the manufacturer's guidelines.

The affinity and kinetic parameters (with background subtracted) are shown in FIGs. 29A and 29B, where k_{on} = rate of association, k_{dis} = rate of dissociation, and K_D = affinity constant, determined by the ratio k_{dis}/k_{on}.

Example 28: Inhibition of c-Kit phosphorylation in human CHO-KIT cells

A standard MSD plate was coated with purified anti-human CD117 (c-Kit) antibody, sealed, shaken at 500 rpm for 10 minutes and incubated at 4°C overnight. A 96-well tissue culture treated plate was seeded with 100,000 CHO cells overexpressing human c-Kit/well and incubated at 37°C/5% CO_2 overnight. Bispecific antibodies were diluted, then added to appropriate wells and incubated for 2 hours at 37°C/5% CO_2. The coating antibody was removed from the MSD plate, washed, then blocked with TBST/5% BSA for 1 hour at room temperature with shaking at 500 RPM. Dilute recombinant human SCF was added to all wells, then incubated for 10 minutes at 37°C/5% CO_2. Following incubation cells were lysed in ice cold PBS/0.1% Triton X-100 plus phosphatase and protease inhibitors and shaken at 4°C for 5 minutes. The blocked MSD plate was washed with TBST. Cell lysates were applied to the MSD plate and shaken at 500 rpm for 1 hour at room temperature. SulfoTag-pY20 detection antibody was added to all wells and shaken at 500 rpm for 1 hour at room temperature. Results were read in 1x Read Buffer using MSD Sector Plate Reader. Representative curves are shown in FIG. 30 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to inhibit c-KIT phosphorylation in human CHO-KIT cells.

Example 29: Inhibition of human mast cell degranulation

Mature human mast cells were cytokine starved overnight at 37°C/5% CO_2. The following day mast cells were washed, resuspended in warm HEPES buffer and transferred to 96-well tissue culture plate. Bispecific antibodies were diluted and incubated with human mast cells at 37°C in air for 1 hour. Next, human IgE was added to human mast cell/antibody mixture for 30 minutes at 37°C in air. Following IgE treatment, human SCF and goat anti-human IgE were diluted and added to appropriate wells to induce crosslinking and incubated with human mast cells for 30 minutes at 37°C in air. Following incubations β-hexosaminidase was read by diluting samples in PNAG solution and incubating for 90 minutes at 37°C in air,

followed by addition of glycine buffer, and analyzed at OD 405nm using a microtiter plate reader. Representative curves are shown in FIG. 31 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to inhibit human mast cell degranulation.

Example 30: Inhibition of M-07e cell proliferation

M-07e cells were incubated with dilutions of bispecific antibodies at 37°C, 5%CO_2 for 1 hour. Following incubation, recombinant human SCF (R&D Systems) were added to all wells and incubated at 37°C, 6%CO_2 for 6 days. After 6 days, CellTiter Glo (Promega) was added according to the kit instructions and luminescence as a result of cell proliferation was detected and quantitated using a microtiter plate reader. Representative inhibition curves are shown in FIG. 32 showing the ability of the bispecific constructs (i.e., the IgG and scFv pairings shown in Table 10) to inhibit M-07e cell proliferation.

Example 31: Inhibition of KIT phosphorylation in M-07e cells stimulated with soluble SCF compared to membrane-associated SCF (SCF^{222})

M-07e cells were incubated with dilutions of bispecific antibody, CDX-622. Following incubation, soluble SCF and membrane-associated SCF (SCF^{222}) were added and incubated according to the kit instructions (CellTiter Glo; Promega). Luminescence as a result of cell proliferation was detected and quantitated using a microtiter plate reader. Representative inhibition data are shown in FIG. 33. As shown, CDX-622 blocks KIT phosphorylation in M-07e cells that have been stimulated with soluble SCF with greater potency than KIT stimulated with SCF^{220}-expressing cells

Example 32: Inhibition of mast cell activity

A pilot study of mAb12 (SCF-12) was conducted in cynomolgus macaques. Prior to the initiation of the dosing, baseline samples were collected from two animals which included skin biopsies from the ear pinna. mAb12 (SCF-12) was administered on Day 1 and on Day 8, at a dose level of 75 mg/kg/dose by a slow intravenous push. Additional skin biopsies were collected on 30 and day 57. Nanostring RNA analysis of the biopsies was performed with a non-human primate immunology panel of genes along with selected mast cell and melanocyte genes. FIGs. 34A and 34B shows the decrease in the expression of several selected genes associated with mast cell function, reflecting significantly reduced mast cell activity.

Example 33: Pilot Study Histology

During the course of the pilot study described in Example 32 punch biopsies from the pinna of the monkey ears were formalin fixed and paraffin embedded. Blocks were sectioned and stained with toluidine blue. Representative images of the biopsy cross sections, from animals treated with mAb12, are shown in FIG. 35A (before treatment) and FIG. 35B (day 30). Mast cells were counted and average data is shown in FIG. 35A, with the aggregate data shown in FIG. 36B.

Example 34: Pilot Study Hematology

Clinical pathology analysis was performed periodically throughout the pilot study described in Example 32. Mild changes in hematology consisted of a transient decrease in Mean Corpuscular Hemoglobin Concentration, a transient increase in Mean Corpuscular Volume with no change in Mean Corpuscular Hemoglobin, following the first dose of mAb12. Results are shown in FIGs. 37A, 37B, and 37C.

Example 35: Pilot Study Pharmacology

Serum samples were collected from the monkeys over the course of the study and were assayed for the presence of mAb12. Circulating levels of the monoclonal antibodies are shown in FIG. 38. Serum samples were also assayed for the presence of anti-drug antibodies (ADAs). Results are shown in FIG. 39 (the red line indicates the cutpoint of the assay).

Example 36: Inhibition of Mast Cell Activity

A pilot study of bispecific antibody, CDX-622, was conducted in cynomolgus macaques. Four cynomolgus macaques were administered 10 mg/kg of CDX-622 on Day 1 by a slow intravenous injection. Blood samples were taken as indicated for determination of circulating test article levels, anti-drug antibodies and clinical pathology. CDX-622 administration did not result in significant decreases in hematological parameters (see FIGs. 40A-F).

Punch biopsies from each ear pinna were collected for histology at days 0 (pre-dose), day 15, and day 29 post-treatment. RNA from each biopsy was isolated and subjected to RNA quantitation by Nanostring analysis. Normalized mast cell specific gene counts are

plotted as a function of baseline values and show mast cell depletion (FIGs. 41A-F). Housekeeping gene b-tubulin is shown as a control.

Example 37: Inhibition of TSLP-Induced CD80 Expression on Human Dendritic Cells

Human dendritic cells (DCs) were isolated from previously frozen peripheral blood mononuclear cell leukopaks (BioIVT®) using a MACS Cell separation Pan DC Enrichment Kit from Miltenyi Biotec. The cells were incubated overnight with recombinant human TSLP (R&D Systems) in the presence of either media, antibodies (bispecific antibody (CDX-622) or 1D10), or an isotype control at 37°C, 6% CO_2. Cells were harvested, washed, and incubated with FITC labeled CD80 (BD Biosciences). After washing, the cell associated fluorescence was determined by analysis using a FACSCanto II™ instrument (BD Biosciences) according to manufacturer's directions. Results are shown in FIG. 42 showing bispecific construct CDX-622 inhibited TSLP-driven upregulation of dendritic cell CD80 cell surface expression comparable to parental mAb 1D10.

Example 38: Inhibition of TSLP Binding to TSLP-R In Vitro

Inhibition by the bispecific antibody CDX-622 of TSLP binding to TSLP-R in vitro was measured by ELISA using a method adapted from Example 23. Results are shown in FIG. 43 showing bispecific construct CDX-622 inhibited TSLP binding to its cognate receptor complex (TSLPR/IL-7Rα) comparable to parental mAb 1D10.

Example 39: Inhibition of TSLP-Mediated Cell Proliferation In Vitro

Inhibition by the bispecific antibody CDX-622 of TSLP-mediated cell proliferation in BaF3 cells in vitro was measured using a method adapted from Example 25. Results are shown in FIG. 44 showing bispecific construct CDX-622 inhibited TSLP-mediated cell proliferation in vitro comparable to parental mAb 1D10.

Example 40: Eosinophil survival

Human eosinophils were isolated from buffy coats using EasySep Direct Human Eosinophil Isolation Kit. Upon isolation, eosinophils were plated with IL-5 (0.1 ng/mL), overnight. Following priming, eosinophils were treated with SCF (25 ng/mL), TSLP (1000 ng/mL), or a combination of both cytokines in the presence of either media, or CDX-622. Eosinophils were cultured for 5 days at 37 °C/5%CO_2 and survival assessed using CellTiter-

Glo. As shown in FIG. 45, bispecific construct CDX-622 inhibited eosinophil survival to a greater extent in cells treated with both chemokines (SCF and TSLP) compared to cells treated with one chemokine (SCF or TLSP).

Example 41: SCF-induced Cytokine Release from Human Primary Mast Cells

Human primary mast cells were plated ($1x10^5$ cells/well) in a 96-well cell culture treated plate and primed in the presence of IL-1α (10 ng/mL)/IL-3 (10 ng/mL)/TNF-α (25 ng/mL). After priming, mast cells were treated with SCF (100 ng/mL), TSLP (5 ng/mL), or a combination of both cytokines in the presence of either media, mAbs, or CDX-622 for 24 hours. Following incubation, supernatants were collected, and production of IL-5 (R&D Systems) was determined by ELISA. As shown in FIG. 46, bispecific construct CDX-622 simultaneously neutralizes TSLP and SCF mediated mast cell activation.

Example 42: MCP-1 Induction with the combination of SCF and TSLP / Simultaneous Blockade of SCF and TSLP

LAD2 cells were incubated with either 12.5ng/mL SCF (Peprotech), 50ng/mL TSLP (R&D Systems) or the combination overnight. Supernatants were harvested and MCP-1 production was quantitated by ELISA (R&D Systems). As shown in FIG. 47, co-addition of SCF and TSLP increases the secretion of a number of pro-inflammatory cytokines and chemokines.

CDX-622, the parental monoclonal antibodies and an isotype control were pre-incubated for 20 minutes at room temperature with either 12.5ng/mL recombinant human SCF (Peprotech), 50ng/mL recombinant human TSLP (R&D Systems) or the combination. The mixture was then added to LAD2 cells and incubated overnight. Supernatants were harvested and MCP-1 production was quantitated by ELISA (R&D Systems). Representative data (FIG. 48) shows that, while addition of anti-SCF or anti-TSLP mAbs inhibited cytokines release elicited by their respective targets, CDX-622 reduced their secretion to a greater extent.

Example 43: Inhibition of TSLP-Induced CD80 Expression on Human Dendritic Cells

Human dendritic cells (DCs) were isolated from previously frozen peripheral blood mononuclear cell leukopaks (BioIVT) using a MACS Cell separation Pan DC Enrichment Kit from Miltenyi Biotec. The cells were incubated overnight with recombinant human TSLP (R&D Systems) in the presence of either media, antibodies or an isotype control at 37°C, 6%

CO_2. Cells were harvested, washed and incubated with FITC labeled CD80 (BD Biosciences). After washing, the cell associated fluorescence was determined by analysis using a FACSCanto II™ instrument (BD Biosciences) according to manufacturer's directions. Representative curves are shown in FIG. 49 showing CDX-622 potently inhibited TSLP-driven upregulation of dendritic cell CD80 cell surface expression.

Table 11: SUMMARY OF SEQUENCE LISTING

SEQ ID NO:1 1D10 VH1	QVQLVQSGAEVKKPGASVKVSCKASTNAFTNYLIEWVRQAPGQGLEWI GVINPGGGGTNYNEKFQGRATLTADKSSSTAYMELSSLRSEDTAVYFC AREDSAGYGFAYWGQGTLVTVSS
SEQ ID NO:2 1D10 VH1-CDR1 (Kabat)	NYLIE
SEQ ID NO:3 1D10 VH1-CDR2 (Kabat)	VINPGGGGTNYNEKFQG
SEQ ID NO:4 1D10 VH1-CDR3 (Kabat)	EDSAGYGFAY
SEQ ID NO:5 1D10 VH2	QVQLVQSGAEVKKPGASVKVSCKASTNAFTNYLIEWVRQAPGQGLEW MGVINPGGGGTNYNEKFQGRVTMTADKSTSTAYMELSSLRSEDTAVY YCAREDSAGYGFAYWGQGTLVTVSS
SEQ ID NO:6 1D10 VH2-CDR1 (Kabat)	NYLIE
SEQ ID NO:7 1D10 VH2-CDR2 (Kabat)	VINPGGGGTNYNEKFQG
SEQ ID NO:8 1D10 VH2-CDR3 (Kabat)	EDSAGYGFAY

SEQ ID NO:9 1D10 VH3	QVQLQQSGPGLVKPSETLSLTCTASTNAFTNYLIEWVRQPPGKGLEWIG VINPGGGGTNYNESLKSRATLSADKSSSTASLKLSSVTAADTAVYFCAR EDSAGYGFAYWGQGTLVTVSS
SEQ ID NO:10 1D10 VH3-CDR1 (Kabat)	NYLIE
SEQ ID NO:11 1D10 VH3-CDR2 (Kabat)	VINPGGGGTNYNEKLKS
SEQ ID NO:12 1D10 VH3-CDR3 (Kabat)	EDSAGYGFAY
SEQ ID NO:13 1D10 VH4	QVQLQESGPGLVKPSETLSLTCTASTNAFTNYLIEWIRQPPGKGLEWIGV INPGGGGTNYNESLKSRVTISADKSKNQASLKLSSVTAADTAVYYCARE DSAGYGFAYWGQGTLVTVSS
SEQ ID NO:14 1D10 VH4-CDR1 (Kabat)	NYLIE
SEQ ID NO:15 1D10 VH4-CDR2 (Kabat)	VINPGGGGTNYNEKLKS
SEQ ID NO:16 1D10 VH4-CDR3 (Kabat)	EDSAGYGFAY
SEQ ID NO:17 1D10 VL1	SIVMTQSPATLSLSPGERATLSCRASQSVSSDVAWYQQKPGQAPRLLIY YASNRYTGVPARFSGSGYGTDFTFTISSLEPEDFAVYFCQQDYAFPYTF GGGTKLEIK
SEQ ID NO:18 1D10 VL1-CDR1 (Kabat)	RASQSVSSDVA
SEQ ID NO:19 1D10	YASNRYT

VL1-CDR2 (Kabat)	
SEQ ID NO:20 1D10 VL1-CDR3 (Kabat)	QQDYAFPYT
SEQ ID NO:21 1D10 VL2	EIVMTQSPATLSLSPGERATLSCRASQSVSSDVAWYQQKPGQAPRLLIY YASNRYTGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQDYAFPYTFG GGTKLEIK
SEQ ID NO:22 1D10 VL2-CDR1 (Kabat)	RASQSVSSDVA
SEQ ID NO:23 1D10 VL2-CDR2 (Kabat)	YASNRYT
SEQ ID NO:24 1D10 VL2-CDR3 (Kabat)	QQDYAFPYT
SEQ ID NO:25 1D10 VL3	SIVMTQSPDSLAVSLGERATINCKASQSVSSDVAWYQQKPGQPPKLLIY YASNRYTGVPDRFSGSGYGTDFTFTISSLQAEDVAVYFCQQDYAFPYTF GGGTKLEIK
SEQ ID NO:26 1D10 VL3-CDR1 (Kabat)	KASQSVSSDVA
SEQ ID NO:27 1D10 VL3-CDR2 (Kabat)	YASNRYT
SEQ ID NO:28 1D10 VL3-CDR3 (Kabat)	QQDYAFPYT
SEQ ID NO:29 1D10 VL4	DIVMTQSPDSLAVSLGERATINCKASQSVSSDVAWYQQKPGQPPKLLIY YASNRYSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQDYAFPYTF GGGTKLEIK

SEQ ID NO:30 1D10 VL4-CDR1 (Kabat)	KASQSVSSDVA
SEQ ID NO:31 1D10 VL4-CDR2 (Kabat)	YASNRYS
SEQ ID NO:32 1D10 VL4-CDR3 (Kabat)	QQDYAFPYT
SEQ ID NO:33 mAb12 VH1	EVQLVQSGGGLVQPGGSLRLSCAASGIDFSRYWMSWVRRAPGKGLEW IGEINPDSNTLNYAPSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYC ARPGGGYYSYALDYWGQGTTVTVSS
SEQ ID NO:34 mAb12 VH1-CDR1 (Kabat)	RYWMS
SEQ ID NO:35 mAb12 VH1-CDR2 (Kabat)	EINPDSNTLNYAPSVKG
SEQ ID NO:36 mAb12 VH1-CDR3 (Kabat)	PGGGYYSYALDY
SEQ ID NO:37 mAb12 VH2	EVQLVESGGGLVQPGGSLRLSCAASGIDFSRYWMSWVRQAPGKGLEW VGEINPDSNTLNYAPSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYY CARPGGGYYSYALDYWGQGTTVTVSS
SEQ ID NO:38 mAb12 VH2-CDR1 (Kabat)	RYWMS
SEQ ID NO:39 mAb12 VH2-CDR2 (Kabat)	EINPDSNTLNYAPSVKG

SEQ ID NO:40 mAb12 VH2-CDR3 (Kabat)	PGGGYYSYALDY
SEQ ID NO:41 mAb12 VH3	QVQLQQSGPGLVKPSGTLSLTCAASGIDFSRYWMSWVRRPPGKGLEWI GEINPDSNTLNYAPSLKSRFTISRDNSKNTLSLKLSSVTAADTAVYYCAR PGGGYYSYALDYWGQGTTVTVSS
SEQ ID NO:42 mAb12 VH3-CDR1 (Kabat)	RYWMS
SEQ ID NO:43 mAb12 VH3-CDR2 (Kabat)	EINPDSNTLNYAPSLKS
SEQ ID NO:44 mAb12 VH3-CDR3 (Kabat)	PGGGYYSYALDY
SEQ ID NO:45 mAb12 VH4	QVQLQESGPGLVKPSGTLSLTCAASGIDFSRYWMSWVRQPPGKGLEWI GEINPDSNTLNYAPSLKSRVTISRDNSKNQLSLKLSSVTAADTAVYYCA RPGGGYYSYALDYWGQGTTVTVSS
SEQ ID NO:46 mAb12 VH4-CDR1 (Kabat)	RYWMS
SEQ ID NO:47 mAb12 VH4-CDR2 (Kabat)	EINPDSNTLNYAPSLKS
SEQ ID NO:48 mAb12 VH4-CDR3 (Kabat)	PGGGYYSYALDY
SEQ ID NO:49 mAb12 VL1	DIQMTQSPSSLSASVGDRVTITCRASEDIYNRLAWYQQKPGKAPKLLMS GTTILETGVPSRFSGSGSGKDYTLTISSLQPEDFATYYCQQYWSTPYTFG GGTKLEIK
SEQ ID NO:50 mAb12	RASEDIYNRLA

VL1-CDR1 (Kabat)	
SEQ ID NO:51 mAb12 VL1-CDR2 (Kabat)	GTTILET
SEQ ID NO:52 mAb12 VL1-CDR3 (Kabat)	QQYWSTPYT
SEQ ID NO:53 mAb12 VL2	DIQMTQSPSSLSASVGDRVTITCRASEDIYNRLAWYQQKPGKAPKLLMS GTTILESGVPSRFSGSGSGKDYTLTISSLQPEDFATYYCQQYWSTPYTFG GGTKLEIK
SEQ ID NO:54 mAb12 VL2-CDR1 (Kabat)	RASEDIYNRLA
SEQ ID NO:55 mAb12 VL2-CDR2 (Kabat)	GTTILES
SEQ ID NO:56 mAb12 VL2-CDR3 (Kabat)	QQYWSTPYT
SEQ ID NO:57 mAb12 VL3	DIVMTQSPDSLAVSLGERATINCKASEDIYNRLAWYQQKPGQPPKLLMS GTTILETGVPDRFSGSGSGKDYTLTISSLQAEDVATYYCQQYWSTPYTF GGGTKLEIK
SEQ ID NO:58 mAb12 VL3-CDR1 (Kabat)	KASEDIYNRLA
SEQ ID NO:59 mAb12 VL3-CDR2 (Kabat)	GTTIRES
SEQ ID NO:60 mAb12	QQYWSTPYT

VL3-CDR3 (Kabat)	
SEQ ID NO:61 mAb12 VL4	DIVMTQSPDSLAVSLGERATINCKASEDIYNRLAWYQQKPGQPPKLLMS GTTIRESGVPDRFSGSGSGKDYTLTISSLQAEDVAVYYCQQYWSTPYTF GGGTKLEIK
SEQ ID NO:62 mAb12 VL4-CDR1 (Kabat)	KASEDIYNRLA
SEQ ID NO:63 mAb12 VL4-CDR2 (Kabat)	GTTIRES
SEQ ID NO:64 mAb12 VL4-CDR3 (Kabat)	QQYWSTPYT
SEQ ID NO:65 5.2 1D10 H2-mAb12 VH1VL4 (ds)	QVQLVQSGAEVKKPGASVKVSCKASTNAFTNYLIEWVRQAPGQGLEW MGVINPGGGGTNYNEKFQGRVTMTADKSTSTAYMELSSLRSEDTAVY YCAREDSAGYGFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAQGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGKGSSGGGGSEVQLVQSGGGLVQPGGSLRLSCAA SGIDFSRYWMSWVRRAPGKCLEWIGEINPDSNTLNYAPSVKGRFTISRD NAKNTLYLQMNSLRAEDTAVYYCARPGGGYYSYALDYWGQGTTVTV SSGGGGSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKAS EDIYNRLAWYQQKPGQPPKLLMSGTTIRESGVPDRFSGSGSGKDYTLTI SSLQAEDVAVYYCQQYWSTPYTFGCGTKLEIK
SEQ ID NO:66 5.2 1D10 H2-mAb12 VH1VL4 (ds)	CAAGTGCAGCTGGTCCAGTCCGGAGCCGAGGTCAAGAAGCCTGGCG CCTCAGTGAAAGTGTCCTGCAAGGCTAGCACCAACGCGTTTACCAAC TACTTGATCGAATGGGTCAGACAGGCCCCCGGACAAGGACTGGAGT GGATGGGAGTGATCAATCCTGGAGGAGGAGGGACCAACTACAATGA GAAGTTCCAGGGACGCGTGACTATGACCGCCGATAAGTCCACTTCA ACCGCCTATATGGAACTGTCGTCCCTGCGATCCGAAGATACCGCCGT GTACTACTGTGCCCGGGAGGATTCTGCCGGATACGGCTTCGCGTACT GGGGACAAGGCACCTTGGTCACCGTGTCCAGCGCCTCAACCAAGGG CCCCTCGGTGTTTCCGCTTGCGCCGTCGAGCAAGAGCACCTCGGGAG GAACAGCAGCCCTGGGTTGCCTCGTGAAGGACTATTTCCCGGAACCC GTGACTGTCTCCTGGAACTCAGGAGCCCTCACCTCCGGAGTGCACAC GTTCCCGGCCGTGCTTCAGTCGTCCGGGCTGTACTCCCTGTCGTCCGT

	GGTCACGGTGCCCAGTTCCTCCCTGGGCACTCAGACTTACATTTGCA ACGTGAACCACAAGCCGTCGAACACCAAGGTCGATAAGAAAGTGGA ACCCAAGTCCTGCGACAAGACCCACACTTGCCCTCCTTGCCCTGCTC CCGAAGCCCAAGGGGGGCCTTCGGTGTTCCTCTTCCCCCCCAAACCA AAGGACACCCTGTACATCACCCGGGAGCCGGAAGTGACCTGTGTGG TGGTCGATGTGTCCCACGAGGATCCGGAAGTCAAGTTCAATTGGTAC GTCGATGGCGTGGAAGTGCACAACGCCAAGACTAAGCCCCGGGAAG AACAGTACAACTCCACCTATCGCGTGGTGTCCGTCCTGACCGTGCTG CACCAGGACTGGCTCAACGGGAAGGAATACAAGTGCCAGGTGTCCA ACAAGGCACTGCCTGCCCCAATCGAAAAGACCATCTCCAAGGCCAA GGGACAACCAAGGGAGCCCCAAGTGTACACCCTGCCTCCCTCACGG GACGAGCTCACCAAAAACCAGGTTTCCCTGACCTGTCTCGTGAAGG GCTTCTATCCCTCCGATATCGCGGTCGAATGGGAGTCCAACGGACAG CCCGAGAACAACTACAAGACTACTCCCCCGGTGTTAGACTCCGACG GCTCCTTCTTCTTGTACTCAAAGCTGACCGTGGACAAGTCGCGCTGG CAACAGGGAAACGTGTTCAGCTGCTCCGTGATGCATGAGGCCCTGC ATAATCATTACACCCAGAAGTCGCTGTCCCTGTCACCGGGGAAGGG GTCCAGCGGTGGAGGAGGTTCGGAGGTGCAGCTTGTGCAGAGCGGA GGCGGATTGGTGCAACCAGGGGGAAGCCTTCGCCTGTCGTGTGCAG CAAGCGGCATTGACTTCTCTCGGTACTGGATGTCCTGGGTCCGGAGA GCTCCAGGGAAGTGCCTCGAATGGATCGGGGAGATCAACCCGGACT CCAACACCCTCAACTACGCACCAAGCGTGAAGGGCCGGTTCACGAT TAGCAGGGACAACGCCAAAAACACTTTGTACCTCCAAATGAACTCG CTGCGCGCTGAGGACACCGCGGTCTACTACTGTGCCAGACCTGGGG GAGGATACTACAGCTACGCCCTGGACTACTGGGGCCAGGGTACCAC CGTGACTGTGTCATCCGGAGGCGGTGGTTCGGGTGGCGGAGGAAGC GGAGGGGGAGGATCAGGAGGCGGCGGATCAGACATCGTGATGACCC AGAGCCCTGACTCGCTGGCTGTGTCCTTGGGTGAACGCGCCACTATC AACTGCAAGGCCTCCGAGGACATCTACAACAGGCTCGCCTGGTACC AGCAGAAACCTGGCCAACCGCCTAAGCTGCTGATGAGCGGGACCAC TATCCGCGAATCAGGAGTCCCGGATAGATTCTCCGGTTCCGGTTCGG GGAAAGACTACACCCTGACCATCAGTTCGCTGCAAGCCGAGGACGT CGCAGTGTACTACTGCCAGCAGTACTGGTCCACTCCCTACACCTTTG GATGCGGCACCAAGCTCGAGATCAAG
SEQ ID NO:675.7 1D10 H2-mAb12 VH4VL3 (ds)	QVQLVQSGAEVKKPGASVKVSCKASTNAFTNYLIEWVRQAPGQGLEW MGVINPGGGGTNYNEKFQGRVTMTADKSTSTAYMELSSLRSEDTAVY YCAREDSAGYGFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAQGGP SVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGKGSSGGGGSQVQLQESGPGLVKPSGTLSLTCAAS GIDFSRYWMSWVRQPPGKCLEWIGEINPDSNTLNYAPSLKSRVTISRDN SKNQLSLKLSSVTAADTAVYYCARPGGGYYSYALDYWGQGTTVTVSS GGGGSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKASEDI YNRLAWYQQKPGQPPKLLMSGTTILETGVPDRFSGSGSGKDYTLTISSL QAEDVATYYCQQYWSTPYTFGCGTKLEIK

