

Summary

The present disclosure relates to anti-tryptase antibodies and pharmaceutical compositions thereof, as well as methods of using the same.

In one aspect, the present disclosure refers to an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6). In some examples, the antibody is defined by the six HVRs comprising the amino acid sequence of SEQ ID NO: 7, 2, 8, 4, 5, and 6. In some examples, the antibody further comprises S43, P46, and W47 in the light chain variable (VL) domain framework region L2 (FR-L2) (Kabat numbering). In some examples, the antibody comprises (a) a heavy chain variable (VH) domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 10; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain framework regions (FRs): (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO: 11); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 12); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 13); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 14). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 9. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRTITC (SEQ ID NO: 15); (b) an FR-L2 comprising the amino acid sequence of WYQKPKGSPKPIY (SEQ ID NO: 16); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFLTISLQPEDFATYYC (SEQ ID NO: 17); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 18). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77. In other examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79.

In another aspect, the present disclosure refers to an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9 and (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises a VH domain comprising the amino acid sequence of

SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77. In other examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79.

In another aspect, the present disclosure refers to an isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 or SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77 or SEQ ID NO: 79.

In another example, the disclosure features an isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79.

In another example, the disclosure features an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RDNYDWYFDV (SEQ ID NO: 29); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVKLVESGGGSVQPGGSRKLSCAASGFTFS (SEQ ID NO: 21); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 22); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNPKNTLFLQMSSLRSEDAMYYCAR (SEQ ID NO: 23); and (d) an FR-H4 comprising the amino acid sequence of WGTGTTVTVSS (SEQ ID NO: 24). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 19. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of QIVLTQSPAIMSASPGEKVTISC (SEQ ID NO: 25); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGSSPKWIY (SEQ ID NO: 26); (c) an FR-L3 comprising the amino acid sequence of GVPARFSGSGSGTSYSLTISMEADAATYYC (SEQ ID NO: 27); and (d) an FR-L4 comprising the amino acid sequence of FGAGTKLELK (SEQ ID NO: 28). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 20.

In another example, the disclosure features an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino sequence having at least 90%, at least 95% sequence, or at least 99% identity to the amino acid sequence of SEQ ID NO: 19; (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 20; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVKLVESGGGSVQPGGSRKLSCAASGFTFS (SEQ ID NO: 21); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 22); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNPKNTLFLQMSSLRSEDAMYYCAR (SEQ ID NO: 23); and (d) an FR-H4 comprising the

amino acid sequence of WGTGTTVTVSS (SEQ ID NO: 24). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 19. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of QIVLTQSPAIMASPGKEKVTISC (SEQ ID NO: 25); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGSSPKPWIY (SEQ ID NO: 26); (c) an FR-L3 comprising the amino acid sequence of GVPARFSGSGSGTSYSLTISSEMEADAATYYC (SEQ ID NO: 27); and (d) an FR-L4 comprising the amino acid sequence of FGAGTKLELK (SEQ ID NO: 28). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 20.

In another example, the disclosure features an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, comprising (a) a VH domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 19 and (b) a VL domain comprising an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 20.

In some examples of any of the preceding aspects, the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising His51 and at least one, at least two, or all three residues selected from the group consisting of Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or all twelve amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises His51, Gln67, Val80, Lys81, Asp82, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating both the small interface of tetrameric human tryptase beta 1 and the large interface of tetrameric human tryptase beta 1.

In another aspect, the present disclosure refers to an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYAIT (SEQ ID NO: 30); (b) an HVR-H2 comprising the amino acid sequence of GISSAATTFYSSWAKS (SEQ ID NO: 31); (c) an HVR-H3 comprising the amino acid sequence of DPRGYGAALDRLDL (SEQ ID NO: 32); (d) an HVR-L1 comprising the amino acid sequence of QSIKSVYNNRLG (SEQ ID NO: 33); (e) an HVR-L2 comprising the amino acid sequence of ETSILTS (SEQ ID NO: 34); and (f) an HVR-L3 comprising the amino acid sequence of AGGFDRSGDTT

(SEQ ID NO: 35). In some examples, the antibody is defined by the six HVRs comprising the amino acid sequence of SEQ ID NO: 30, 31, 32, 33, 34, and 35. In some examples, the antibody further comprises Arg71 and Val78 in VH domain FR-H3 (Kabat numbering). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGPGGLVKPSETLSLTCTVSRFSLI (SEQ ID NO: 38); (b) an FR-H2 comprising the amino acid sequence of WIRQPPGKGLEWIG (SEQ ID NO: 42); (c) an FR-H3 comprising the amino acid sequence of RVTISRDTSKNQVSLKLSSVTAADTAVYYCAR (SEQ ID NO: 43); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 41). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 36. In some examples, the antibody comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 64); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 65); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFLTISLQPEDFATYYC (SEQ ID NO: 66); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 63). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81. In other examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83.

In another aspect, the present disclosure refers to an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 36, 47, 48, 49, 50, 51, and 52; (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of any one of SEQ ID NO: 37, 53, 58, or 59; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGPGGLVKPSETLSLTCTVSRFSLI (SEQ ID NO: 38); (b) an FR-H2 comprising the amino acid sequence of WIRQPPGKGLEWIG (SEQ ID NO: 42); (c) an FR-H3 comprising the amino acid sequence of RVTISRDTSKNQVSLKLSSVTAADTAVYYCAR (SEQ ID NO: 43); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 41). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 36. In some examples, the antibody comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 64); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 65); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFLTISLQPEDFATYYC (SEQ ID NO: 66); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 63). In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81. In other examples, the antibody comprises

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83.

In another aspect, the present disclosure refers to an isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 36 and (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and a VL domain comprising the amino acid sequence of SEQ ID NO: 37.

In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81. In other examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83.

In another aspect, the present disclosure refers to an isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 or SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 83.

In another example, the disclosure features an isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83.

In another example, the disclosure features an isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 52 and (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 53.

In some examples of any of the preceding aspects, the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, or all fourteen amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope comprises Gln35, Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Gln100, Leu101, Leu102, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, Glu129, and Arg216 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is relative to a human tryptase beta 1 tetramer, and the epitope on human tryptase beta 1 further comprises one or both of Gln35 and Arg216 of SEQ ID NO: 71. In some

examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating the small interface and/or the large interface of human tryptase beta 1.

In some examples of any of the preceding aspects, the antibody further binds cynomolgus monkey (cyno) tryptase. In some examples, the antibody further binds human tryptase alpha. In some
5 examples, the antibody further binds human tryptase beta 2 or human tryptase beta 3. In some examples, the antibody binds human tryptase beta 2 and human tryptase beta 3.

