No preclinical results or clinical efficacy, however, has been demonstrated either by using any one of the anti-IL-13/IL-17 DVD antibodies or by proving the concept of targeting both IL-13 and IL-17, in these diseases.

[0012] Therefore, moderate to severe asthmatic patients are still in need of alternative treatment options. Thus, there is a need to identify better therapies for treating asthma and improved methods for understanding how to treat asthma patients.

[0013] Another inflammation disease in the airway idiopathic pulmonary fibrosis (IPF) is a restrictive lung disease characterized by progressive interstitial fibrosis of lung parenchyma, affecting approximately 100,000 patients in the United States (Raghu et al., *Am J Respir Crit Care Med* 174:810-816 (2006)). This interstitial fibrosis associated with IPF leads to progressive loss of lung function, resulting in death due to respiratory failure in most patients. The median survival from the time of diagnosis is 2-3 years (Raghu et al., *Am J Respir Crit Care Med* 183:788-824 (2011)). The etiology and key molecular and pathophysiological drivers of IPF are unknown. The only treatment shown to prolong survival in IPF patients is lung transplantation (Thabut et al., *Annals of internal medicine* 151:767-774 (2009)). Lung transplantation, however, is associated with considerable morbidity. Further, not all IPF patients are appropriate candidates for transplantation, and there is a relative paucity of suitable donor lungs. Despite numerous attempts, no drug therapies to date have been shown to substantially prolong survival in a randomized, placebo-controlled interventional trial in IPF patients, although some interventions have appeared to slow the rate of lung function decline in some patients (Raghu et al., *Am J Respir Crit Care Med* 183:788-824 (2011); Richeldi et al., *The New England J. of Med.* 365:1079-1087 (2011)).

[0014] IPF patients are still in need of alternative treatment options. Thus, there is a need to identify better therapies for treating IPF and improved methods for understanding how to treat IPF patients

[0015] All references cited herein, including patent applications and publications, are incorporated by reference herein in their entirety for any purpose.

SUMMARY

[0016] ~~In one aspect, the invention~~The present disclosure provides methods of treatment using anti-IL-13/IL-17 multispecific antibodies, in particular, bispecific antibodies that bind and inhibit IL-13 and

IL-17AA, AF and FF, and the anti-IL-13/IL-17 multispecific antibodies. The ~~invention~~ disclosure described herein is partly based on the discovery of an improved therapy for asthma using the anti-IL-13/IL-17 bispecific antibodies. In certain embodiments, the asthma is eosinophilic asthma. In certain embodiments, the anti-IL-13/IL-17 bispecific antibody retains the wild-type full-length antibody format, but differs from the wild-type monospecific bivalent antibody in that the bispecific antibody is a monovalent binder to each target. Yet, the bispecific antibody maintains comparable affinity and potency with regard to each target as compared to each of the parent monospecific bivalent antibody. In certain embodiments, the ~~invention~~ disclosure also relates to the surprising findings that the anti-IL-13/IL-17 bispecific antibody was difficult to make as further described herein.

[0017] In one ~~aspect of the invention~~embodiment, the antibodies described herein are provided for use as a medicament. In some embodiments, the antibodies described herein are provided for use in the preparation of a medicament for treating an eosinophilic disorder, an IL-13 mediated disorder, an IL-17 mediated disorder, and/or a respiratory disorder. In some embodiments, the antibodies described herein are provided for use in treating an eosinophilic disorder, an IL-13 mediated disorder, an IL-17 mediated disorder, and/or a respiratory disorder. In some embodiments, use of the antibodies described herein in the manufacture of a medicament for treating an eosinophilic disorder, an IL-13 mediated disorder, an IL-17 mediated disorder, and/or a respiratory disorder is provided. In some embodiments, methods of treating an eosinophilic disorder, an IL-13 mediated disorder, an IL-17 mediated disorder, and/or a respiratory disorder in an individual are provided comprising administering to the individual an effective amount of an antibody described herein. In certain embodiments, the antibodies described herein are provided for use in treating an eosinophilic disorder and a neutrophilic disorder. In certain embodiments, the antibodies described herein are provided for use in treating eosinophilic asthma, neutrophilic asthma, eosinophilic and neutrophilic asthma, mixed asthma and/or mixed granulocytic asthma. In certain embodiments, methods of treating an eosinophilic disorder and a neutrophilic disorder are provided comprising administering to an individual in need thereof an effective amount of an antibody described herein. In certain embodiments, methods of treating eosinophilic asthma, neutrophilic asthma, eosinophilic and neutrophilic asthma, mixed asthma and/or mixed granulocytic asthma are provided comprising administering to an individual in need thereof an effective amount of an antibody described herein.