SEQ ID NO:68 5.7 1D10 H2-mAb12 VH4VL3 (ds)	CAGGTCCAGCTGGTGCAGTCCGGTGCCGAAGTGAAGAAGCCGGGAG CTTCAGTCAAAGTGTCCTGCAAGGCTTCAACCAACGCCTTCACTAAC TACTTGATTGAATGGGTGCGCCAAGCACCAGGACAGGGTCTGGAAT GGATGGGAGTCATTAATCCGGGAGGAGGGGGAACGAACTATAACGA AAAGTTCCAAGGCCGCGTGACTATGACCGCCGATAAGTCGACATCC ACTGCTTACATGGAACTGAGCTCCCTGCGCTCGGAGGACACTGCCGT TTACTACTGCGCCCGCGAGGATTCCGCAGGATACGGCTTTGCCTATT GGGGACAGGGGACCCTCGTGACTGTGTCCTCGGCGTCCACGAAGGG CCCCAGCGTGTTCCCTCTGGCGCCAAGCTCTAAGTCGACCTCCGGTG GAACTGCCGCCCTTGGGTGTCTCGTGAAGGACTACTTCCCTGAGCCG GTCACGGTGTCCTGGAACTCCGGCGCCTTGACCAGCGGAGTCCACAC CTTTCCCGCCGTGCTCCAGTCATCGGGGCTCTACAGCCTGTCCTCCGT GGTCACCGTCCCGTCCTCATCCCTCGGCACCCAAACCTACATCTGCA ACGTCAACCACAAGCCATCGAACACCAAAGTGGACAAGAAAGTGGA ACCCAAGTCGTGTGATAAGACCCACACTTGCCCACCTTGCCCTGCCC CTGAAGCGCAGGGTGGACCGAGCGTGTTCCTGTTCCCGCCGAAGCCT AAGGATACCCTGTACATCACCCGGGAACCCGAAGTGACCTGTGTGG TGGTCGACGTGTCACATGAGGATCCTGAGGTCAAATTCAATTGGTAC GTCGACGGGGTGGAAGTGCATAACGCCAAGACAAAGCCGCGCGAG GAACAGTACAACTCCACTTACCGCGTGGTGTCCGTGCTGACCGTGCT GCACCAGGACTGGCTGAACGGGAAGGAGTACAAGTGCCAGGTGTCC AATAAGGCCCTGCCTGCTCCTATCGAAAAGACTATCTCCAAGGCCAA GGGACAGCCGAGGGAGCCTCAGGTGTACACCCTGCCGCCTTCGAGG GATGAACTCACGAAGAACCAGGTGTCACTGACTTGCCTTGTGAAGG GCTTCTATCCGAGCGACATTGCAGTGGAATGGGAGTCAAACGGACA GCCTGAGAACAACTACAAGACCACTCCTCCCGTGCTGGATTCAGAC GGGTCCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCAGATG GCAGCAGGGCAACGTATTCTCGTGCTCCGTGATGCACGAAGCTCTCC ATAACCACTACACCCAAAAGAGCCTGTCCCTGAGCCCCGGAAAGGG CTCGTCCGGAGGAGGAGGGTCACAAGTGCAGTTGCAGGAATCAGGA CCCGGACTCGTGAAGCCGTCGGGGACCTTGAGCTTGACTTGTGCCGC CTCCGGAATCGACTTCTCCCGGTATTGGATGTCCTGGGTCCGGCAAC CACCCGGAAAATGCCTGGAGTGGATCGGGGAGATCAACCCCGACTC TAACACCCTCAACTACGCGCCGTCCCTGAAGTCGAGAGTCACCATCT CGCGCGACAATTCCAAAAACCAACTGAGTCTGAAGCTGAGCTCAGT GACCGCCGCCGATACTGCGGTGTACTACTGCGCAAGACCCGGTGGC GGATATTACTCCTACGCGCTGGACTACTGGGGCCAGGGCACTACTGT CACTGTGTCCAGTGGAGGGGGTGGATCCGGTGGAGGCGGAAGCGGA GGAGGCGGTTCCGGTGGTGGTGGCAGCGACATTGTGATGACTCAGT CCCCTGACTCACTGGCGGTGTCTCTGGGAGAGAGAGCCACCATTAAC TGCAAAGCCTCCGAGGACATCTACAACCGGCTTGCTTGGTACCAACA GAAGCCCGGACAACCTCCCAAGCTGCTGATGTCCGGAACCACCATC CTCGAGACTGGCGTGCCAGACCGGTTCTCCGGATCGGGATCCGGCA AAGACTACACCCTGACCATCAGCAGCCTCCAGGCCGAGGATGTGGC CACCTACTACTGCCAGCAGTACTGGTCGACTCCTTACACCTTCGGCT GTGGGACCAAGCTGGAGATCAAG
SEQ ID NO:69 1D10 VL1	TCCATCGTGATGACACAGTCCCCGGCCACTCTCTCACTCTCCCCTGG GGAGAGAGCAACCCTGAGCTGTAGGGCCTCGCAGTCCGTGTCATCC GACGTCGCCTGGTACCAGCAGAAGCCGGGTCAAGCCCCACGCCTGC TGATCTACTACGCGAGCAACCGCTATACTGGAGTGCCTGCCCGGTTC

	TCCGGATCGGGCTACGGGACGGATTTTACCTTCACTATTTCGAGCTT GGAACCCGAGGATTTCGCTGTGTACTTCTGCCAACAAGACTACGCCT TCCCGTACACCTTCGGTGGCGGAACCAAGCTGGAGATCAAGAGAAC CGTGGCTGCCCCTAGCGTGTTCATTTTCCCGCCGTCTGACGAACAGC TGAAGTCCGGCACTGCCTCGGTGGTCTGCCTCCTGAACAACTTTTAC CCCCGGGAAGCCAAAGTGCAGTGGAAGGTCGACAACGCGCTCCAGT CCGGAAATAGCCAGGAATCAGTGACCGAGCAGGACTCCAAGGACTC AACCTATTCCCTGTCCTCGACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCATAAAGTGTACGCCTGCGAAGTGACCCACCAGGGACTGTC CTCCCCCGTCACTAAGAGCTTCAACCGCGGGGAGTGC
SEQ ID NO: 70 Q969D9 TSLP_HUMAN Thymic stromal lymphopoietin	MFPFALLYVLSVSFRKIFILQLVGLVLTYDFTNCDFEKIKAAYLSTISKDL ITYMSGTKSTEFNNTVSCSNRPHCLTEIQSLTFNPTAGCASLAKEMFAM KTKAALAIWCPGYSETQINATQAMKKRRKRKVTTNKCLEQVSQLQGL WRRFNRPLLKQQ
SEQ ID NO: 71 UniProt accession no. P21583 Human SCF	MKKTQTWILTCIYLQLLLFNPLVKTEGICRNRVTNNVKDVTKLVANLP KDYMITLKYVPGMDVLPSHCWISEMVVQLSDSLTDLLDKFSNISEGLSN YSIIDKLVNIVDDLVECVKENSSKDLKKSFKSPEPRLFTPEEFFRIFNRSID AFKDFVVASETSDCVVSSTLSPEKDSRVSVTKPFMLPPVAASSLRNDSSS SNRKAKNPPGD SSLHWAAMAL PALFSLIIGFAFGALYWKKRQPSLTRAVEN IQINEEDNEI SMLQEKEREF QEV
SEQ ID NO:72 1D10 VH1-CDR1 (Chothia)	TNAFTNY
SEQ ID NO:73 1D10 VH1-CDR2 (Chothia)	NPGGGG
SEQ ID NO:74 1D10 VH1-CDR3 (Chothia)	EDSAGYGFAY
SEQ ID NO:75 1D10 VH2-CDR1 (Chothia)	TNAFTNY
SEQ ID NO:76 1D10 VH2-CDR2 (Chothia)	NPGGGG
SEQ ID NO:77	EDSAGYGFAY

1D10 VH2-CDR3 (Chothia)	
SEQ ID NO:78 1D10 VH3-CDR1 (Chothia)	TNAFTNY
SEQ ID NO:79 1D10 VH3-CDR2 (Chothia)	NPGGGG
SEQ ID NO:80 1D10 VH3-CDR3 (Chothia)	EDSAGYGFAY
SEQ ID NO:81 1D10 VH4-CDR1 (Chothia)	TNAFTNY
SEQ ID NO:82 1D10 VH4-CDR2 (Chothia)	NPGGGG
SEQ ID NO:83 1D10 VH4-CDR3 (Chothia)	EDSAGYGFAY
SEQ ID NO:84 1D10 VH1-CDR1 (AbM)	TNAFTNYLIE
SEQ ID NO:85 1D10 VH1-CDR2 (AbM)	VINPGGGGTN
SEQ ID NO:86 1D10 VH1-CDR3 (AbM)	EDSAGYGFAY

SEQ ID NO:87 1D10 VH2-CDR1 (AbM)	TNAFTNYLIE
SEQ ID NO:88 1D10 VH2-CDR2 (AbM)	VINPGGGGTN
SEQ ID NO:89 1D10 VH2-CDR3 (AbM)	EDSAGYGFAY
SEQ ID NO:90 1D10 VH3-CDR1 (AbM)	TNAFTNYLIE
SEQ ID NO:91 1D10 VH3-CDR2 (AbM)	VINPGGGGTN
SEQ ID NO:92 1D10 VH3-CDR3 (AbM)	EDSAGYGFAY
SEQ ID NO:93 1D10 VH4-CDR1 (AbM)	TNAFTNYLIE
SEQ ID NO:94 1D10 VH4-CDR2 (AbM)	VINPGGGGTN
SEQ ID NO:95 1D10 VH4-CDR3 (AbM)	EDSAGYGFAY
SEQ ID NO:96 1D10 VH1-CDR1 (Contact)	TNYLIE

SEQ ID NO:97 1D10 VH1-CDR2 (Contact)	WIGVINPGGGGTN
SEQ ID NO:98 1D10 VH1-CDR3 (Contact)	AREDSAGYGFA
SEQ ID NO:99 1D10 VH2-CDR1 (Contact)	TNYLIE
SEQ ID NO:100 1D10 VH2-CDR2 (Contact)	WMGVINPGGGGTN
SEQ ID NO:101 1D10 VH2-CDR3 (Contact)	AREDSAGYGFA
SEQ ID NO:102 1D10 VH3-CDR1 (Contact)	TNYLIE
SEQ ID NO:103 1D10 VH3-CDR2 (Contact)	WIGVINPGGGGTN
SEQ ID NO:104 1D10 VH3-CDR3 (Contact)	AREDSAGYGFA
SEQ ID NO:105 1D10 VH4-CDR1 (Contact)	TNYLIE
SEQ ID NO:106 1D10	WIGVINPGGGGTN

VH4-CDR2 (Contact)	
SEQ ID NO:107 1D10 VH4-CDR3 (Contact)	AREDSAGYGFA
SEQ ID NO:108 1D10 VH1-CDR1 (IMGT)	TNAFTNYL
SEQ ID NO:109 1D10 VH1-CDR2 (IMGT)	INPGGGGT
SEQ ID NO:110 1D10 VH1-CDR3 (IMGT)	AREDSAGYGFAY
SEQ ID NO:111 1D10 VH2-CDR1 (IMGT)	TNAFTNYL
SEQ ID NO:112 1D10 VH2-CDR2 (IMGT)	INPGGGGT
SEQ ID NO:113 1D10 VH2-CDR3 (IMGT)	AREDSAGYGFAY
SEQ ID NO:114 1D10 VH3-CDR1 (IMGT)	TNAFTNYL
SEQ ID NO:115 1D10 VH3-CDR2 (IMGT)	INPGGGGT
SEQ ID NO:116	AREDSAGYGFAY

1D10 VH3-CDR3 (IMGT)	
SEQ ID NO:117 1D10 VH4-CDR1 (IMGT)	TNAFTNYL
SEQ ID NO:118 1D10 VH4-CDR2 (IMGT)	INPGGGGT
SEQ ID NO:119 1D10 VH4-CDR3 (IMGT)	AREDSAGYGFAY
SEQ ID NO:120 1D10 VL1-CDR1 (Chothia)	RASQSVSSDVA
SEQ ID NO:121 1D10 VL1-CDR2 (Chothia)	YASNRYT
SEQ ID NO:122 1D10 VL1-CDR3 (Chothia)	QQDYAFPYT
SEQ ID NO:123 1D10 VL2-CDR1 (Chothia)	RASQSVSSDVA
SEQ ID NO:124 1D10 VL2-CDR2 (Chothia)	YASNRYT
SEQ ID NO:125 1D10 VL2-CDR3 (Chothia)	QQDYAFPYT

SEQ ID NO:126 1D10 VL3-CDR1 (Chothia)	KASQSVSSDVA
SEQ ID NO:127 1D10 VL3-CDR2 (Chothia)	YASNRYT
SEQ ID NO:128 1D10 VL3-CDR3 (Chothia)	QQDYAFPYT
SEQ ID NO:129 1D10 VL4-CDR1 (Chothia)	KASQSVSSDVA
SEQ ID NO:130 1D10 VL4-CDR2 (Chothia)	YASNRYS
SEQ ID NO:131 1D10 VL4-CDR3 (Chothia)	QQDYAFPYT
SEQ ID NO:132 1D10 VL1-CDR1 (AbM)	RASQSVSSDVA
SEQ ID NO:133 1D10 VL1-CDR2 (AbM)	YASNRYT
SEQ ID NO:134 1D10 VL1-CDR3 (AbM)	QQDYAFPYT
SEQ ID NO:135 1D10 VL2-CDR1 (AbM)	RASQSVSSDVA

SEQ ID NO:136 1D10 VL2-CDR2 (AbM)	YASNRYT
SEQ ID NO:137 1D10 VL2-CDR3 (AbM)	QQDYAFPYT
SEQ ID NO:138 1D10 VL3-CDR1 (AbM)	KASQSVSSDVA
SEQ ID NO:139 1D10 VL3-CDR2 (AbM)	YASNRYT
SEQ ID NO:140 1D10 VL3-CDR3 (AbM)	QQDYAFPYT
SEQ ID NO:141 1D10 VL4-CDR1 (AbM)	KASQSVSSDVA
SEQ ID NO:142 1D10 VL4-CDR2 (AbM)	YASNRYS
SEQ ID NO:143 1D10 VL4-CDR3 (AbM)	QQDYAFPYT
SEQ ID NO:144 1D10 VL1-CDR1 (Contact)	SSDVAWY
SEQ ID NO:145 1D10	LLIYYASNRY

VL1-CDR2 (Contact)	
SEQ ID NO:146 1D10 VL1-CDR3 (Contact)	QQDYAFPY
SEQ ID NO:147 1D10 VL2-CDR1 (Contact)	SSDVAWY
SEQ ID NO:148 1D10 VL2-CDR2 (Contact)	LLIYYASNRY
SEQ ID NO:149 1D10 VL2-CDR3 (Contact)	QQDYAFPY
SEQ ID NO:150 1D10 VL3-CDR1 (Contact)	SSDVAWY
SEQ ID NO:151 1D10 VL3-CDR2 (Contact)	LLIYYASNRY
SEQ ID NO:152 1D10 VL3-CDR3 (Contact)	QQDYAFPY
SEQ ID NO:153 1D10 VL4-CDR1 (Contact)	SSDVAWY
SEQ ID NO:154 1D10 VL4-CDR2 (Contact)	LLIYYASNRY
SEQ ID NO:155	QQDYAFPY

1D10 VL4-CDR3 (Contact)	
SEQ ID NO:156 1D10 VL1-CDR1 (IMGT)	QSVSSD
SEQ ID NO:157 1D10 VL1-CDR2 (IMGT)	YA
SEQ ID NO:158 1D10 VL1-CDR3 (IMGT)	QQDYAFPYT
SEQ ID NO:159 1D10 VL2-CDR1 (IMGT)	QSVSSD
SEQ ID NO:160 1D10 VL2-CDR2 (IMGT)	YA
SEQ ID NO:161 1D10 VL2-CDR3 (IMGT)	QQDYAFPYT
SEQ ID NO:162 1D10 VL3-CDR1 (IMGT)	QSVSSD
SEQ ID NO:163 1D10 VL3-CDR2 (IMGT)	YA
SEQ ID NO:164 1D10 VL3-CDR3 (IMGT)	QQDYAFPYT

SEQ ID NO:165 1D10 VL4-CDR1 (IMGT)	QSVSSD
SEQ ID NO:166 1D10 VL4-CDR2 (IMGT)	YA
SEQ ID NO:167 1D10 VL4-CDR3 (IMGT)	QQDYAFPYT
SEQ ID NO:168 mAb12 VH1-CDR1 (Chothia)	GIDFSRY
SEQ ID NO:169 mAb12 VH1-CDR2 (Chothia)	NPDSNT
SEQ ID NO:170 mAb12 VH1-CDR3 (Chothia)	PGGGYYSYALDY
SEQ ID NO:171 mAb12 VH2-CDR1 (Chothia)	GIDFSRY
SEQ ID NO:172 mAb12 VH2-CDR2 (Chothia)	NPDSNT
SEQ ID NO:173 mAb12 VH2-CDR3 (Chothia)	PGGGYYSYALD
SEQ ID NO:174 mAb12 VH3-CDR1 (Chothia)	GIDFSRY

SEQ ID NO:175 mAb12 VH3-CDR2 (Chothia)	NPDSNT
SEQ ID NO:176 mAb12 VH3-CDR3 (Chothia)	PGGGYYSYALDY
SEQ ID NO:177 mAb12 VH4-CDR1 (Chothia)	GIDFSRY
SEQ ID NO:178 mAb12 VH4-CDR2 (Chothia)	NPDSNT
SEQ ID NO:179 mAb12 VH4-CDR3 (Chothia)	PGGGYYSYALDY
SEQ ID NO:180 mAb12 VH1-CDR1 (AbM)	GIDFSRYWMS
SEQ ID NO:181 mAb12 VH1-CDR2 (AbM)	EINPDSNTLN
SEQ ID NO:182 mAb12 VH1-CDR3 (AbM)	PGGGYYSYALDY
SEQ ID NO:183 mAb12 VH2-CDR1 (AbM)	GIDFSRYWMS
SEQ ID NO:184 mAb12	EINPDSNTLN

VH2-CDR2 (AbM)	
SEQ ID NO:185 mAb12 VH2-CDR3 (AbM)	PGGGYYSYALDY
SEQ ID NO:186 mAb12 VH3-CDR1 (AbM)	GIDFSRYWMS
SEQ ID NO:187 mAb12 VH3-CDR2 (AbM)	EINPDSNTLN
SEQ ID NO:188 mAb12 VH3-CDR3 (AbM)	PGGGYYSYALDY
SEQ ID NO:189 mAb12 VH4-CDR1 (AbM)	GIDFSRYWMS
SEQ ID NO:190 mAb12 VH4-CDR2 (AbM)	EINPDSNTLN
SEQ ID NO:191 mAb12 VH4-CDR3 (AbM)	PGGGYYSYALDY
SEQ ID NO:192 mAb12 VH1-CDR1 (Contact)	SRYWMS
SEQ ID NO:193 mAb12 VH1-CDR2 (Contact)	WIGEINPDSNTLN
SEQ ID NO:194	ARPGGGYYSYALD

mAb12 VH1-CDR3 (Contact)	
SEQ ID NO:195 mAb12 VH2-CDR1 (Contact)	SRYWMS
SEQ ID NO:196 mAb12 VH2-CDR2 (Contact)	WVGEINPDSNTLN
SEQ ID NO:197 mAb12 VH2-CDR3 (Contact)	ARPGGGYYSYALD
SEQ ID NO:198 mAb12 VH3-CDR1 (Contact)	SRYWMS
SEQ ID NO:199 mAb12 VH3-CDR2 (Contact)	WIGEINPDSNTLN
SEQ ID NO:200 mAb12 VH3-CDR3 (Contact)	ARPGGGYYSYALD
SEQ ID NO:201 mAb12 VH4-CDR1 (Contact)	SRYWMS
SEQ ID NO:202 mAb12 VH4-CDR2 (Contact)	WIGEINPDSNTLN
SEQ ID NO:203 mAb12 VH4-CDR3 (Contact)	ARPGGGYYSYALD

SEQ ID NO:204 mAb12 VH1-CDR1 (IMGT)	GIDFSRYW
SEQ ID NO:205 mAb12 VH1-CDR2 (IMGT)	INPDSNTL
SEQ ID NO:206 mAb12 VH1-CDR3 (IMGT)	ARPGGGYYSYALD
SEQ ID NO:207 mAb12 VH2-CDR1 (IMGT)	GIDFSRYW
SEQ ID NO:208 mAb12 VH2-CDR2 (IMGT)	INPDSNTL
SEQ ID NO:209 mAb12 VH2-CDR3 (IMGT)	ARPGGGYYSYALDY
SEQ ID NO:210 mAb12 VH3-CDR1 (IMGT)	GIDFSRYW
SEQ ID NO:211 mAb12 VH3-CDR2 (IMGT)	INPDSNTL
SEQ ID NO:212 mAb12 VH3-CDR3 (IMGT)	ARPGGGYYSYALDY
SEQ ID NO:213 mAb12 VH4-CDR1 (IMGT)	GIDFSRYW

SEQ ID NO:214 mAb12 VH4-CDR2 (IMGT)	INPDSNTL
SEQ ID NO:215 mAb12 VH4-CDR3 (IMGT)	ARPGGGYYSYALDY
SEQ ID NO:216 mAb12 VL1-CDR1 (Chothia)	RASEDIYNRLA
SEQ ID NO:217 mAb12 VL1-CDR2 (Chothia)	GTTILET
SEQ ID NO:218 mAb12 VL1-CDR3 (Chothia)	QQYWSTPYT
SEQ ID NO:219 mAb12 VL2-CDR1 (Chothia)	RASEDIYNRLA
SEQ ID NO:220 mAb12 VL2-CDR2 (Chothia)	GTTILES
SEQ ID NO:221 mAb12 VL2-CDR3 (Chothia)	QQYWSTPYT
SEQ ID NO:222 mAb12 VL3-CDR1 (Chothia)	KASEDIYNRLA
SEQ ID NO:223 mAb12	GTTIRES

VL3-CDR2 (Chothia)	
SEQ ID NO:224 mAb12 VL3-CDR3 (Chothia)	QQYWSTPYT
SEQ ID NO:225 mAb12 VL4-CDR1 (Chothia)	KASEDIYNRLA
SEQ ID NO:226 mAb12 VL4-CDR2 (Chothia)	GTTIRES
SEQ ID NO:227 mAb12 VL4-CDR3 (Chothia)	QQYWSTPYT
SEQ ID NO:228 mAb12 VL1-CDR1 (AbM)	RASEDIYNRLA
SEQ ID NO:229 mAb12 VL1-CDR2 (AbM)	GTTILET
SEQ ID NO:230 mAb12 VL1-CDR3 (AbM)	QQYWSTPYT
SEQ ID NO:231 mAb12 VL2-CDR1 (AbM)	RASEDIYNRLA
SEQ ID NO:232 mAb12 VL2-CDR2 (AbM)	GTTILES
SEQ ID NO:233	QQYWSTPYT

mAb12 VL2-CDR3 (AbM)	
SEQ ID NO:234 mAb12 VL3-CDR1 (AbM)	KASEDIYNRLA
SEQ ID NO:235 mAb12 VL3-CDR2 (AbM)	GTTIRES
SEQ ID NO:236 mAb12 VL3-CDR3 (AbM)	QQYWSTPYT
SEQ ID NO:237 mAb12 VL4-CDR1 (AbM)	KASEDIYNRLA
SEQ ID NO:238 mAb12 VL4-CDR2 (AbM)	GTTIRES
SEQ ID NO:239 mAb12 VL4-CDR3 (AbM)	QQYWSTPYT
SEQ ID NO:240 mAb12 VL1-CDR1 (Contact)	YNRLAWY
SEQ ID NO:241 mAb12 VL1-CDR2 (Contact)	LLMSGTTILE
SEQ ID NO:242 mAb12 VL1-CDR3 (Contact)	QQYWSTPY