In some examples of any of the preceding aspects, the antibody binds the tryptase with a K_D of about 1 nM or less. In some examples, the K_D is measured by a surface plasmon resonance (SPR) assay. In some examples, the antibody binds the tryptase with a K_D of between about 120 pM and about
10 0.5 nM. In some examples, the antibody binds the tryptase with a K_D of between about 120 pM and about 300 pM. In some examples, the antibody binds the tryptase with a K_D of between about 120 pM and about 200 pM. In some examples, the antibody binds the tryptase with a K_D of about 180 pM. In some examples, the antibody binds tryptase with a K_D of about 400 pM. In some examples, the SPR assay is performed at 25°C. In some examples, the K_D is measured using a BIAcore® SPR assay, for example,
15 as described in Example 1, Section (A)(vii). In some examples, the SPR assay can use a BIAcore® T200 or an equivalent device. In some examples, BIAcore® Series S CM5 sensor chips (or equivalent sensor chips) are immobilized with monoclonal mouse anti-human IgG (Fc) antibody and anti-tryptase antibodies are subsequently captured on the flow cell. Serial 3-fold dilutions of the His-tagged human tryptase beta 1 monomer (SEQ ID NO: 128) are injected at a flow rate of 30 μ l/min. Each sample is analyzed with 3
20 min association and 10 min dissociation. The assay is performed at 25°C. After each injection, the chip is regenerated using 3 M $MgCl_2$. Binding response is corrected by subtracting the response units (RU) from a flow cell capturing an irrelevant IgG at similar density. A 1:1 Langmuir model of simultaneous fitting of k_{on} and k_{off} is used for kinetics analysis.

In some examples of any of the preceding aspects, the antibody is capable of inhibiting the
25 enzymatic activity of human tryptase beta 1. In some examples, the antibody inhibits the activity of tryptase with an IC_{50} of about 2.5 nM or lower as determined by a human tryptase beta enzymatic assay using a synthetic peptide S-2288 as a substrate. In some examples, the antibody inhibits the activity of tryptase with an IC_{50} of between about 550 pM and about 2.5 nM. In some examples, the antibody inhibits the activity of tryptase with an IC_{50} of between about 500 pM and about 2 nM. In some
30 examples, the antibody inhibits the activity of tryptase with an IC_{50} of between about 550 nM and 1.5 nM. In some examples, the antibody inhibits the activity of tryptase with an IC_{50} of between about 500 pM and about 700 pM. In some examples, the inhibitory activity of the antibody is determined as described in Example 1(A)(viii)(a)). In some examples, the final concentration of heparin in the human tryptase beta enzymatic assay using the synthetic peptide S-2288 is 66 μ g/ml. In some examples, recombinant human
35 tryptase beta 1 tetramer active enzyme is diluted to 0.75 nM in TNH Buffer (200 mM Tris, 150 mM NaCl, 0.1 mg/mL heparin, 0.01% TRITON™ X-100, pH 8.0), and combined 1:1 with anti-tryptase antibodies (diluted in PBS) in 384-well plates. Plates are incubated for 1 h at ambient temperature with gentle agitation. Colorimetric substrate S-2288 (Chromogenix, Part No. 82-0852-39), or an equivalent substrate, is diluted to 1200 μ M in TNH Buffer and added to the plate. In some examples, the final in-well
40 concentrations are 400 μ M S-2288, 0.25 nM recombinant human

tryptase beta 1 tetramer, 66 µg/mL heparin, and from 0.10 to 222 nM anti-tryptase antibody. Plates are incubated for 40 min at ambient temperature with gentle agitation and then read at A₄₀₅. The IC₅₀ of the anti-tryptase antibodies is determined from a four-parameter fit of their respective curves.

In some examples of any of the preceding aspects, the antibody is capable of inhibiting the enzymatic activity of human tryptase beta 1 at pH 6. In particular, the inhibitory activity of the antibody may be determined at pH 6.

In some examples, the antibody is capable inhibiting tryptase-mediated stimulation of bronchial smooth muscle cell proliferation and/or collagen-based contraction. In some examples, the antibody is capable of inhibiting mast cell histamine release. In some examples, the antibody is capable of inhibiting IgE-triggered histamine release and/or tryptase-triggered histamine release. In some examples, the antibody is capable of inhibiting cyno tryptase D1 as assessed by an active tryptase ELISA assay. In some examples, the antibody is capable of inhibiting tryptase activity in cynomolgus monkey broncheolar lavage (BAL) or nasosorption samples. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1 when in a monovalent format. In some examples, the monovalent format is a Fab format. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1 in the presence of heparin. In some examples, the antibody is capable of dissociating tetrameric tryptase beta in the presence of 66 µg/ml heparin.

In another aspect, the present disclosure refers to an antibody that binds to the same epitope as any one of the preceding antibodies or that competes for binding to human tryptase beta 1 with, or cross-blocks or is cross-blocked by, any one of the preceding antibodies. In some examples, whether the antibody binds to the same epitope or competes for binding to human tryptase beta 1 is determined by an epitope binning assay. In some examples, the epitope binning assay is an OCTET® epitope binning assay such as described in Example 3, Section C. In some examples, human tryptase beta 1 monomer protein is biotinylated at Lys residue by reacting with NHS-PEG4-biotin. Biotinylated monomer is diluted to 5 µg/ml in kinetics buffer (ForteBio, Inc.) and immobilized onto streptavidin sensor tips (ForteBio, Inc.). After the immobilization step, human tryptase beta 1-immobilized sensors are saturated with the first antibody, diluted at 10-20 µg/ml, followed by binding with second antibody diluted at 2.5 µg/ml. In some examples, the epitope binning assay is performed at 30°C.

In another example, the disclosure features an antibody that competes for binding to human tryptase beta 1 with, or cross-blocks or is cross-blocked by any one of the preceding antibodies.

In some examples of any of the preceding aspects, the antibody is monoclonal, human, humanized, or chimeric. In some examples, the antibody is humanized.

In some examples of any of the preceding aspects, the antibody is an antibody fragment that binds tryptase. In some examples, the antibody fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

In some examples of any of the preceding aspects, the antibody is a full-length antibody. In some examples, the antibody is an IgG antibody. In some examples, the IgG antibody is an IgG1 antibody. In some examples, the IgG antibody is an IgG4 antibody. In some examples, the IgG4 antibody comprises a mutation in the hinge region. In some examples, the mutation is a substitution

mutation. In some examples, the substitution mutation is at amino acid residue S228 (EU numbering). In some examples, the IgG4 antibody comprises an S228P mutation (EU numbering).

In some examples of any of the preceding aspects, the antibody is a monospecific antibody.

