

SUMMARY

[0006] Monitoring of antibody therapeutics in formulation over time is important to determine storage conditions that reduce any breakdown of the therapeutic and maintain the integrity of the product. The present disclosure provides a study of attributes of an anti-TSLP antibody that can change over time in storage and attributes that can be beneficial or detrimental to antibody stability.

[0006a] In one aspect, the disclosure provides an anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof comprising (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; (ii) a heavy chain CDR2 sequence comprising an amino acid sequence set forth in SEQ ID NO:7 but with a mutation at one of the following residues equivalent to D54 or G55 set forth in SEQ ID NO:10, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8.

[0006b] In another aspect, the disclosure provides a composition comprising the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure and a pharmaceutically acceptable carrier, excipient or diluent.

[0006c] In another aspect, the disclosure provides an isolated nucleic acid comprising a polynucleotide sequence encoding, the heavy chain variable domain, of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure.

[0006d] In another aspect, the disclosure provides an isolated nucleic acid comprising a polynucleotide sequence encoding the heavy chain variable domain and light chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure.

[0006e] In another aspect, the disclosure provides an isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable

domain, or both, of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure.

[0006f] In another aspect, the disclosure provides a recombinant expression vector comprising the nucleic acid of the disclosure.

[0006g] In another aspect, the disclosure provides a host cell comprising the vector of the disclosure.

[0006h] In another aspect, the disclosure provides a method of producing an immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof that specifically binds to a TSLP polypeptide comprising amino acids 29-159 of SEQ ID NO: 2, comprising incubating the host cell of the disclosure under conditions that allow it to express the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof, wherein said host cell comprises (i) a recombinant expression vector encoding the light chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure and a recombinant expression vector encoding the heavy chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure, or (ii) a recombinant expression vector encoding both the light chain variable domain and the heavy chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure.

[0006i] In another aspect, the disclosure provides a use of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of the disclosure or a composition of the disclosure in the manufacture of a medicament for treating an inflammatory disease.

[0007] In one example, the disclosure provides an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof comprising (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; (ii) a heavy chain CDR2 sequence comprising an amino acid sequence with a mutation at at least one of the following residues, D54 or G55 set forth in SEQ ID NO:7, and (iii)

a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8. In various examples, the HCDR2 has the sequence VIWYX₁X₂SNKHYADSVKG (SEQ ID NO: 13), wherein X₁ is D or E and X₂ is G or A. In various examples, the HCDR2 has the following sequence: VIWYEGSNKHYADSVKG (SEQ ID NO: 14), VIWYDASNKHYADSVKG (SEQ ID NO: 15) or VIWYEASNKHYADSVKG (SEQ ID NO: 16).

[0008] In various examples, the mutation in HCDR2 is D54E. In various examples, the mutation in HCDR2 is G55A. In various examples, the anti-TSLP antigen binding protein or fragment thereof optionally comprises a mutation in at least one of the following residues of LCDR2 D49, D50, or S51 of SEQ ID NO: 4. In various examples, the mutation of LCDR2 is one or more of D49E, D50E, or S51A. In various examples, the LCDR2 has the sequence X₁X₂X₃DRPS, wherein X₁ is D or E, X₂ is D or E, and X₃ is S or A (SEQ ID NO: 17). In various examples, the LCDR2 has the following sequence: EDSRPS (SEQ ID NO: 18), DESRPS (SEQ ID NO: 19), EESRPS (SEQ ID NO: 20), DDADRPS (SEQ ID NO: 21), DEADRPS (SEQ ID NO: 22), EDADRPS (SEQ ID NO: 23) or EEADRPS (SEQ ID NO: 24).

[0009] In various examples, the disclosure provides an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof comprising (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a light chain CDR2 sequence comprising an amino

acid sequence with a mutation in at least one of the following residues D49, D50, or S51 of SEQ ID NO: 4; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7 and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8.

[0010] In various examples, the LCDR2 has the sequence $X_1X_2X_3$ DRPS, wherein X_1 is D or E, X_2 is D or E, and X_3 is S or A (SEQ ID NO: 17). Optionally the LCDR2 has the following sequence: EDSRPS (SEQ ID NO: 18), DESRPS (SEQ ID NO: 19), EESRPS (SEQ ID NO: 20), DDADRPS (SEQ ID NO: 21), DEADRPS (SEQ ID NO: 22), EDADRPS (SEQ ID NO: 23) or EEADRPS (SEQ ID NO: 24). In various examples, the mutation in LCDR2 is D49E. In various examples, the mutation in LCDR2 is D50E. In various examples, the mutation in LCDR2 is S51A. In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof optionally comprises a mutation at one of the following residues D54 or G55 in HCDR2 set out in SEQ ID NO: 7. In various examples, the mutation in HCDR2 is one or more of D54E or G55A in SEQ ID NO: 7. In various examples, the HCDR2 has the sequence VIWYX₁X₂SNKHYSVKG (SEQ ID NO: 13), wherein X_1 is D or E and X_2 is G or A. In various examples, the HCDR2 has the following sequence: VIWYEGSNKHYSVKG (SEQ ID NO: 14), VIWYDASNKHYSVKG (SEQ ID NO: 15) or VIWYEASNKHYSVKG (SEQ ID NO: 16).