SEQ ID NO:243 mAb12 VL2-CDR1 (Contact)	YNRLAWY
SEQ ID NO:244 mAb12 VL2-CDR2 (Contact)	LLMSGTTILE
SEQ ID NO:245 mAb12 VL2-CDR3 (Contact)	QQYWSTPY
SEQ ID NO:246 mAb12 VL3-CDR1 (Contact)	YNRLAWY
SEQ ID NO:247 mAb12 VL3-CDR2 (Contact)	LLMSGTTIRE
SEQ ID NO:248 mAb12 VL3-CDR3 (Contact)	QQYWSTPY
SEQ ID NO:249 mAb12 VL4-CDR1 (Contact)	YNRLAWY
SEQ ID NO:250 mAb12 VL4-CDR2 (Contact)	LLMSGTTIRE
SEQ ID NO:251 mAb12 VL4-CDR3 (Contact)	QQYWSTPY
SEQ ID NO:252 mAb12 VL1-CDR1 (IMGT)	EDIYNR

SEQ ID NO:253 mAb12 VL1-CDR2 (IMGT)	GT
SEQ ID NO:254 mAb12 VL1-CDR3 (IMGT)	QQYWSTPYT
SEQ ID NO:255 mAb12 VL2-CDR1 (IMGT)	EDIYNR
SEQ ID NO:256 mAb12 VL2-CDR2 (IMGT)	GT
SEQ ID NO:257 mAb12 VL2-CDR3 (IMGT)	QQYWSTPYT
SEQ ID NO:258 mAb12 VL3-CDR1 (IMGT)	EDIYNR
SEQ ID NO:259 mAb12 VL3-CDR2 (IMGT)	GT
SEQ ID NO:260 mAb12 VL3-CDR3 (IMGT)	QQYWSTPYT
SEQ ID NO:261 mAb12 VL4-CDR1 (IMGT)	EDIYNR
SEQ ID NO:262 mAb12	GT

VL4-CDR2 (IMGT)	
SEQ ID NO:263 mAb12 VL4-CDR3 (IMGT)	QQYWSTPYT
SEQ ID NO:264 1D10 Parental VH	QVQLQQSGAELVRPGTSVKVSCKASTNAFTNYLIEWVKQRPGQGLEWI GVINPGGGGTNYNEKFKDKATLTADKSSSTAYMQLSSLTSDDSAVYFC AREDSAGYGFAYWGQGTLVTVSA
SEQ ID NO:265 1D10 VH3 Removed N-glycosylation by returning to mouse amino acid	QVQLQQSGPGLVKPSETLSLTCTASTNAFTNYLIEWVRQPPGKGLEWIG VINPGGGGTNYNEKLKSRATLSADKSSSTASLKLSSVTAADTAVYFCAR EDSAGYGFAYWGQGTLVTVSS
SEQ ID NO:266 1D10 VH4 Removed N-glycosylation by returning to mouse amino acid	QVQLQESGPGLVKPSETLSLTCTASTNAFTNYLIEWIRQPPGKGLEWIGV INPGGGGTNYNEKLKSRVTISADKSKNQASLKLSSVTAADTAVYYCAR EDSAGYGFAYWGQGTLVTVSS
SEQ ID NO:267 1D10 Parental VL	SIVMTQTPKFLLVSAGDRVTLTCKASQSVSSDVAWYQQKPGQSPKLLIY YASNRYTGVPDRFTGSGYGTDFTFTISTVQAEDLAVYFCQQDYAFPYTF GGGTKLEIR
SEQ ID NO:268 1D10 Parental VH	CAAGTGCAGCTGCAGCAGAGCGGCGCCGAGCTGGTGAGACCTGGCA CAAGCGTGAAGGTGAGCTGCAAGGCAAGCACCAACGCCTTCACCAA CTACCTGATCGAGTGGGTGAAGCAGAGACCTGGCCAAGGCCTGGAG TGGATCGGCGTGATCAACCCTGGCGGCGGCGGCACCAACTACAACG AGAAGTTCAAGGACAAGGCCACCCTGACCGCCGACAAGAGCAGCAG CACCGCCTACATGCAGCTGAGCAGCCTGACAAGCGACGACAGCGCC GTGTACTTCTGCGCTAGAGAGGACAGCGCCGGCTACGGCTTCGCCTA CTGGGGCCAAGGCACCCTGGTGACCGTGAGCGCC
SEQ ID NO:269 1D10 VH1	CAAGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCTGGCG CAAGCGTGAAGGTGAGCTGCAAGGCAAGCACCAACGCCTTCACCAA CTACCTGATCGAGTGGGTGAGACAAGCCCCTGGCCAAGGCCTGGAG TGGATCGGCGTGATCAACCCTGGCGGCGGCGGCACCAACTACAACG AGAAGTTCCAAGGCAGAGCCACCCTGACCGCCGACAAGAGCAGCAG CACCGCCTACATGGAGCTGAGCAGCCTGAGAAGCGAGGACACCGCC GTGTACTTCTGCGCTAGAGAGGACAGCGCCGGCTACGGCTTCGCCTA CTGGGGCCAAGGCACCCTGGTGACCGTGAGCAGC

SEQ ID NO:270 1D10 VH2	CAAGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCTGGCG CAAGCGTGAAGGTGAGCTGCAAGGCAAGCACCAACGCCTTCACCAA CTACCTGATCGAGTGGGTGAGACAAGCCCCTGGCCAAGGCCTGGAG TGGATGGGCGTGATCAACCCTGGCGGCGGCGGCACCAACTACAACG AGAAGTTCCAAGGCAGAGTGACCATGACCGCCGACAAGAGCACAAG CACCGCCTACATGGAGCTGAGCAGCCTGAGAAGCGAGGACACCGCC GTGTACTACTGCGCTAGAGAGGACAGCGCCGGCTACGGCTTCGCCT ACTGGGGCCAAGGCACCCTGGTGACCGTGAGCAGC
SEQ ID NO:271 1D10 VH3 Removed N-glycosylation by returning to mouse amino acid	CAAGTGCAGCTGCAGCAGAGCGGCCCTGGCCTGGTGAAGCCTAGCG AGACCCTGAGCCTGACCTGCACCGCAAGCACCAACGCCTTCACCAA CTACCTGATCGAGTGGGTGAGACAGCCTCCTGGCAAGGGCCTGGAG TGGATCGGCGTGATCAACCCTGGCGGCGGCGGCACCAACTACAACG AGAAGCTGAAGAGCAGAGCCACCCTGAGCGCCGACAAGAGCAGCA GCACCGCAAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGC CGTGTACTTCTGCGCTAGAGAGGACAGCGCCGGCTACGGCTTCGCCT ACTGGGGCCAAGGCACCCTGGTGACCGTGAGCAGC
SEQ ID NO:272 1D10 VH4 Removed N-glycosylation by returning to mouse amino acid	CAAGTGCAGCTGCAAGAGAGCGGCCCTGGCCTGGTGAAGCCTAGCG AGACCCTGAGCCTGACCTGCACCGCAAGCACCAACGCCTTCACCAA CTACCTGATCGAGTGGATCAGACAGCCTCCTGGCAAGGGCCTGGAG TGGATCGGCGTGATCAACCCTGGCGGCGGCGGCACCAACTACAACG AGAAGCTGAAGAGCAGAGTGACCATCAGCGCCGACAAGAGCAAGA ACCAAGCAAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGC CGTGTACTACTGCGCTAGAGAGGACAGCGCCGGCTACGGCTTCGCCT ACTGGGGCCAAGGCACCCTGGTGACCGTGAGCAGC
SEQ ID NO:273 1D10 Parental VL	AGCATCGTGATGACACAGACCCCTAAGTTCCTGCTGGTGAGCGCCG GCGACAGAGTGACCCTGACCTGCAAGGCTTCTCAGAGCGTGAGCAG CGACGTGGCCTGGTATCAGCAGAAGCCTGGACAGAGCCCTAAGCTG CTGATCTACTACGCTAGCAACAGATACACCGGCGTGCCTGACAGATT CACCGGCAGCGGCTACGGCACCGACTTCACCTTCACCATCAGCACCG TGCAAGCCGAGGACCTGGCCGTGTACTTCTGTCAGCAAGACTACGCC TTCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAGA
SEQ ID NO:274 1D10 VL1	AGCATCGTGATGACACAGAGCCCTGCGACCCTGAGCCTGAGCCCTG GCGAGAGAGCTACCCTGAGCTGCAGAGCTTCTCAGAGCGTGAGCAG CGACGTGGCCTGGTATCAGCAGAAGCCTGGCCAAGCCCCTAGACTG CTGATCTACTACGCTAGCAACAGATACACCGGCGTGCCTGCTAGATT CAGCGGCAGCGGCTACGGCACCGACTTCACCTTCACCATCAGCAGC CTGGAGCCTGAGGACTTCGCCGTGTACTTCTGTCAGCAAGACTACGC CTTCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:275 1D10 VL2	GAGATCGTGATGACACAGAGCCCTGCGACCCTGAGCCTGAGCCCTG GCGAGAGAGCTACCCTGAGCTGCAGAGCTTCTCAGAGCGTGAGCAG CGACGTGGCCTGGTATCAGCAGAAGCCTGGCCAAGCCCCTAGACTG CTGATCTACTACGCTAGCAACAGATACACCGGCATCCCTGCTAGATT CAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGC

	CTGGAGCCTGAGGACTTCGCCGTGTACTACTGTCAGCAAGACTACGC CTTCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:276 1D10 VL3	AGCATCGTGATGACACAGAGCCCTGACAGCCTGGCCGTGAGCCTGG GCGAGAGAGCCACCATCAACTGCAAGGCTTCTCAGAGCGTGAGCAG CGACGTGGCCTGGTATCAGCAGAAGCCTGGACAGCCTCCTAAGCTG CTGATCTACTACGCTAGCAACAGATACACCGGCGTGCCTGACAGATT CAGCGGCAGCGGCTACGGCACCGACTTCACCTTCACCATCAGCAGC CTGCAAGCCGAGGACGTGGCCGTGTACTTCTGTCAGCAAGACTACG CCTTCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:277 1D10 VL4	GACATCGTGATGACACAGAGCCCTGACAGCCTGGCCGTGAGCCTGG GCGAGAGAGCCACCATCAACTGCAAGGCTTCTCAGAGCGTGAGCAG CGACGTGGCCTGGTATCAGCAGAAGCCTGGACAGCCTCCTAAGCTG CTGATCTACTACGCTAGCAACAGATACAGCGGCGTGCCTGACAGATT CAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGC CTGCAAGCCGAGGACGTGGCCGTGTACTACTGTCAGCAAGACTACG CCTTCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:278 mAb12 Parental mouse VH	EVKLLQSGGGLVQPGGSLKLSCAASGIDFSRYWMSWVRRAPRKGLEWI GEINPDSNTLNYAPSLEDKFIISRDNAKNTLYLQMNKVKSEDTALYYCA RPGGGYYSYALDYWGQGTSVTVSS
SEQ ID NO:279 mAb12 Parental mouse VL	DIQMTQSSSSFSVSLGDRVTITCKASEDIYNRLAWYQQKPGNAPRLLMS GTTILETGVPSRFSGSGSGKDYTLSITSLQTEDFVTYYCQQYWSTPYTFG GGTKLEIK
SEQ ID NO:280 mAb12 Parental mouse VH	GAGGTAAAGCTGCTGCAGAGCGGCGGCGGCCTGGTGCAACCTGGTG GCAGTCTGAAGCTGAGCTGCGCCGCAAGCGGCATCGACTTCAGCAG ATACTGGATGAGCTGGGTGAGAAGAGCCCCTAGAAAGGGCCTGGAG TGGATCGGCGAGATCAACCCTGACAGCAACACCCTGAACTACGCCC CTAGCCTGGAGGACAAGTTCATCATCAGCAGAGACAACGCCAAGAA CACCCTGTACCTGCAGATGAACAAGGTGAAGAGCGAGGACACCGCC CTGTACTACTGCGCTAGACCTGGCGGCGGCTACTACAGCTACGCCCT GGACTACTGGGGCCAAGGCACAAGCGTGACCGTGAGCAGC
SEQ ID NO:281 mAb12 VH1	GAGGTGCAGCTTGTACAAAGCGGCGGGGGCTTAGTTCAGCCTGGCG GCTCCCTGAGACTGAGCTGCGCCGCAAGCGGCATCGACTTCAGCAG ATACTGGATGAGCTGGGTGAGAAGAGCCCCTGGCAAGGGCCTGGAG TGGATCGGCGAGATCAACCCTGACAGCAACACCCTGAACTACGCCC CTAGCGTGAAGGGCAGATTCACCATCAGCAGAGACAACGCCAAGAA CACCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGCGCTAGACCTGGCGGCGGCTACTACAGCTACGCCCT GGACTACTGGGGCCAAGGCACCACCGTGACCGTGAGCAGC
SEQ ID NO:282 mAb12 VH2	GAGGTGCAGCTTGTAGAAAGCGGCGGGGGCTTAGTTCAGCCTGGCG GCTCCCTGAGACTGAGCTGCGCCGCAAGCGGCATCGACTTCAGCAG ATACTGGATGAGCTGGGTGAGACAAGCCCCTGGCAAGGGCCTGGAG TGGGTGGGCGAGATCAACCCTGACAGCAACACCCTGAACTACGCCC CTAGCGTGAAGGGCAGATTCACCATCAGCAGAGACAACGCCAAGAA

	CAGCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGCGCTAGACCTGGCGGCGGCTACTACAGCTACGCCCT GGACTACTGGGGCCAAGGCACCACCGTGACCGTGAGCAGC
SEQ ID NO:283 mAb12 VH3	CAAGTGCAGCTGCAGCAGAGCGGCCCTGGCCTGGTGAAGCCTAGCG GCACGCTGAGCCTGACCTGCGCCGCAAGCGGCATCGACTTCAGCAG ATACTGGATGAGCTGGGTGAGAAGGCCTCCTGGCAAGGGCCTGGAG TGGATCGGCGAGATCAACCCTGACAGCAACACCCTGAACTACGCCC CTAGCCTGAAGAGCAGATTCACCATCAGCAGAGACAACAGCAAGAA CACACTGAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCC GTGTACTACTGCGCTAGACCTGGCGGCGGCTACTACAGCTACGCCCT GGACTACTGGGGCCAAGGCACCACCGTGACCGTGAGCAGC
SEQ ID NO:284 mAb12 VH4	CAAGTGCAGCTGCAAGAGAGCGGCCCTGGCCTGGTGAAGCCTAGCG GCACCCTGAGCCTGACCTGCGCCGCAAGCGGCATCGACTTCAGCAG ATACTGGATGAGCTGGGTGAGACAGCCTCCTGGCAAGGGCCTGGAG TGGATCGGCGAGATCAACCCTGACAGCAACACCCTGAACTACGCCC CTAGCCTGAAGAGCAGAGTGACCATCAGCAGAGACAACAGCAAGA ATCAGCTGAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGC CGTGTACTACTGCGCTAGACCTGGCGGCGGCTACTACAGCTACGCCC TGGACTACTGGGGCCAAGGCACCACCGTGACCGTGAGCAGC
SEQ ID NO:285 mAb12 Parental mouse VL	GACATTCAGATGACACAGAGCAGCAGCAGCTTCAGCGTGAGCCTGG GCGACAGAGTGACCATCACCTGCAAGGCAAGCGAGGACATCTACAA CAGACTGGCCTGGTATCAGCAGAAGCCTGGCAACGCCCCTAGACTG CTGATGAGCGGCACCACCATCCTGGAGACCGGCGTGCCTAGCAGAT TCAGCGGCAGCGGCAGCGGCAAGGACTACACCCTGAGCATCACAAG CCTGCAGACCGAGGACTTCGTGACCTACTACTGTCAGCAGTACTGGA GCACCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:286 mAb12 VL1	GACATTCAGATGACACAGAGCCCTAGCAGCCTGAGCGCTAGCGTGG GCGACAGAGTGACCATCACCTGCAGAGCTAGCGAGGACATCTACAA CAGACTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCCCCTAAGCTG CTGATGAGCGGCACCACCATCCTGGAGACCGGCGTGCCTAGCAGAT TCAGCGGCAGCGGCAGCGGCAAGGACTACACCCTGACCATCAGCAG CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCAGCAGTACTGGA GCACCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:287 mAb12 VL2	GACATTCAGATGACACAGAGCCCTAGCAGCCTGAGCGCTAGCGTGG GCGACAGAGTGACCATCACCTGCAGAGCTAGCGAGGACATCTACAA CAGACTGGCCTGGTATCAGCAGAAGCCTGGCAAGGCCCCTAAGCTG CTGATGAGCGGCACCACCATCCTGGAGAGCGGCGTGCCTAGCAGAT TCAGCGGCAGCGGCAGCGGCAAGGACTACACCCTGACCATCAGCAG CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCAGCAGTACTGGA GCACCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:288 mAb12 VL3	GACATCGTGATGACACAGAGCCCTGACAGCCTGGCCGTGAGCCTGG GCGAGAGAGCCACCATCAACTGCAAGGCTAGCGAGGACATCTACAA CAGACTGGCCTGGTATCAGCAGAAGCCTGGACAGCCTCCTAAGCTG

	CTGATGAGCGGCACCACCATCCTGGAGACCGGCGTGCCTGACAGAT TCAGCGGCAGCGGCAGCGGCAAGGACTACACCCTGACCATCAGCAG CCTGCAAGCCGAGGACGTGGCCACCTACTACTGTCAGCAGTACTGG AGCACCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:289 mAb12 VL4	GACATCGTGATGACACAGAGCCCTGACAGCCTGGCCGTGAGCCTGG GCGAGAGAGCCACCATCAACTGCAAGGCTAGCGAGGACATCTACAA CAGACTGGCCTGGTATCAGCAGAAGCCTGGACAGCCTCCTAAGCTG CTGATGAGCGGCACCACCATCAGAGAGAGCGGCGTGCCTGACAGAT TCAGCGGCAGCGGCAGCGGCAAGGACTACACCCTGACCATCAGCAG CCTGCAAGCCGAGGACGTGGCCGTGTACTACTGTCAGCAGTACTGG AGCACCCCTTACACCTTCGGCGGCGGCACCAAGCTGGAGATCAAG
SEQ ID NO:290 1D10 Parental VH-CDR1 (Kabat)	NYLIE
SEQ ID NO:291 1D10 Parental VH-CDR2 (Kabat)	VINPGGGGTNYNEKFKD
SEQ ID NO:292 1D10 Parental VH-CDR3 (Kabat)	EDSAGYGFAY
SEQ ID NO:293 1D10 Parental VH-CDR1 (Chothia)	TNAFTNY
SEQ ID NO:294 1D10 Parental VH-CDR2 (Chothia)	NPGGGG
SEQ ID NO:295 1D10 Parental VH-CDR3 (Chothia)	EDSAGYGFAY
SEQ ID NO:296 1D10 Parental VH-CDR1 (AbM)	TNAFTNYLIE
SEQ ID NO:297	VINPGGGGTN

1D10 Parental VH-CDR2 (AbM)	
SEQ ID NO:298 1D10 Parental VH-CDR3 (AbM)	EDSAGYGFAY
SEQ ID NO:299 1D10 Parental VH-CDR1 (Contact)	TNYLIE
SEQ ID NO:300 1D10 Parental VH-CDR2 (Contact)	WIGVINPGGGGTN
SEQ ID NO:301 1D10 Parental VH-CDR3 (Contact)	AREDSAGYGFA
SEQ ID NO:302 1D10 Parental VH-CDR1 (IMGT)	TNAFTNYL
SEQ ID NO:303 1D10 Parental VH-CDR2 (IMGT)	INPGGGGT
SEQ ID NO:304 1D10 Parental VH-CDR3 (IMGT)	AREDSAGYGFAY
SEQ ID NO:305 1D10 Parental VL-CDR1 (Kabat)	KASQSVSSDVA
SEQ ID NO:306 1D10 Parental VL-CDR2 (Kabat)	YASNRYT

SEQ ID NO:307 1D10 Parental VL-CDR3 (Kabat)	QQDYAFPYT
SEQ ID NO:308 1D10 Parental VL-CDR1 (Chothia)	KASQSVSSDVA
SEQ ID NO:309 1D10 Parental VL-CDR2 (Chothia)	YASNRYT
SEQ ID NO:310 1D10 Parental VL-CDR3 (Chothia)	QQDYAFPYT
SEQ ID NO:311 1D10 Parental VL-CDR1 (AbM)	KASQSVSSDVA
SEQ ID NO:312 1D10 Parental VL-CDR2 (AbM)	YASNRYT
SEQ ID NO:313 1D10 Parental VL-CDR3 (AbM)	QQDYAFPYT
SEQ ID NO:314 1D10 Parental VL-CDR1 (Contact)	SSDVAWY
SEQ ID NO:315 1D10 Parental VL-CDR2 (Contact)	LLIYYASNRY
SEQ ID NO:316 1D10 Parental VL-CDR3 (Contact)	QQDYAFPY

SEQ ID NO:317 1D10 Parental VL-CDR1 (IMGT)	QSVSSD
SEQ ID NO:318 1D10 Parental VL-CDR2 (IMGT)	YA
SEQ ID NO:319 1D10 Parental VL-CDR3 (IMGT)	QQDYAFPYT
SEQ ID NO:320 mAb12 Parental VH-CDR1 (Kabat)	RYWMS
SEQ ID NO:321 mAb12 Parental VH-CDR2 (Kabat)	EINPDSNTLNYAPSLED
SEQ ID NO:322 mAb12 Parental VH-CDR3 (Kabat)	PGGGYYSYALDY
SEQ ID NO:323 mAb12 Parental VH-CDR1 (Chothia)	GIDFSRY
SEQ ID NO:324 mAb12 Parental VH-CDR2 (Chothia)	NPDSNT
SEQ ID NO:325 mAb12 Parental VH-CDR3 (Chothia)	PGGGYYSYALDY
SEQ ID NO:326 mAb12 Parental	GIDFSRYWMS

VH-CDR1 (AbM)	
SEQ ID NO:327 mAb12 Parental VH-CDR2 (AbM)	EINPDSNTLN
SEQ ID NO:328 mAb12 Parental VH-CDR3 (AbM)	PGGGYYSYALDY
SEQ ID NO:329 mAb12 Parental VH-CDR1 (Contact)	YNRLAWY
SEQ ID NO:330 mAb12 Parental VH-CDR2 (Contact)	LLMSGTTILE
SEQ ID NO:331 mAb12 Parental VH-CDR3 (Contact)	QQYWSTPY
SEQ ID NO:332 mAb12 Parental VH-CDR1 (IMGT)	GIDFSRYW
SEQ ID NO:333 mAb12 Parental VH-CDR2 (IMGT)	INPDSNTL
SEQ ID NO:334 mAb12 Parental VH-CDR3 (IMGT)	ARPGGGYYSYALDY
SEQ ID NO:335 mAb12 Parental VL-CDR1 (Kabat)	KASEDIYNRLA
SEQ ID NO:336	GTTILET

mAb12 Parental VL-CDR2 (Kabat)	
SEQ ID NO:337 mAb12 Parental VL-CDR3 (Kabat)	QQYWSTPYT
SEQ ID NO:338 mAb12 Parental VL-CDR1 (Chothia)	KASEDIYNRLA
SEQ ID NO:339 mAb12 Parental VL-CDR2 (Chothia)	GTTILET
SEQ ID NO:340 mAb12 Parental VL-CDR3 (Chothia)	QQYWSTPYT
SEQ ID NO:341 mAb12 Parental VL-CDR1 (AbM)	KASEDIYNRLA
SEQ ID NO:342 mAb12 Parental VL-CDR2 (AbM)	GTTILET
SEQ ID NO:343 mAb12 Parental VL-CDR3 (AbM)	QQYWSTPYT
SEQ ID NO:344 mAb12 Parental VL-CDR1 (Contact)	SRYWMS
SEQ ID NO:345 mAb12 Parental VL-CDR2 (Contact)	WIGEINPDSNTLN