In some examples of any of the preceding aspects, the antibody is a multispecific antibody. In some examples, the antibody is a bispecific antibody. In some examples, the antibody comprises a first binding domain that binds to tryptase and a second binding domain that binds to a second biological molecule, wherein the second biological molecule is selected from the group consisting of interleukin-13 (IL-13), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-17 (IL-17), IgE, and interleukin-33 (IL-33). In some examples, the second biological molecule is IL-13. In some examples, the second biological molecule is IL-33. In some examples, the second biological molecule is IgE.

In another aspect, the present disclosure refers to an isolated nucleic acid, or a set of isolated nucleic acids, encoding any of the antibodies described herein.

In another aspect, the present disclosure refers to an isolated nucleic acid, or a set of isolated nucleic acids, encoding an antibody comprising a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and/or a VL domain comprising the amino acid sequence of SEQ ID NO: 10, wherein the nucleic acid or set comprises a sequence that is at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 104 and/or SEQ ID NO: 105. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 and/or (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77, and wherein the nucleic acid or set comprises a sequence that is at least 85%, at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 106 and/or SEQ ID NO: 107. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and/or (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79, and wherein the nucleic acid or set comprises a sequence that is at least 85%, at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 108 and/or SEQ ID NO: 107. In some examples, the nucleic acid or set comprises the sequence of SEQ ID NO: 108 and/or SEQ ID NO: 107.

In another aspect, the present disclosure refers to an isolated nucleic acid, or a set of nucleic acids, encoding the antibody comprising a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and/or a VL domain comprising the amino acid sequence of SEQ ID NO: 37, wherein the nucleic acid or set comprises a sequence that is at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 109 and/or SEQ ID NO: 110. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and/or (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81, and wherein the nucleic acid or set comprises a sequence that is at least 85%, at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 111 and/or SEQ ID NO: 112. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and/or (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83, and wherein the nucleic acid or set comprises a sequence that is at least 85%, at least 90%, at least 95%, or at least 99%

identical to the sequence of SEQ ID NO: 113 and/or SEQ ID NO: 112. In some examples, the nucleic acid or set comprises the sequence of SEQ ID NO: 113 and/or SEQ ID NO: 112.

In another example, the disclosure features a vector (e.g., an expression vector) or set of vectors comprising any of the isolated nucleic acids or set of isolated nucleic acids described herein. In one aspect, the present disclosure refers to a vector or set of vectors comprising any of the isolated nucleic acids or sets of isolated nucleic acids described herein. In another example, the disclosure features host cells comprising the preceding nucleic acids and/or vectors and/or sets of nucleic acids and/or sets of vectors. In one aspect, the present disclosure refers to a host cell comprising any of the vectors or sets of vectors described herein. In some examples, the host cell is a mammalian cell. In some examples, the mammalian cell is a Chinese hamster ovary (CHO) cell. In some examples, the host cell is a prokaryotic cell. In some examples, the prokaryotic cell is *E. coli*.

In another example, the disclosure features a method of producing any of the antibodies described herein, the method comprising culturing a host cell that comprises any of the preceding vectors (e.g., expression vectors) or set of vectors in a culture medium under suitable conditions that allow production of the antibody. In one aspect, the present disclosure refers to a method of producing any of the antibodies described herein, the method comprising culturing any of the host cells described herein in a culture medium under suitable conditions that allow production of the antibody. In some examples, the method further comprises recovering the antibody from the host cell or the culture medium.

In another example, the disclosure features composition (e.g., a pharmaceutical composition) comprising any one of the preceding antibodies. In some examples, the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any of the antibodies described herein and a pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising an isolated monoclonal antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to monomeric tryptase beta 1 with a K_D of about 0.1 nM to about 1 nM, and/or wherein the antibody is capable of inhibiting the enzymatic activity of the tryptase with a half-maximal inhibitory concentration (IC₅₀) of about 0.1 nM to about 5 nM as determined by an in vitro tryptase enzymatic assay using S-2288 as a substrate.

In some examples of the preceding aspect, the antibody binds the tryptase with a K_D between about 0.5 nM to about 1 nM. In some examples, the antibody binds the tryptase with a K_D between about 0.1 nM to about 0.5 nM. In some examples, the antibody binds the tryptase with a K_D of about 0.4 nM. In some examples, the antibody binds the tryptase with a K_D of about 0.2 nM. In some examples, the K_D is measured by a surface plasmon resonance (SPR) assay. In some examples, the SPR assay is performed at 25°C. In some examples, the K_D is measured using a BIACORE® SPR assay, for example, as described in Example 1, Section (A)(vii). In some examples, the SPR assay can use a BIAcore® T200 or an equivalent device. In some examples, BIAcore® Series S CM5 sensor chips (or equivalent sensor chips) are immobilized with monoclonal mouse anti-human IgG (Fc) antibody and anti-tryptase antibodies are subsequently captured on the flow cell. Serial 3-fold dilutions of the His-tagged human tryptase beta 1 monomer (SEQ ID NO: 128) are injected at a flow rate of 30 µl/min. Each sample is analyzed with 3 min association and 10 min dissociation. The assay is performed at 25°C. After each injection, the chip is regenerated using 3 M MgCl₂. Binding response is corrected by subtracting the response units (RU) from a flow cell capturing an irrelevant IgG at similar density. A 1:1 Langmuir model of simultaneous fitting of k_{on} and k_{off} is used for kinetics analysis.

In some examples of the preceding aspect, the antibody is capable of inhibiting the activity of the tryptase with an IC₅₀ of about 0.5 nM to about 5 nM. In some examples, the antibody is capable of inhibiting the activity of the tryptase with an IC₅₀ of about 0.1 nM to about 2 nM. In some

examples, the antibody is capable of inhibiting the activity of human tryptase with an IC₅₀ of about 4 nM. In some examples, the antibody is capable of inhibiting the activity of the tryptase with an IC₅₀ of about 0.6 nM. In some examples, the antibody is capable of inhibiting the tryptase activity at pH 6 in an in vitro tryptase enzymatic assay using S-2288 as a substrate. In some examples, the inhibitory activity of the antibody is determined as described in the Examples (e.g., Example 1, Section (A)(viii)(a)). In some examples, recombinant human tryptase beta 1 tetramer active enzyme is diluted to 0.75 nM in TNH Buffer (200 mM Tris, 150 mM NaCl, 0.1 mg/mL heparin, 0.01% TRITON™ X-100, pH 8.0), and combined 1:1 with anti-tryptase antibodies (diluted in PBS) in 384-well plates. Plates are incubated for 1 h at ambient temperature with gentle agitation. Colorimetric substrate S-2288 (Chromogenix, Part No. 82-0852-39), or an equivalent substrate, is diluted to 1200 μM in TNH Buffer and added to the plate. In some examples, the final in-well concentrations are 400 μM S-2288, 0.25 nM recombinant human tryptase beta 1 tetramer, 66 μg/mL heparin, and from 0.10 to 222 nM anti-tryptase antibody. Plates are incubated for 40 min at ambient temperature with gentle agitation and then read at A₄₀₅. The IC₅₀ of the anti-tryptase antibodies is determined from a four-parameter fit of their respective curves. In some examples, the final concentration of heparin in the human tryptase beta enzymatic assay using the synthetic peptide S-2288 is 66 μg/ml.

