

THERAPEUTIC AND DIAGNOSTIC METHODS FOR MAST CELL-MEDIATED INFLAMMATORY DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims benefit to U.S. Provisional Application No. 62/628,564, filed on February 9, 2018, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

10 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 4, 2019, is named 50474-161WO2_Sequence_Listing_2.4.19_ST25 and is 47,396 bytes in size.

FIELD OF THE INVENTION

15 The present invention relates to therapeutic and diagnostic methods for mast cell-mediated inflammatory diseases, including asthma.

BACKGROUND

20 Asthma has canonically been described as an allergic inflammatory disorder of the airways, characterized clinically by episodic, reversible airway obstruction. The therapeutic rationale for targeting mediators of allergic inflammation in asthma has been borne out by the clinical efficacy achieved by anti-Type 2 cytokine therapies, e.g. anti-IL-5. These studies have supported the therapeutic strategy of targeting the Type 2 pathway to provide meaningful clinical benefit, especially in subjects selected on the basis of Type 2 biomarkers. Despite these advances, substantial interest remains to discover and develop new asthma therapies having greater efficacy in Type 2^{HIGH} asthma as well as for asthma patients with low levels of Type 2 biomarkers, for whom currently developed therapies are anticipated to provide less clinical benefit.

30 Mast cell infiltration of airway smooth muscles is a defining pathophysiologic feature of asthma. IgE/FcεRI-dependent and IgE/FcεRI-independent mechanisms instigate the release of soluble mast cell asthma mediators. Demonstrating the therapeutic importance of targeting mast cell biology, XOLAIR® (omalizumab), an anti-IgE monoclonal antibody therapy, is effective at reducing asthma exacerbations.

 There remains a need in the art for improved therapeutic and diagnostic approaches for asthma and other mast cell-mediated inflammatory diseases.

SUMMARY

35 The present disclosure features, *inter alia*, methods of treating patients having a mast cell-mediated inflammatory disease, methods of determining whether patients having a mast cell-mediated inflammatory disease are likely to respond to a therapy (e.g., a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an Fc epsilon receptor (FcεR) antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, an IgE antagonist, and a combination thereof), methods of selecting a therapy for a patient

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having a mast cell-mediated inflammatory disease, methods for assessing a response of a patient having mast cell-mediated inflammatory disease, and methods for monitoring the response of a patient having a mast cell-mediated inflammatory disease.

5 In one example, the disclosure features a method of treating a patient having a mast cell-mediated inflammatory disease who has been identified as having (i) a genotype comprising an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) an expression level of tryptase in a sample from the patient that is at or above a reference level of tryptase, the method comprising administering to a patient having a mast cell-mediated inflammatory disease a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof.

In another example, the disclosure features a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof, the method comprising: (a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and (b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the patient's active tryptase allele count, wherein an active tryptase allele count at or above a reference active tryptase allele count indicates that the patient has an increased likelihood of being responsive to the therapy. In one aspect, the present disclosure refers to a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising: (a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and (b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the patient's active tryptase allele count, wherein an active tryptase allele count at or above a reference active tryptase allele count indicates that the patient has an increased likelihood of being responsive to the therapy.

15 In another example, the disclosure features a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and (b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the expression level of tryptase in the sample from the patient, wherein an expression level of tryptase in the sample at or above a reference level of tryptase indicates that the patient has an increased likelihood of being responsive to the therapy. In one aspect, the present disclosure refers to a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and (b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the expression level of tryptase in the sample from the patient, wherein an expression level of tryptase in the sample at or above a reference level of tryptase indicates that the patient has an increased likelihood of being responsive to the therapy.

35 In some examples of any of the preceding aspects, the method further comprises administering the therapy to the patient.

In some examples of any of the preceding aspects, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker. In some examples, the agent is administered to the patient as a monotherapy.

40 In some examples of any of the preceding aspects, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type

2 biomarker. In some examples, the method further comprises administering a T_H2 pathway inhibitor to the patient.

In another example, the disclosure features a method of treating a patient having a mast cell-mediated inflammatory disease who has been identified as having (i) a genotype comprising an active tryptase allele count that is below a reference active tryptase allele count; or (ii) an expression level of tryptase in a sample from the patient that is below a reference level of tryptase, the method comprising administering to a patient having a mast cell-mediated inflammatory disease a therapy comprising an IgE antagonist or an Fc epsilon receptor (FcεR) antagonist.

In another aspect, the disclosure refers to a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the method comprising: (a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and (b) identifying the patient as likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist based on the patient's active tryptase allele count, wherein an active tryptase allele count below a reference active tryptase allele count indicates that the patient has an increased likelihood of being responsive to the therapy.

In another aspect, the disclosure refers to a method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and (b) identifying the patient as likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist based on the expression level of tryptase in the sample from the patient, wherein an expression level of tryptase in the sample from the patient below a reference level of tryptase indicates that the patient has an increased likelihood of being responsive to the therapy.

In some examples of any of the preceding aspects, the method further comprises administering the therapy to the patient.

In some examples of any of the preceding aspects, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker. In some examples, the method further comprises administering an additional T_H2 pathway inhibitor to the patient.

In another example, the disclosure features a method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising: (a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and (b) selecting for the patient: (i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof if the patient's active tryptase allele count is at or above a reference active tryptase allele count, or (ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the patient's active tryptase allele count is below a reference active tryptase allele count. In one aspect, the present disclosure refers to a method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising: (a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and (b) selecting for the patient: (i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof if the patient's active tryptase allele count is at or above a reference active tryptase allele count, or (ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the patient's active tryptase allele count is below a reference active tryptase allele count.

In another example, the disclosure features a method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and (b) selecting for the patient: (i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof if the expression level of tryptase in the sample from the patient is at or above a reference level of tryptase, or (ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the expression level of tryptase in the sample from the patient is below a reference level of tryptase. In one aspect, the present disclosure refers to a method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and (b) selecting for the patient: (i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof if the expression level of tryptase in the sample from the patient is at or above a reference level of tryptase, or (ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the expression level of tryptase in the sample from the patient is below a reference level of tryptase.