SEQ ID NO:346 mAb12 Parental VL-CDR3 (Contact)	ARPGGGYYSYALD
SEQ ID NO:347 mAb12 Parental VL-CDR1 (IMGT)	EDIYNR
SEQ ID NO:348 mAb12 Parental VL-CDR2 (IMGT)	GT
SEQ ID NO:349 mAb12 Parental VL-CDR3 (IMGT)	QQYWSTPYT
SEQ ID NO:350 Constant domain amino acid sequence of bispecific	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPEAQGGPSVFLFPPKPKDTLYITREPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO:351 Omalizumab XOLAIR™ Anti-IgE VH (US 6267958)	E V Q L V E S G G GL V Q P G G S L R LS C A V S G Y S I TS G Y S W N W I R QA P G K G L E W V AS I T Y D G S T N YN P S V K G R I T IS R D D S K N T F YL Q M N S L R A E DT A V Y Y C A R G SH Y F G H W H F A VW G Q G T L V T V SS A S T K G P S V FP L A P S S K S T SG G T A A L G C L VK D Y F P E P V T VS W N S G A L T S GV H T F P A V L Q S S G L Y S L S S V VT V P S S S L G T QT Y I C N V N H K PS N T K V D K K V EP K S C D K T H T CP P C P A P E L L GG P S V F L F P P KP K D T L M I S R TP E V T C V V V D VS H E D P E V K F NW Y V D G V E V H NA K T K P R E E Q YN S T Y R V V S V LT V L H Q D W L N GK E Y K C K V S N KA L P A P I E K T IS K A K G Q P R E PQ V Y T L P P S R E E M T K N Q V S L TC L V K G F Y P S DI A V E W E S N G QP E N N Y K T T P PV L D S D G S F F LY S K L T V D K S RW Q Q G N V F S C SV M H E A L H N H YT Q K S L S L S P GK
SEQ ID NO:352 Omalizumab XOLAIR™ Anti-IgE VL (US 6267958)	D I Q L T Q S P S S L S A S V G D R V T I T C R A S Q S V D Y D G D S Y M N W YQ Q K P G K A P K LL I Y A A S Y L E SG V P S R F S G S GS G T D F T L T I SS L Q P E D F A T YY C Q Q S H E D P YT F G Q G T K V E IK R T V A A P S V FI F P P S D E Q L KS G T A S V V C L LN N F Y P R E A K VQ W K V D N A L Q SG N S Q E S V T E QD S K D S

	T Y S L SS T L T L S K A D YE K H K V Y A C E VT H Q G L S S P V TK S F N R G E C
SEQ ID NO:353 Adalimumab HUMIRA™ Anti-TNF VH (US 6090382)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEW VSAITWNSGHIDYADSVEGRFTISRDNAKNSLYLQMNSLRAEDTAVYY CAKVSYLSTASSLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHY TQKSLSLSPG K
SEQ ID NO:354 Adalimumab HUMIRA™ Anti-TNF VL (US 6090382)	DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIY AASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRAPYTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQG LSSPVTKSFN RGEC
SEQ ID NO:355 Oxelumab Anti-OX40L VH (US 7501496)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEW VSIISGSGGFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYC AKDRLVAPGTFDYWGQGALVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYT QKSLSLSPG
SEQ ID NO:356 Oxelumab Anti-OX40L VL (US 7501496)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFG QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQG LSSPVTKSFN RGEC
SEQ ID NO:357 Lebrikizumab EBGLYSS™ Anti-IL-13 VH (US 8088618)	QVTLRESGPALVKPTQTLTLTCTVSGFSLSAYSVNWIRQPPGKALEWLA MIWGDGKIVYNSALKSRLTISKDTSKNQVVLTMTNMDPVDTATYYCA GDGYYPYAMDNWGQGSLVTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTKTYT CNVDHKPSNT KVDKRVESKY GPPCPPCPAP EFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG

	SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
SEQ ID NO:358 Lebrikizumab EBGLYSS™ Anti-IL-13 VL (US 8088618)	DIVMTQSPDSLSVSLGERATINCRASKSVDSYGNSFMHWYQQKPGQPP KLLIYLASNLESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQNNE DPRTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEV THQGLSSPVT KSFNRGEC
SEQ ID NO:359 Vedolizumab ENTYVIO™ Anti-integrin α4β7 VH (US 7147851)	QVQLVQSGAEVKKPGASVKVSCKGSGYTFTSYWMHWVRQAPGQRLE WIGEIDPSESNTNYNQKFKGRVTLTVDISASTAYMELSSLRSEDTAVYY CARGGYDGWDYAIDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLV KDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELA GAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPG
SEQ ID NO:360 Vedolizumab ENTYVIO™ Anti-integrin α4β7 VL (US 7147851)	DVVMTQSPLSLPVTPGEPASISCRSSQSLAKSYGNTYLSWYLQKPGQSP QLLIYGISNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCLQGTHQ PYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACE VTHQGLSSPV TKSFNRGEC
SEQ ID NO:361 Ustekinumab STELARA™ Anti-IL-12 and IL-23 VH (US 6902734)	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDW IGIMSPVDSDIRYSPSFQGQVTMSVDKSITTAYLQWNSLKASDTAMYYC ARRRPGQGYFDFWGQGTLVTVSSSSTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQ KSLSLSPGK
SEQ ID NO:362 Ustekinumab STELARA™ Anti-IL-12 and IL-23 VL (US 6902734)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNIYPYTFG QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KV DNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF N RGEC

SEQ ID NO:363 Secukinumab COSENTYX™ Anti-IL-17A VH (US 7807155)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEW VAAINQDGSEKYYVGSVKGRFTISRDNAKNSLYLQMNSLRVEDTAVYY CVRDYYDILTDYYIHYWYFDLWGRGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHE ALHNHYTQKS LSLSPGK
SEQ ID NO:364 Secukinumab COSENTYX™ Anti-IL-17A VL (US 7807155)	EIVLTQSPGT LSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY GASSRATGIPDRFSGSGSGT DFTLTISRLE PEDFAVYYCQQYGSSPCTFG QGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQ GLSSPVTKSF NRGEC
SEQ ID NO:365 Guselkumab TREMFYA™ Anti-IL-23 VH (US 7935344)	EVQLVQSGAEVKKPGESLKISCKGSGYSFSNYWIGWVRQMPGKGLEW MGIIDPSNSYTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC ARWYYKPFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQGNVFSCSVMHE ALHNHYTQKS LSLSPGK
SEQ ID NO:366 Guselkumab TREMFYA™ Anti-IL-23 VL (US 7935344)	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGSGYDVHWYQQLPGTAPKLLI YGNSKRPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCASWTDGLSL VVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQV THEGSTVEKT VAPTECS
SEQ ID NO:367 Tildrakizumab ILUMYA™ Anti-IL-23 VH (US 8404813)	QVQLVQSGAE VKKPGASVKVSCKASGYIFI TYWMTWVRQA PGQGLEWMGQ IFPASGSADY NEKFEGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARGG GGFAYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSLSLSPGK
SEQ ID NO:368	DIQMTQSPSS LSASVGDRVTITCRTSENIY SYLAWYQQKP

Tildrakizumab ILUMYA™ Anti-IL-23 VL (US 8404813)	GKAPKLLIYN AKTLAEGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQH HYGIPFTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
SEQ ID NO:369 Tralokinumab ADTRALZA™ Anti-IL-13 VH (US 7935343)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGLSWVRQAPGQGLE WMGWISANNGDTNYGQEFQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARDS SSSWARWFFD LWGRGTLVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQEGNVFSCSVM HEALHNHYTQ KSLSLSLGK
SEQ ID NO:370 Tralokinumab ADTRALZA™ Anti-IL-13 VL (US 7935343)	SYVLTQPPSVSVAPGKTARITCGGNIIGSKLVHWYQQKPGQAPVLVIYD DGDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDTGSDPVV FGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVT VAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSC QVTHE GSTVEKTVAP TECS
SEQ ID NO:371 Risankizumab SKYRIZI™ Anti-IL-23A VH (US 8778346)	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEW IGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVYYC AIPDRSGYAWFIYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYT QKSLSLSPG
SEQ ID NO:372 Risankizumab SKYRIZI™ Anti-IL-23A VL (US 8778346)	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLLIY WASTRHTGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSYPFTFG SGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQG LSSPVTKSFN RGEC
SEQ ID NO:373 Tezepelumab TEZSPIRE™ Anti-TSLP VH (US 7982016)	QMQLVESGGGVVQPGRSLRLSCAASGFTFRTYGMHWVRQAPGKGLE WVAVIWYDGSNKHYADSVKGRFTITRDNSKNTLNLQMNSLRAEDTAV YYCARAP QWELVHEAFD IWGQGTMVTVSSASTKGPSV FPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV HNAKT KPREEQFNSTFRVVSVLTVV HQDWLNGKEY KCKVSNKGLP

	APIEKTISKT KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MH EALHNHYTQK SLSLSPGK
SEQ ID NO:374 Tezepelumab TEZSPIRE™ Anti-TSLP VL (US 7982016)	SYVLTQPPSVSVAPGQTARITCGGNNLGSKSVHWYQQKPGQAPVLVVY DDSDRPSWIPERFSGSNSGNTATLTISRGEAGDEADYYCQVWDSSSDHV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS CQVTHE GSTVEKTVAP TECS

Equivalents

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS:

1. A bispecific construct comprising an anti-TSLP antibody, or binding domain thereof, linked to an anti-SCF antibody, or binding domain thereof,, wherein:

(a) the anti-TSLP antibody, or binding domain thereof, comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 6, 7, and 8, (ii) SEQ ID NOs: 2, 3, and 4, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (v) SEQ ID NOs: 18, 19, and 20, (vi) SEQ ID NOs: 22, 23, and 24, (vii) SEQ ID NOs: 26, 27, and 28, (viii) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof; and

(b) the anti-SCF antibody, or binding domain thereof, comprises heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 46, 47, and 48, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, (iv) SEQ ID NOs: 34, 35, and 36, or conservative sequence modifications thereof, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (v) SEQ ID NOs: 58, 59, and 60, (vi) SEQ ID NOs: 54, 55, and 56, (vii) SEQ ID NOs: 50, 51, and 52, (viii) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof.

2. A bispecific construct comprising an anti-TSLP antibody, or binding domain thereof, linked to an anti-SCF antibody, or binding domain thereof,, wherein:

(a) the anti-TSLP antibody, or binding domain thereof, comprises a heavy chain variable region having the amino acid sequences set forth in SEQ ID NOs: 5, 1, 9, 13, or a sequence at least 90% identical thereto, and a light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 17, 21, 25, 29, or a sequence at least 90% identical thereto; and

(b) the anti-SCF antibody, or binding domain thereof, comprises a heavy chain variable region having the amino acid sequences set forth in SEQ ID NOs:45, 33, 37, 41, or a sequence at least 90% identical thereto, and a light chain variable region

having the amino acid sequences set forth in SEQ ID NOs: 57, 49, 53, 61, or a sequence at least 90% identical thereto.

3. The bispecific construct of claim 1 or 2, wherein the anti-TSLP antibody, or binding domain thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 5 and 17, (b) SEQ ID NOs: 1 and 21, (c) SEQ ID NOs: 1 and 25, (d) SEQ ID NOs: 1 and 29, (e) SEQ ID NOs: 1 and 17, (f) SEQ ID NOs: 5 and 21, (g) SEQ ID NOs: 5 and 25, (h) SEQ ID NOs: 5 and 29, (i) SEQ ID NOs: 9 and 17, (j) SEQ ID NOs: 9 and 21, (k) SEQ ID NOs: 9 and 25, (l) SEQ ID NOs: 9 and 29, (m) SEQ ID NOs: 13 and 17, (n) SEQ ID NOs: 13 and 21, (o) SEQ ID NOs: 13 and 25, or (p) SEQ ID NOs: 13 and 29.

4. The bispecific construct of claim 1 or 2, wherein the anti-TSLP antibody, or binding domain thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 5 and 17, (b) SEQ ID NOs: 1 and 21, (c) SEQ ID NOs: 1 and 25, (d) SEQ ID NOs: 1 and 17, (e) SEQ ID NOs: 5 and 21, (f) SEQ ID NOs: 5 and 25, (g) SEQ ID NOs: 9 and 17, (h) SEQ ID NOs: 9 and 21, or (i) SEQ ID NOs: 9 and 25.

5. The bispecific construct of any one of claims 1-4, wherein the anti-SCF antibody, or binding domain thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 45 and 57, (b) SEQ ID NOs: 33 and 53, (c) SEQ ID NOs: 33 and 57, (d) SEQ ID NOs: 33 and 61, (e) SEQ ID NOs: 37 and 49, (f) SEQ ID NOs: 37 and 53, (g) SEQ ID NOs: 37 and 57, (h) SEQ ID NOs: 33 and 61, (i) SEQ ID NOs: 41 and 49, (j) SEQ ID NOs: 41 and 53, (k) SEQ ID NOs: 41 and 57, (l) SEQ ID NOs: 41 and 61, (m) SEQ ID NOs: 45 and 49, (n) SEQ ID NOs: 45 and 53, (o) SEQ ID NOs: 33 and 49, or (p) SEQ ID NOs: 45 and 61.

6. The bispecific construct of any one of claims 1-4, wherein the anti-SCF antibody, or binding domain thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 45 and 57, (b) SEQ ID NOs: 33 and 61, (c) SEQ ID NOs: 37 and 57, (d) SEQ ID NOs: 37 and 61, (e) SEQ ID NOs:

41 and 57, (f) SEQ ID NOs: 41 and 61, (g) SEQ ID NOs: 33 and 57, or (h) SEQ ID NOs: 45 and 61.

7. The bispecific construct of any one of claims 1-6, wherein (a) the anti-TSLP antibody, or binding domain thereof, further comprises a human IgG1 constant domain or (b) the anti-SCF antibody, or binding domain thereof, further comprises a human IgG1 constant domain.

8. The bispecific construct of any one of claims 1-7, wherein (a) the anti-SCF antibody, or binding domain thereof, is linked to the C-terminus of the heavy chain of the anti-TSLP antibody, or binding domain thereof, or (b) the anti-TSLP antibody, or binding domain thereof, is linked to the C-terminus of the heavy chain of the anti-SCF antibody, or binding domain thereof,.

9. The bispecific construct of any one of claims 1-8, wherein the anti-SCF binding domain is a scFv or (b) the anti-TSLP binding domain is a scFv.

10. The bispecific construct of any one of claims 1-9, wherein the anti-TSLP antibody, or binding domain thereof, and the anti-SCF antibody, or binding domain thereof, are genetically fused.

11. The bispecific construct of any one of claims 1-9, wherein the anti-TSLP antibody, or binding domain thereof, and the anti-SCF antibody, or binding domain thereof, are chemically conjugated.

12. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 34, 35, and 36, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs:

2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

13. The bispecific construct of claim 12, wherein:

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 33 and 61; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17, and a human IgG1 constant domain.

14. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 38, 39, and 40, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

15. The bispecific construct of claim 14, wherein:

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 37 and 61; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17, and a human IgG1 constant domain.

16. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 46, 47, and 48, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 58, 59, and 60, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

17. The bispecific construct of claim 16, wherein:

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 45 and 57; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17, and a human IgG1 constant domain.

18. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 34, 35, and 36, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

19. The bispecific construct of claim 18, wherein

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 33 and 61; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17, and a human IgG1 constant domain.

20. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 38, 39, and 40, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

21. The bispecific construct of claim 20, wherein:

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 37 and 61; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17, and a human IgG1 constant domain.

22. A bispecific construct comprising an anti-TSLP antibody linked to an anti-SCF scFv, wherein:

(a) the anti-SCF scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 46, 47, and 48, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 58, 59, and 60, respectively; and

(b) the anti-TSLP antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively, and a human IgG1 constant domain.

23. The bispecific construct of claim 22, wherein:

(a) the anti-SCF scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 45 and 57; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17, and a human IgG1 constant domain.

24. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 34, 35, and 36, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

25. The bispecific construct of claim 24, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 33 and 61, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17.

26. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 38, 39, and 40, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

27. The bispecific construct of claim 26, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 37 and 61, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17.

28. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 46, 47, and 48, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 58, 59, and 60, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 2, 3, and 4, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

29. The bispecific construct of claim 28, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 45 and 57, and a human IgG1 constant domain; and

(b) the anti-TSLP antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 17.

30. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 34, 35, and 36, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

31. The bispecific construct of claim 30, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 33 and 61, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17.

32. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 38, 39, and 40, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 62, 63, and 64, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

33. The bispecific construct of claim 32, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 37 and 61, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17.

34. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, wherein:

(a) the anti-SCF antibody comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 46, 47, and 48, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 58, 59, and 60, respectively, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and light chain variable region CDR1, CDR2 and CDR3 domains comprising the amino acid sequences as set forth in SEQ ID NOs: 18, 19, and 20, respectively.

35. The bispecific construct of claim 34, wherein:

(a) the anti-SCF antibody comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 45 and 57, and a human IgG1 constant domain; and

(b) the anti-TSLP scFv comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in SEQ ID NOs: 5 and 17.

36. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, comprising the amino acid sequence set forth in SEQ ID NO: 65 or encoded by the nucleotide sequence set forth in SEQ ID NO: 66.

37. A bispecific construct comprising an anti-SCF antibody linked to an anti-TSLP scFv, comprising the amino acid sequence set forth in SEQ ID NO: 67 or encoded by the nucleotide sequence set forth in SEQ ID NO: 68.

38. The bispecific construct of any one of claims 12-23, wherein the anti-SCF scFv is linked to the C-terminus of the heavy chain of the anti-TSLP antibody.

39. The bispecific construct of any one of claims 24-35, wherein the anti-TSLP scFv is linked to the C-terminus of the heavy chain of the anti-SCF antibody.

40. The bispecific construct of any one of claims 12-35, wherein the antibody and scFv are genetically fused.

41. The bispecific construct of any one of claims 12-35, wherein the antibody and scFv are chemically conjugated.

42. An anti-TSLP antibody, or antigen-binding fragment thereof, comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 2, 3, and 4, (ii) SEQ ID NOs: 6, 7, and 8, (iii) SEQ ID NOs: 10, 11, and 12, (iv) SEQ ID NOs: 14, 15, and 16, or conservative sequence modifications thereof, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (v) SEQ ID NOs: 18, 19, and 20,

(vi) SEQ ID NOs: 22, 23, and 24, (vii) SEQ ID NOs: 26, 27, and 28, (viii) SEQ ID NOs: 30, 31, and 32, or conservative sequence modifications thereof.

43. The anti-TSLP antibody, or antigen-binding fragment thereof, of claim 42, comprising a heavy chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1, 5, 9, 13, or a sequence at least 90% identical thereto, and a light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 17, 21, 25, 29, or a sequence at least 90% identical thereto.

44. The anti-TSLP antibody, or antigen-binding fragment thereof, of claim 42 or 43, wherein the anti-TSLP antibody, or antigen-binding fragment thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 1 and 17, (b) SEQ ID NOs: 1 and 21, (c) SEQ ID NOs: 1 and 25, (d) SEQ ID NOs: 1 and 29, (e) SEQ ID NOs: 5 and 17, (f) SEQ ID NOs: 5 and 21, (g) SEQ ID NOs: 5 and 25, (h) SEQ ID NOs: 5 and 29, (i) SEQ ID NOs: 9 and 17, (j) SEQ ID NOs: 9 and 21, (k) SEQ ID NOs: 9 and 25, (l) SEQ ID NOs: 9 and 29, (m) SEQ ID NOs: 13 and 17, (n) SEQ ID NOs: 13 and 21, (o) SEQ ID NOs: 13 and 25, or (p) SEQ ID NOs: 13 and 29.

45. The anti-TSLP antibody, or antigen-binding fragment thereof, of claim 42 or 43, wherein the anti-TSLP antibody, or antigen-binding fragment thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 1 and 17, (b) SEQ ID NOs: 1 and 21, (c) SEQ ID NOs: 1 and 25, (d) SEQ ID NOs: 5 and 17, (e) SEQ ID NOs: 5 and 21, (f) SEQ ID NOs: 5 and 25, (g) SEQ ID NOs: 9 and 17, (h) SEQ ID NOs: 9 and 21, or (i) SEQ ID NOs: 9 and 25.

46. A bispecific construct comprising the anti-TSLP antibody, or antigen binding fragment thereof, of any one of claims 42-45 linked to a second antibody, or antigen binding fragment thereof.

47. The bispecific construct of claim 46, wherein the second antibody, or antigen binding fragment thereof, binds to (a) a member of the TNF superfamily (e.g., TNFα), (b) a tumor necrosis factor (TNF) receptor (e.g., TNFRSF4), (c) an interleukin (e.g., IL-23, IL-17A, or IL-13), (d) an immunoglobulin (e.g., IgE), or (e) an integrin (e.g., integrin α4β7).

48.. The bispecific construct of claim 47, further comprising one or more additional binding agents.

49. An anti-SCF antibody, or antigen-binding fragment thereof, comprising heavy chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (i) SEQ ID NOs: 34, 35, and 36, (ii) SEQ ID NOs: 38, 39, and 40, (iii) SEQ ID NOs: 42, 43, and 44, (iv) SEQ ID NOs: 46, 47, and 48, or conservative sequence modifications thereof, and light chain variable region CDR1, CDR2 and CDR3 domains having the amino acid sequences respectively set forth in (v) SEQ ID NOs: 50, 51, and 52, (vi) SEQ ID NOs: 54, 55, and 56, (vii) SEQ ID NOs: 58, 59, and 60, (viii) SEQ ID NOs: 62, 63, and 64, or conservative sequence modifications thereof.

50. The anti-SCF antibody, or antigen-binding fragment thereof, of claim 49, comprising a heavy chain variable region having the amino acid sequences set forth in SEQ ID NOs: 33, 37, 41, 45, or a sequence at least 90% identical thereto, and a light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 49, 53, 57, 61, or a sequence at least 90% identical thereto.

51. The anti-SCF antibody, or antigen-binding fragment thereof, of claim 49 or 50, wherein the anti-SCF antibody, or antigen-binding fragment thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 33 and 49, (b) SEQ ID NOs: 33 and 53, (c) SEQ ID NOs: 33 and 57, (d) SEQ ID NOs: 33 and 61, (e) SEQ ID NOs: 37 and 49, (f) SEQ ID NOs: 37 and 53, (g) SEQ ID NOs: 37 and 57, (h) SEQ ID NOs: 33 and 61, (i) SEQ ID NOs: 41 and 49, (j) SEQ ID NOs: 41 and 53, (k) SEQ ID NOs: 41 and 57, (l) SEQ ID NOs: 41 and 61, (m) SEQ ID NOs: 45 and 49, (n) SEQ ID NOs: 45 and 53, (o) SEQ ID NOs: 45 and 57, or (p) SEQ ID NOs: 45 and 61.

52. The anti-SCF antibody, or antigen-binding fragment thereof, of claim 49 or 50, wherein the anti-SCF antibody, or antigen-binding fragment thereof, comprises heavy and light chain variable regions respectively comprising the amino acid sequences set forth in (a) SEQ ID NOs: 33 and 57, (b) SEQ ID NOs: 33 and 61, (c) SEQ ID NOs: 37 and 57, (d) SEQ

ID NOs: 37 and 61, (e) SEQ ID NOs: 41 and 57, (f) SEQ ID NOs: 41 and 61, (g) SEQ ID NOs: 45 and 57, or (h) SEQ ID NOs: 45 and 61.

53. A bispecific construct comprising the anti-SCF antibody, or antigen binding fragment thereof, of any one of claims 49-52 linked to a second antibody, or antigen binding fragment thereof.

54. The bispecific construct of claim 53, wherein the second antibody, or antigen binding fragment thereof, binds to (a) a member of the TNF superfamily (e.g., TNFα), (b) a tumor necrosis factor (TNF) receptor (e.g., TNFRSF4), (c) an interleukin (e.g., IL-23, IL-17A, or IL-13), (d) an immunoglobulin (e.g., IgE), or (e) an integrin (e.g., integrin α4β7).

55. The bispecific construct of claim 54, further comprising one or more additional binding agents.

56. A composition comprising the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50 and a pharmaceutically acceptable carrier.

57. A kit comprising the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50 and instructions for use.

58. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody variable region, wherein the antibody variable region comprises the amino acid sequence as set forth in SEQ ID NO: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, or 61.

59. An isolated nucleic acid molecule comprising a nucleotide sequence encoding heavy and light chain variable regions of an antibody, wherein the heavy and light chain variable regions respectively comprise the amino acid sequences depicted in (a) SEQ ID NOs: 1 and 17, (b) SEQ ID NOs: 1 and 21, (c) SEQ ID NOs: 1 and 25, (d) SEQ ID NOs: 1 and 29, (e) SEQ ID NOs: 5 and 17, (f) SEQ ID NOs: 5 and 21, (g) SEQ ID NOs: 5 and 25, (h) SEQ ID

NOs: 5 and 29, (i) SEQ ID NOs: 9 and 17, (j) SEQ ID NOs: 9 and 21, (k) SEQ ID NOs: 9 and 25, (l) SEQ ID NOs: 9 and 29, (m) SEQ ID NOs: 13 and 17, (n) SEQ ID NOs: 13 and 21, (o) SEQ ID NOs: 13 and 25, (p) SEQ ID NOs: 13 and 29, (q) SEQ ID NOs: 33 and 49, (r) SEQ ID NOs: 33 and 53, (s) SEQ ID NOs: 33 and 57, (t) SEQ ID NOs: 33 and 61, (u) SEQ ID NOs: 37 and 49, (v) SEQ ID NOs: 37 and 53, (w) SEQ ID NOs: 37 and 57, (x) SEQ ID NOs: 33 and 61, (y) SEQ ID NOs: 41 and 49, (z) SEQ ID NOs: 41 and 53, (aa) SEQ ID NOs: 41 and 57, (bb) SEQ ID NOs: 41 and 61, (cc) SEQ ID NOs: 45 and 49, (dd) SEQ ID NOs: 45 and 53, (ee) SEQ ID NOs: 45 and 57, or (ff) SEQ ID NOs: 45 and 61.

