Therefore, antagonists to TSLP would be expected to be useful for treating these inflammatory and fibrotic disorders. The present disclosure provides such treatments and methods of treating.

SUMMARY ~~OF THE INVENTION~~

In one aspect, there is provided an antigen binding protein comprising:

A.

a. a light chain variable domain comprising:

i. a light chain CDR1 sequence comprising the amino acid sequence of SEQ ID NO:13;

ii a light chain CDR2 sequence comprising the amino acid sequence of SEQ ID NO:60; and

iii. a light chain CDR3 sequence comprising the amino acid sequence of SEQ ID NO:105; and

b. a heavy chain variable domain comprising:

i. a heavy chain CDR1 sequence comprising the amino acid sequence of SEQ ID NO:145;

ii. a heavy chain CDR2 sequence comprising the amino acid sequence of SEQ ID NO:173, and

iii. a heavy chain CDR3 sequence comprising the amino acid sequence of SEQ ID NO:212;

B.

a. a light chain variable domain sequence selected from the group consisting of:

i. amino acids having a sequence at least 80% identical to SEQ ID NO:363;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:362;

iii. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:362;

and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:361;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:360;

iii. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:360; or

C.

a light chain variable domain comprising the sequence of SEQ ID NO:363 and a heavy chain variable domain comprising the sequence of SEQ ID NO:361;

wherein the antigen binding protein according to items A., B., or C. specifically binds to TSLP.

In one ~~aspect~~example, the present disclosure provides an isolated antigen binding protein comprising a. a light chain CDR3 sequence selected from i. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of A1 to A27; ii. $QQAX_8SFPLT$ (SEQ ID NO: 251); and b. a heavy chain CDR3 sequence selected from i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain CDR3 sequences of A1 to A27; ii.$GGGIX_{12}VADYYX_{13}YGMDV$ (SEQ ID NO: 255); iii. $DX_{21}GX_{22}SGWPLFX_{23}Y$ (SEQ ID NO: 259); wherein X_8 is an N residue or a D residue;X_{12} is a P residue or an A residue; X_{13} is a Y residue or an F residue; X_{21} is a G residue or an R residue;X_{22} is an S residue or a T residue; X_{23} is an A residue or a D residue, and wherein said antigen binding protein specifically binds to TSLP.

In another ~~aspect~~example, the isolated antigen binding protein of the present disclosure further comprises at least one of the following: a. a light chain CDR1 sequence selected from i. a light chain CDR1 sequence that differs by no more than three amino acids additions, substitutions, and/or deletions from a light chain CDR1 sequence of A1-A27; ii. $RSSQSLX_1YSDGX_2TYLN$ (SEQ ID NO: 246);

iii. $RASQX_4X_5SSWLA$ (SEQ ID NO: 249); b. a light chain CDR2 sequence selected from i. a light chain CDR2 sequence that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of A1-A27; ii. $KVSX_3$ (residues 1-4 of SEQ ID NO: 247); iii. X_6X_7SSLQS (SEQ ID NO: 250); or iv. QDX_9KRPS (SEQ ID NO: 252); and c. a heavy chain CDR1 sequence selected from i. a heavy chain CDR1 sequence that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of A1-A27; ii. $X_{10}YGMH$ (SEQ ID

NO: 253); and iii. $X_{15}X_{16}YMX_{17}$ (SEQ ID NO: 257); and d. a heavy chain CDR2 sequence selected from i. a heavy chain CDR2 sequence that differs by no more than three amino acid additions, substitutions, and /or deletions from a CDR2 sequence of A1-A27; ii. $VIWX_{11}DGSNKYYADSVKG$ (SEQ ID NO: 254); iii. $VISYDGSX_{14}KYYADSVKG$ (SEQ ID NO: 256); and iv. $WINPNSGGTNX_{18}X_{19}X_{20}KFQG$ (SEQ ID NO: 258); wherein X_1 is a V residue or an I residue; X_2 is an N residue or a D residue; X_3 is a Y residue or an N residue; X_4 is a G residue or a S residue; X_5 is a L residue or an I residue; X_6 is an N residue or a T residue; X_7 is a T residue or an A residue; X_9 is a K residue or an N residue; X_{10} is an S residue or an N residue; X_{11} is a Y residue or an F residue; X_{14} is a Y residue or a N residue; X_{15} is a D residue or G residue; X_{16} is a Y residue or a D residue; X_{17} is a Y residue or an H residue; X_{18} is a Y residue or an H residue; X_{19} is a V residue or an A residue; X_{20} is a Q residue or an R residue,and wherein said antigen binding protein specifically binds to TSLP.

In another ~~aspect~~example of the present disclosure, the isolated antigen binding protein of claim 1 comprises either: a. a light chain variable domain comprising: i. a light chain CDR1 sequence selected from A1-A27; ii a light chain CDR2 sequence selected from A1-A27; iii. a light chain CDR3 sequence selected from A1-A27; or b. a heavy chain variable domain comprising i. a heavy chain CDR1 sequence selected from A1-A27; ii. a heavy chain CDR2 sequence selected from A1-A27, and iii. a heavy chain CDR3 sequence selected from A1-A27; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

In a further ~~aspect~~example, the isolated antigen binding protein comprises either a. a light chain variable domain sequence selected from i. amino acids having a sequence at least 80% identical to a light chain variable domain sequence selected from L1-L27; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the light chain variable domain sequence of L1-L27; iii. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L27; b. a heavy chain variable domain sequence selected from i. a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of H1-H27; ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of H1-H27; iii. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H27; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein said antigen binding protein specifically binds to TSLP.