In some examples of any of the preceding aspects, the method further comprises administering the therapy selected in accordance with (b) to the patient.

In some examples of any of the preceding aspects, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker. In some examples, the agent is administered to the patient as a monotherapy.

In some examples of any of the preceding aspects, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the method further comprises selecting a combination therapy that comprises a T_H2 pathway inhibitor. In some examples, the method further comprises administering a T_H2 pathway inhibitor (or an additional T_H2 pathway inhibitor) to the patient.

In another example, the disclosure features a method for assessing a response of a patient having a mast cell-mediated inflammatory disease to treatment with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease at a time point during or after administration of a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and (b) maintaining, adjusting, or stopping the treatment based on a comparison of the expression level of tryptase in the sample with a reference level of tryptase, wherein a change in the expression level of tryptase in the sample from the patient compared to the reference level is indicative of a response to treatment with the therapy. In one aspect, the disclosure refers to a method for assessing a response of a patient having a mast cell-mediated inflammatory disease to treatment with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease at a time point during or after administration of a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and (b) maintaining, adjusting, or stopping the treatment based on a comparison of the expression level of tryptase in the sample with a reference level of tryptase, wherein a change in the expression level of tryptase in the sample from the patient compared to the reference level is indicative of a response to treatment with the therapy. In some examples, the change is an increase in the expression level of tryptase and the treatment is maintained. In some examples, the change is a decrease in the expression level of tryptase and the treatment is adjusted or stopped.

In another example, the disclosure features a method for monitoring the response of a patient having a mast cell-mediated inflammatory disease treated with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from the patient at a time point during or after administration of the therapy comprising an agent selected

from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and (b) comparing the expression level of tryptase in the sample from the patient with a reference level of tryptase, thereby monitoring the response of the patient undergoing treatment with the therapy. In one aspect, the disclosure refers to a method for monitoring the response of a patient having a mast cell-mediated inflammatory disease treated with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising: (a) determining the expression level of tryptase in a sample from the patient at a time point during or after administration of the therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and (b) comparing the expression level of tryptase in the sample from the patient with a reference level of tryptase, thereby monitoring the response of the patient undergoing treatment with the therapy. In some examples, the change is an increase in the level of tryptase and the treatment is maintained. In some examples, the change is a decrease in the expression level of tryptase and the treatment is adjusted or stopped.

In another example, the disclosure features an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy. In some examples, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the agent is for use in combination with a T_H2 pathway inhibitor. In some examples, the tryptase antagonist is an anti-tryptase antibody, e.g., any of the anti-tryptase antibodies disclosed herein. In some examples, the IgE antagonist is an anti-IgE antibody. e.g., any of the anti-IgE antibodies disclosed herein.

In another example, the disclosure features an agent selected from an IgE antagonist or an FcεR antagonist for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or FcεR antagonist is for use in combination with an additional T_H2 pathway inhibitor.

In another example, the disclosure provides for the use of an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase. In one aspect, the present disclosure refers to use of an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein the patient has been identified as having (i) a genotype comprising an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) an expression level of tryptase in a sample from the patient that is at or above a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy. In some examples, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and

the agent is for use in combination with a T_H2 pathway inhibitor. In some examples, the tryptase antagonist is an anti-tryptase antibody, e.g., any of the anti-tryptase antibodies disclosed herein. In some examples, the IgE antagonist is an anti-IgE antibody. e.g., any of the anti-IgE antibodies disclosed herein. In some examples, the tryptase antagonist is to be administered in combination with an IgE antagonist.

5 In some examples, the agent is a tryptase antagonist, and the medicament is formulated for administration with an IgE antagonist.

In another aspect, the disclosure refers to use of an agent selected from an IgE antagonist or an $Fc\epsilon R$ antagonist in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein: (i) the genotype of the patient has been determined to comprise an active
10 tryptase allele count that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase. In one example, the disclosure provides for the use of an IgE antagonist or an $Fc\epsilon R$ antagonist in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count
15 that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or $Fc\epsilon R$ antagonist is for use in combination with an additional T_H2 pathway inhibitor.

20 In some examples of any of the preceding aspects, the active tryptase allele count is determined by sequencing the *TPSAB1* and *TPSB2* loci of the patient's genome. In some examples, the sequencing is Sanger sequencing or massively parallel sequencing. In some examples, the *TPSAB1* locus is sequenced by a method comprising (i) amplifying a nucleic acid from the subject in the presence of a first forward primer comprising the nucleotide sequence of 5'-CTG GTG TGC AAG GTG AAT GG-3' (SEQ ID
25 NO: 31) and a first reverse primer comprising the nucleotide sequence of 5'-AGG TCC AGC ACT CAG GAG GA-3' (SEQ ID NO: 32) to form a *TPSAB1* amplicon, and (ii) sequencing the *TPSAB1* amplicon. In some examples, sequencing the *TPSAB1* amplicon comprises using the first forward primer and the first reverse primer. In some examples, the *TPSB2* locus is sequenced by a method comprising (i) amplifying a nucleic acid from the subject in the presence of a second forward primer comprising the nucleotide
30 sequence of 5'-GCA GGT GAG CCT GAG AGT CC-3' (SEQ ID NO: 33) and a second reverse primer comprising the nucleotide sequence of 5'-GGG ACC TTC ACC TGC TTC AG-3' (SEQ ID NO: 34) to form a *TPSB2* amplicon, and (ii) sequencing the *TPSB2* amplicon. In some examples, sequencing the *TPSB2* amplicon comprises using the second forward primer and a sequencing reverse primer comprising the nucleotide sequence of 5'-CAG CCA GTG ACC CAG CAC-3' (SEQ ID NO: 35).