60. A nucleic acid molecule coding for the bispecific construct as set forth in any one of claims 1-41, 46-48, and 55-55, e.g., an isolated nucleic acid molecule comprising the nucleotide sequence as set forth in SEQ ID NO: 65-69, 269-272, 274-277, 281-284, 286-289, or 350.

61. A nucleic acid molecule as set forth in any one of claims 58-60 in the form of an expression vector.

62. A method of blocking TSLP from binding to TLSPR expressed on immune cells in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to block TSLP from binding to TSLPR.

63. A method of blocking SCF from binding to c-Kit expressed on immune cells in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to block SCF from binding to c-Kit.

64. A method for inhibiting activation of immune cells in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50,

or the composition of claim 56, in an amount effective to inhibit activation of immune cells in the subject.

65. A method for reducing the accumulation of immune cells within organs or tissues in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to reduce the accumulation of immune cells within organs or tissues in the subject.

66. A method for reducing inflammation in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to reduce inflammation in the subject.

67. A method for treating an inflammatory disease in a subject, comprising administering to the subject the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to treat the subject.

68. The method of any one of claims 63-67, wherein the method results in at least one of the following biological activities in the subject: (a) inhibition of TSLP-induced activation and/or proliferation of mast cells, dendritic cells (DC), and/or natural killer T cells (NKT); (b) inhibition of TSLP-induced osteoprotegerin (OPG) secretion; (c) inhibition of TSLP-induced secretion of Th2 cytokines (such as TARC, CCL22, IL-4, IL-13 or IL-5); or (d) inhibition of SCF-induced secretion of mast cells, eosinophils, type 2 innate lymphoid (ILC2) cells, and/or type 3 innate lymphoid (ILC3) cells.

69. The method of any one of claims 64-67, wherein the subject is diagnosed with a disorder of the immune system, allergic inflammation, allergic airway inflammation, DC-mediated inflammatory Th2 responses, atopic dermatitis, atopic eczema, asthma, obstructive airways disease, chronic obstructive pulmonary disease, a food allergy, inflammatory arthritis, rheumatoid arthritis, psoriasis, an IgE-mediated disorder, rhino-conjunctivitis, a fibrotic disease, a disease associated with tissue remodeling, idiopathic pulmonary fibrosis,

chronic obstructive pulmonary disease, acute respiratory distress syndrome, cystic fibrosis, peribronchial fibrosis, hypersensitivity pneumonitis, asthma, sclerodoma, inflammation, liver cirrhosis, renal fibrosis, parenchymal fibrosis, endomyocardial fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, fibrous histiocytoma, fibrothorax, hepatic fibrosis, fibromyalgia, gingival fibrosis, radiation-induced fibrosis, a cardiovascular disease, a gastrointestinal disease, lung disease, a metabolic disease (such as Type 2 diabetes), a neurodegenerative disease (such as Parkinson's disease), or colon cancer.

70. The method of any one of claims 63-69, further comprising administration of one or more additional therapeutics.

71. The method of claim 70, wherein the additional therapeutic is selected from, but not limited to: immunosuppressants (for example, corticosteroids, non-steroidal glucocorticoid receptor agonists, leukotriene D4 antagonists, leukotriene B4 antagonists, A2A agonists, A2B antagonists, dopamine receptor agonists, pirfenidone, nintedanib, or avB6 antagonists), bronchodilators (for example, β-2 adrenergic receptor agonists, muscarinic antagonists, short-acting β2 receptor agonists, long-acting β2 receptor agonists, short-acting anticholinergic drugs, methyl xanthine drugs, long-acting anticholinergic drugs), other cytokine or cytokine receptor antagonists or antibodies (for example, IL-13 antagonists, IL-6 antagonists, antagonists of IL-1, IL-33, IL-25 or TNF-α, anti-IgE antibodies, anti-IL31 antibodies, anti-IL31R antibodies, anti-IL13 antibodies, anti-endoglin antibodies, anti-ILlb antibodies, another anti-TSLP antibody or anti-hTSLPR antibodies), antibiotics, radiotherapy, leukotriene antagonists (for example, montelukast, zafirlukast or pranlukast), PDE4 inhibitors (for example, roflumilast, xanthene), antihistamines or antitussive drugs.

72. An *in vitro* method of blocking TSLP from binding to TLSPR, comprising contacting cells expressing TSLPR with the bispecific construct of any one of claims 1-41, 46-48, 53-55, or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to block TSLP from binding to TSLPR.

73. An *in vitro* method of blocking SCF from binding to c-Kit, comprising contacting cells expressing c-Kit with the bispecific construct of any one of claims 1-41, 46-48, 53-55,

or the antibody, or antigen binding fragment thereof, of any one of claims 42-45 and 47-50, or the composition of claim 56, in an amount effective to block SCF from binding to c-Kit.

74. A human, humanized or chimeric antibody or bispecific construct thereof which binds to soluble human SCF ($hSCF^{165}$) with greater affinity than to membrane bound human SCF ($hSCF^{222}$).

75. A human, humanized or chimeric antibody or bispecific construct thereof which binds to an epitope comprising residue K100 of human SCF.

76. A bispecific construct comprising an anti-TSLP antibody, or binding domain thereof, linked to an anti-SCF antibody, or binding domain thereof.

77. A method for reducing mast cell activity by administering an antibody or bispecific construct as claimed in any of claims 74-76 to a patient in need thereof.

78. A method for treating an inflammatory disorder by administering an antibody or bispecific construct as claimed in any of claims 74-76 to a patient in need thereof.

79. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to TSLP.

80. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a member of the TNF superfamily.

81. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a tumor necrosis factor (TNF) receptor.

82. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-12 and/or IL-23.

83. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-23A.

84. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-17A.

85. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-13.

86. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IgE.

87. A construct comprising an anti-SCF antibody (or binding domain) linked to a second antibody (or binding domain) that binds to an integrin.

88. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to a member of the TNF superfamily.

89. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-12 and/or IL-23.

90. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-23A.

91. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-17A.

92. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IL-13.

93. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to IgE.

94. A construct comprising an anti-TSLP antibody (or binding domain) linked to a second antibody (or binding domain) that binds to an integrin.

FIG. 1

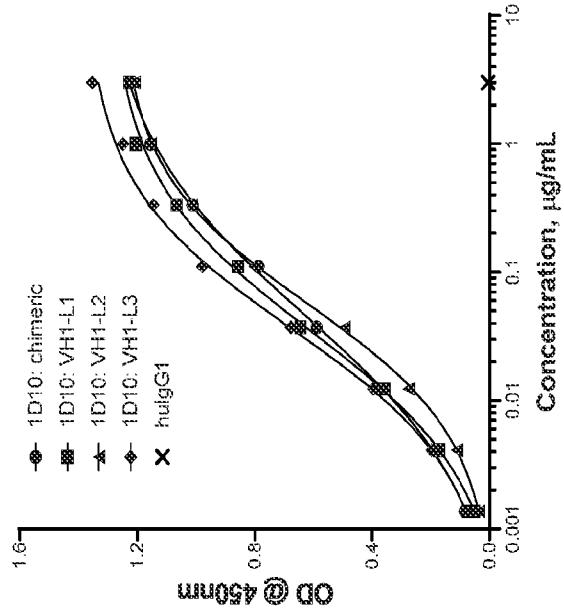


FIG. 2

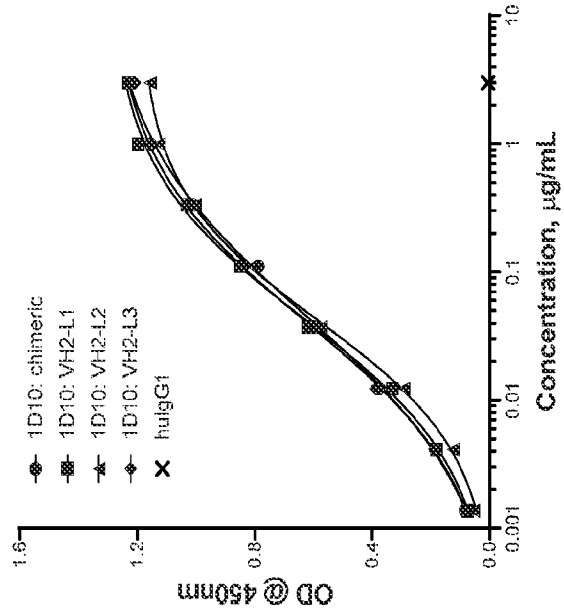


FIG. 3

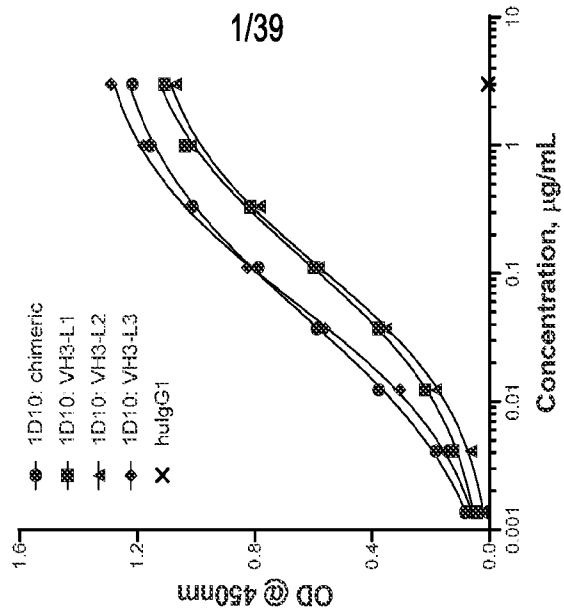


FIG. 6

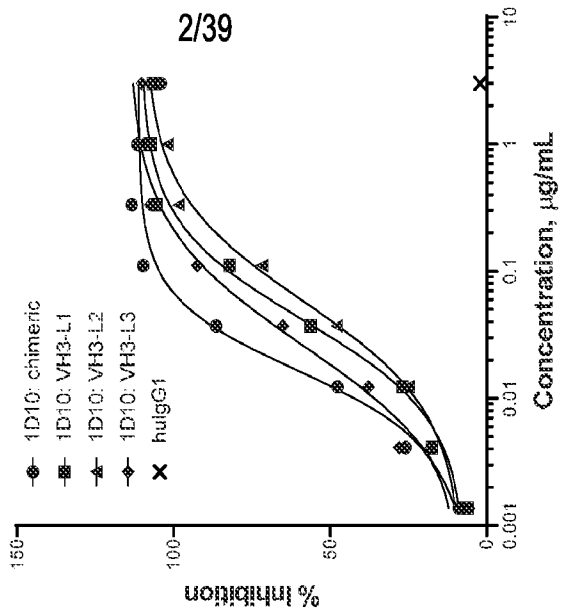


FIG. 5

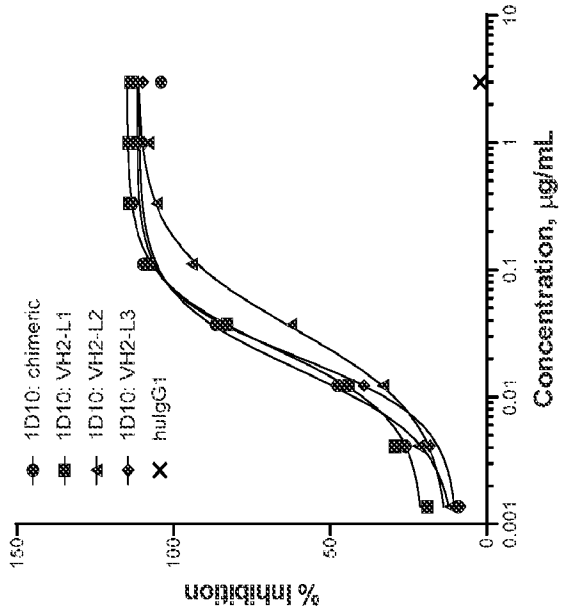


FIG. 4

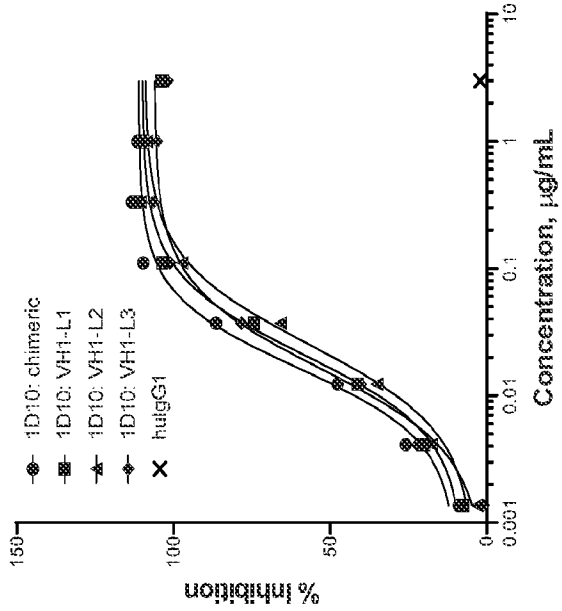


FIG. 8

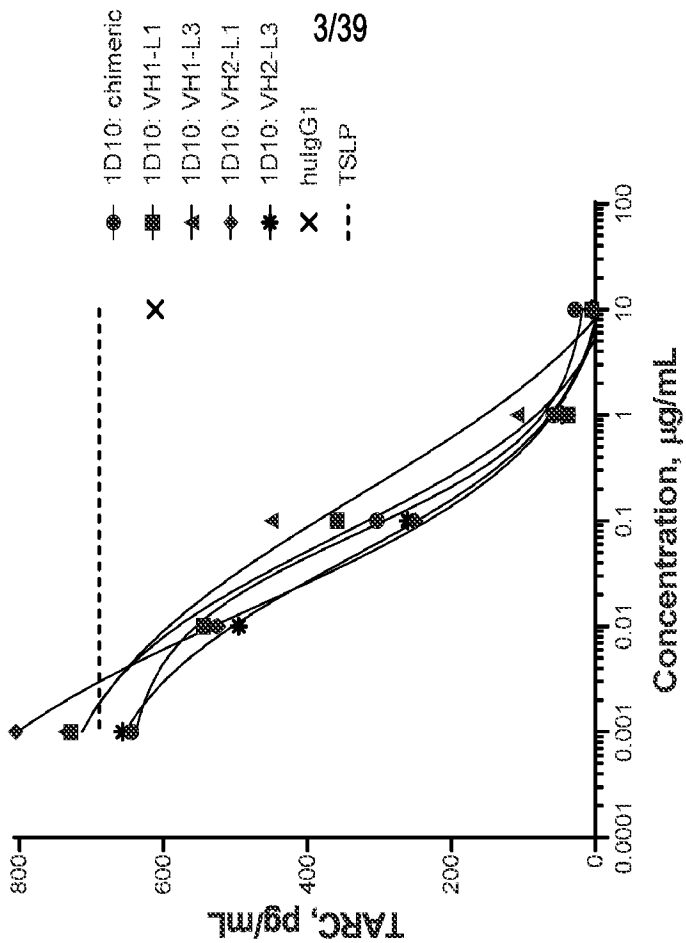

1D10: chimeric
1D10: VH1-L1
1D10: VH1-L3
1D10: VH2-L1
1D10: VH2-L3
huIgG1
TSLP
TARC, pg/mL
800
600
400
200
0
0.0001
0.001
0.01
0.1
1
10
100
Concentration, µg/mL

FIG. 7

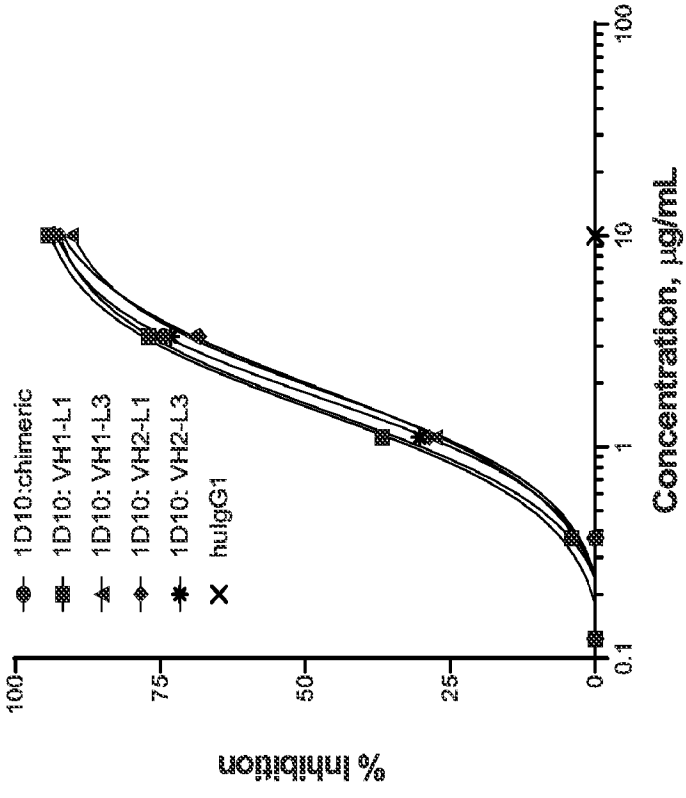

1D10:chimeric
1D10: VH1-L1
1D10: VH1-L3
1D10: VH2-L1
1D10: VH2-L3
huIgG1
% inhibition
100
75
50
25
0
0.1
1
10
100
Concentration, µg/mL

FIG. 9A

mAb	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
1D10: chimeric	725	1.48E+06	1.07E-03
1D10: VH1-L1	1448	1.26E+06	1.83E-03
1D10: VH1-L3	966	1.28E+06	1.23E-03
1D10: VH2-L1	1151	1.34E+06	1.54E-03
1D10: VH2-L3	1112	1.05E+06	1.17E-03

human

FIG. 9B

mAb	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
1D10: chimeric	17000	1.21E+06	2.05E-02
1D10: VH1-L1	15600	1.01E+06	1.57E-02
1D10: VH1-L3	13000	1.06E+06	1.38E-02
1D10: VH2-L1	17500	1.03E+06	1.805E-02
1D10: VH2-L3	13800	1.17E+06	1.61E-02

cyno

FIG. 11

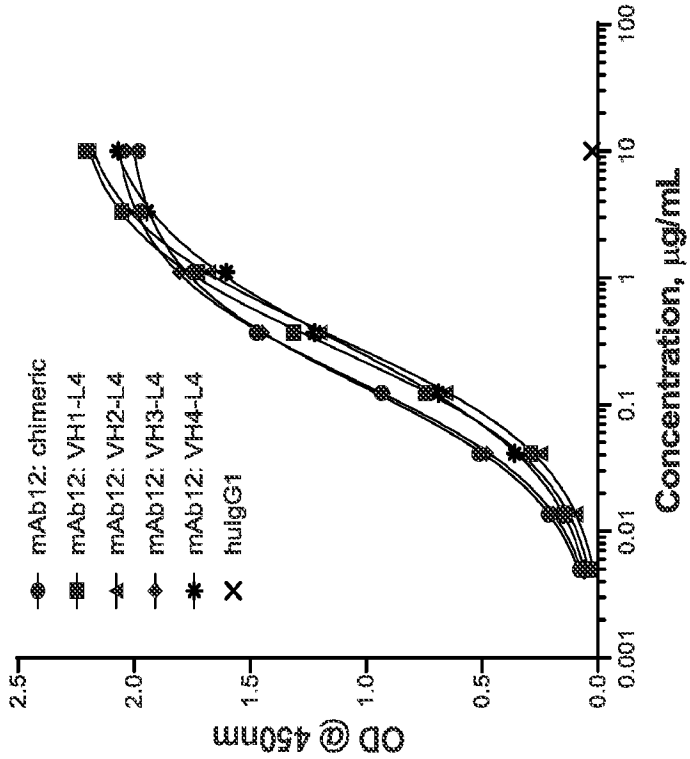

mAb12: chimeric
mAb12: VH1-L4
mAb12: VH2-L4
mAb12: VH3-L4
mAb12: VH4-L4
huIgG1
OD @ 450nm
Concentration, µg/mL
0.0
0.5
1.0
1.5
2.0
2.5
0.001
0.01
0.1
1
10
100

FIG. 10

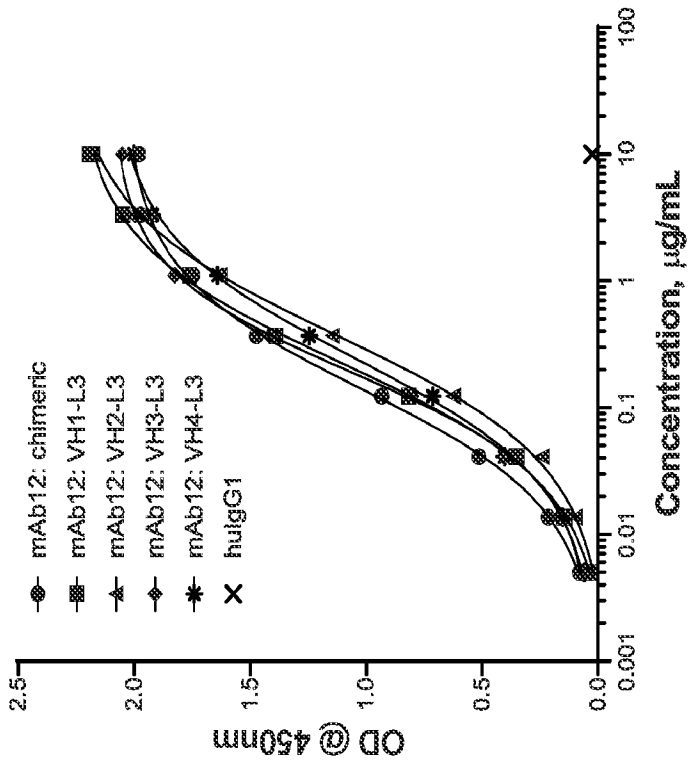

mAb12: chimeric
mAb12: VH1-L3
mAb12: VH2-L3
mAb12: VH3-L3
mAb12: VH4-L3
huIgG1
OD @ 450nm
Concentration, µg/mL
0.0
0.5
1.0
1.5
2.0
2.5
0.001
0.01
0.1
1
10
100

FIG. 13

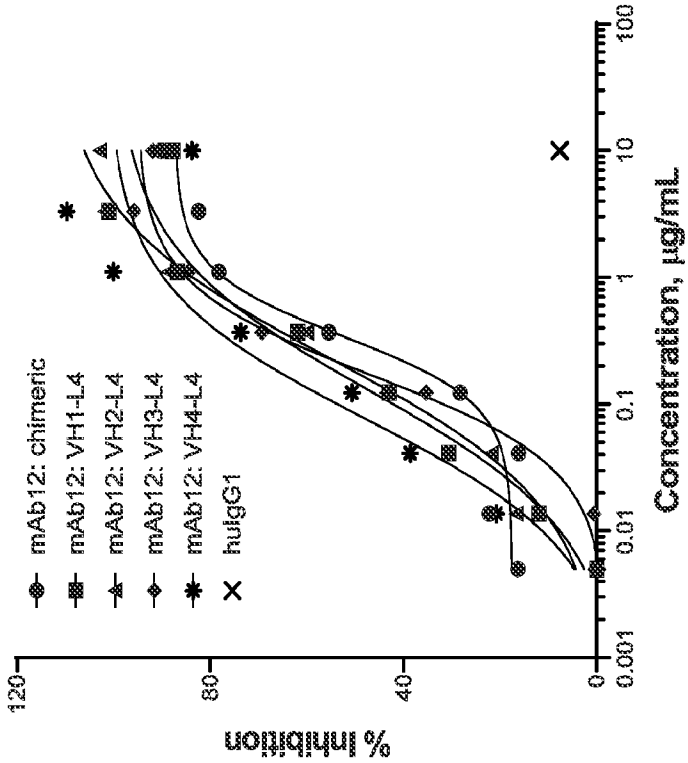

mAb12: chimeric
mAb12: VH1-L4
mAb12: VH2-L4
mAb12: VH3-L4
mAb12: VH4-L4
huIgG1
% inhibition
120
80
40
0
0.001
0.01
0.1
1
10
100
Concentration, µg/mL

FIG. 12

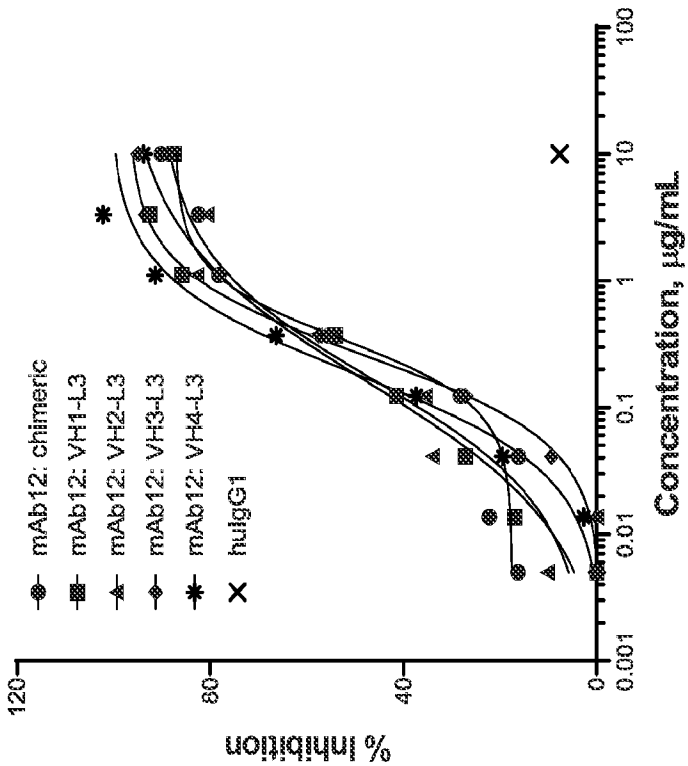

mAb12: chimeric
mAb12: VH1-L3
mAb12: VH2-L3
mAb12: VH3-L3
mAb12: VH4-L3
huIgG1
% inhibition
120
80
40
0
0.001
0.01
0.1
1
10
100
Concentration, µg/mL