[0017a] In one aspect, there is provided use of an anti-IL-13/IL-17 antibody in the manufacture of a medicament for treating an eosinophilic disorder in a patient, the anti-IL-13/IL-17 antibody comprising a first half antibody and a second half antibody, wherein the first half antibody comprises a first VH/VL unit that specifically binds to IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20.

[0018] In certain embodiments, a patient suffering from an eosinophilic inflammation or disorder may exhibit elevated level of one or more of the eosinophilic signature genes. In certain embodiments, the patient is identified as an Eosinophilic Inflammation Positive (EIP) patient that shows elevated serum periostin levels and/or elevated levels of one or more selected from CSF1 (macrophage colony stimulating factor 1, Entrez ID 1435), MEIS2 (Meis homeobox 2, Entrez ID 4212), LGALS12 (lectin, galactoside-binding, soluble, 12, Entrez ID 85329), IDO1 (indoleamine 2,3-dioxygenase 1, Entrez ID 3620), THBS4 (thrombospondin 4, Entrez ID 7060), OLIG2 (oligodendrocyte lineage transcription factor 2, Entrez ID 10215), ALOX15 (arachidonate 15-lipoxygenase , Entrez ID 246), SIGLEC8 (sialic acid binding Ig-like lectin 8, Entrez ID 27181), CCL23 (chemokine (C-C motif) ligand 23, Entrez ID 6368), PYROXD2 (pyridine nucleotide-disulphide oxidoreductase domain 2, Entrez ID 84795), HSD3B7 (hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7, Entrez ID 80270), SORD (sorbitol dehydrogenase, Entrez ID 6652), ASB2 (ankyrin repeat and SOCS box containing 2, Entrez ID 51676), CACNG6 (calcium channel, voltage-dependent, gamma subunit 6, Entrez ID 59285), GPR44 (G protein-coupled receptor 44, Entrez ID 11251), MGAT3 (mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase , Entrez ID 4248), SLC47A1 (solute carrier family 47, member 1, Entrez ID 55244), SMPD3 (sphingomyelin phosphodiesterase 3, neutral membrane, Entrez ID 55512), CCR3 (chemokine (C-C motif) receptor 3, Entrez ID 1232), CLC (Charcot-Leyden crystal protein , Entrez ID 1178), CYP4F12 (cytochrome P450, family 4, subfamily F, polypeptide 12, Entrez ID 66002), and ABTB2 (ankyrin repeat and BTB (POZ) domain containing 2, Entrez ID 25841), as compared to a control. Alternatively or additionally, the patient may exhibit elevated levels of one or more of the neutrophilic signature genes such as CXCR1, CXCR2, neutrophil elastase, or CEACAM6. Accordingly, in certain embodiments, the methods provided herein further comprise the step of measuring in the patient the levels of serum periostin and/or one or more of the eosinophil signature genes or one or more of neutrophil signature genes. In certain embodiments, the methods provided herein further comprise the step of measuring in the patient the levels of serum periostin. In certain embodiments, the serum periostin is Total Periostin. In certain embodiments, the methods provided herein further comprise the step of measuring in the patient blood eosinophil counts. In certain embodiments, the methods provided herein further comprise the step of measuring in the patient blood neutrophil counts.

(LAMA), theophylline, and an oral corticosteroids (OCS). In some embodiments, the LABD is selected from budesonide/formoterol fumarate dehydrate (e.g., Symbicort®), fluticasone propionate and salmeterol (e.g., Advair®), arformoterol tartrate (e.g., Brovana®), formoterol fumarate (e.g., Foradil®, Performist®), and salmeterol xinafoate (e.g., Serevent®). In certain embodiments, the method of treating asthma comprises administering to a patient the anti-IL-13/IL-17 multispecific antibody described herein and further comprises administering to the patient a corticosteroid.