35 In some examples of any of the preceding aspects, the active tryptase allele count is determined by the formula: 4 – the sum of the number of tryptase α and tryptase βIII^{FS} alleles in the patient's genotype. In some examples, tryptase α is detected by detecting the c733 G>A SNP at *TPSAB1* comprising the nucleotide sequence
40 CTGCAGGCGGGCGTGGTCAGCTGGG[G/A]CGAGGGCTGTGCCCAGCCCAACCGG (SEQ ID NO: 36), wherein the presence of an A at the c733 G>A SNP indicates tryptase α . In some examples, tryptase βIII^{FS} is detected by detecting a c980_981insC mutation at *TPSB2* comprising the nucleotide sequence CACACGGTCACCCTGCCCCCTGCCTCAGAGACCTTCCCCC (SEQ ID NO: 37).

In some examples of any of the preceding aspects, the reference active tryptase allele count is determined in a group of patients having the mast cell-mediated inflammatory disease. In some examples, the reference active tryptase allele count is 3.

5 In some examples of any of the preceding aspects, the patient has an active tryptase allele count of 3 or 4.

In some examples of any of the preceding aspects, the patient has an active tryptase allele count of 0, 1, or 2.

In some examples of any of the preceding aspects, the tryptase is tryptase beta I, tryptase beta II, tryptase beta III, tryptase alpha I, or a combination thereof.

10 In some examples of any of the preceding aspects, the expression level of tryptase is a protein expression level. In some examples, the protein expression level of tryptase is an expression level of active tryptase. In some examples, the protein expression level of tryptase is an expression level of total tryptase. In some examples, the protein expression level is measured using an immunoassay, enzyme-linked immunosorbent assay (ELISA), Western blot, or mass spectrometry. In some examples, the
15 expression level of the tryptase is an mRNA expression level. In some examples, the mRNA expression level is measured using a polymerase chain reaction (PCR) method or a microarray chip. In some examples, the PCR method is qPCR.

In some examples of any of the preceding aspects, the reference level of tryptase is a level determined in a group of individuals having the mast cell-mediated inflammatory disease. In some
20 examples, the reference level of tryptase is a median level.

In some examples of any of the preceding aspects, the sample from the patient is selected from the group consisting of a blood sample, a tissue sample, a sputum sample, a bronchiolar lavage sample, a mucosal lining fluid (MLF) sample, a bronchosorption sample, and a nasosorption sample. In some
25 examples, the blood sample is a whole blood sample, a serum sample, a plasma sample, or a combination thereof. In some examples, the blood sample is a serum sample or a plasma sample.

In some examples of any of the preceding aspects, the agent is a tryptase antagonist. In some examples, the tryptase antagonist is a tryptase alpha antagonist or a tryptase beta antagonist. In some examples, the tryptase antagonist is a tryptase beta antagonist. In some examples, the tryptase beta antagonist is an anti-tryptase beta antibody or an antigen-binding fragment thereof. In some examples,
30 the antibody comprises the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 1); (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: 3); (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
35 (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 acid sequence having at least 90%, at least 95%, or at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 7; (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: 8; or (c) a VH domain as
40 in (a) and a VL domain as in (b). In some examples, the VH domain

comprises the amino acid sequence of SEQ ID NO: 7. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 8. In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 7 and the VL domain comprises the amino acid sequence of SEQ ID NO: 8. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and (b) a light chain 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: 11 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 10. In some examples, the antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYAIT (SEQ ID NO: 12); (b) an HVR-H2 comprising the amino acid sequence of GISSAATTFYSSWAKS (SEQ ID NO: 13); (c) an HVR-H3 comprising the amino acid sequence of DPRGYGAALDRLDL (SEQ ID NO: 14); (d) an HVR-L1 comprising the amino acid sequence of QSIKSVYNNRLG (SEQ ID NO: 15); (e) an HVR-L2 comprising the amino acid sequence of ETSILTS (SEQ ID NO: 16); and (f) an HVR-L3 comprising the amino acid sequence of AGGFDRSGDTT (SEQ ID NO: 17). In some examples, the antibody comprises (a) a heavy chain variable (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: 18; (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: 19; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 18. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 19. In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 18 and the VL domain comprises the amino acid sequence of SEQ ID NO: 19. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 21. In some examples, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 22 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 21. In some examples, the therapy further comprises an IgE antagonist.

In some examples of any of the preceding aspects, the agent is an FcεR antagonist. In some examples, the FcεR antagonist is a Bruton's tyrosine kinase (BTK) inhibitor. In some examples, the BTK inhibitor is GDC-0853, acalabrutinib, GS-4059, spebrutinib, BGB-3111, or HM71224. In some examples, the agent is an IgE⁺ B cell depleting antibody. In some examples, the IgE⁺ B cell depleting antibody is an anti-M1' domain antibody.

In some examples of any of the preceding aspects, the agent is a mast cell or basophil depleting antibody.

In some examples of any of the preceding aspects, the agent is a PAR2 antagonist.

In some examples of any of the aspects disclosed herein, the therapy or the combination comprises a tryptase antagonist (e.g., an anti-tryptase antibody, including any of the anti-tryptase antibodies described herein) and an IgE antagonist (e.g., an anti-IgE antibody, including any of the anti-IgE antibodies described herein, e.g., omalizumab (e.g., XOLAIR®)).

In some examples of any of the aspects disclosed herein, the agent is an IgE antagonist. In some examples, the IgE antagonist is an anti-IgE antibody. In some examples, the anti-IgE antibody is an IgE blocking antibody and/or an IgE depleting antibody. In some examples, the anti-IgE antibody comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of GYSWN (SEQ ID NO: 40); (b) an HVR-H2 comprising the amino acid sequence of SITYDGSTNYPNPSVK (SEQ ID NO: 41); (c) an HVR-H3 comprising the amino acid sequence of GSHYFGHWHFAV (SEQ ID NO: 42); (d) an HVR-L1 comprising the amino acid sequence of RASQSVDYDGDSYMN (SEQ ID NO: 43); (e) an HVR-L2 comprising the amino acid sequence of AASYLES (SEQ ID NO: 44); and (f) an HVR-L3 comprising the amino acid sequence of QQSHEDPYT (SEQ ID NO: 45). In some examples, the anti-IgE antibody comprises (a) a heavy chain variable (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: 38; (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: 39; or (c) a VH domain as in (a) and a VL domain as in (b). In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 38. In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 39. In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 38 and the VL domain comprises the amino acid sequence of SEQ ID NO: 39. In some examples, the anti-IgE antibody is omalizumab (XOLAIR®) or XmAb7195. In some examples, the anti-IgE antibody is omalizumab (XOLAIR®).