[0011] In various examples, the disclosure provides an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof comprising (A) a light chain variable domain selected from the group consisting of: i. a sequence of amino acids at least 80% identical to SEQ ID NO:12; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:11; or iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:11; or (B) a heavy chain variable domain selected from the group consisting of: i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:10; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:9; or iii. a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:9; or (C) a light chain variable domain of (A) and a heavy chain variable domain of (B), wherein the anti-TSLP immunoglobulin,

antigen binding protein or fragment thereof, or antibody or fragment thereof retains one or more of CDRs of the anti-TSLP antigen binding proteins or fragment thereof and comprises a mutation at one or more of HCDR2 D54 or G55 of SEQ ID NO: 7, or LCDR2 D49, D50, or S51 of SEQ ID NO: 4.

[0012] In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 25-28, and a light chain comprising the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 29-36.

[0013] In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof comprises an anti-TSLP antigen binding protein selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

[0014] In various examples, the immunoglobulin, antigen binding protein or antibody is a human antibody. In various examples, the antibody is an IgG2 antibody. In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO: 2. In various examples, both binding sites of the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof have identical binding to TSLP.

[0015] In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof binds TSLP with an affinity of that is numerically no more than 10^{-8} M Kd.

[0016] Further contemplated is a composition comprising the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof of described herein and a pharmaceutically acceptable carrier, excipient or diluent.

[0017] The disclosure also provides an isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the immunoglobulin, antigen binding protein or antibody described herein.

[0018] The disclosure further contemplates a recombinant expression vector comprising the nucleic acid encoding an anti-TSLP immunoglobulin, antigen binding protein or antibody as described herein. Also provided is a host cell comprising the expression vector.

[0019] Further contemplated herein is a method of producing an immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof that specifically binds to a TSLP polypeptide comprising amino acids 29-159 of SEQ ID NO: 2, comprising incubating the host cell under conditions that allow it to express the immunoglobulin, antigen binding protein, or antibody, wherein said host cell comprises (i) a recombinant expression vector encoding the light chain variable domain of the antigen binding protein of as described herein and a recombinant expression vector encoding the heavy chain variable domain of the antigen binding protein as described herein, or (ii) a recombinant expression vector encoding both the light chain variable domain and the heavy chain variable domain of the immunoglobulin, antigen binding protein or antibody as described herein.

[0020] In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof has increased stability at 25° C compared to an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12. In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof has increased stability at 40° C after 4 weeks compared to an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12. In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof has decreased high molecular weight species at 40° C after 4 weeks compared to an anti-TSLP antigen binding protein or fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

[0021] In various examples, the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof had decreased isomerization at 50° C compared to an anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

[0022] In various examples, less than 2% of the anti-TSLP immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof shows isomerization after at least 2 weeks (optionally, after at least 1 month, after at least 2 months, after at least 3 months,

after at least 4 months, after at least 5 months or after at least 6 months) of storage at about 25°C, as determined by SEC, e.g. SEC of antibody-antigen complex. In various examples, less than 2% of the antigen binding protein or fragment thereof shows isomerization after about 22 months to about 36 months of storage at 2° C to 8° C followed by at least 2 weeks or at least 1 month or at least 2 months or at least 3 months of storage at about 25° C, as determined by SEC.

[0023] Also provided herein is a method for treating an inflammatory disease in a subject comprising administering to the subject a therapeutically effective amount of the immunoglobulin, antigen binding protein or fragment thereof, or antibody or fragment thereof as described herein or a composition thereof. In various examples, the inflammatory disease is selected from the group consisting of: asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis (EoE), nasal polyps, chronic spontaneous urticaria, Ig-driven disease, IgA nephropathy, lupus nephritis, eosinophilic gastritis, chronic sinusitis without nasal polyps and idiopathic pulmonary fibrosis (IPF). In various examples, the asthma is mild, moderate or severe asthma. In various examples, the asthma is severe asthma. In various examples, the asthma is eosinophilic or non-eosinophilic asthma.