[0023] In one ~~aspect of the invention~~embodiment, multispecific antibodies are provided, wherein the antibodies comprise a first half antibody and a second half antibody, wherein the first half-antibody comprises a first VH/VL unit that specifically binds IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13. In some embodiments, the first half antibody does not bind IL-13, and wherein the second half antibody does not bind IL-17. In some embodiments, a multispecific antibody provided herein binds to IL-17AA and IL-17AF, inhibits IL-17AA- and IL-17AF-induced activity, and/or inhibits IL-13-induced activity. In some embodiments, the multispecific antibody further binds to IL-17FF. In certain embodiments, the multispecific antibody provided herein binds to IL-17AA and IL-17AF, inhibits IL-17AA- and IL-17AF – induced activity, and inhibits IL-13-induced activity. In certain particular embodiments, the multispecific antibody provided herein binds to IL-17AA, IL-17AF and IL-17FF, inhibits IL-17AA- , IL-17AF, and IL-17FF – induced activity, and inhibits IL-13-induced activity. In certain such embodiments, the anti-IL-13/IL-17AA, AF and FF bispecific antibody advantageously block activities induced by all of IL-17A and F cytokines as opposed to activities induced by IL-17A or IL-17F alone. In some embodiments, the IL-17AA-induced activity is IL-17AA-induced gene expression and/or proliferation of cells *in vivo* or *in vitro*. In some embodiments, the IL-17AF-induced activity is IL-17AF-induced gene expression and/or proliferation of cells *in vivo* or *in vitro*. In some embodiments, the IL-13-induced activity is IL-13-induced gene expression and/or proliferation of cells *in vivo* or *in vitro*. In some embodiments, a multispecific antibody provided herein binds to IL-17AA, IL-17AF, and IL-17FF. In some embodiments, a multispecific antibody provided herein further inhibits IL-17FF-induced activity. In some such embodiments, the IL-17FF-induced activity is IL-17FF-induced gene expressing and/or proliferation of cells *in vivo* or *in vitro*. In some embodiments, a multispecific antibody provided herein does not inhibit binding of IL-13 to IL-13Rα1.

the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the first half antibody does not bind IL-13, and the second half antibody does not bind IL-17.

[0036] In ~~some embodiments~~one aspect, a multispecific antibody is provided, comprising a first half antibody and a second half antibody, wherein the first half-antibody comprises a first VH/VL unit that specifically binds IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the first half antibody does not bind IL-13, and the second half antibody does not bind IL-17.

[0037] In some embodiments, an anti-IL13/IL-17 bispecific antibody is provided, comprising a first half-antibody and a second half-antibody, wherein the first half-antibody comprises a first VH/VL unit and the second half-antibody comprises a second VH/VL unit, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20. In certain

can form pyroglutamate and C-terminal lysine residues can be clipped during manufacturing processes. Thus, in certain embodiments, the N-terminal glutamine may be optionally removed. In addition, heavy chains with or without the C-terminal lysine residues are both contemplated by the current ~~invention~~disclosure.

[0044] In one aspect, there is provided an isolated nucleic acid encoding: (a) any of the multispecific antibodies described herein; (b) the first VH/VL unit of any of the multispecific antibodies described herein; or (c) the second VH/VL unit of any of the multispecific antibodies described herein. In some embodiments, an isolated nucleic acid is provided that encodes any of the multispecific antibodies or isolated antibodies described herein. In some embodiments, an isolated nucleic acid is provided that encodes a first VH/VL unit of any of the multispecific antibodies described herein. In some embodiments, an isolated nucleic acid is provided that encodes a second VH/VL unit of any of the multispecific antibodies described herein. In ~~some embodiments~~one aspect, a host cell is provided that comprises the isolated nucleic acid(s). In some embodiments, the host cell is a prokaryotic cell or a eukaryotic cell. In some embodiments, the host cell is an *E. coli* cell or a CHO cell. In certain embodiments, the multispecific antibody comprises a first VH/VL unit and a second VH/VL unit, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14. In ~~some embodiments~~one aspect, a method of producing an antibody is provided comprising culturing the host cell as described herein under conditions sufficient to produce the antibody. In certain embodiments, the host cell is an *E. coli* cell. In some embodiments, the host cell is an E. coli cell, and the multispecific antibody is aglycosylated. In certain embodiments, the method further comprises recovering the half-antibody or multispecific antibody.