In some examples of the preceding aspect, the antibody is capable inhibiting tryptase-mediated stimulation of bronchial smooth muscle cell proliferation and/or collagen-based contraction. In some examples, the antibody is capable of inhibiting mast cell histamine release. In some examples, the antibody is capable of inhibiting IgE-triggered histamine release and/or tryptase-triggered histamine release. In some examples, the antibody is capable of inhibiting tryptase activity in cynomolgus monkey broncheolar lavage (BAL) or nasosorption samples. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1 when in a monovalent format. In some examples, the monovalent format is a Fab format. In some examples, the antibody is capable of dissociating tetrameric human tryptase beta 1 in the presence of heparin. In some examples, the antibody is capable of dissociating tetrameric tryptase beta in the presence of 66 μg/ml heparin.

In some examples of the preceding aspect, the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6). In some examples, the antibody comprises (a) a heavy chain variable (VH) domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 10; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1

comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO: 11); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 12); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 13); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14). In some examples, the VH domain of the antibody comprises the amino acid sequence of SEQ ID NO: 9. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 15); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKSPKPIWY (SEQ ID NO: 16); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDFATYYC (SEQ ID NO: 17); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 18). In some examples, the VL domain of the antibody comprises the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising His51 and at least one, at least two, or all three residues selected from the group consisting of Val 80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or all twelve amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises His51, Gln67, Val80, Lys81, Asp82, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating both the small interface of tetrameric human tryptase beta 1 and the large interface of tetrameric human tryptase beta 1.

In other examples of the preceding aspect, the antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYAIT (SEQ ID NO: 30); (b) an HVR-H2 comprising the amino acid sequence of GISSAATTFYSSWAKS (SEQ ID NO: 31); (c) an HVR-H3 comprising the amino acid sequence of DPRGYGAALDRLDL (SEQ ID NO: 32); (d) an HVR-L1 comprising the amino acid sequence of QSIKSVYNNRLG (SEQ ID NO: 33); (e) an HVR-L2 comprising the amino acid sequence of ETSILTS (SEQ ID NO: 34); and (f) an HVR-L3 comprising the amino acid sequence of AGGFDRSGDIT (SEQ ID NO: 35). In some examples, the antibody comprises (a) a VH domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to

the amino acid sequence of any one of SEQ ID NOs: 36, 47, 48, 49, 50, 51, and 52; (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of any one of SEQ ID NO: 37, 53, 58, or 59; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGPGLVKPSSETLSLTCTVSRFSLI (SEQ ID NO: 38); (b) an FR-H2 comprising the amino acid sequence of WIRQPPGKGLEWIG (SEQ ID NO: 42); (c) an FR-H3 comprising the amino acid sequence of RVTISRDTSKNQVSLKLSSVTAADTAVYYCAR (SEQ ID NO: 43); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVTVSS (SEQ ID NO: 41). In some examples, the VH domain of the antibody comprises the amino acid sequence of SEQ ID NO: 36. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 64); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 65); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFLTITSSLPEDFATYYC (SEQ ID NO: 66); and (d) an FR-L4 comprising the amino acid sequence of FGQGTVKVEIK (SEQ ID NO: 63). In some examples, the VL domain of the antibody comprises the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, or all fourteen amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope comprises Gln35, Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Gln100, Leu101, Leu102, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, Glu129, and Arg216 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is relative to a human tryptase beta 1 tetramer, and the epitope on human tryptase beta 1 further comprises one or both of Gln35 and Arg216 of SEQ ID NO: 71. In some examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating the small interface and/or the large interface of human tryptase beta 1.

In another example, the disclosure features a composition (e.g., a pharmaceutical composition) comprising an isolated monoclonal antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all

four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71. In one aspect, the present disclosure refers to a pharmaceutical composition comprising an isolated monoclonal antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the antibody binds to an epitope on human tryptase beta 1 comprising His51 and at least one, at least two, or all three residues selected from the group consisting of Val80, Lys81, and Asp82 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or all twelve amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises His51, Gln67, Val80, Lys81, Asp82, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating both the small interface of tetrameric human tryptase beta 1 and the large interface of tetrameric human tryptase beta 1. In some examples, the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6). In some examples, the antibody comprises (a) a heavy chain variable (VH) domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 10; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFS (SEQ ID NO: 11); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 12); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNSKNTLYQMNSLRAEDTAVYYCTR (SEQ ID NO: 13); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 14). In some examples, the VH domain of the antibody comprises the amino acid sequence of SEQ ID NO: 9. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 15); (b) an FR-L2 comprising the amino acid sequence of WYQKPKGKSPKPIY (SEQ ID NO: 16); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDFATYYC (SEQ ID NO: 17); and (d) an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 18). In some examples, the VL domain of the antibody comprises the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 and (b) a light chain

comprising the amino acid sequence of SEQ ID NO: 77. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 79.

In another example, the disclosure features a composition (e.g., a pharmaceutical composition) comprising an isolated monoclonal antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71. In one aspect, the present disclosure refers to a pharmaceutical composition comprising an isolated monoclonal antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope on human tryptase beta 1 comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, or all fourteen amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71. In some examples, the epitope comprises Gln35, Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Gln100, Leu101, Leu102, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, Glu129, and Arg216 of SEQ ID NO: 71. In some examples, the epitope is relative to a human tryptase beta 1 monomer or tetramer. In some examples, the epitope is relative to a human tryptase beta 1 tetramer, and the epitope on human tryptase beta 1 further comprises one or both of Gln35 and Arg216 of SEQ ID NO: 71. In some examples, the epitope is determined by an X-ray crystallography model. In some examples, the antibody is capable of dissociating the small interface and/or the large interface of human tryptase beta 1. In some examples, the antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYAIT (SEQ ID NO: 30); (b) an HVR-H2 comprising the amino acid sequence of GISSAATTFYSSWAKS (SEQ ID NO: 31); (c) an HVR-H3 comprising the amino acid sequence of DPRGYGAALDRLDL (SEQ ID NO: 32); (d) an HVR-L1 comprising the amino acid sequence of QSIKSVYNNRLG (SEQ ID NO: 33); (e) an HVR-L2 comprising the amino acid sequence of ETSILTS (SEQ ID NO: 34); and (f) an HVR-L3 comprising the amino acid sequence of AGGFDRSGDTT (SEQ ID NO: 35). In some examples, the antibody comprises (a) a VH domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 36, 47, 48, 49, 50, 51, and 52; (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of any one of SEQ ID NO: 37, 53, 58, or 59; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the antibody further comprises the following VH domain FRs: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGPGGLVKPSETLSLTCTVSRFSLI (SEQ ID NO: 38); (b) an FR-H2 comprising the amino acid sequence of WIRQPPGKGLEWIG (SEQ ID NO: 42); (c) an FR-H3 comprising the amino acid sequence of RVTISRDTSKNQVSLKLSSVTAADTAVYYCAR (SEQ ID NO: 43); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 41). In some examples, the VH domain of the antibody comprises the amino acid sequence of SEQ ID NO: 36. In some examples, the antibody further comprises the following VL domain FRs: (a) an FR-L1

comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 64); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKLLIY (SEQ ID NO: 65); (c) an FR-L3 comprising the amino acid sequence of GVPSRFGSGSGTDFLTITSLQPEDFATYYC (SEQ ID NO: 66); and (d) an FR-L4 comprising the amino acid sequence of FGQGKVEIK (SEQ ID NO: 63). In some examples, the VL domain of the antibody comprises the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 83.

In some examples, the antibody is capable of further binding to human tryptase alpha, tryptase beta 2, tryptase beta 3 and/or cyno tryptase D1.

In any of the preceding compositions (e.g., pharmaceutical compositions), the antibody may be monoclonal, human, humanized, or chimeric. In some examples, the antibody is humanized.

In any of the preceding compositions (e.g., pharmaceutical compositions), the composition may be for use in a human.

Any of the preceding compositions (e.g., pharmaceutical compositions) may be lyophilized. In other examples, any of the preceding compositions (e.g., pharmaceutical compositions) may be a liquid.

In any of the preceding compositions (e.g., pharmaceutical compositions), the excipient may be an antioxidant. In some examples, the composition comprises one or more antioxidants selected from the group consisting of N-acetyltryptophan, tryptophan, methionine, cysteine, glutathione, thiosorbitol, ascorbic acid, monothioglycerol, cyclodextrins, Trolox (6-hydroxy-2,5,7,8- tetramethylchroman-2-carboxylic acid), pyridoxine, mannitol, and a metal chelator. In some examples, the composition comprises N-acetyltryptophan or methionine. In some examples, the composition comprises N-acetyltryptophan and methionine.

In another example, the disclosure features a composition (e.g., a pharmaceutical composition) comprising: (i) an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6), wherein the oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is no more than 30%. In one aspect, the present disclosure refers to a pharmaceutical composition comprising: (i) an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6), wherein the oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is no more than 30%. In some examples, the oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is no more than 28%, 25%, 20%, 15%, 10%, or 6%. In some examples, the oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is determined following an AAPH stress test. In some examples, the oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is determined within one year from the initial production of the composition.

Any of the preceding compositions (e.g., pharmaceutical compositions) may comprise N-acetyltryptophan at a concentration of about 0.1 mM to about 5 mM. In some examples, the concentration of N-acetyltryptophan is about 0.1 mM to about 1 mM. In some examples, the concentration of N-acetyltryptophan is about 0.3 mM. In some examples, the composition comprises methionine at a concentration of about 1 mM to about 20 mM. In some examples, the concentration of methionine is about 1 mM to about 10 mM. In some examples, the concentration of methionine is about 5 mM.

In another example, the disclosure features a composition (e.g., a pharmaceutical composition) comprising: (i) an isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and

(f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6); (ii) N-acetyltryptophan at a concentration of about 0.1 mM to about 1 mM; and (iii) methionine at a concentration of about 1 mM to about 10 mM. In one aspect, the present disclosure refers to a pharmaceutical composition comprising: (i) an isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7); (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8); (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6); (ii) N-acetyltryptophan at a concentration of about 0.1 mM to about 1 mM; and (iii) methionine at a concentration of about 1 mM to about 10 mM.

In any of the preceding compositions (e.g., pharmaceutical compositions), the antibody concentration may be about 1 mg/ml to about 250 mg/ml. In some examples, the antibody concentration is about 150 mg/ml.

Any of the preceding compositions (e.g., pharmaceutical compositions) may further include one or more additional excipients selected from the group consisting of a stabilizer, a buffer, a surfactant, and a tonicity agent. In some examples, the composition further comprises a buffer. In some examples, the buffer is arginine succinate and/or histidine succinate. In some examples, the buffer comprises arginine succinate and histidine succinate. In some examples, the concentration of arginine succinate is about 50 mM to about 500 mM. In some examples, the concentration of arginine succinate is about 100 mM to about 300 mM. In some examples, the concentration of arginine succinate is about 200 mM. In some examples, the concentration of histidine succinate is about 1 mM to about 50 mM. In some examples, the concentration of histidine succinate is about 15 mM to about 25 mM. In some examples, the concentration of histidine succinate is about 20 mM. In some examples, the composition further comprises a surfactant. In some examples, the surfactant is poloxamer 188 or polysorbate 20. In some examples, the surfactant is poloxamer 188. In some examples, the concentration of poloxamer 188 is about 0.005% to about 0.1%. In some examples, the concentration of poloxamer 188 is about 0.005% to about 0.05%. In some examples, the concentration of poloxamer 188 is about 0.02%. In some examples, the pH of the composition is about 4.5 to about 7.0. In some examples, the pH of the composition is about 4.5 to about 6.5. In some examples, the pH of the composition is about 5.5. In some examples, the composition is in a light-proof container. In some examples, the composition is in a pre-filled syringe.

Any of the preceding compositions (e.g., pharmaceutical compositions) may further include an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some instances, the IgE antagonist is omalizumab (XOLAIR®).

Any of the preceding compositions (e.g., pharmaceutical compositions) may be formulated for administration to a human. In certain examples, the pharmaceutical compositions comprise antibodies that do not comprise non-human constant region sequences. In certain examples, the pharmaceutical compositions comprise antibodies that do not comprise non-human framework and non-human constant region sequences. In certain examples, the pharmaceutical compositions comprise antibodies that are human antibodies, humanized antibodies, or chimeric antibodies.

In some examples, any one of the preceding antibodies can be used as a medicament. In one aspect, the present disclosure refers to any one of the preceding antibodies for use as a medicament.