In a further ~~aspect~~example, an isolated antigen binding protein of the present disclosure comprises either: a. a light chain variable domain sequence selected from : L1-L27; b. a heavy chain variable domain sequence selected from H1-H27; or, c. the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds to TSLP.

In a further ~~aspect~~example, the isolated binding protein comprises a light chain variable domain sequence and a heavy chain variable domain sequence selected from L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13.1H13, L13.2H13, L14.1H14, L14.2H14, L15.1H15, L15.2H15, L16.1H16, L16.2H16, L17H17, L18.1H18, L18.2H18, L19.1H19, L19.2H19, L20.1H20, L20.2H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, and L27H27.

In a further ~~aspect~~example, the isolated antigen binding protein comprises a binding protein that binds to TSLP with substantially the same Kd as a reference antibody selected from A2, A3, A4, and A5. In another aspect, the isolated antigen binding protein comprises a binding protein that inhibits TSLP activity according to the primary cell OPG assay with the same IC50 as a reference antibody selected from A2, A3, A4 or A5.

In still a further ~~aspect~~example, the isolated antigen binding protein cross-competes for binding of TSLP with a reference antibody. In another ~~aspect~~example, the isolated antigen binding protein binds the same epitope as a reference antibody, e.g., A2, A4, A5, A6, A7, A10, A21, A23, or A26.

In one ~~aspect~~example, the isolated antigen binding protein is selected from a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an F(fa')x fragment, a domain antibody, an IgD antibody, an IgE antibody, and IgM antibody, and IgG1 antibody, and IgG2 antibody, and IgG3 antibody, and IgG4 antibody, and IgG4 antibody having at least one mutation in the hinge region that alleviates a tendency to for intra H-chain disulfide bonds. In one ~~aspect~~example, the isolated antigen binding protein is a human antibody.

In one aspect, there is provided a nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the antigen binding agent as defined herein; or wherein the sequence is SEQ ID NO:362; SEQ ID NO:360; or both.

Also provided is an isolated nucleic acid molecule comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the antigen binding agent of the present disclosure. In one ~~embodiment~~example, the polynucleotide comprises a light chain variable sequence L1-L27, and/or a heavy chain variable sequence H1-H27, or both.

In one aspect, there is provided a recombinant expression vector comprising the nucleic acid as defined above.

In one aspect, there is provided a host cell comprising the vector as defined above.

In one aspect, there is provided a hybridoma capable of producing the human antibody as defined above.

In one aspect, there is provided a method of producing the antibody as defined above, comprising incubating the host cell as defined above under conditions that allow it to express the antibody.

Also provided are vectors comprising the polynucleotides of the present disclosure. In one ~~embodiment~~example the vector is an expression vector. Also provided is a host cell comprising the vector. Also provided is a hybridoma capable of producing the antigen binding protein of the present ~~invention~~disclosure. Also provided is a method of making the antigen binding protein comprising culturing the host cell under conditions that allow it to express the antigen binding protein.

In one aspect, there is provided a pharmaceutical composition comprising the antigen binding protein as defined above.

In one aspect, there is provided a composition as defined above for use in treating

a. a TSLP-related inflammatory condition in a subject in need of such treatment; or

b. a TSLP-related fibrotic disorder in a subject in need of such treatment.

Also provided is a pharmaceutical composition comprising the antigen binding proteins of the present ~~invention~~disclosure. In one ~~embodiment~~example the pharmaceutical composition comprises a human antibody, Also provided is a method of treating a TSLP-related inflammatory condition in a subject in need of such treatment comprising administering a therapeutically effective amount of the composition to the subject. In one ~~embodiment~~example, the inflammatory condition is allergic asthma, allergic rhinosinusitis, allergic conjunctivitis, or atopic dermatitis. Also provided is a method of treating a TSLP-related fibrotic disorder in a subject in need of such treatment comprising administering a therapeutically effective amount of the composition to the subject. In one ~~embodiment~~example, the fibrotic disorder is scleroderma, interstitial lung disease, idiopathic pulmonary fibrosis, fibrosis arising from chronic hepatitis B or C, radiation-induced fibrosis, and fibrosis arising from wound healing.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A-FIG. 1F. The figure provides the amino acid sequence of the light chain CDR1, CDR2, and CDR3 regions of A1-A27. Further provided is an exemplary nucleotide sequence encoding each CDR.

FIG. 2A-FIG. 2F. The figure provides the amino acid sequence of the heavy chain CDR1, CDR2, and CDR3 regions of A1-A27. Further provided is an exemplary nucleotide sequence encoding each CDR.

i. a sequence of amino acids that is at least 80% identical to SEQ ID NO:361;

ii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO:360;

iii. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO:360; or

C.

a light chain variable domain comprising the sequence of SEQ ID NO:363 and a heavy chain variable domain comprising the sequence of SEQ ID NO:361;

wherein the antigen binding protein according to items A., B., or C. specifically binds to TSLP.

2. The antigen binding protein of claim 1, wherein

a. the binding protein binds to TSLP with substantially the same Kd as a reference antibody, and/or

b. wherein the binding protein inhibits TSLP activity according to the primary cell OPG assay with the same IC50 as a reference antibody,

wherein said reference antibody is an antibody comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:363 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:361.

3. The antigen binding protein of claim 1 or claim 2, wherein the antigen binding protein is selected from the group consisting of a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal 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 F(fa')x fragment, a domain antibody, an IgD antibody, an IgE antibody, and IgM antibody, and IgG1 antibody, and IgG2 antibody, and IgG3 antibody, and IgG4 antibody, and and IgG4 antibody having at least one mutation in the hinge region that alleviates a tendency to form intra H-chain disulfide bonds.