In some examples of any of the preceding aspects, the Type 2 biomarker is a T_H2 cell-related cytokine, periostin, eosinophil count, an eosinophil signature, FeNO, or IgE. In some examples, the T_H2 cell-related cytokine is IL-13, IL-4, IL-9, or IL-5. In some examples, the T_H2 pathway inhibitor inhibits any of the targets selected from interleukin-2-inducible T cell kinase (ITK), Bruton's tyrosine kinase (BTK), Janus kinase 1 (JAK1) (e.g., ruxolitinib, tofacitinib, oclacitinib, baricitinib, filgotinib, gandotinib, lestaurtinib, momelotinib, pacritinib, upadacitinib, peficitinib, and fedratinib), GATA binding protein 3 (GATA3), IL-9 (e.g., MEDI-528), IL-5 (e.g., mepolizumab, CAS No. 196078-29-2; reslizumab), IL-13 (e.g., IMA-026, IMA-638 (also referred to as anrukinzumab, INN No. 910649-32-0; QAX-576; IL-4/IL-13 trap), tralokinumab (also referred to as CAT-354, CAS No. 1044515-88-9); AER-001, ABT-308 (also referred to as humanized 13C5.5 antibody)), IL-4 (e.g., AER-001, IL-4/IL-13 trap), OX40L, TSLP, IL-25, IL-33, and IgE (e.g., XOLAIR®, QGE-031; and MEDI-4212); and receptors such as: IL-9 receptor, IL-5 receptor (e.g., MEDI-563 (benralizumab, CAS No. 1044511-01-4)), IL-4 receptor alpha (e.g., AMG-317, AIR-645), IL-13 receptor alpha1 (e.g., R-1671) and IL-13 receptor alpha2, OX40, TSLP-R, IL-7R alpha (a co-receptor for TSLP), IL-17RB (receptor for IL-25), ST2 (receptor for IL-33), CCR3, CCR4, CRTH2 (e.g., AMG-853, AP768, AP-761, MLN6095, ACT129968), FcεRI, FcεRII/CD23 (receptors for IgE), Flap (e.g., GSK2190915), Syk kinase (R-343, PF3526299); CCR4 (AMG-761), TLR9 (QAX-935) and multi-cytokine inhibitor of CCR3, IL-5, IL-3, and GM-CSF (e.g., TPI ASM8).

In some examples of any of the preceding aspects, the method further comprises administering an additional therapeutic agent to the patient. In some examples, the additional therapeutic agent is selected from the group consisting of a corticosteroid, an IL-33 axis binding

antagonist, a TRPA1 antagonist, a bronchodilator or asthma symptom control medication, an immunomodulator, a tyrosine kinase inhibitor, and a phosphodiesterase inhibitor. In some examples, the additional therapeutic agent is a corticosteroid. In some examples, the corticosteroid is an inhaled corticosteroid.

In some examples of any of the preceding aspects, the mast cell-mediated inflammatory disease is selected from the group consisting of asthma, atopic dermatitis, chronic spontaneous urticaria (CSU), systemic anaphylaxis, mastocytosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and eosinophilic esophagitis. In some examples, the mast cell-mediated inflammatory disease is asthma. In some examples, the asthma is moderate to severe asthma. In some examples, the asthma is uncontrolled on a corticosteroid. In some examples, the asthma is T_H2 high asthma or T_H2 low asthma.

In another example, the disclosure features a kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof, the kit comprising: (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally, (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof. In some examples, the agent is a tryptase antagonist, and the therapy further comprises an IgE antagonist. In some examples, the therapy comprises a tryptase antagonist and an IgE antagonist. In one aspect, the disclosure refers to a kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the kit comprising: (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally, (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, optionally wherein the agent is a tryptase antagonist, and the therapy further comprises an IgE antagonist, further optionally comprising reagents for determining the level of a Type 2 biomarker in a sample from the patient.

In another example, the disclosure features a kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the kit comprising: (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally, (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist.

In some examples of any of the preceding aspects, the kit further comprises reagents for determining the level of a Type 2 biomarker in a sample from the patient.

In one aspect, the disclosure refers to a kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the kit comprising: (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally, (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, further optionally comprising reagents for determining the level of a Type 2 biomarker in a sample from the patient.

In another example, the disclosure features an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy. In some examples, the patient has been identified as

having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the agent is for use in combination with a T_H2 pathway inhibitor. In one aspect, the disclosure refers to an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase, optionally wherein: (a) the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy; (b) the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the agent is for use in combination with a T_H2 pathway inhibitor; or (c) the IgE+ B cell depleting antibody is an anti-M1' domain antibody.

In another example, the disclosure features an agent selected from an IgE antagonist or an FcεR antagonist for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or FcεR antagonist is for use in combination with an additional T_H2 pathway inhibitor. In one aspect, the disclosure refers to an agent selected from an IgE antagonist or an FcεR antagonist for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase, optionally wherein the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or FcεR antagonist is for use in combination with an additional T_H2 pathway inhibitor, further optionally wherein the FcεR antagonist is a BTK inhibitor, further optionally wherein the BTK inhibitor is GDC-0853, acalabrutinib, GS-4059, spebrutinib, BGB-3111, or HM71224.

In another example, the disclosure provides for the use of an agent selected from the group consisting of a tryptase antagonist, an IgE antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy. In some examples, the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the agent is for use in combination with a T_H2 pathway inhibitor.

In another example, the disclosure provides for the use of an IgE antagonist or an FcεR antagonist in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase. In some examples, the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or FcεR antagonist is for use in combination with an additional T_H2 pathway inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing active tryptase allele count for moderate to severe asthma patients. Active tryptase allele count is plotted by barplot for BOBCAT, EXTRA, and MILLY moderate to severe asthma subjects.