In some examples, any of the preceding antibodies can be used in treating a disorder. In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In one aspect, the present disclosure refers to any of the preceding antibodies for use in treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis. In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU, also known as chronic spontaneous urticaria, CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples, the disorder is a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the antibody is for use in combination with an additional therapeutic agent. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an

immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some
5 examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some examples, the antibody is for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the
10 antibody is for administration subcutaneously. In some examples, the antibody is for use in a human subject.

In some examples, any one of the preceding compositions (e.g., pharmaceutical compositions) can be used as a medicament. In one aspect, the present disclosure refers to any one of the preceding pharmaceutical compositions for use as a medicament.

15 In some examples, any of the preceding compositions (e.g., pharmaceutical compositions) can be used in treating a disorder. In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as
20 mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In one aspect, the present disclosure refers to any of the preceding pharmaceutical compositions for use in treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated
25 with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis. In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the
30 autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU or CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples, the disorder is a disorder associated with increased numbers or distribution of
35 normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the composition (e.g., pharmaceutical composition) is for use in combination with an additional therapeutic agent. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33
40 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding
45 antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding

antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some examples, the composition (e.g., pharmaceutical composition) is for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the composition (e.g., pharmaceutical composition) is for administration subcutaneously. In some examples, the composition (e.g., pharmaceutical composition) is for use in a human subject.

In some examples, any one of the preceding antibodies can be used in the manufacture of a medicament for treating a disorder. In one aspect, the present disclosure refers to use of any one of the preceding antibodies in the manufacture of a medicament for treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis. In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU or CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples, the disorder is a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the medicament is formulated for use in combination with an additional therapeutic agent. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some examples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the medicament is formulated for administration subcutaneously. In some examples, the medicament is formulated for use in a human subject.

In some examples, any one of the preceding compositions (e.g., pharmaceutical compositions) can be used in the manufacture of a medicament for treating a disorder. In one aspect, the present disclosure refers to use of any one of the preceding pharmaceutical compositions in the manufacture of a medicament for treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, or mastocytosis. In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU or CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples the disorder is a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the medicament is formulated for use in combination with an additional therapeutic agent. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some examples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the medicament is formulated for administration subcutaneously. In some examples, the medicament is formulated for use in a human subject.

In another example, the disclosure features a method of treating a disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the preceding antibodies. In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts,

smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU or CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples, the disorder is a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the method further comprises administering an additional therapeutic agent to the subject. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is quilizumab. In some embodiments, the IgE antagonist is omalizumab (Xolair®). In some examples, the antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

In another example, the disclosure features a method of treating a disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the preceding compositions (e.g., pharmaceutical compositions). In some examples, the disorder is selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, or a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is a pulmonary disorder. In some examples, the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD). In some examples, the pulmonary disorder is asthma. In some examples, the asthma is Th2-high asthma or Th2-low asthma. In some examples, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel

disease (IBD), and Crohn's disease. In some examples, the inflammatory disorder is chronic idiopathic urticaria (CIU or CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis. In some examples, the fibrotic disorder is idiopathic pulmonary fibrosis (IPF). In some examples the disorder is a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells (such as mast cells, macrophages, or lymphocytes) or stromal cells (such as fibroblasts, myofibroblasts, smooth muscle cells, epithelia, or endothelia). In some examples, the disorder is mastocytosis. In some examples, the method further comprises administering an additional therapeutic agent to the subject. In some examples, the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor. In some examples, the IL-13 axis binding antagonist is an anti-IL-13 antibody. In some examples, the anti-IL-13 antibody is lebrikizumab. In some examples, the IL-5 axis binding antagonist is an IL-5 binding antagonist or an IL-5 receptor binding antagonist. In some examples, the IL-33 axis binding antagonist is an IL-33 binding antagonist or an ST2 binding antagonist. In some examples, the IL-33 binding antagonist is an anti-IL-33 antibody. In some examples, the M1 prime antagonist is omalizumab (Xolair®). In some examples, the composition is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

Brief Description of the Drawings

FIG. 1 is a sequence alignment of the VH and VL domains of hu31A.v11 and huE104.v2 showing the complementarity determining regions (CDRs) according to the Kabat, Chothia and Contact designations. The hypervariable regions (HVRs) are underlined.

FIG. 2A is a series of graphs showing the results of an inhibition analysis of hu31A.v11 and huE104.v2 IgG as determined by a human tryptase enzymatic assay. Both antibodies completely inhibited tryptase enzymatic activity.

FIGS. 2B and **2C** are graphs showing the results of human primary airway smooth muscle cell (SMC) proliferation (Fig. 2B) and contraction (Fig. 2C) assays. Addition of tryptase beta stimulated human primary airway SMC proliferation, which was inhibited in a dose-dependent manner by addition of the anti-tryptase antibody hu31A.v11 IgG4 or huE104.v2 IgG4 (Fig. 2B). Addition of tryptase also stimulated human primary airway SMC contraction, which was also inhibited by addition of hu31A.v11 IgG4 and huE104.v2 IgG4 (Fig. 2C).

FIGS. 2D and **2E** are graphs showing the results of mast cell degranulation assays in which mast cells were stimulated in vitro by addition of tryptase beta or anti-4-hydroxy-3-nitrophenylacetyl (NP) IgE and NP. Addition of tryptase resulted in histamine release, which was blocked by addition of hu31A.v11 (Fig. 2D). A catalytically-inactive mutant tryptase (S195A) served as a control. Addition of IgE and NP also resulted in histamine release, which was inhibited (30-50%) by addition of a tryptase small molecule inhibitor (SMI) or hu31A.v11 (Fig. 2E).

What is claimed is:

1. An isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs):

- (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7);
- (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2);
- (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8);
- (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4);
- (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and
- (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6).

2. The antibody of claim 1, wherein the antibody comprises (a) a heavy chain variable (VH) domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 10; or (c) a VH domain as in (a) and a VL domain as in (b).

3. The antibody of claim 1 or 2, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 9.

4. The antibody of any one of claims 1-3, wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 10.

5. An isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 9 and (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 10.

6. The antibody of claim 5, wherein the antibody comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10.

7. An isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 76 or SEQ ID NO: 78 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 77 or SEQ ID NO: 79.

8. An isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six HVRs:

- (a) an HVR-H1 comprising the amino acid sequence of GYAIT (SEQ ID NO: 30);
- (b) an HVR-H2 comprising the amino acid sequence of GISSAATTFYSSWAKS (SEQ ID NO: 31);

- (c) an HVR-H3 comprising the amino acid sequence of DPRGYGAALDRLDL (SEQ ID NO: 32);
- (d) an HVR-L1 comprising the amino acid sequence of QSIKSVYNNRLG (SEQ ID NO: 33);
- (e) an HVR-L2 comprising the amino acid sequence of ETSILTS (SEQ ID NO: 34); and
- (f) an HVR-L3 comprising the amino acid sequence of AGGFDRSGDTT (SEQ ID NO: 35).