[0044a] In one aspect, there is provided an isolated nucleic acid comprising: a) the sequence of SEQ ID NO: 107; b) the sequence of SEQ ID NO: 108; or c) the sequence of (a) and the sequence of (b). In one aspect, there is provided an isolated nucleic acid comprising: a) the sequence of SEQ ID NO: 105; b) the sequence of SEQ ID NO: 106; or c) the sequence of (a) and the sequence of (b). In one aspect, there is provided an isolated nucleic acid comprising: a) the sequence of SEQ ID NO: 103; b) the sequence of SEQ ID NO: 104; or c) the sequence of (a) and the sequence of (b). In one aspect, there is provided an isolated nucleic acid comprising: a) the sequence of SEQ ID NO: 99 or 101; b) the sequence of SEQ ID NO: 100 or 102; or c) the sequence of (a) and the sequence of (b).

[0045] In some embodiments, an isolated nucleic acid is provided, comprising (a) a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 107 or 103 or 118; (b) a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 108 or 104; or (c) the sequence of (a) and the sequence of (b). In some embodiments, an isolated nucleic acid is provided, comprising (a) a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 105 or 99 or 119; (b) a sequence that is at least 90%,

at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 106 or 100; or (c) the sequence of (a) and the sequence of (b). In some embodiments, a host cell comprising a first nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 107 or 103 or 108 and a second nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 108 or 104 is provided, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules. In some embodiments, a host cell comprising a first nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 105 or 99 or 119 and a second nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 106 or 100 is provided, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules. In one aspect, there is provided a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules. In another aspect, there is provided a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99, or 101 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules. In some embodiments, the host cell is a prokaryotic cell or a eukaryotic cell. In some embodiments, the prokaryotic cell is an *E. coli* cell and wherein the eukaryotic cell is a CHO cell. In ~~some embodiments~~one aspect, a method of producing a half antibody or a multispecific antibody is provided, comprising culturing the host cell under conditions sufficient to produce the half antibody or multispecific antibody. In some embodiments, the method further comprises recovering the half antibody or multispecific antibody.

[0045a] In one aspect, there is provided a method of producing a multispecific antibody comprising (i) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 99, 101 or 105 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a first half antibody, and (ii) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a second half antibody. In another aspect, there is provided a method of producing a multispecific antibody comprising (a) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99 or 101 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a first half antibody, and (b) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a second half antibody; (c) recovering the first half antibody and recovering the second half antibody; and (d) forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce the multispecific antibody.

[0046] In some embodiments, a method of producing a multispecific antibody is provided, comprising (i) culturing a first host cell comprising a first nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 105 or 99 and a second nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 106 or 100 to produce a first half antibody, and (ii) culturing a second host cell comprising a first

nucleic acid comprising a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 107 or 103 or 118 and a second nucleic acid comprising the sequence a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, to produce a second half antibody. In some embodiments, a method of producing a multispecific antibody is provided, comprising (i) culturing a first host cell comprising a first nucleic acid comprising a sequence of SEQ ID NO: 105, 99,119 or 101 and a second nucleic acid comprising a sequence of SEQ ID NO: 106, 100 or 102 to produce a first half antibody, and (ii) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 or 118 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, to produce a second half antibody. In some embodiments, a method of producing a multispecific antibody is provided, comprising (i) culturing a first host cell comprising a first nucleic acid comprising a sequence of SEQ ID NO: 105 or 99 or 119 and a second nucleic acid comprising a sequence of SEQ ID NO: 106 or 100 to produce a first half antibody, and (ii) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 or 118 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, to produce a second half antibody. In some embodiments, the method further comprises recovering the first half antibody and recovering the second half antibody. In some embodiments, the method comprises forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce a multispecific antibody. In some ~~embodiments~~aspects, a multispecific antibody produced by the methods described herein is provided. In certain embodiments, the multispecific antibody comprises a first VH/VL unit and a second VH/VL unit, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14. In certain

embodiments, the same or different nucleic acid molecules can be one or more vectors, in particular expression vectors.