FIGS. 2A and 2B are a series of graphs showing that total peripheral tryptase protein level is associated with tryptase copy number in moderate to severe asthma. Protein Quantitative Trait Linkage (pQTL) analyses were conducted for plasma total tryptase from BOBCAT (Fig. 2A) and serum total tryptase from MILLY studies (Fig. 2B). Linear regression line (95% CI) are indicated in gray shading. The P -value of r^2 from linear regression is annotated on the plots. r^2 is the coefficient of determination of

CLAIMS

What is claimed is:

1. Use of an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a protease activated receptor 2 (PAR2) antagonist, and a combination thereof in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein the patient has been identified as having (i) a genotype comprising an active tryptase allele count that is at or above a reference active tryptase allele count; or (ii) an expression level of tryptase in a sample from the patient that is at or above a reference level of tryptase.

2. The use of claim 1, wherein:

- (a) the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the medicament is for use as a monotherapy;
- (b) the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the medicament is for use in combination with a T_H2 pathway inhibitor; or
- (c) the IgE+ B cell depleting antibody is an anti-M1' domain antibody.

3. Use of an agent selected from an IgE antagonist or an FcεR antagonist in the manufacture of a medicament for treating a patient having a mast cell-mediated inflammatory disease, wherein:

- (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or
- (ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase.

4. The use of claim 3, wherein the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the medicament is for use in combination with an additional T_H2 pathway inhibitor, further optionally wherein the FcεR antagonist is a Bruton's tyrosine kinase (BTK) inhibitor, further optionally wherein the BTK inhibitor is GDC-0853, acalabrutinib, GS-4059, spebrutinib, BGB-3111, or HM71224.

5. The use of any one of claims 1-4, wherein:

- (i) the active tryptase allele count is determined by sequencing the *TPSAB1* and *TPSB2* loci of the patient's genome;
- (ii) the active tryptase allele count is determined by the formula: 4 – the sum of the number of tryptase α and tryptase βIII frame-shift (βIII^{FS}) alleles in the patient's genotype;
- (iii) the reference active tryptase allele count is determined in a group of patients having the mast cell-mediated inflammatory disease;
- (iv) the reference active tryptase allele count is 3; and/or

(v) (a) the patient has an active tryptase allele count of 3 or 4 or (b) the patient has an active tryptase allele count of 0, 1, or 2.

6. The use of claim 5, wherein:

(i) the sequencing is Sanger sequencing or massively parallel sequencing;

(ii) the *TPSAB1* locus is sequenced by a method comprising (a) amplifying a nucleic acid from the subject in the presence of a first forward primer comprising the nucleotide sequence of 5'-CTG GTG TGC AAG GTG AAT GG-3' (SEQ ID NO: 31) and a first reverse primer comprising the nucleotide sequence of 5'-AGG TCC AGC ACT CAG GAG GA-3' (SEQ ID NO: 32) to form a *TPSAB1* amplicon, and (b) sequencing the *TPSAB1* amplicon, optionally wherein sequencing the *TPSAB1* amplicon comprises using the first forward primer and the first reverse primer;

(iii) the *TPSB2* locus is sequenced by a method comprising (a) amplifying a nucleic acid from the subject in the presence of a second forward primer comprising the nucleotide sequence of 5'-GCA GGT GAG CCT GAG AGT CC-3' (SEQ ID NO: 33) and a second reverse primer comprising the nucleotide sequence of 5'-GGG ACC TTC ACC TGC TTC AG-3' (SEQ ID NO: 34) to form a *TPSB2* amplicon, and (b) sequencing the *TPSB2* amplicon, optionally wherein sequencing the *TPSB2* amplicon comprises using the second forward primer and a sequencing reverse primer comprising the nucleotide sequence of 5'-CAG CCA GTG ACC CAG CAC-3' (SEQ ID NO: 35);

(iv) tryptase alpha is detected by detecting the c733 G>A SNP at *TPSAB1* comprising the nucleotide sequence CTGCAGGCGGGCGTGGTCAGCTGGG[G/A]CGAGGGCTGTGCCCAGCCCAACCGG (SEQ ID NO: 36), wherein the presence of an A at the c733 G>A SNP indicates tryptase alpha; and/or

(v) tryptase beta III^{FS} is detected by detecting a c980_981insC mutation at *TPSB2* comprising the nucleotide sequence CACACGGTCACCCTGCCCCCTGCCTCAGAGACCTTCCCCCCC (SEQ ID NO: 37).

7. The use of any one of claims 1-6, wherein:

(i) the tryptase is tryptase beta I, tryptase beta II, tryptase beta III, tryptase alpha I, or a combination thereof;

(ii) the expression level of tryptase is a protein expression level;

(iii) the expression level of tryptase is an mRNA expression level; or

(iv) the reference level of tryptase is a level determined in a group of individuals having the mast cell-mediated inflammatory disease, optionally wherein:

(a) the protein expression level of tryptase is an expression level of active tryptase;

(b) the protein expression level of tryptase is an expression level of total tryptase;

(c) the protein expression level of tryptase is measured using an immunoassay, enzyme-linked immunosorbent assay (ELISA), Western blot, or mass spectrometry;

(d) the mRNA expression level of tryptase is measured using a polymerase chain reaction (PCR) method or a microarray chip, optionally wherein the PCR method is qPCR; or

(e) the reference level of tryptase is a median level.

8. The use of any one of claims 1-7, wherein the sample from the patient is selected from the group consisting of a blood sample, a tissue sample, a sputum sample, a bronchiolar lavage sample, a mucosal lining fluid (MLF) sample, a bronchosorption sample, and a nasosorption sample, optionally wherein the blood sample is a whole blood sample, a serum sample, a plasma sample, or a combination thereof.

9. The use of any one of claims 1, 2, and 5-8, wherein the agent is a tryptase antagonist, optionally wherein the tryptase antagonist is a tryptase alpha antagonist or a tryptase beta antagonist, further optionally wherein the tryptase antagonist is to be administered in combination with an IgE antagonist.