9. An isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 36, 47, 48, 49, 50, 51, and 52; (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of any one of SEQ ID NO: 37, 53, 58, or 59; or (c) a VH domain as in (a) and a VL domain as in (b).

10. An isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 36 and (b) a VL domain comprising an amino acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 37.

11. The antibody of claim 10, wherein the antibody comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and a VL domain comprising the amino acid sequence of SEQ ID NO: 37.

12. An isolated antibody comprising (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 or SEQ ID NO: 82 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 83.

13. The antibody of any one of claims 1-7, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71.

14. The antibody of claim 13, wherein the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Gln67, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71.

15. The antibody of claim 14, wherein the epitope on human tryptase beta 1 comprises His51, Gln67, Val80, Lys81, Asp82, Leu83, Ala84, Ala85, Arg87, Pro103, Val104, Ser105, Arg106, Glu128, Glu129, and Pro130 of SEQ ID NO: 71.

16. The antibody of any one of claims 1-7 or 13-15, wherein the antibody is capable of dissociating both the small interface of tetrameric human tryptase beta 1 and the large interface of tetrameric human tryptase beta 1.

17. The antibody of any one of claims 8-12, wherein the antibody binds to an epitope on human tryptase beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71.

18. The antibody of claim 17, wherein the epitope on human tryptase beta 1 further comprises one or more amino acid residues selected from the group consisting of Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, and Glu129 of SEQ ID NO: 71.

19. The antibody of claim 18, wherein the epitope comprises Gln35, Trp55, Gln67, Asp82, Leu83, Ala84, Arg87, Gln100, Leu101, Leu102, Pro103, Val104, Ser105, Arg106, Glu126, Leu127, Glu128, Glu129, and Arg216 of SEQ ID NO:71.

20. The antibody of any one of claims 1-19, wherein the antibody further binds cynomolgus monkey (cyno) tryptase, human tryptase alpha, human tryptase beta 2 and/or human tryptase beta 3.

21. The antibody of any one of claims 1-20, wherein the antibody binds the tryptase with a K_D of about 1 nM or less.

22. The antibody of claim 21, wherein the antibody binds the tryptase with a K_D of between about 120 pM and about 0.5 nM.

23. The antibody of claim 22, wherein the antibody binds tryptase with a K_D of about 400 pM.

24. The antibody of any one of claims 1-23, wherein the antibody is capable of inhibiting the enzymatic activity of human tryptase beta 1.

25. The antibody of claim 24, wherein the antibody inhibits the activity of tryptase with an IC_{50} of about 2.5 nM or lower as determined by a human tryptase beta enzymatic assay using a synthetic peptide S-2288 as a substrate.

26. The antibody of any one of claims 1-25, wherein:

- (i) the antibody is capable of inhibiting the enzymatic activity of human tryptase beta 1 at pH 6;
- (ii) the antibody is capable of inhibiting tryptase-mediated stimulation of bronchial smooth muscle cell proliferation and/or collagen-based contraction;
- (iii) the antibody is capable of inhibiting mast cell histamine release;
- (iv) the antibody is capable of inhibiting IgE-triggered histamine release and/or tryptase-triggered histamine release;
- (v) the antibody is capable of inhibiting tryptase activity in cynomolgus monkey broncheolar lavage (BAL) or nasosorption samples;
- (vi) the antibody is capable of dissociating tetrameric human tryptase beta 1;

(vii) the antibody is capable of dissociating tetrameric human tryptase beta 1 when in a monovalent format; and/or

(viii) the antibody is capable of dissociating tetrameric human tryptase beta 1 in the presence of heparin.

27. An antibody that binds to the same epitope as the antibody of any one of claim 1-26 or that competes for binding to human tryptase beta 1 with, or cross-blocks or is cross-blocked by, the antibody of any one of claims 1-26.

28. The antibody of any one of claims 1-27, wherein the antibody is monoclonal or humanized.

29. The antibody of any one of claims 1-6, 8-11, and 13-28, wherein the antibody is an antibody fragment that binds human tryptase beta 1.

30. The antibody of any one of claims 1-28, wherein the antibody is a full-length antibody.

31. The antibody of claim 30, wherein the antibody is an IgG antibody.

32. The antibody of claim 31, wherein the IgG antibody is an IgG1 antibody or an IgG4 antibody.

33. The antibody of claim 32, wherein the IgG4 antibody comprises an S228P mutation (EU numbering).

34. The antibody of any one of claims 1-33, wherein the antibody is a monospecific antibody or a multispecific antibody.

35. The antibody of claim 34, wherein the antibody is a bispecific antibody.

36. The antibody of claim 35, wherein the antibody comprises a first binding domain that binds to human tryptase beta 1 and a second binding domain that binds to a second biological molecule, wherein the second biological molecule is selected from the group consisting of interleukin-13 (IL-13), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-17 (IL-17), IgE, and interleukin-33 (IL-33).

37. An isolated nucleic acid, or a set of isolated nucleic acids, encoding the antibody of any one of claims 1-36.

38. An isolated nucleic acid, or a set of isolated nucleic acids, encoding an antibody comprising a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and/or a VL domain comprising the amino acid sequence of SEQ ID NO: 10, wherein the nucleic acid or set comprises a sequence that is at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 104 and/or SEQ ID NO: 105.

39. An isolated nucleic acid, or a set of isolated nucleic acids, encoding the antibody comprising a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and/or a VL domain comprising the amino acid sequence of SEQ ID NO: 37, wherein the nucleic acid or set comprises a sequence that is at least 90%, at least 95%, or at least 99% identical to the sequence of SEQ ID NO: 109 and/or SEQ ID NO: 110.

40. A vector or set of vectors comprising the isolated nucleic acid or set of isolated nucleic acids of any one of claims 37-39.

41. A host cell comprising the vector or set of vectors of claim 40.

42. The host cell of claim 41, wherein the host cell is a mammalian cell or a prokaryotic cell.

43. A method of producing the antibody of any one of claims 1-36, the method comprising culturing the host cell of claim 41 in a culture medium under suitable conditions that allow production of the antibody.

44. A pharmaceutical composition comprising the antibody of any one of claims 1-36 and a pharmaceutically acceptable carrier, excipient, or diluent.

45. A pharmaceutical composition comprising an isolated monoclonal antibody that binds to human trypsin beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to monomeric trypsin beta 1 with a K_D of about 0.1 nM to about 1 nM, and/or wherein the antibody is capable of inhibiting the enzymatic activity of the trypsin with a half-maximal inhibitory concentration (IC₅₀) of about 0.1 nM to about 5 nM as determined by an in vitro trypsin enzymatic assay using S-2288 as a substrate.