[0047] In some ~~embodiments~~aspects, an immunoconjugate is provided, wherein the immunoconjugate comprises any of the multispecific antibodies or isolated antibodies described herein and a cytotoxic agent.

[0048] In some ~~embodiments~~aspects, pharmaceutical formulations are provided, comprising any of the multispecific antibodies or isolated antibodies described herein and a pharmaceutically acceptable carrier.

[0049]

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] **Fig. 1A-C** show pairwise comparisons of bronchial biopsy tissue counts for (A) neutrophils and eosinophils, (B) eosinophils and IL-17A+ cells, and (C) IL-17F+ and IL-17A+ cells, as described in Example 1.

[0051] **Fig. 2A-B** show (A) IL-17A and (B) IL-17F expression in matched biopsy neutrophil samples with respect to undetectable (less than the lower limit of quantitation; <LLOQ) and detectable (greater than or equal to the lower limit of quantitation, ≥LLOQ), as described in Example 2.

[0052] **Fig. 3** shows two-way hierarchical clustering of certain neutrophil-associated gene expression from microarray analyses of UK cohort bronchial biopsies, as described in Example 2. Open circles correspond asthmatics not taking steroids. Closed circles indicate asthmatics taking steroids (inhaled corticosteroids (ICS) or oral corticosteroids (OCS)).

[0053] **Fig. 4A-B** show (A) CXCL1 levels in healthy controls and moderate-severe asthmatics from the BOBCAT study, and (B) plasma CXCL1 levels in asthmatic patients with serum periostin levels below 50 ng/ml or equal to or above 50 ng/ml, as described in Example 3. CXCL1 levels above 160 pg/ml (dashed line) tend to have elevated serum periostin levels (p=0.02 by Fisher's exact test).

[0054] **Fig. 5** shows serum periostin levels in the UK Cohort with undetectable (<LLOQ) or detectable (≥LLOQ) IL-17A expression in matching samples, as described in Example 3. Serum periostin is elevated in subjects with detectable bronchial biopsy IL-17A mRNA (P=0.03, Kruskal-Wallis).

[0055] **Fig. 6A-D** show (A, C) eosinophil numbers and (B, D) neutrophil numbers in bronchoalveolar lavage (BAL; A, B) and blood (C, D) in a mouse house dust mite asthma

WHAT IS CLAIMED IS:

1. A method of treating an eosinophilic disorder in a patient comprising administering to the patient an effective amount of an anti-IL-13/IL-17 antibody comprising a first half antibody and a second half antibody, wherein the first half antibody comprises a first VH/VL unit that specifically binds to IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20.

2. The method of claim 1, wherein the first VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 14.

3. The method of claim 1 or 2, wherein the first VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 14.

4. The method of any one of the preceding claims, wherein the first VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 14

5. The method of any one of the preceding claims, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14.

6. The method of any one of the preceding claims, wherein the antibody is an IgG antibody.

7. The method of any one of the preceding claims, wherein the antibody is an IgG1 or IgG4 antibody.

8. The method of any one of the preceding claims, wherein the antibody is an IgG4 antibody.

9. The method of any one of preceding claims wherein the first half antibody comprises a first heavy chain comprising the sequence of SEQ ID NO: 72, and a first light chain comprising the sequence of SEQ ID NO: 73, and wherein the second half antibody comprises a second heavy chain comprising the sequence of SEQ ID NO: 21, and a second light chain comprising the sequence of SEQ ID NO: 22.

10. The method of any one of the preceding claims, wherein the eosinophilic disorder is asthma.

11. The method of any one of the preceding claims, wherein the eosinophilic disorder is moderate to severe asthma.

12. The method of any one of the preceding claims, wherein the asthma is uncontrolled on a corticosteroid.

13. The method of any one of the preceding claims, further comprising administering to the patient a corticosteroid.

14. The method of claim 13, wherein the corticosteroid is an inhaled corticosteroid.

15. The method of any one of the preceding claims, wherein the patient has been determined to have a serum periostin level of 20 ng/ml or higher.

16. The method of any one of the preceding claims, wherein the patient has been determined to have a serum periostin level of 50 ng/ml or higher.