[0024] In various examples, the method comprises administering the composition at an interval of every 2 weeks or every 4 weeks. In various examples, the composition is administered for a period of at least 4 months, 6 months, 9 months, 1 year or more.

[0025] In various examples, the disclosure provides a method of making a composition comprising a plurality of anti-TSLP monoclonal antibodies or antigen binding fragments thereof each comprising: a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ IDNO:5; a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, the method comprising enriching the composition for IgG2 anti-TSLP monoclonal antibodies that comprise at least one of: L-aspartate at HC position 54, relative to isoAspartate (isoAsp) or cyclic aspartate (cAsp) in HCDR2 set out in SEQ ID NO: 7; non-oxidized HC W102, relative to oxidized W102 in HCDR3 set out in SEQ ID NO: 8; L-aspartate at LC position 49 or position 50, relative to isoAsp or cAsp in LCDR2 set out in SEQ ID NO: 4; LC N65 relative to deamidated N65 set out in LC SEQ ID NO: 12; or L-aspartate at LC position 91

of LCDR3 set out in SEQ ID NO: 5, relative to isoAsp or cAsp. cAsp is also known as succinimide featuring H₂O loss relative to Asp or isoAsp.

[0026] In various examples, less than 2.0% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54. In various examples, no more than 2% of the anti-TSLP monoclonal antibodies comprise oxidized HC W102. In various examples, less than 2.0% of the anti-TSLP monoclonal antibodies comprise isomerized LC D49 or D50. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D49 or D50. In various examples, no more than 0.5% of the anti-TSLP monoclonal antibodies comprise deamidated LC N65. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D91.

[0027] Further contemplated is a composition comprising anti-TSLP monoclonal antibodies each comprising: a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4; a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8, the composition comprising a limited content of isomerized HC D54 (SEQ ID NO: 7) and/or a limited content of isomerized LC D49 or D50 (SEQ ID NO: 4), effective for the anti-TSLP monoclonal antibodies of the composition to bind to TSLP with a K_d that is numerically less than or equal to 10⁻⁸ M.

[0028] Also provided is a composition comprising IgG2 anti-TSLP monoclonal antibodies, each comprising a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4; a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8, wherein at least one of: no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54; no more than 2% of the anti-TSLP monoclonal antibodies comprise oxidized HC W102; no more than 6.7 % of the anti-TSLP monoclonal antibodies comprise isomerized LC D49 or D50; no more than 0.5% of the anti-TSLP

monoclonal antibodies comprise deamidated LC N65; or no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D91. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54. In various examples, no more than 2% of the anti-TSLP monoclonal antibodies comprise oxidized HC W102. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LCD49 or LC D50. In various examples, no more than 0.5% of the anti-TSLP monoclonal antibodies comprise deamidated LC N65. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D91.

[0029] Also provided is a composition comprising IgG2 anti-TSLP monoclonal antibodies, each comprising a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4; a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein at least one of: no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54; no more than 2% of the anti-TSLP monoclonal antibodies comprise oxidized HC W102; no more than 12.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D49 or D50; no more than 0.5% of the anti-TSLP monoclonal antibodies comprise deamidated LC N65; or no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D91. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized HC D54. In various examples, no more than 2% of the anti-TSLP monoclonal antibodies comprise oxidized HC W102. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LCD49 or LC D50. In various examples, no more than 0.5% of the anti-TSLP monoclonal antibodies comprise deamidated LC N65. In various examples, no more than 0.9% of the anti-TSLP monoclonal antibodies comprise isomerized LC D91.

[0030] In various examples, the anti-TSLP antibody comprises a combination of L-aspartate at HC D54 and L-aspartate at LC D49 or D50. In various examples, the anti-TSLP antibody is enriched in L-aspartate at HC D54 to at least 6-fold over the levels of isoAsp.

[0031] In various examples, the antibody is an IgG2 antibody. In various examples, the anti-TSLP antibody comprises a heavy chain variable region set out in SEQ ID NO: 10 or

SEQ ID NOs: 25-28 and a light chain variable region set out in SEQ ID NO: 12 or SEQ ID NOs: 29-36, and comprises one or more of the sequence modifications described herein.