46. A pharmaceutical composition comprising an isolated monoclonal antibody that binds to human trypsin beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human trypsin beta 1 comprising at least one, at least two, at least three, or all four residues selected from the group consisting of His51, Val80, Lys81, and Asp82 of SEQ ID NO: 71.

47. A pharmaceutical composition comprising an isolated monoclonal antibody that binds to human trypsin beta 1, or an antigen-binding fragment thereof, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the antibody binds to an epitope on human trypsin beta 1 comprising at least one, at least two, or all three residues selected from the group consisting of Gln100, Leu101, and Leu102 of SEQ ID NO: 71.

48. The composition of any one of claims 44-47, wherein the excipient is an antioxidant.

49. A pharmaceutical composition comprising:

(i) an isolated antibody that binds to human tryptase beta 1, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs):

- (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7);
- (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2);
- (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8);
- (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4);
- (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and
- (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6), wherein the

oxidation of tryptophan at position 6 of HVR-H3 (SEQ ID NO: 8) is no more than 30%.

50. A pharmaceutical composition comprising:

(i) an isolated antibody that binds to human tryptase, or an antigen-binding fragment thereof, wherein the antibody comprises the following six hypervariable regions (HVRs):

- (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 7);
- (b) an HVR-H2 comprising the amino acid sequence of FISSGSSTVYYADTMKG (SEQ ID NO: 2);
- (c) an HVR-H3 comprising the amino acid sequence of RNYDDWYFDV (SEQ ID NO: 8);
- (d) an HVR-L1 comprising the amino acid sequence of SASSSVTYMY (SEQ ID NO: 4);
- (e) an HVR-L2 comprising the amino acid sequence of RTSDLAS (SEQ ID NO: 5); and
- (f) an HVR-L3 comprising the amino acid sequence of QHYHSYPLT (SEQ ID NO: 6);

(ii) N-acetyltryptophan at a concentration of about 0.1 mM to about 1 mM; and

(iii) methionine at a concentration of about 1 mM to about 10 mM.

51. The composition of any one of claims 44-50, wherein the composition is in a light-proof container or pre-filled syringe.

52. The composition of any one of claims 44-51, wherein the composition further comprises an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor.

53. The antibody of any one of claims 1-36 for use as a medicament.

54. The antibody of any one of claims 1-36 for use in treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis.

55. The antibody for use of claim 54, wherein the disorder is a pulmonary disorder.

56. The antibody for use of claim 55, wherein the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD).

57. The antibody for use of claim 56, wherein the pulmonary disorder is asthma.

58. The antibody for use of claim 54, wherein the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease.

59. The antibody for use of claim 54, wherein the inflammatory disorder is chronic spontaneous urticaria (CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis.

60. The antibody for use of claim 54, wherein the fibrotic disorder is idiopathic pulmonary fibrosis (IPF).

61. The antibody for use of any one of claims 54-60, which is for use in combination with an additional therapeutic agent.

62. The antibody for use of claim 61, wherein the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor.

63. The antibody for use of any one of claims 54-62, which is for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

64. The pharmaceutical composition of any one of claims 44-52 for use as a medicament.

65. The pharmaceutical composition of any one of claims 44-52 for use in treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis.

66. The pharmaceutical composition for use of claim 65, wherein the disorder is a pulmonary disorder.

67. The pharmaceutical composition for use of claim 66, wherein the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD).

68. The pharmaceutical composition for use of claim 67, wherein the pulmonary disorder is asthma.

69. The pharmaceutical composition for use of claim 65, wherein the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease.

70. The pharmaceutical composition for use of claim 65, wherein the inflammatory disorder is chronic spontaneous urticaria (CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis.

71. The pharmaceutical composition for use of claim 65, wherein the fibrotic disorder is idiopathic pulmonary fibrosis (IPF).

72. The pharmaceutical composition for use of any one of claims 65-71, which is for use in combination with an additional therapeutic agent.

73. The pharmaceutical composition for use of claim 72, wherein the additional therapeutic agent is an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor.

74. The pharmaceutical composition for use of any one of claims 65-73, which is for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

75. Use of an antibody of any one of claims 1-36 in the manufacture of a medicament for treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, and mastocytosis.

76. The use of claim 75, wherein the disorder is a pulmonary disorder.

77. The use of claim 76, wherein the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD).

78. The use of claim 77, wherein the pulmonary disorder is asthma.

79. The use of claim 75, wherein the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease.

80. The use of claim 75, wherein the inflammatory disorder is chronic spontaneous urticaria (CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis.

81. The use of claim 75, wherein the fibrotic disorder is idiopathic pulmonary fibrosis (IPF).

82. The use of any one of claims 75-81, wherein the medicament is formulated for use in combination with an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor.

83. Use of a pharmaceutical composition of any one of claims 44-52 in the manufacture of a medicament for treating a disorder selected from the group consisting of a pulmonary disorder, an autoimmune disorder, an inflammatory disorder, a fibrotic disorder, a granulocytic (neutrophilic or eosinophilic) disorder, a monocytic disorder, a lymphocytic disorder, a disorder associated with increased numbers or distribution of normal or aberrant tissue resident cells or stromal cells, or mastocytosis.

84. The use of claim 83, wherein the disorder is a pulmonary disorder.

85. The use of claim 84, wherein the pulmonary disorder is selected from the group consisting of asthma, airway hyperresponsiveness, and chronic obstructive pulmonary disease (COPD).

86. The use of claim 85, wherein the pulmonary disorder is asthma.

87. The use of claim 83, wherein the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, psoriasis, eosinophilic esophagitis, inflammatory bowel disease (IBD), and Crohn's disease.

88. The use of claim 83, wherein the inflammatory disorder is chronic spontaneous urticaria (CSU), anaphylaxis, anaphylactic shock, atopic dermatitis, or allergic rhinitis.

89. The use of claim 83, wherein the fibrotic disorder is idiopathic pulmonary fibrosis (IPF).

90. The use of any one of claims 83-89, wherein the medicament is formulated for use in combination with an IL-13 axis binding antagonist, an IL-5 axis binding antagonist, an IL-33 axis binding antagonist, an M1 prime antagonist, an IgE antagonist, a TRPA1 antagonist, a CRTH2 antagonist, a broncodilator or

asthma symptom controller medication, an immunomodulator, a corticosteroid, a Th2 pathway inhibitor, a tyrosine kinase inhibitor, or a phosphodiesterase inhibitor.

91. The use of any one of claims 75-90, wherein the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.