10. The use of claim 9, wherein the tryptase beta antagonist is an anti-tryptase beta antibody or an antigen-binding fragment thereof.

11. The use of claim 10, wherein:

(i) the antibody comprises the following six hypervariable regions (HVRs):

- (a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 1);
- (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: 3);
- (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) the antibody comprises (a) a heavy chain variable (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: 7; (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: 8; or (c) a VH domain as in (a) and a VL domain as in (b), optionally wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 7, the VL domain comprises the amino acid sequence of SEQ ID NO: 8, or the VH domain comprises the amino acid sequence of SEQ ID NO: 7 and the VL domain comprises the amino acid sequence of SEQ ID NO: 8;

(iii) the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 10; or

(iv) the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 11 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 10.

12. The use of any one of claims 3, 4, and 9, wherein the IgE antagonist is an anti-IgE antibody, optionally wherein the anti-IgE antibody is an IgE blocking antibody and/or an IgE depleting antibody; further optionally wherein:

(i) the anti-IgE antibody comprises the following six HVRs:

- (a) an HVR-H1 comprising the amino acid sequence of GYSWN (SEQ ID NO: 40);
- (b) an HVR-H2 comprising the amino acid sequence of SITYDGSTNYPNVKVG (SEQ ID NO: 41);
- (c) an HVR-H3 comprising the amino acid sequence of GSHYFGHWHFAV (SEQ ID NO: 42);
- (d) an HVR-L1 comprising the amino acid sequence of RASQSVDDYDGDSYMN (SEQ ID NO: 43);

- (e) an HVR-L2 comprising the amino acid sequence of AASYLES (SEQ ID NO: 44); and
- (f) an HVR-L3 comprising the amino acid sequence of QQSHEDPYT (SEQ ID NO: 45);
- (ii) the anti-IgE antibody comprises (a) a heavy chain variable (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: 38; (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: 39; or (c) a VH domain as in (a) and a VL domain as in (b), optionally wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 38, the VL domain comprises the amino acid sequence of SEQ ID NO: 39, or the VH domain comprises the amino acid sequence of SEQ ID NO: 38 and the VL domain comprises the amino acid sequence of SEQ ID NO: 39; or
- (iii) the anti-IgE antibody is omalizumab (XOLAIR®) or XmAb7195.

13. The use of any one of claims 2 and 4-12, wherein:

- (i) the Type 2 biomarker is a T_H2 cell-related cytokine, periostin, eosinophil count, an eosinophil signature, FeNO, or IgE, optionally wherein the T_H2 cell-related cytokine is IL-13, IL-4, IL-9, or IL-5; or
- (ii) the T_H2 pathway inhibitor inhibits interleukin-2-inducible T cell kinase (ITK), Bruton's tyrosine kinase (BTK), Janus kinase 1 (JAK1), GATA binding protein 3 (GATA3), IL-9, IL-5, IL-13, IL-4, IL-33, OX40L, TSLP, IL-25, IL-9 receptor, IL-5 receptor, IL-4 receptor alpha, IL-13 receptoralpha1, IL-13 receptoralpha2, OX40, TSLP-R, IL-7Ralpha, IL-17RB, ST2, CCR3, CCR4, CRTH2, Flap, Syk kinase, CCR4, TLR9, or GM-CSF.

14. The use of any one of claims 1-13, wherein:

- (i) the medicament is formulated for administration with an additional therapeutic agent, optionally wherein the additional therapeutic agent is selected from the group consisting of a corticosteroid, an IL-33 axis binding antagonist, a TRPA1 antagonist, a bronchodilator or asthma symptom control medication, an immunomodulator, a tyrosine kinase inhibitor, and a phosphodiesterase inhibitor; further optionally wherein the additional therapeutic agent is a corticosteroid, further optionally wherein the corticosteroid is an inhaled corticosteroid; or
- (ii) the mast cell-mediated inflammatory disease is selected from the group consisting of asthma, atopic dermatitis, chronic spontaneous urticaria (CSU), systemic anaphylaxis, mastocytosis, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and eosinophilic esophagitis, optionally wherein the mast cell-mediated inflammatory disease is asthma, further optionally wherein:
 - (a) the asthma is moderate to severe asthma;
 - (b) the asthma is uncontrolled on a corticosteroid; or
 - (c) the asthma is T_H2 high asthma or T_H2 low asthma.

15. A method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising:

(a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and

(b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the patient's active tryptase allele count, wherein an active tryptase allele count at or above a reference active tryptase allele count indicates that the patient has an increased likelihood of being responsive to the therapy.

16. A method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising:

(a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and

(b) identifying the patient as likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof based on the expression level of tryptase in the sample from the patient, wherein an expression level of tryptase in the sample at or above a reference level of tryptase indicates that the patient has an increased likelihood of being responsive to the therapy.

17. A method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the method comprising:

(a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and

(b) identifying the patient as likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist based on the patient's active tryptase allele count, wherein an active tryptase allele count below a reference active tryptase allele count indicates that the patient has an increased likelihood of being responsive to the therapy.

18. A method of determining whether a patient having a mast cell-mediated inflammatory disease is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the method comprising:

(a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and

(b) identifying the patient as likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist based on the expression level of tryptase in the sample from the patient, wherein an expression level of tryptase in the sample from the patient below a reference level of tryptase indicates that the patient has an increased likelihood of being responsive to the therapy.

19. The method of claim 17 or 18, wherein the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker.

20. A method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising:

(a) determining in a sample from a patient having a mast cell-mediated inflammatory disease the patient's active tryptase allele count; and

(b) selecting for the patient:

(i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof if the patient's active tryptase allele count is at or above a reference active tryptase allele count, or

(ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the patient's active tryptase allele count is below a reference active tryptase allele count.

21. A method of selecting a therapy for a patient having a mast cell-mediated inflammatory disease, the method comprising:

(a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease; and

(b) selecting for the patient:

(i) a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof if the expression level of tryptase in the sample from the patient is at or above a reference level of tryptase, or

(ii) a therapy comprising an IgE antagonist or an FcεR antagonist if the expression level of tryptase in the sample from the patient is below a reference level of tryptase.