17. The method of claim 15 or 16, wherein the serum periostin level is determined by ELISA.

18. The method of any one of claims 15-17, wherein the serum periostin level is determined by the E4 assay or ELECSYS® periostin assay.

19. The method of any one of claims 15-18, wherein the serum periostin is Total Periostin.

20. The method of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 150/μl.

21. The method of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 200/μl.

22. The method of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 300/μl.

23. A multispecific antibody comprising a first half antibody and a second half antibody, wherein the first half antibody comprises a first VH/VL unit that specifically binds to IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20.

24. The multispecific antibody of claim 23, wherein the first VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 95% sequence

identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 14.

25. The multispecific antibody of claim 23 or 24, wherein the first VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 14.

26. The multispecific antibody of any one of claims 23-25, wherein the first VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 14

27. The multispecific antibody of any one of claims 23-26, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14.

28. The multispecific antibody of any one of claims 23-27, wherein the antibody is an IgG antibody.

29. The multispecific antibody of any one of claims 23-28, wherein the antibody is an IgG1 or IgG4 antibody.

30. The multispecific antibody of any one of claims 23-29, wherein the antibody is an IgG4 antibody.

31. The multispecific antibody of any one of claims 23-30 wherein the first half antibody comprises a first heavy chain comprising the sequence of SEQ ID NO: 72, and a first light chain comprising the sequence of SEQ ID NO: 73, and wherein the second half antibody comprises a second heavy chain comprising the sequence of SEQ ID NO: 21, and a second light chain comprising the sequence of SEQ ID NO: 22.

32. An isolated nucleic acid encoding:

(a) the multispecific antibody of any one of claims 23-31;

(b) the first VH/VL unit of the multispecific antibody of any one of claims 23-31; or

(c) the second VH/VL unit of the multispecific antibody of any one of claims 23-31.

33. A host cell comprising the nucleic acid of claim 32.

34. The host cell of claim 33, wherein the host cell is a prokaryotic cell preferably an *E. coli* cell.

35. The host cell of claim 33, wherein the host cell is a eukaryotic cell preferably a CHO cell.

36. The host cell of claim 33 or 34, wherein the host cell is an *E. coli* cell.

37. A method of producing an antibody comprising culturing the host cell of any one of claims 33-36 under conditions sufficient to produce the antibody.

38. The method of claim 37, further comprising the step of recovering the antibody.

39. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 107;

b) the sequence of SEQ ID NO: 108; or

c) the sequence of (a) and the sequence of (b).

40. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 105;

b) the sequence of SEQ ID NO: 106; or

c) the sequence of (a) and the sequence of (b).

41. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 103;

b) the sequence of SEQ ID NO: 104; or

c) the sequence of (a) and the sequence of (b).

42. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 99 or 101;

b) the sequence of SEQ ID NO: 100 or 102; or

c) the sequence of (a) and the sequence of (b).

43. A host cell comprising the nucleic acid of claim 39 or 41.

44. A host cell comprising the nucleic acid of claim 40 or 42.

45. A host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules.

46. A host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99, or 101 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules.

47. The host cell of any one of claims 43-46, wherein the host cell is a prokaryotic cell.

48. The host cell of any one of claims 43-46, wherein the host cell is a eukaryotic cell preferably a CHO cell.

49. The host cell of claim 47, wherein the host cell is an *E. coli* cell.

50. A method of producing a half antibody or a multispecific antibody comprising culturing the host cell of any one of claims 43-49 under conditions sufficient to produce the half antibody or multispecific antibody.

51. The method of claim 50, further comprising recovering the half antibody or multispecific antibody.

52. A method of producing a multispecific antibody comprising (i) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 99, 101 or 105 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a first half antibody, and (ii) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a second half antibody.

53. The method of claim 52, comprising recovering the first half antibody and recovering the second half antibody.

54. The method of claim 52 or 53, comprising forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce a multispecific antibody.

55. The method of claim 54, further comprising the step of recovering the multispecific antibody.

56. A method of producing a multispecific antibody comprising (a) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99 or 101 and a

second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a first half antibody, and (b) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a second half antibody; (c) recovering the first half antibody and recovering the second half antibody; and (d) forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce the multispecific antibody.