[0032] The disclosure also provides a composition comprising anti-TSLP monoclonal antibodies, each comprising a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3; a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6; a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:8, wherein at least one of: greater than 98% of the anti-TSLP monoclonal antibodies of the composition comprise L-aspartate at HC position 54, relative to isoAsp or cAsp at position 54 (SEQ ID NO: 7); at least 99% of the anti-TSLP monoclonal antibodies of the composition comprise non-oxidized HC W102 relative to oxidized W102 (SEQ ID NO: 8); at least 97% of the anti-TSLP monoclonal antibodies of the composition comprise L-aspartate at LC position 49 or position 50, relative to isoAsp or cAsp at position 49 or 50 (SEQ ID NO: 4); at least 99.1% of the anti-TSLP monoclonal antibodies of the composition comprise LC N65 relative to deamidated LC N65 (SEQ ID NO: 12); or at least 99.1% of the anti-TSLP monoclonal antibodies of the composition comprise L-aspartate at LC position 91, relative to isoAsp or cAsp at position 91 (SEQ ID NO: 5).

[0033] The disclosure also provides a composition comprising an anti-TSLP antibody or antigen binding fragment thereof as described herein for use in treating an inflammatory disease as described herein. In certain examples, the disclosure provides use of a composition comprising an anti-TSLP antibody or antigen binding fragment thereof as described herein in the preparation of a medicament for treating an inflammatory disease.

[0034] Syringes, e.g., single use or pre-filled syringes, sterile sealed containers, e.g. vials, bottle, vessel, and/or kits or packages comprising any of the foregoing antibodies or compositions, optionally with suitable instructions for use, are also contemplated.

[0035] It is understood that each feature or example, or combination, described herein is a non-limiting, illustrative example of any of the examples of the invention and, as such, is meant to be combinable with any other feature or example, or combination, described herein. For example, where features are described with language such as “one example”, “some examples”, “certain examples”, “further example”, “specific exemplary examples”, and/or “another example”, each of these types of examples is a non-

limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the examples of the invention. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

[0036] The headings herein are for the convenience of the reader and not intended to be limiting. Additional examples, examples, and variations of the invention will be apparent from the Detailed Description and/or Drawings and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] Figure 1 illustrates the workflow for characterizing residues and modifications that potentially impact binding determined by the SEC affinity binding of heat stressed AMG157 (40C4W) and TSLP. *In silico* sequence analysis is shown (top). Several mutations of residues with modifications were considered to improve the stability of AMG 157 at room temperature (bottom).

[0038] Figure 2 shows relative abundance of potential attributes in the T0, 40C4W and 22M5C+2M25C samples of AMG 157 as determined by SEC of antigen-antibody complex. These attributes were predicted as potentially impacting TSLP stability according to *in silico* sequence (as shown in Figure 1). White, black and gray bars represent the modification percentages in AMG 157 T0, 40C4W and 22M5C+2M25C samples, respectively. A dashed line is shown to represent 2%.

[0039] Figure 3A shows SEC-UV profiles of AMG157 T0, AMG157 40C4W, TSLP, AMG157 T0 + TSLP mixture, and AMG157 40C4W + TSLP mixture. Five SEC-UV peak regions are assigned based on the peak shape and molecular weight. Peak 3 represents the bound fraction of AMG 157 with TSLP, and peak 5 corresponds to the unbound fraction of AMG 157. The cartoon of each assigned peak is shown on top of the corresponding peak. Figure 3B shows modification percentages of five attributes in the bound and unbound fractions of the SEC binding.

[0040] Figure 4 is a volcano plot showing how the attributes of AMG 157 are distributed in statistics for impacting the TSLP binding. Attributes appearing in the top right corner are the modifications of AMG 157 that potentially impact TSLP binding. X-axis is log₂ value of the

WHAT IS CLAIMED:

1. An anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof comprising
 - (A) a light chain variable domain comprising:
 - (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:3;
 - (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:4; and
 - (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:5; and
 - (B) a heavy chain variable domain comprising:
 - (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:6;
 - (ii) a heavy chain CDR2 sequence comprising an amino acid sequence set forth in SEQ ID NO:7 but with a mutation at one of the following residues equivalent to D54 or G55 set forth in SEQ ID NO:10, and
 - (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8.
2. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of claim 1, wherein the mutation in HCDR2 is D54E.
3. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of claim 1, wherein the mutation in HCDR2 is G55A.
4. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 3, wherein the HCDR2 has the following sequence: VIWYEGSNKHYADSVKG (SEQ ID NO: 14), VIWYDASNKHYADSVKG (SEQ ID NO: 15) or VIWYEASNKHYADSVKG (SEQ ID NO: 16).

5. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 4 wherein the LCDR2 of SEQ ID NO: 4 comprises a mutation in at least one of the following residues equivalent to D49, D50, or S51 of SEQ ID NO: 12, preferably wherein the mutation is any one of D49E, D50E, and S51A.

6. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of claim 5, wherein the mutation is any one of D49E, D50E, and/or S51A.

7. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of claim 5 or 6, wherein the LCDR2 has the sequence $X_1X_2X_3$ DRPS, wherein X_1 is D or E, X_2 is D or E, and X_3 is S or A (SEQ ID NO: 17), optionally the LCDR2 has the following sequence: EDSRPS (SEQ ID NO: 18), DESRPS (SEQ ID NO: 19), EESRPS (SEQ ID NO: 20), DDADRPS (SEQ ID NO: 21), DEADRPS (SEQ ID NO: 22), EDADRPS (SEQ ID NO: 23) or EEADRPS (SEQ ID NO: 24).

8. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1-7 comprising:

(A) a light chain variable domain selected from the group consisting of:

- i. a sequence of amino acids at least 80% identical to SEQ ID NO: 12;
- ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 11; or

(B) a heavy chain variable domain selected from the group consisting of:

- i. a sequence of amino acids that is at least 80% identical to SEQ ID NO: 10;
- ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 9; or

(C) a light chain variable domain of (A) and a heavy chain variable domain of (B), wherein the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof retains the CDRs of the anti-TSLP antigen binding proteins or antigen binding fragment thereof.

9. The antigen binding protein or antigen binding fragment thereof of any one of claims 1 to 8, wherein the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 25-28, and a light chain comprising the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 29-36.

10. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 9 wherein the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody.

11. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 9, wherein the antigen binding protein is a human antibody.

12. The antibody of claim 10 or 11 that is an IgG2 antibody.

13. The immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 12, wherein the anti-TSLP antigen binding protein or antigen binding fragment thereof specifically binds to a TSLP polypeptide as set forth in amino acids 29-159 of SEQ ID NO: 2.

14. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 13, wherein both binding sites of the anti-TSLP antigen binding protein or antigen binding fragment thereof have identical binding to TSLP.

15. A composition comprising the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14 and a pharmaceutically acceptable carrier, excipient or diluent.

16. An isolated nucleic acid comprising a polynucleotide sequence encoding, the heavy chain variable domain, of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14.

17. An isolated nucleic acid comprising a polynucleotide sequence encoding the heavy chain variable domain and light chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14.

18. An isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 5 to 7.

19. A recombinant expression vector comprising the nucleic acid of any of claims 16 to 18.

20. A host cell comprising the vector of claim 19.

21. A method of producing an immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof that specifically binds to a TSLP polypeptide comprising amino acids 29-159 of SEQ ID NO: 2, comprising incubating the host cell of claim 20 under conditions that allow it to express the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof, wherein said host cell comprises (i) a recombinant expression vector encoding the light chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1-14 and a recombinant expression vector encoding the heavy chain variable domain of the

immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1-14, or (ii) a recombinant expression vector encoding both the light chain variable domain and the heavy chain variable domain of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of claims 1 to 14.

22. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, having increased stability at 25° C compared to an anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

23. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, having increased stability at 40° C after 4 weeks compared to an anti- immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

24. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, having decreased high molecular weight species at 40° C after 4 weeks compared to an anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

25. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, wherein the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof had decreased isomerization at 50° C compared to an anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof having the amino acid sequences set out in SEQ ID NO: 10 and SEQ ID NO: 12.

26. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, wherein less than 2% of the anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof shows isomerization and/or deamidation after at least 2 weeks (optionally, after at least 1 month, after at least 2 months, after at least 3 months, after at least 4 months, after at least 5 months or after at least 6 months) of storage at about 25°C, as determined by SEC.

27. The anti-TSLP immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of claims 1 to 14, wherein less than 2% of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof shows isomerization and/or deamidation after about 22 months to about 36 months of storage at 2°C to 8°C followed by at least 2 weeks or at least 1 month or at least 2 months of storage at about 25°C, as determined by SEC.

28. Use of the immunoglobulin, antigen binding protein or antigen binding fragment thereof, or antibody or antigen binding fragment thereof of any one of the claims 1-14 or a composition of claim 15 in the manufacture of a medicament for treating an inflammatory disease, wherein the inflammatory disease is selected from the group consisting of: asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis (EoE), nasal polyps, chronic spontaneous urticaria, Ig-driven disease, IgA nephropathy, lupus nephritis, eosinophilic gastritis, chronic sinusitis without nasal polyps and idiopathic pulmonary fibrosis (IPF).

29. The use of claim 28, wherein the medicament is to be administered at an interval of every 2 weeks or every 4 weeks.

30. The use of any one of claims 28 to 29, wherein the medicament is to be administered for a period of at least 4 months, 6 months, 9 months, 1 year or more.

31. The use of any one of claims 28 to 30, wherein the asthma is severe asthma.

32. The use of any one of claims 28 to 31, wherein the asthma is eosinophilic or non-eosinophilic asthma.