FIG. 14A

mAb	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
mAb12: chimeric	9900	4.04E+04	3.99E-04
mAb12: VH3-L3	20200	2.86E+04	5.77E-04
mAb12: VH3-L4	13000	3.61E+04	4.71E-04
mAb12: VH4-L3	14800	3.64E+04	5.38E-04
mAb12: VH4-L4	16600	3.64E+04	6.05E-04

human

FIG. 14B

mAb	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
mAb12: chimeric	4200	8.19E+04	3.41E-04
mAb12: VH3-L3	2900	7.61E+04	2.21E-04
mAb12: VH3-L4	2100	9.21E+04	1.92E-04
mAb12: VH4-L3	1500	7.84E+04	1.15E-04
mAb12: VH4-L4	6200	7.36E+04	4.54E-04

cyno

FIG. 15

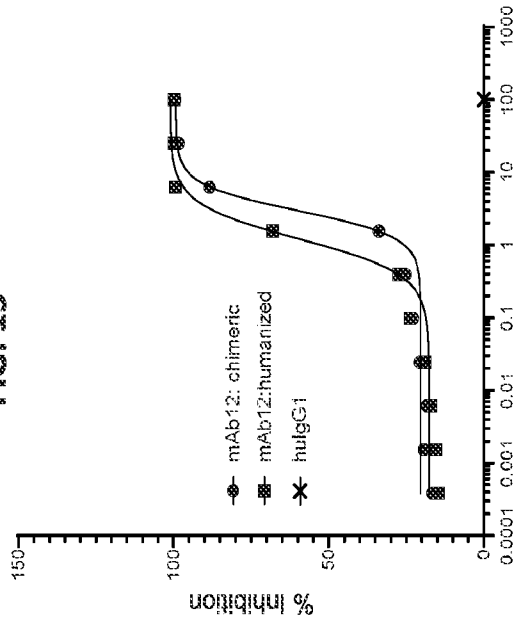


FIG. 16

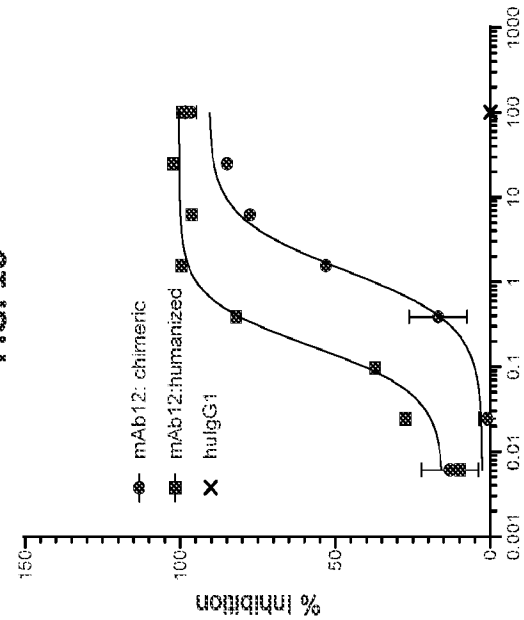


FIG. 17

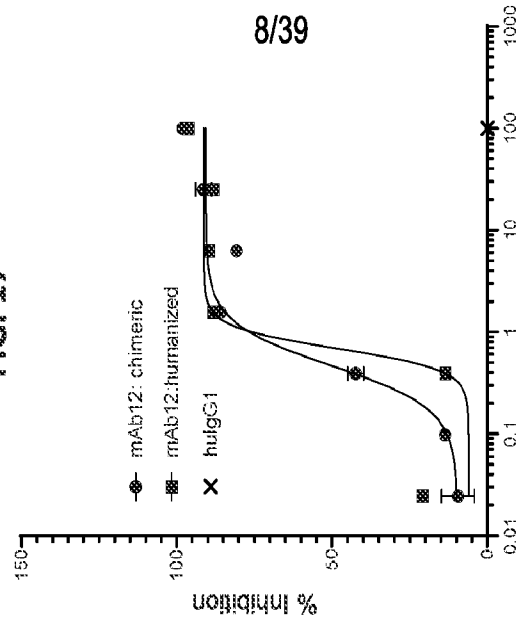


FIG. 18B

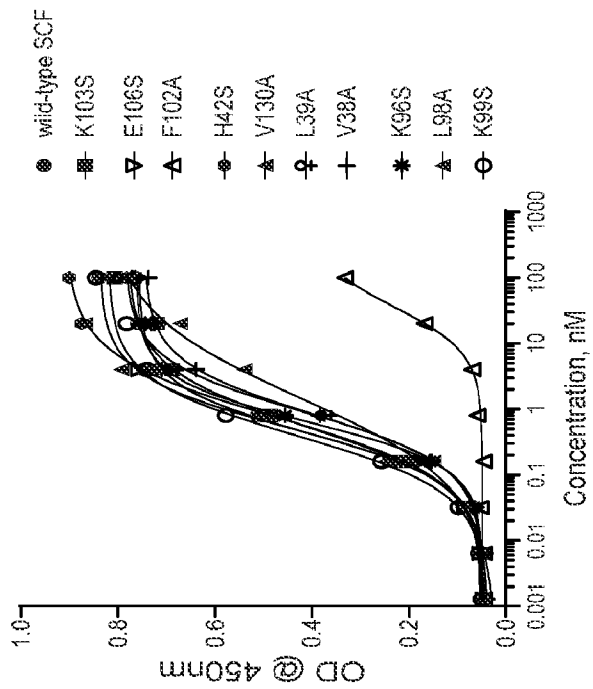


FIG. 18A

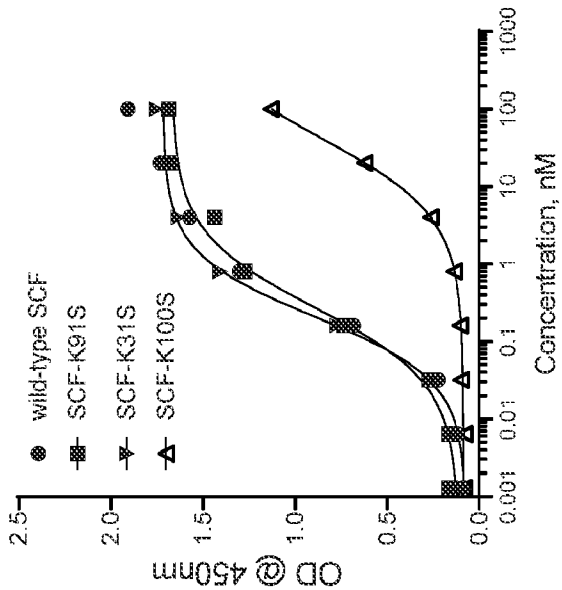


FIG. 18C

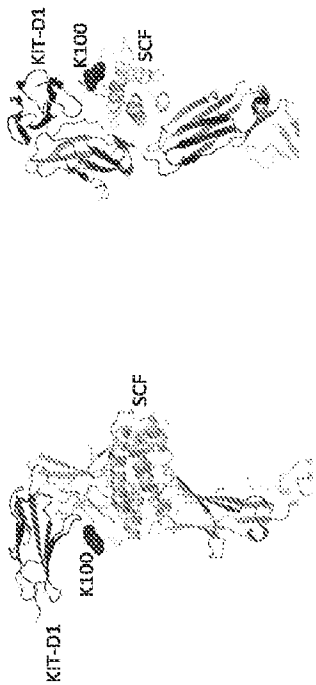


FIG. 19B

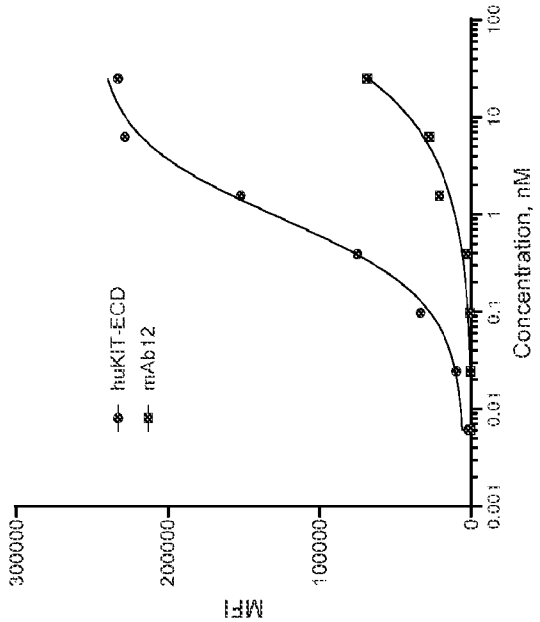


FIG. 19A

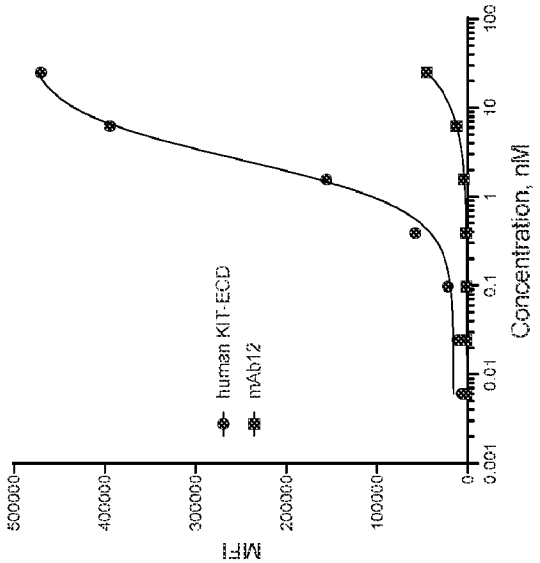


FIG. 20

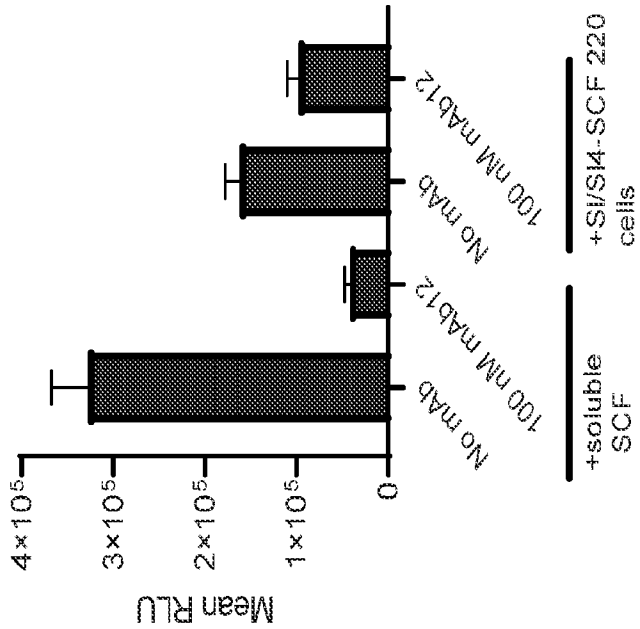

Mean RLU
4×10^5
3×10^5
2×10^5
1×10^5
0
No mAb
100 nM mAb12
No mAb
100 nM mAb12
+soluble SCF
+SI/SI4-SCF 220 cells

FIG. 21A

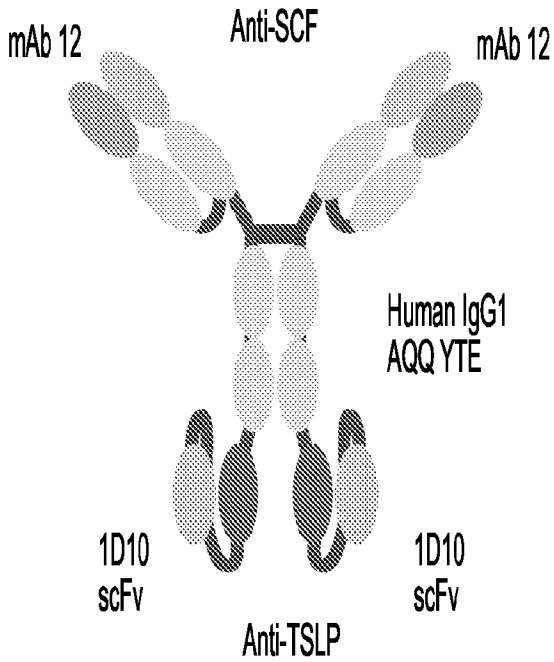


FIG. 21B

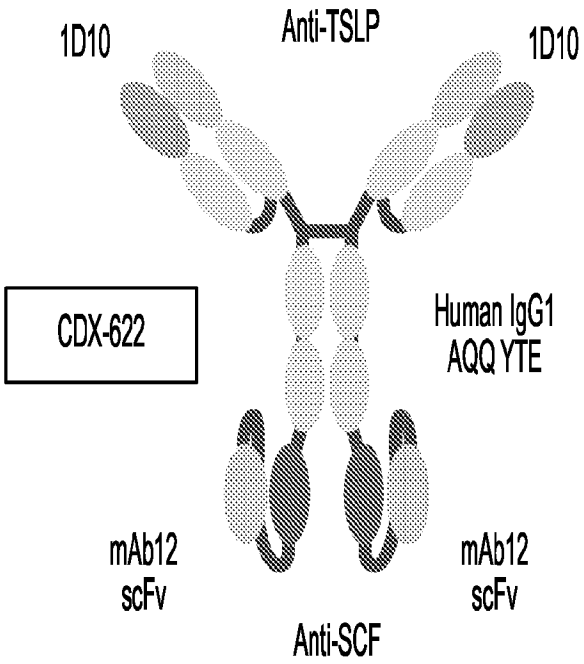


FIG. 24

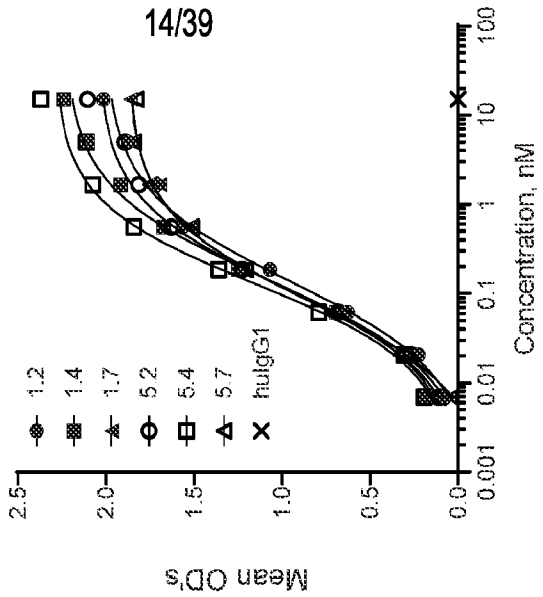


FIG. 23

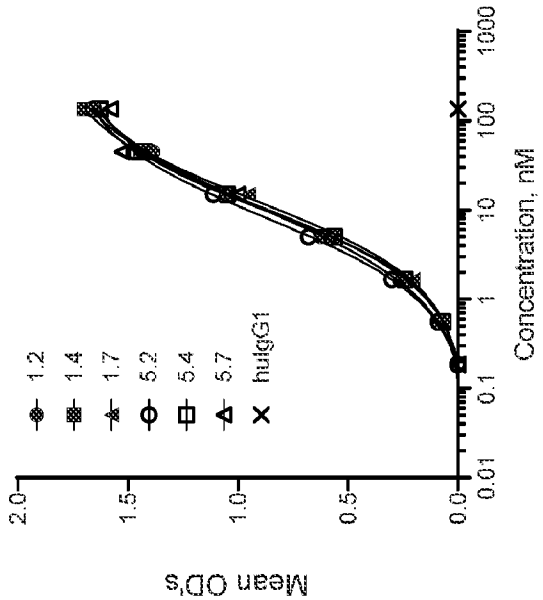


FIG. 22

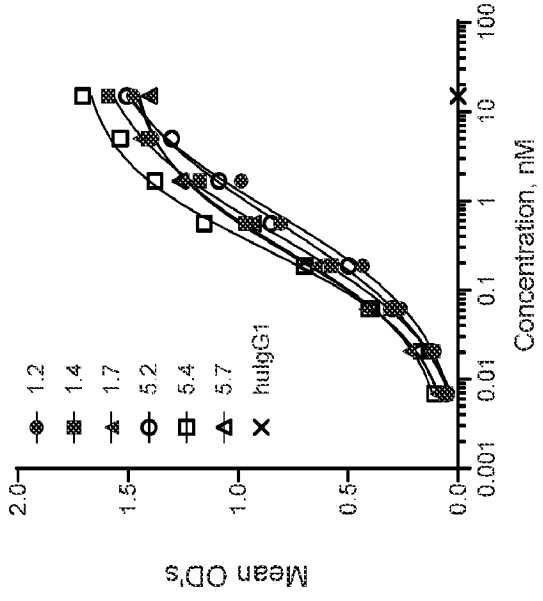


FIG. 25B

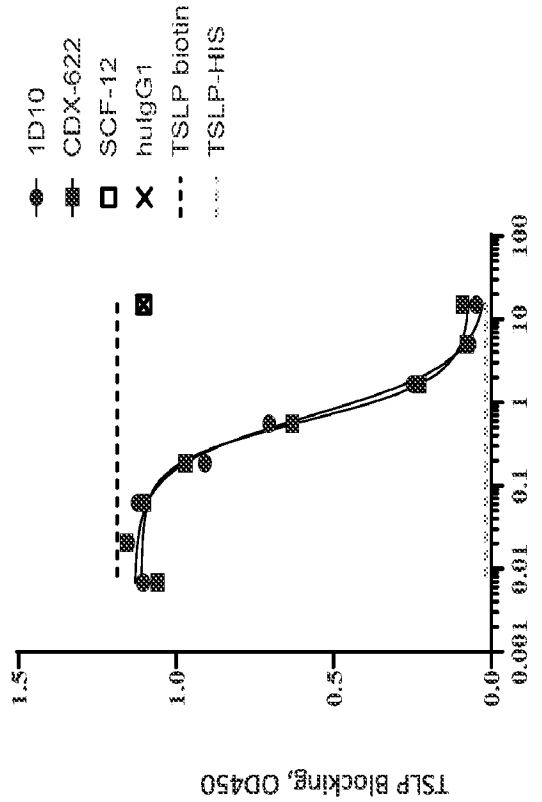
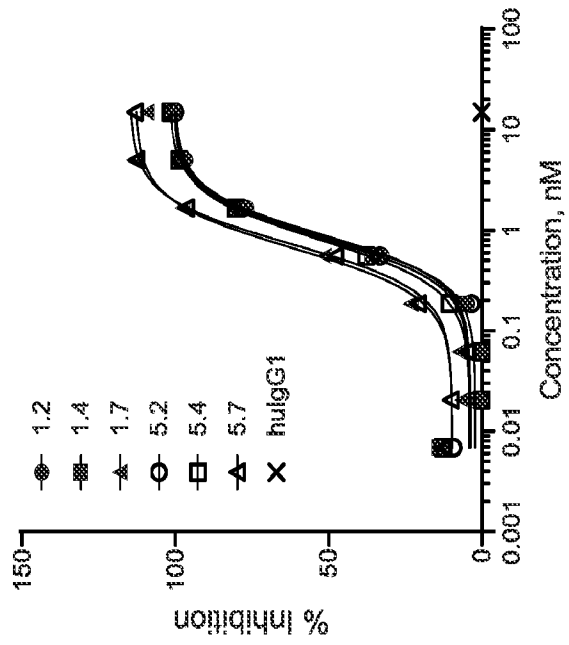


FIG. 25A



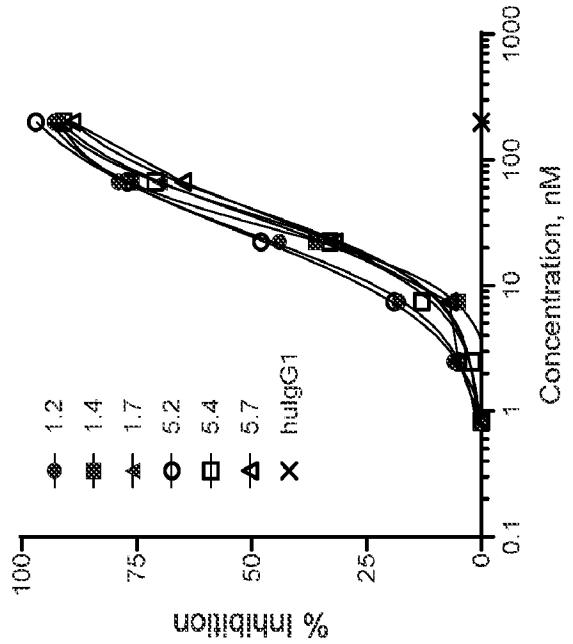

% inhibition
100
75
50
25
0
0.1
1
10
100
1000
Concentration, nM
1.2
1.4
1.7
5.2
5.4
5.7
huIgG1

FIG. 26

FIG. 27B

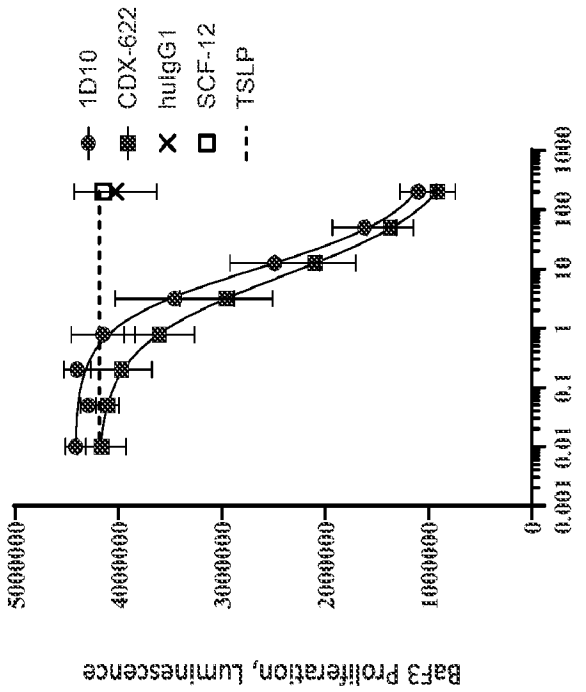


FIG. 27A

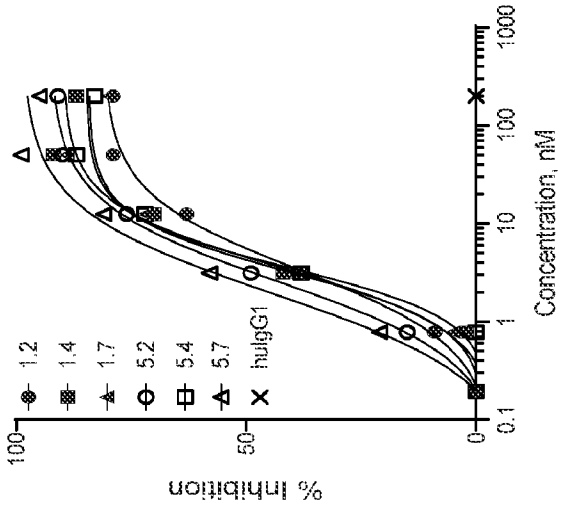


FIG. 28A

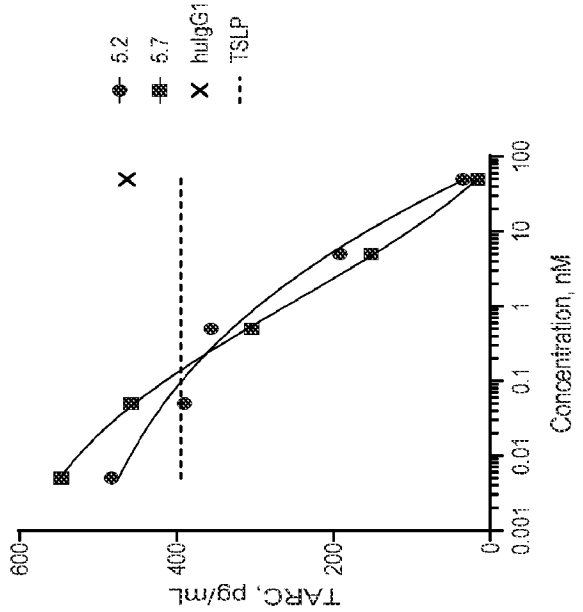


FIG. 28B

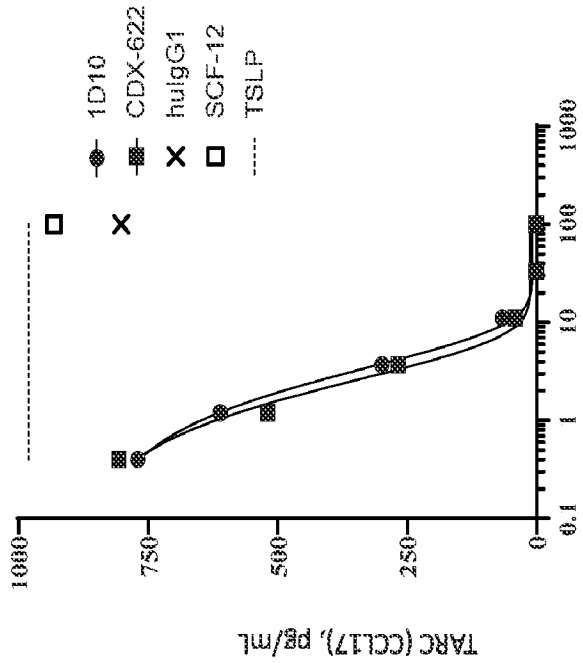


FIG. 29A

Antigen	Construct	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
Human TSLP HIS	5.2	456	1.38E+04	1.27E-04
	5.7	540	1.32E+04	6.87E-05
Human SCF HIS	5.2	9200	1.67E+06	7.60E-04
	5.7	5210	1.87E+06	1.01E-03

human

FIG. 29B

Antigen	Construct	K_D (pM)	k_{on}(1/Ms)	k_{dis}(1/s)
Cyno TSLP HIS	5.2	30900	E+04	E-04
	5.7	33700	E+04	E-05
Cyno SCF HIS	5.2	324	E+06	E-04
	5.7	1160	E+06	E-03