57. The method of claim 56, further comprising the step of recovering the multispecific antibody.

58. A multispecific antibody produced by the methods of any one of claims 37-38 and 50-57.

59. An immunoconjugate comprising the antibody of any one of claims 23 to 31 and 58 and a cytotoxic agent.

60. A pharmaceutical formulation comprising the antibody of any one of claims 23-31 and 58 and a pharmaceutically acceptable carrier.

WHAT IS CLAIMED IS:

1. Use of an anti-IL-13/IL-17 antibody in the manufacture of a medicament for treating an eosinophilic disorder in a patient, the anti-IL-13/IL-17 antibody comprising a first half antibody and a second half antibody, wherein the first half antibody comprises a first VH/VL unit that specifically binds to IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20.

2. The use of claim 1, wherein the first VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 14.

3. The use of claim 1 or 2, wherein the first VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 14.

4. The use of any one of the preceding claims, wherein the first VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 39

and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 14

5. The use of any one of the preceding claims, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14.

6. The use of any one of the preceding claims, wherein the antibody is an IgG antibody.

7. The use of any one of the preceding claims, wherein the antibody is an IgG1 or IgG4 antibody.

8. The use of any one of the preceding claims, wherein the antibody is an IgG4 antibody.

9. The use of any one of preceding claims wherein the first half antibody comprises a first heavy chain comprising the sequence of SEQ ID NO: 72, and a first light chain comprising the sequence of SEQ ID NO: 73, and wherein the second half antibody comprises a second heavy chain comprising the sequence of SEQ ID NO: 21, and a second light chain comprising the sequence of SEQ ID NO: 22.

10. The use of any one of the preceding claims, wherein the eosinophilic disorder is asthma or chronic obstructive pulmonary disease (COPD).

11. The use of any one of the preceding claims, wherein the eosinophilic disorder is moderate to severe asthma.

12. The use of any one of the preceding claims, wherein the asthma is uncontrolled on a corticosteroid.

13. The use of any one of the preceding claims, wherein the medicament is to be administered to the patient with a corticosteroid.

14. The use of claim 13, wherein the corticosteroid is an inhaled corticosteroid.

15. The use of any one of the preceding claims, wherein the patient has been determined to have a serum periostin level of 20 ng/ml or higher.

16. The use of any one of the preceding claims, wherein the patient has been determined to have a serum periostin level of 50 ng/ml or higher.

17. The use of claim 15 or 16, wherein the serum periostin level is determined by ELISA.

18. The use of any one of claims 15-17, wherein the serum periostin level is determined by the E4 assay or ELECSYS® periostin assay.

19. The use of any one of claims 15-18, wherein the serum periostin is Total Periostin.

20. The use of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 150/μl.

21. The use of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 200/μl.

22. The use of any one of the preceding claims wherein the patient has been determined to have a blood eosinophil count of at least 300/μl.

23. The use of any one of claims 1-10, wherein the eosinophilic disorder is COPD.

24. A multispecific antibody comprising a first half antibody and a second half antibody, wherein the first half antibody comprises a first VH/VL unit that specifically binds to IL-17 and the second half antibody comprises a second VH/VL unit that specifically binds IL-13, wherein the first VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 40, HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 43, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47, and wherein the second VH/VL unit comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 16, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 20.

25. The multispecific antibody of claim 24, wherein the first VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 14.

26. The multispecific antibody of claim 24 or 25, wherein the first VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO:

38, and the second VH/VL unit comprises the VH sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 98% sequence identity to the sequence of SEQ ID NO: 14.

27. The multispecific antibody of any one of claims 24-26, wherein the first VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 39 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 13 and the VL sequence having at least 99% sequence identity to the sequence of SEQ ID NO: 14

28. The multispecific antibody of any one of claims 24-27, wherein the first VH/VL unit comprises the VH sequence of SEQ ID NO: 39 and the VL sequence of SEQ ID NO: 38, and the second VH/VL unit comprises the VH sequence of SEQ ID NO: 13 and the VL sequence of SEQ ID NO: 14.