22. The method of any one of claims 15, 16, 20, and 21, wherein:

(i) the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, optionally wherein the method comprises selecting the agent for administration as a monotherapy; or

(ii) the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the method further comprises selecting a combination therapy that comprises a T_H2 pathway inhibitor.

23. A method for assessing a response of a patient having a mast cell-mediated inflammatory disease to treatment with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising:

(a) determining the expression level of tryptase in a sample from a patient having a mast cell-mediated inflammatory disease at a time point during or after administration of a therapy comprising an

agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and

(b) maintaining, adjusting, or stopping the treatment based on a comparison of the expression level of tryptase in the sample with a reference level of tryptase,

wherein a change in the expression level of tryptase in the sample from the patient compared to the reference level is indicative of a response to treatment with the therapy.

24. A method for monitoring the response of a patient having a mast cell-mediated inflammatory disease treated with a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the method comprising:

(a) determining the expression level of tryptase in a sample from the patient at a time point during or after administration of the therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE⁺ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof to the patient; and

(b) comparing the expression level of tryptase in the sample from the patient with a reference level of tryptase, thereby monitoring the response of the patient undergoing treatment with the therapy.

25. The method of claim 23 or 24, wherein:

- (i) the change is an increase in the expression level of tryptase and the treatment is maintained; or
- (ii) the change is a decrease in the expression level of tryptase and the treatment is adjusted or stopped.

26. The method of any one of claims 15, 17, 19, 20, and 22, wherein:

- (i) the active tryptase allele count is determined by sequencing the *TPSAB1* and *TPSB2* loci of the patient's genome;
- (ii) the active tryptase allele count is determined by the formula: 4 – the sum of the number of tryptase α and tryptase β III frame-shift (β IIIF^S) alleles in the patient's genotype;
- (iii) the reference active tryptase allele count is determined in a group of patients having the mast cell-mediated inflammatory disease;
- (iv) the reference active tryptase allele count is 3; and/or
- (v) (a) the patient has an active tryptase allele count of 3 or 4 or (b) the patient has an active tryptase allele count of 0, 1, or 2.

27. The method of claim 26, wherein:

- (i) the sequencing is Sanger sequencing or massively parallel sequencing;
- (ii) the *TPSAB1* locus is sequenced by a method comprising (a) amplifying a nucleic acid from the subject in the presence of a first forward primer comprising the nucleotide sequence of 5'-CTG GTG TGC AAG GTG AAT GG-3' (SEQ ID NO: 31) and a first reverse primer comprising the nucleotide sequence of 5'-AGG TCC AGC ACT CAG GAG GA-3' (SEQ ID NO: 32) to form a *TPSAB1* amplicon, and (b)

sequencing the *TPSAB1* amplicon, optionally wherein sequencing the *TPSAB1* amplicon comprises using the first forward primer and the first reverse primer;

(iii) the *TPSB2* locus is sequenced by a method comprising (a) amplifying a nucleic acid from the subject in the presence of a second forward primer comprising the nucleotide sequence of 5'-GCA GGT GAG CCT GAG AGT CC-3' (SEQ ID NO: 33) and a second reverse primer comprising the nucleotide sequence of 5'-GGG ACC TTC ACC TGC TTC AG-3' (SEQ ID NO: 34) to form a *TPSB2* amplicon, and (b) sequencing the *TPSB2* amplicon, optionally wherein sequencing the *TPSB2* amplicon comprises using the second forward primer and a sequencing reverse primer comprising the nucleotide sequence of 5'-CAG CCA GTG ACC CAG CAC-3' (SEQ ID NO: 35);

(iv) tryptase alpha is detected by detecting the c733 G>A SNP at *TPSAB1* comprising the nucleotide sequence CTGCAGGCGGGCGTGGTCAGCTGGG[G/A]CGAGGGCTGTGCCCAGCCCCAACCGG (SEQ ID NO: 36), wherein the presence of an A at the c733 G>A SNP indicates tryptase alpha; and/or

(v) tryptase beta III^{FS} is detected by detecting a c980_981insC mutation at *TPSB2* comprising the nucleotide sequence CACACGGTCACCCTGCCCCCTGCCTCAGAGACCTTCCCCCCC (SEQ ID NO: 37).

28. The method of any one of claims 16, 18, 19, and 21-25, wherein:

- (i) the tryptase is tryptase beta I, tryptase beta II, tryptase beta III, tryptase alpha I, or a combination thereof;
- (ii) the expression level of tryptase is a protein expression level;
- (iii) the expression level of tryptase is an mRNA expression level; or
- (iv) the reference level of tryptase is a level determined in a group of individuals having the mast cell-mediated inflammatory disease.

29. The method of claim 28, wherein:

- (i) the protein expression level of tryptase is an expression level of active tryptase;
- (ii) the protein expression level of tryptase is an expression level of total tryptase;
- (iii) the protein expression level of tryptase is measured using an immunoassay, ELISA, Western blot, or mass spectrometry;
- (iv) the mRNA expression level of tryptase is measured using a PCR method or a microarray chip, optionally wherein the PCR method is qPCR; or
- (v) the reference level of tryptase is a median level.

30. The method of any one of claims 15-29, wherein the sample from the patient is selected from the group consisting of a blood sample, a tissue sample, a sputum sample, a bronchiolar lavage sample, an MLF sample, a bronchosorption sample, and a nasosorption sample, optionally wherein the blood sample is a whole blood sample, a serum sample, a plasma sample, or a combination thereof.

31. The method of any one of claims 15, 16, and 20-30, wherein the agent is a tryptase antagonist.

32. The method of claim 31, wherein the tryptase antagonist is a tryptase alpha antagonist or a tryptase beta antagonist.

33. The method of claim 32, wherein the tryptase beta antagonist is an anti-tryptase beta antibody or an antigen-binding fragment thereof.