Cyno

FIG. 30

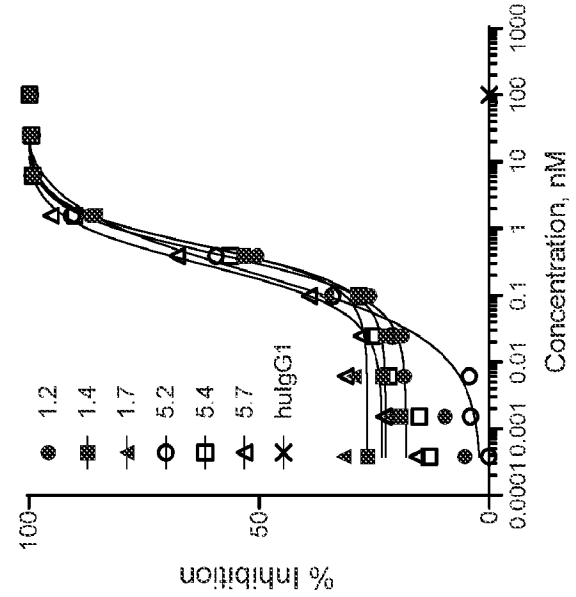


FIG. 31

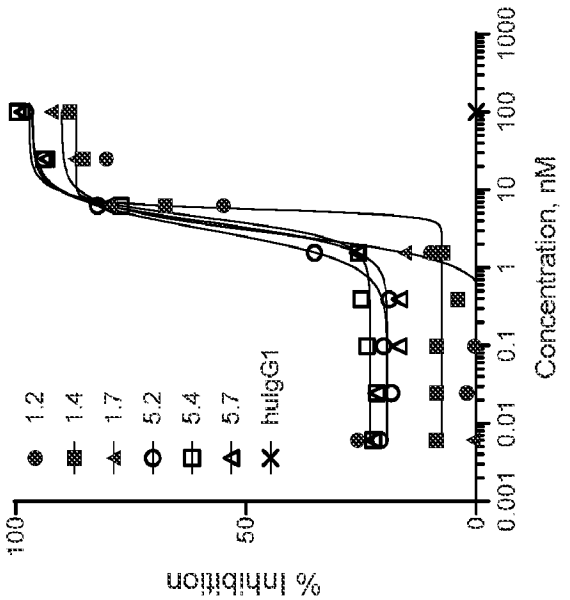


FIG. 32

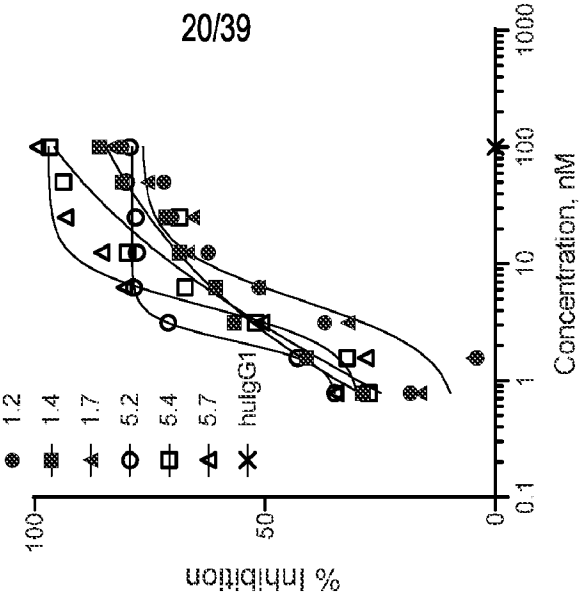


FIG. 33

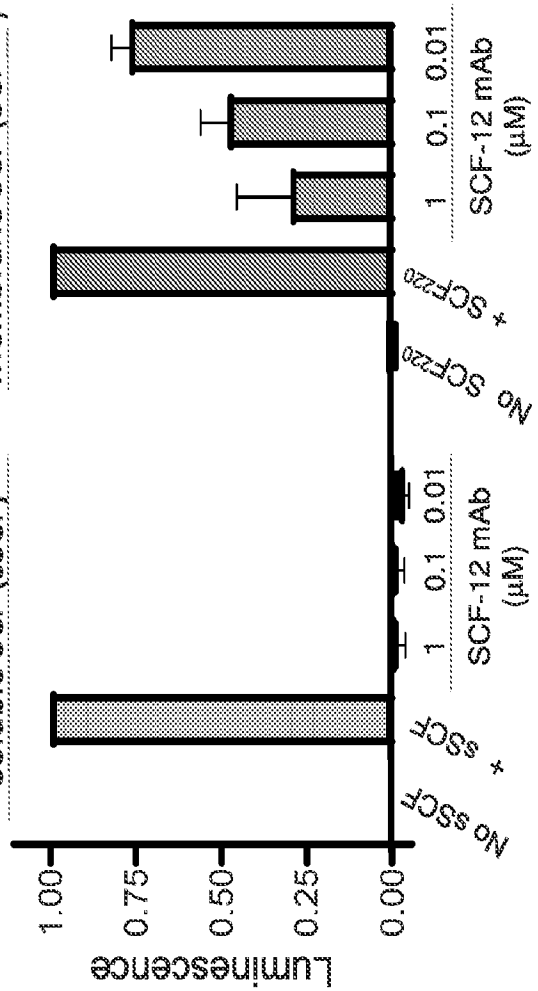

Luminescence
1.00
0.75
0.50
0.25
0.00
Soluble SCF (sSCF)
Membrane SCF (SCF220)
No sSCF
+ sSCF
No SCF220
+ SCF220
SCF-12 mAb (μM)
1
0.1
0.01

FIG. 34B

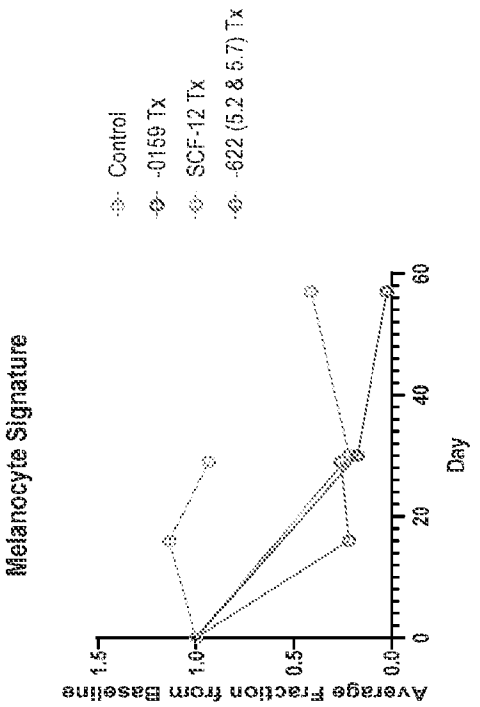
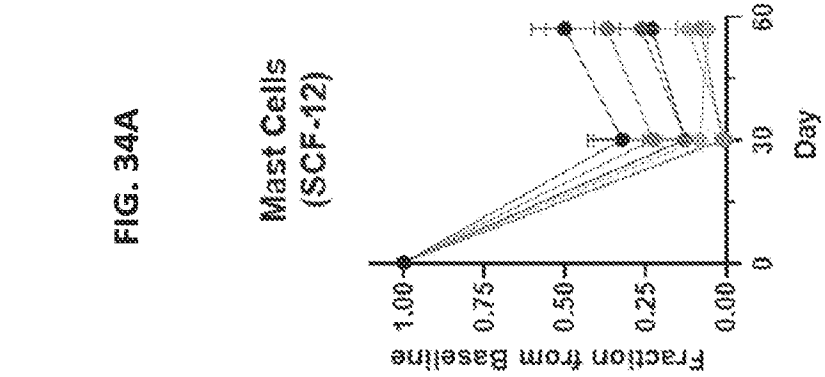


FIG. 34A



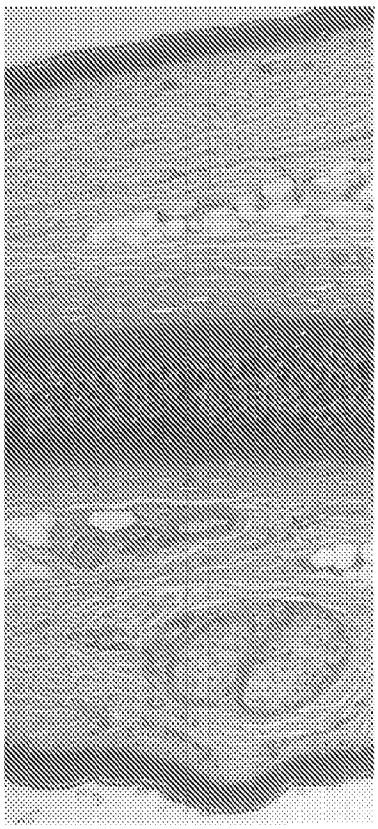


FIG. 35B

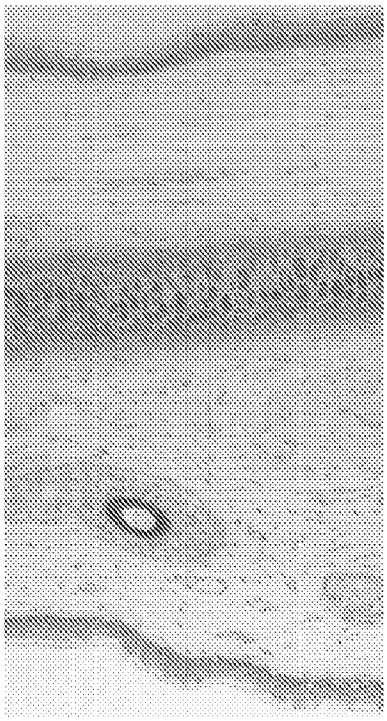


FIG. 35A

Group	% Change D2 to D0	% Change D0 to D57	% Change D2 to D57
mAb12	-36.6	53.6	-2.2

FIG. 36A

Group	Animal	Day2 Average	Day 0 Average	Day 57 Average	% Change D2 to D0	% Change D0 to D57	% Change D2 to D57
mAb12	19-080	130.8	86.4	146.2	-33.9%	69.2%	11.8%
	EC248	116.3	76.3	116.8	-34.4%	53.1%	0.4%
	SBZ429	139.1	81.6	113.1	-41.3%	38.6%	-18.7%

FIG. 36B

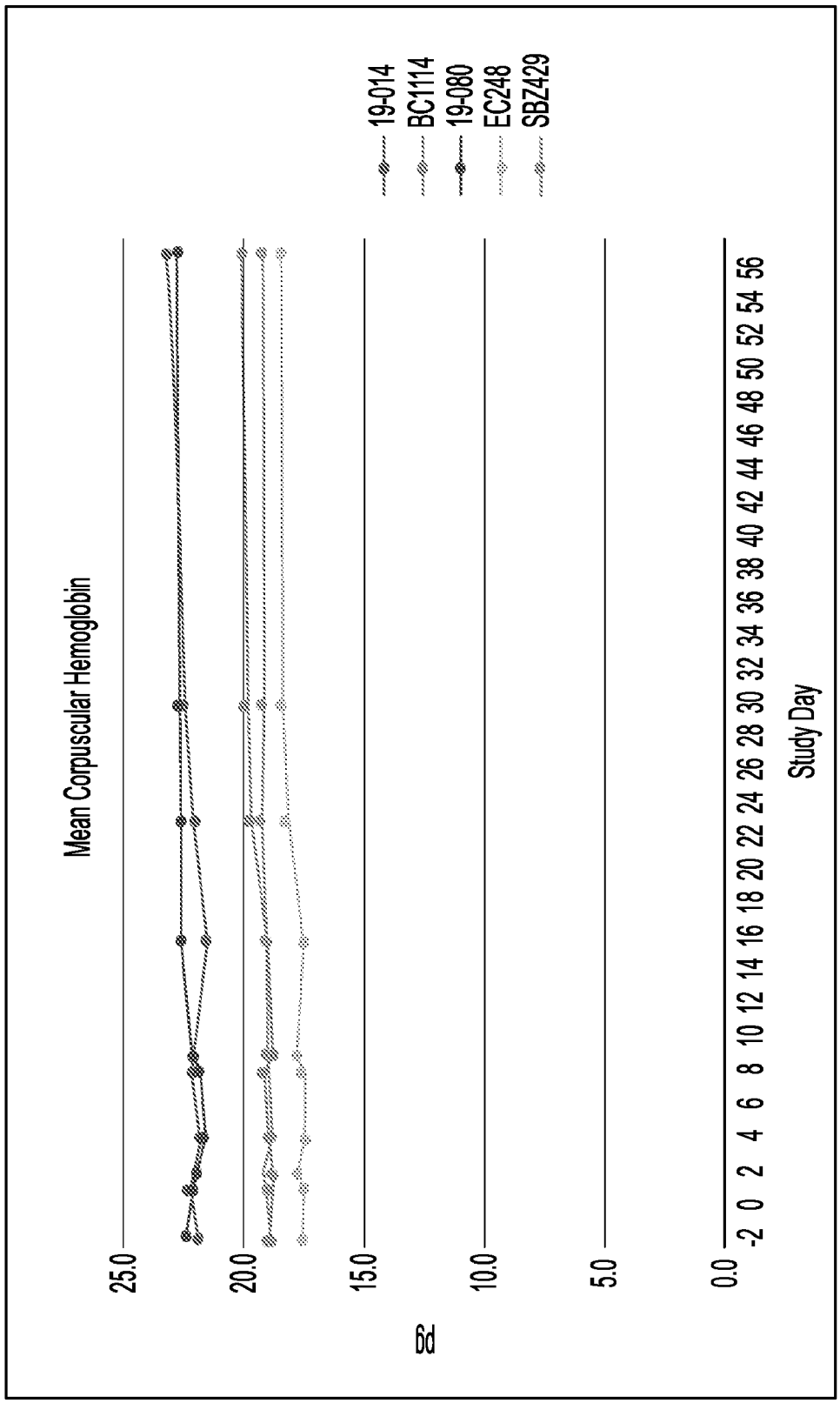

Mean Corpuscular Hemoglobin
25.0
20.0
15.0
10.0
5.0
0.0
-2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56
Study Day
19-014
BC1114
19-080
EC248
SBZ429
6d

FIG. 37A

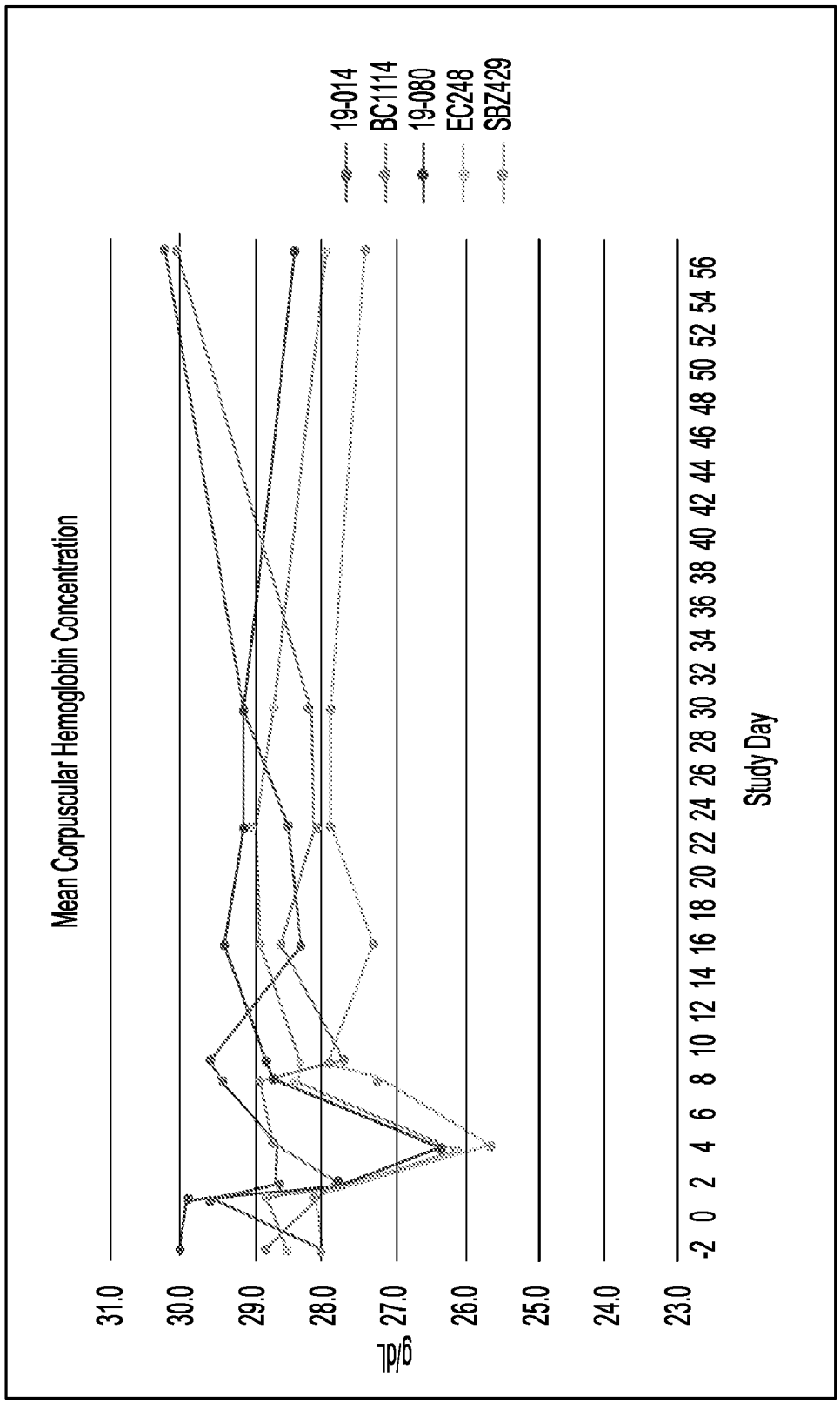

Mean Corpuscular Hemoglobin Concentration
19-014
BC1114
19-080
EC248
SBZ429
g/dL
31.0
30.0
29.0
28.0
27.0
26.0
25.0
24.0
23.0
-2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56
Study Day

FIG. 37B

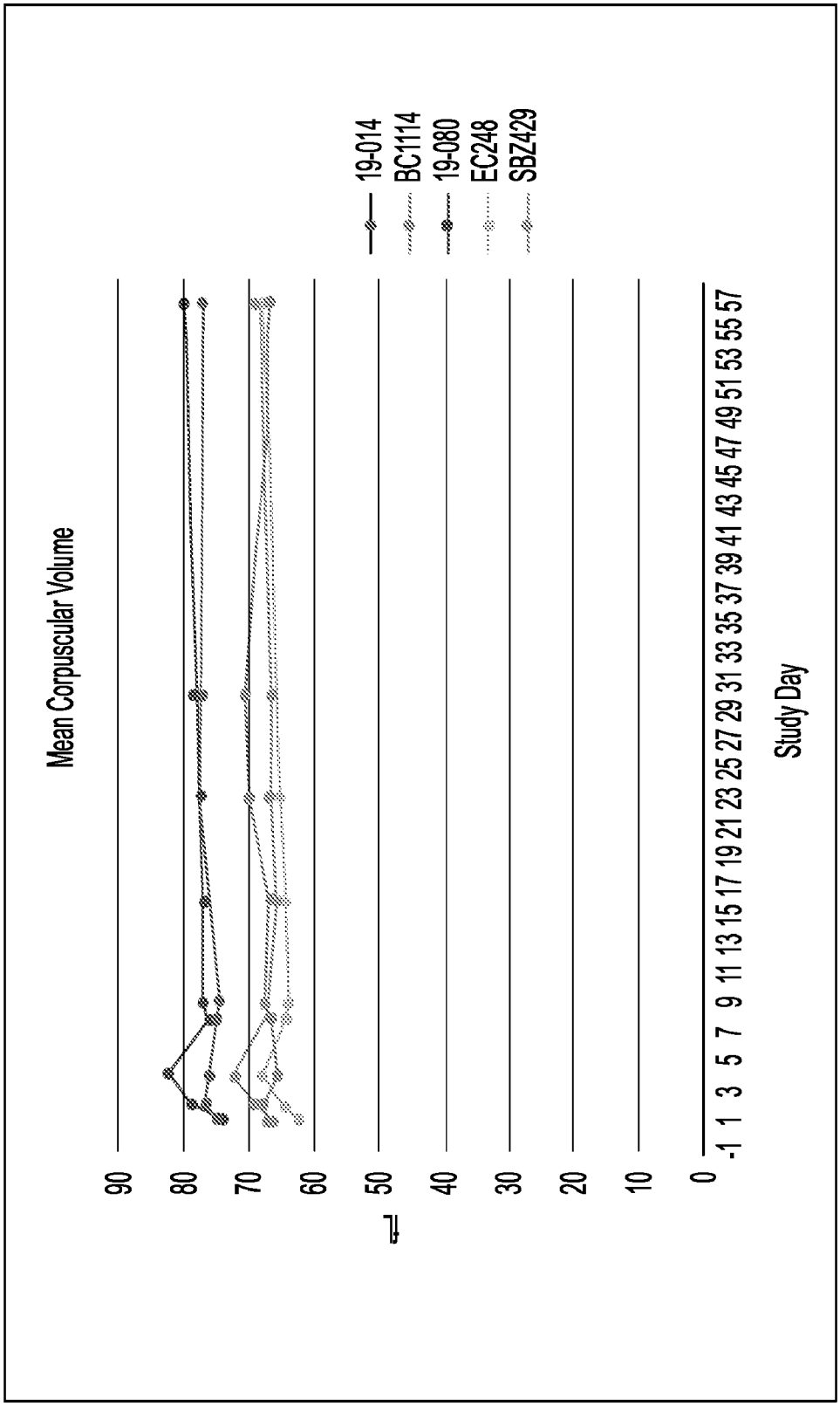

Mean Corpuscular Volume
fL
90
80
70
60
50
40
30
20
10
0
-1 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57
Study Day
19-014
BC1114
19-080
EC248
SBZ429

FIG. 37C

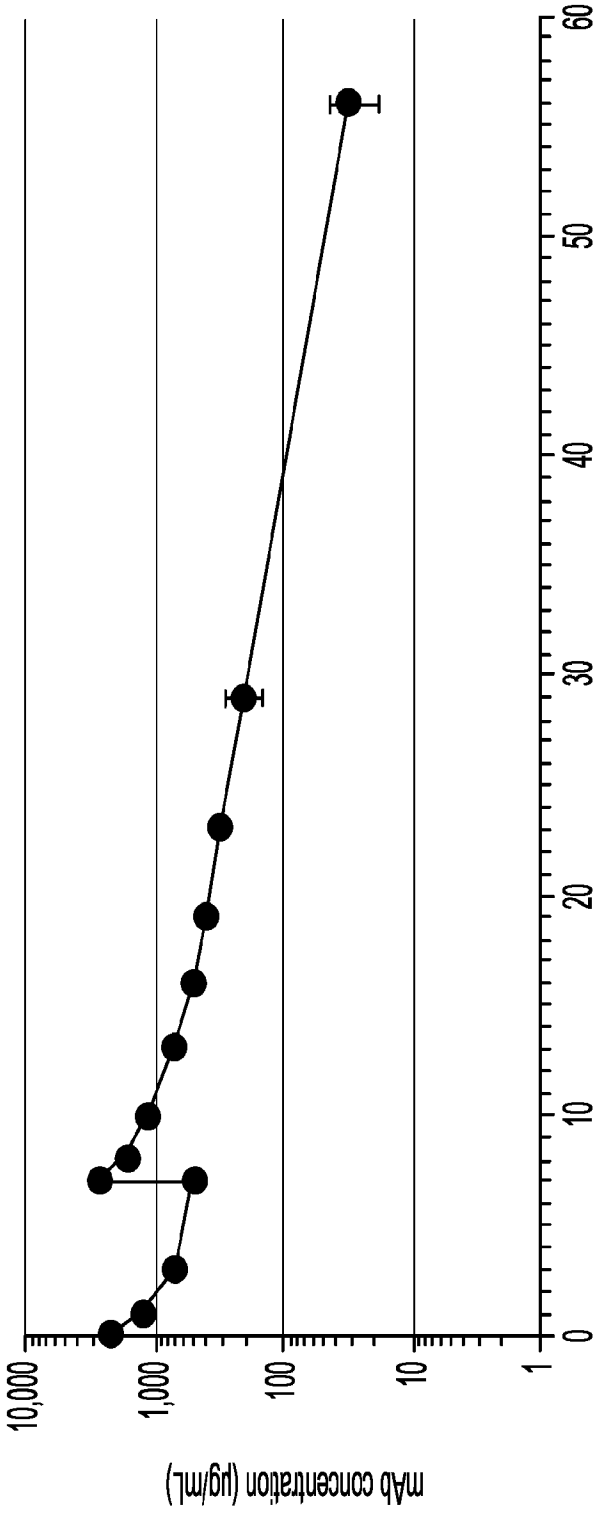

mAb concentration (µg/mL)
10,000
1,000
100
10
1
0
10
20
30
40
50
60
Time (days)