29. The multispecific antibody of any one of claims 24-28, wherein the antibody is an IgG antibody.

30. The multispecific antibody of any one of claims 24-29, wherein the antibody is an IgG1 or IgG4 antibody.

31. The multispecific antibody of any one of claims 24-30, wherein the antibody is an IgG4 antibody.

32. The multispecific antibody of any one of claims 24-31 wherein the first half antibody comprises a first heavy chain comprising the sequence of SEQ ID NO: 72, and a first light chain comprising the sequence of SEQ ID NO: 73, and wherein the second half antibody comprises a second heavy chain comprising the sequence of SEQ ID NO: 21, and a second light chain comprising the sequence of SEQ ID NO: 22.

33. An isolated nucleic acid encoding:

(a) the multispecific antibody of any one of claims 24-32;

(b) the first VH/VL unit of the multispecific antibody of any one of claims 24-32; or

(c) the second VH/VL unit of the multispecific antibody of any one of claims 24-32.

34. A host cell comprising the nucleic acid of claim 33.

35. The host cell of claim 34, wherein the host cell is a prokaryotic cell preferably an *E. coli* cell.

36. The host cell of claim 34, wherein the host cell is a eukaryotic cell preferably a CHO cell.

37. The host cell of claim 34 or 35, wherein the host cell is an *E. coli* cell.

38. A method of producing an antibody comprising culturing the host cell of any one of claims 34-37 under conditions sufficient to produce the antibody.

39. The method of claim 38, further comprising the step of recovering the antibody.

40. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 107;

b) the sequence of SEQ ID NO: 108; or

c) the sequence of (a) and the sequence of (b).

41. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 105;

b) the sequence of SEQ ID NO: 106; or

c) the sequence of (a) and the sequence of (b).

42. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 103;

b) the sequence of SEQ ID NO: 104; or

c) the sequence of (a) and the sequence of (b).

43. An isolated nucleic acid comprising:

a) the sequence of SEQ ID NO: 99 or 101;

b) the sequence of SEQ ID NO: 100 or 102; or

c) the sequence of (a) and the sequence of (b).

44. A host cell comprising the nucleic acid of claim 40 or 42.

45. A host cell comprising the nucleic acid of claim 41 or 43.

46. A host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules.

47. A host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99, or 101 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules.

48. The host cell of any one of claims 44-47, wherein the host cell is a prokaryotic cell.

49. The host cell of any one of claims 44-47, wherein the host cell is a eukaryotic cell preferably a CHO cell.

50. The host cell of claim 48, wherein the host cell is an *E. coli* cell.

51. A method of producing a half antibody or a multispecific antibody comprising culturing the host cell of any one of claims 44-50 under conditions sufficient to produce the half antibody or multispecific antibody.

52. The method of claim 51, further comprising recovering the half antibody or multispecific antibody.

53. A method of producing a multispecific antibody comprising (i) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 99, 101 or 105 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a first half antibody, and (ii) culturing a second host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules, under conditions sufficient to produce a second half antibody.

54. The method of claim 53, comprising recovering the first half antibody and recovering the second half antibody.

55. The method of claim 53 or 54, comprising forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce a multispecific antibody.

56. The method of claim 55, further comprising the step of recovering the multispecific antibody.

57. A method of producing a multispecific antibody comprising (a) culturing a host cell comprising a first nucleic acid comprising the sequence of SEQ ID NO: 105, 99 or 101 and a second nucleic acid comprising the sequence of SEQ ID NO: 106, 100 or 102, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a first half antibody, and (b) culturing a second host cell comprising a first nucleic acid comprising

the sequence of SEQ ID NO: 107 or 103 and a second nucleic acid comprising the sequence of SEQ ID NO: 108 or 104, wherein the first nucleic acid and the second nucleic acid are comprised on the same nucleic acid molecule or on different nucleic acid molecules under conditions sufficient to produce a second half antibody; (c) recovering the first half antibody and recovering the second half antibody; and (d) forming a mixture comprising the first half antibody and the second half antibody under conditions sufficient to produce the multispecific antibody.

58. The method of claim 57, further comprising the step of recovering the multispecific antibody.

59. A multispecific antibody produced by the methods of any one of claims 38-39 and 51-58.

60. An immunoconjugate comprising the antibody of any one of claims 24 to 32 and 59 and a cytotoxic agent.

61. A pharmaceutical formulation comprising the antibody of any one of claims 24-32 and 59 and a pharmaceutically acceptable carrier.