FIG. 38

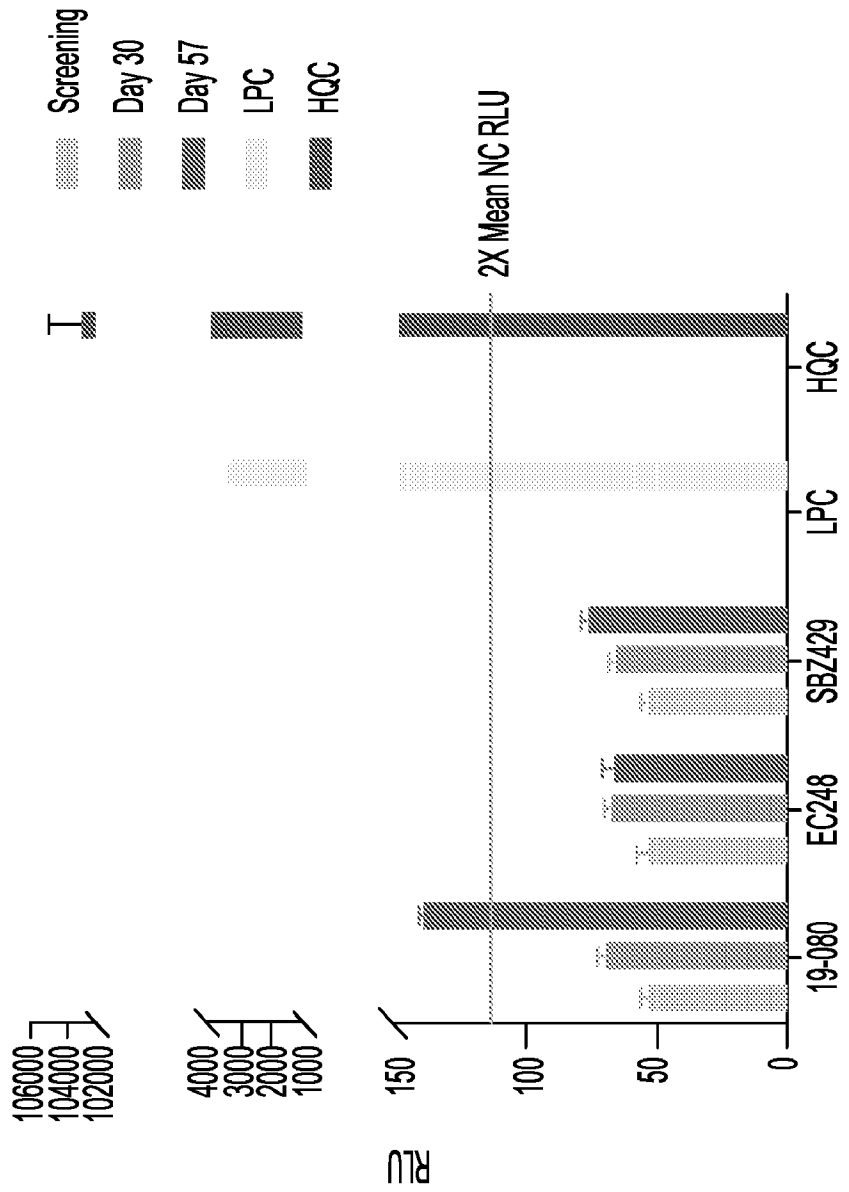

mAb12 ADA
Screening
Day 30
Day 57
LPC
HQC
2X Mean NC RLU
RLU
106000
104000
102000
4000
3000
2000
1000
150
100
50
0
19-080
EC248
SBZ429
LPC
HQC
Group 2 - mab12 infused

FIG. 39

FIG. 40A
White Blood Cells

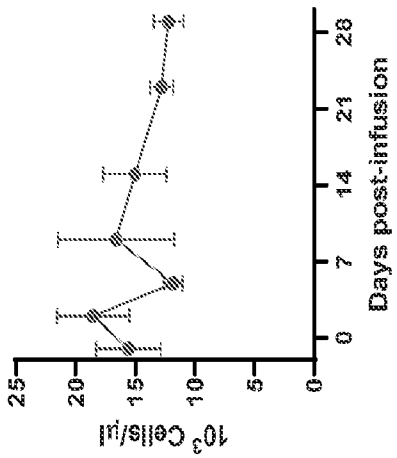


FIG. 40B
Neutrophils

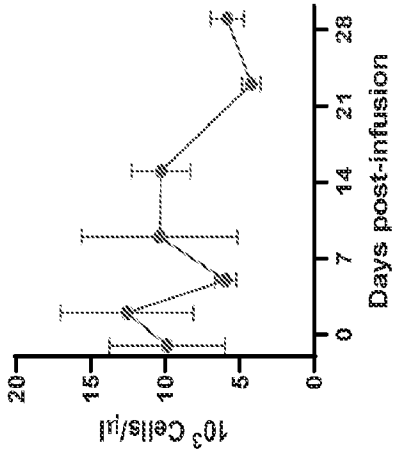


FIG. 40C
Platelets

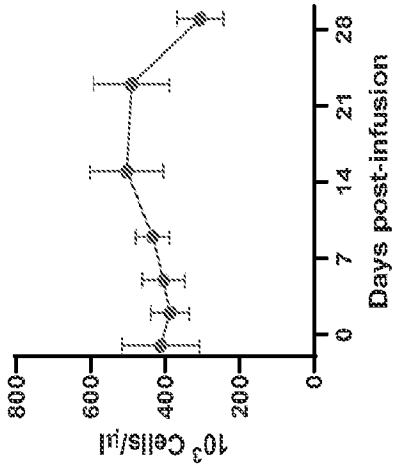


FIG. 40D
Red Blood Cells

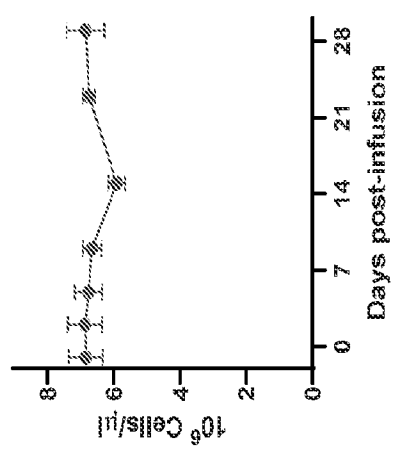


FIG. 40E
Hemoglobin

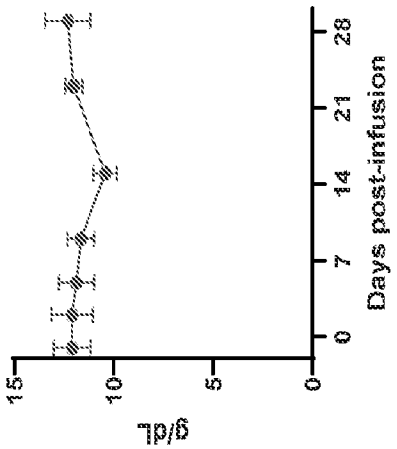
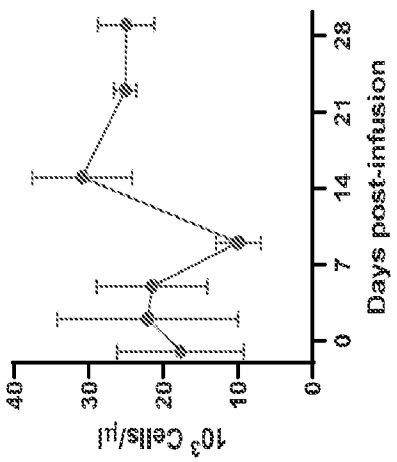


FIG. 40F
Reticulocytes



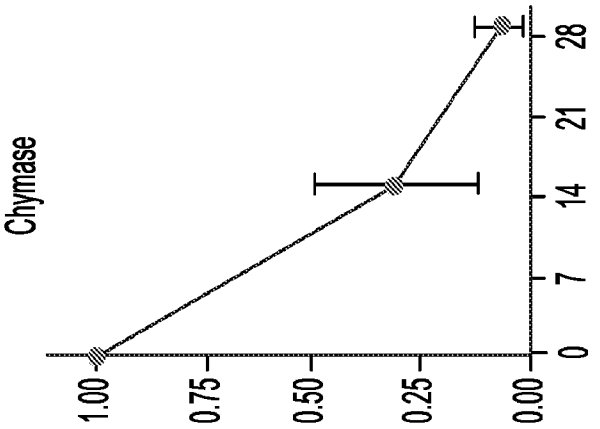


FIG. 41C

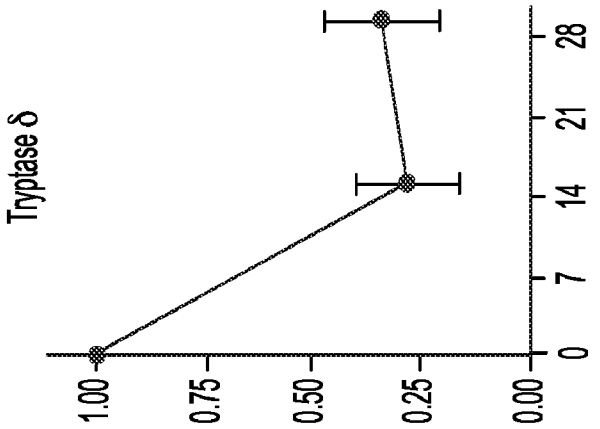


FIG. 41B

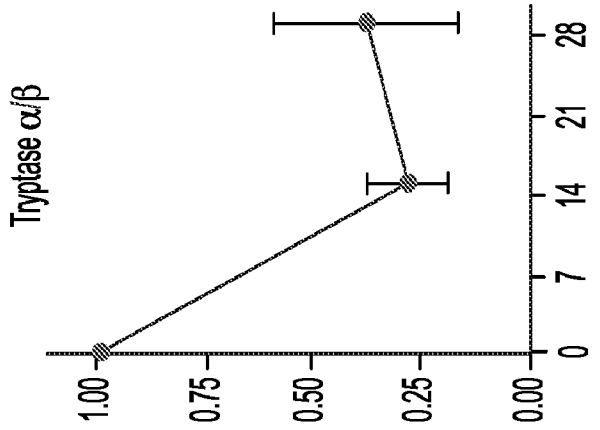


FIG. 41A

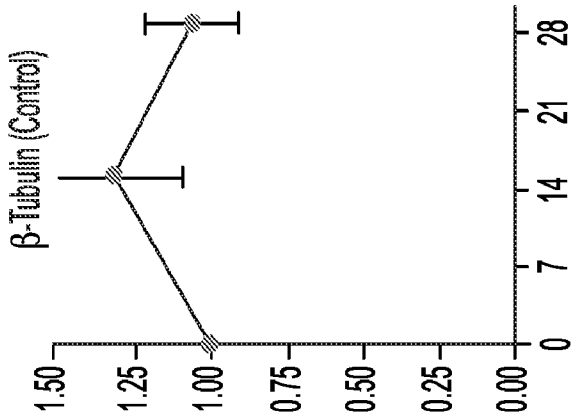


FIG. 41F

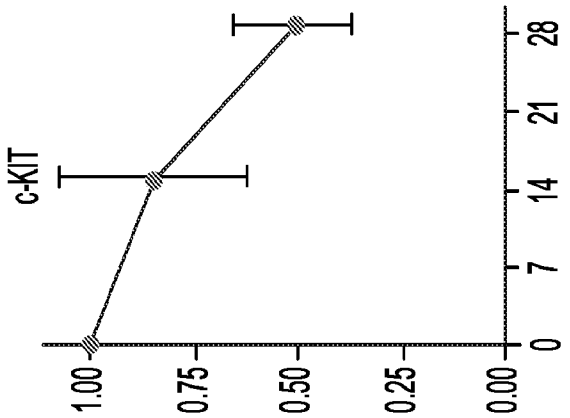


FIG. 41E

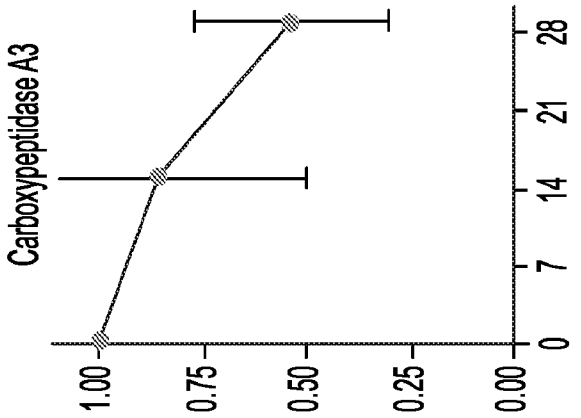


FIG. 41D

FIG. 42

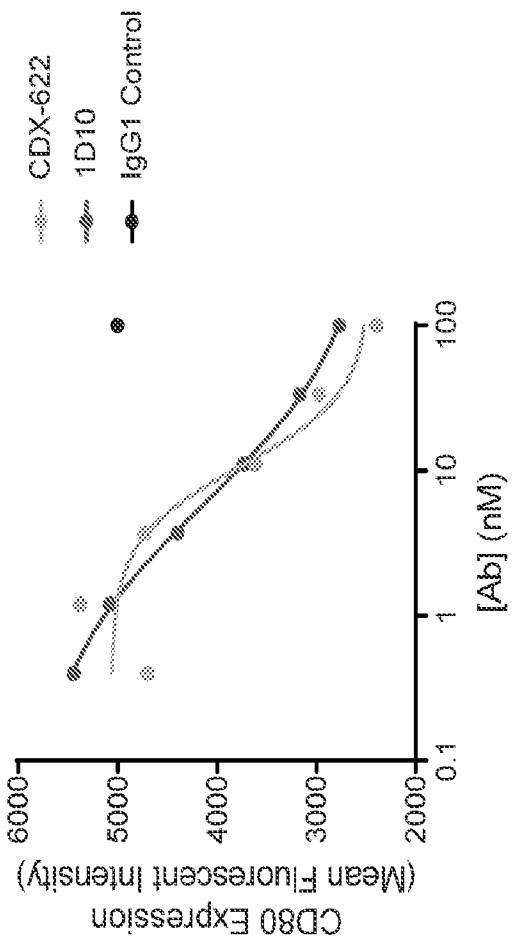

CDX-622
1D10
IgG1 Control
CD80 Expression
(Mean Fluorescent Intensity)
6000
5000
4000
3000
2000
0.1
1
10
100
[Ab] (nM)

FIG. 43

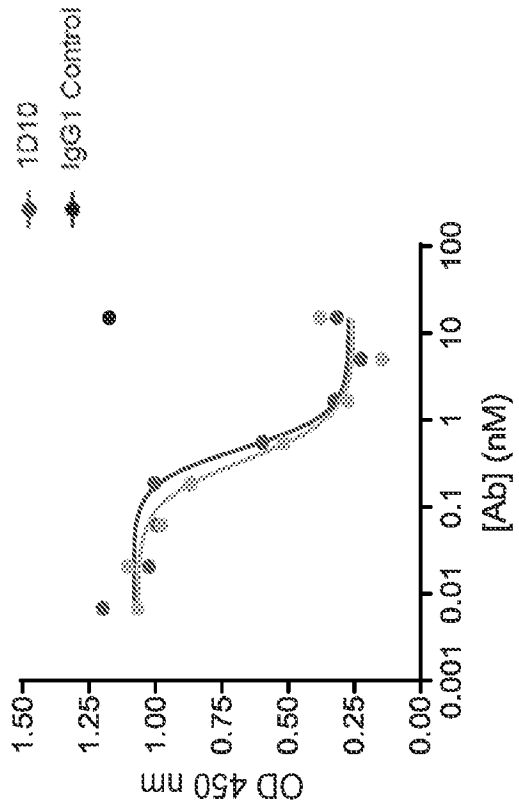
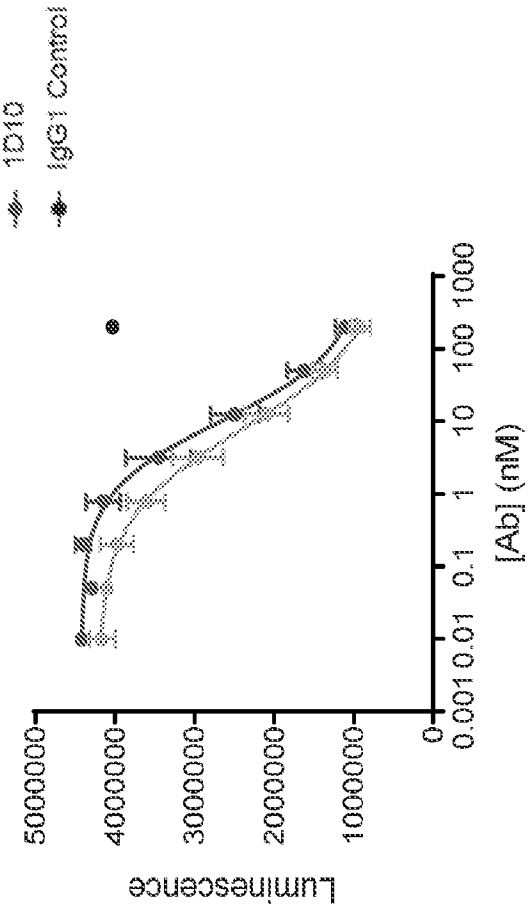

COX-622
1D10
IgG1 Control
OD 450 nm
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0.001
0.01
0.1
1
10
100
[Ab] (nM)

FIG. 44


CDX-622
1D10
IgG1 Control
Luminescence
5000000
4000000
3000000
2000000
1000000
0
0.001 0.01 0.1 1 10 100 1000
[Ab] (nM)

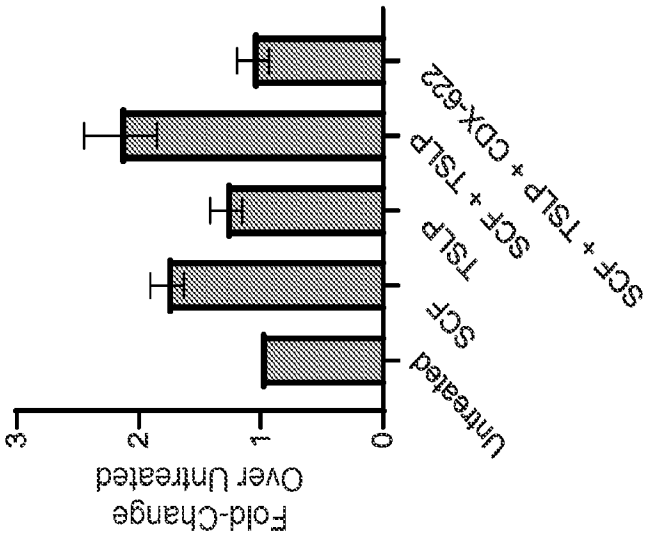

Fold-Change
Over Untreated
0
1
2
3
Untreated
SCF
TSLP
SCF + TSLP
SCF + TSLP + CDX-622

FIG. 45

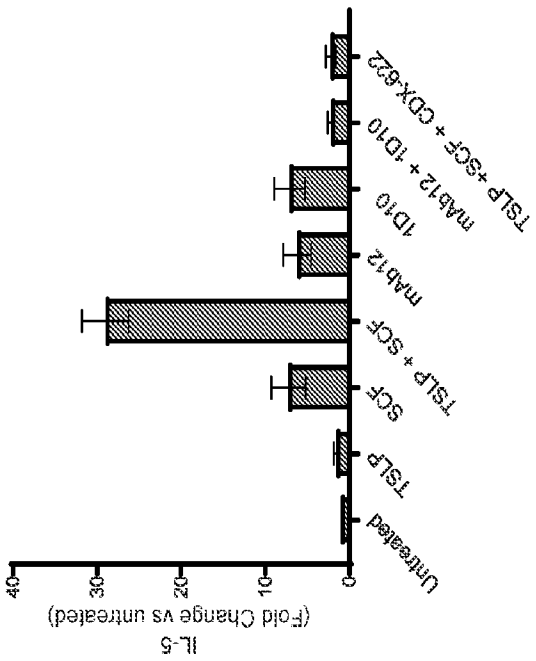
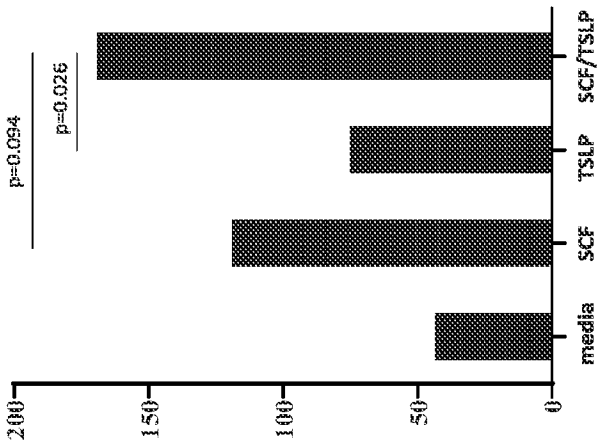

IL-5
(Fold Change vs untreated)
0
10
20
30
40
Untreated
TSLP
SCF
TSLP + SCF
mAb12
1D10
mAb12 + 1D10
TSLP +SCF + CDX-622

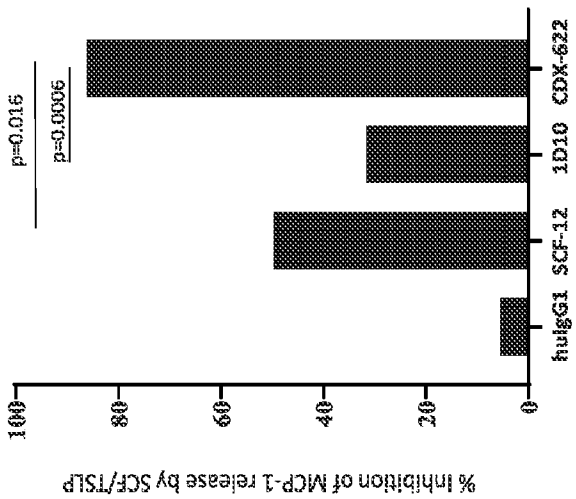
FIG. 46

FIG. 47



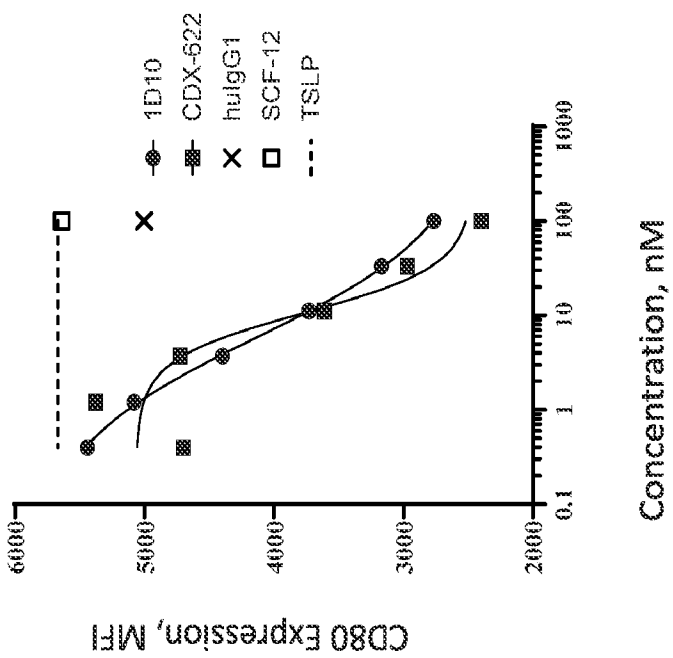
MCP-1 induction with SCF and TSLP

FIG. 48



Simultaneous blockade of SCF and TSLP

FIG. 49


1D10
CDX-622
huIgG1
SCF-12
TSLP
6000
5000
4000
3000
2000
CD80 Expression, MFI
0.1
1
10
100
1000
Concentration, nM