34. The method of claim 33, wherein:

(i) the antibody comprises the following six HVRs:

(a) an HVR-H1 comprising the amino acid sequence of DYGMV (SEQ ID NO: 1);

(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: 3);

(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) 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: 7; (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 SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b), optionally wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 7, the VL domain comprises the amino acid sequence of SEQ ID NO: 8, or the VH domain comprises the amino acid sequence of SEQ ID NO: 7 and the VL domain comprises the amino acid sequence of SEQ ID NO: 8;

(iii) the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 10; or

(iv) the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 11 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 10.

35. The method of any one of claims 31-34, wherein the therapy further comprises an IgE antagonist.

36. The method of any one of claims 17-22 and 26-35, wherein:

(i) the agent is an FcεR antagonist, optionally wherein the FcεR antagonist is a BTK inhibitor, further optionally wherein the BTK inhibitor is GDC-0853, acalabrutinib, GS-4059, spebrutinib, BGB-3111, or HM71224; or

(ii) the agent is an IgE antagonist.

37. The method of any one of claims 15, 16, and 20-30, wherein:

(i) the agent is an IgE⁺ B cell depleting antibody, optionally wherein the IgE⁺ B cell depleting antibody is an anti-M1' domain antibody;

(ii) the agent is a mast cell or basophil depleting antibody; or

(iii) the agent is a PAR2 antagonist.

38. The method of claim 35 or 36, wherein the IgE antagonist is an anti-IgE antibody.

39. The method of claim 38, wherein the anti-IgE antibody is an IgE blocking antibody and/or an IgE depleting antibody.

40. The method of claim 39, wherein:

(i) the anti-IgE antibody comprises the following six HVRs:

- (a) an HVR-H1 comprising the amino acid sequence of GYSWN (SEQ ID NO: 40);
- (b) an HVR-H2 comprising the amino acid sequence of SITYDGSTNYPNPSVKG (SEQ ID NO: 41);
- (c) an HVR-H3 comprising the amino acid sequence of GSHYFGHWHFAV (SEQ ID NO: 42);
- (d) an HVR-L1 comprising the amino acid sequence of RASQSVDDYDGD SYMN (SEQ ID NO: 43);
- (e) an HVR-L2 comprising the amino acid sequence of AASYLES (SEQ ID NO: 44); and
- (f) an HVR-L3 comprising the amino acid sequence of QQSHEDPYT (SEQ ID NO: 45);

(ii) the anti-IgE 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: 38; (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 SEQ ID NO: 39; or (c) a VH domain as in (a) and a VL domain as in (b), optionally wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 38, the VL domain comprises the amino acid sequence of SEQ ID NO: 39, or the VH domain comprises the amino acid sequence of SEQ ID NO: 38 and the VL domain comprises the amino acid sequence of SEQ ID NO: 39; or

(iii) the anti-IgE antibody is omalizumab (XOLAIR®) or XmAb7195.

41. The method of any one of claims 19, 22, and 26-40, wherein:

- (i) the Type 2 biomarker is a T_H2 cell-related cytokine, periostin, eosinophil count, an eosinophil signature, FeNO, or IgE, optionally wherein the T_H2 cell-related cytokine is IL-13, IL-4, IL-9, or IL-5; or
- (ii) the T_H2 pathway inhibitor inhibits ITK, BTK, JAK1, GATA3, IL-9, IL-5, IL-13, IL-4, IL-33, OX40L, TSLP, IL-25, IL-9 receptor, IL-5 receptor, IL-4 receptor alpha, IL-13 receptor alpha1, IL-13 receptor alpha2, OX40, TSLP-R, IL-7R alpha, IL-17RB, ST2, CCR3, CCR4, CRTH2, Flap, Syk kinase, CCR4, TLR9, or GM-CSF.

42. The method of any one of claims 15-41, wherein the therapy further comprises an additional therapeutic agent.

43. The method of claim 42, wherein the additional therapeutic agent is selected from the group consisting of a corticosteroid, an IL-33 axis binding antagonist, a TRPA1 antagonist, a bronchodilator or asthma symptom control medication, an immunomodulator, a tyrosine kinase inhibitor, and a phosphodiesterase inhibitor; optionally wherein the additional therapeutic agent is a corticosteroid, further optionally wherein the corticosteroid is an inhaled corticosteroid.

44. The method of any one of claims 15-43, wherein the mast cell-mediated inflammatory disease is selected from the group consisting of asthma, atopic dermatitis, CSU, systemic anaphylaxis, mastocytosis, COPD, idiopathic pulmonary fibrosis (IPF), and eosinophilic esophagitis.

45. The method of claim 44, wherein the mast cell-mediated inflammatory disease is asthma.

46. The method of claim 44 or 45, wherein:

- (i) the asthma is moderate to severe asthma;
- (ii) the asthma is uncontrolled on a corticosteroid; or
- (iii) the asthma is T_H2 high asthma or T_H2 low asthma.

47. A kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, the kit comprising:

- (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally,
- (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof, optionally wherein the agent is a tryptase antagonist, and the therapy further comprises an IgE antagonist, further optionally comprising reagents for determining the level of a Type 2 biomarker in a sample from the patient.

48. A kit for identifying a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, the kit comprising:

- (a) reagents for determining the patient's active tryptase allele count or for determining the expression level of tryptase in a sample from the patient; and, optionally,
- (b) instructions for using the reagents to identify a patient having a mast cell-mediated inflammatory disease who is likely to respond to a therapy comprising an IgE antagonist or an FcεR antagonist, further optionally comprising reagents for determining the level of a Type 2 biomarker in a sample from the patient.

49. An agent selected from the group consisting of a tryptase antagonist, an IgE+ B cell depleting antibody, a mast cell or basophil depleting antibody, a PAR2 antagonist, and a combination thereof for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein

- (i) the genotype of the patient has been determined to comprise an active tryptase allele count that is at or above a reference active tryptase allele count; or
- (ii) a sample from the patient has been determined to have an expression level of tryptase that is at or above a reference level of tryptase, optionally wherein:

(a) the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is below a reference level of the Type 2 biomarker, and the agent is for use as a monotherapy;

(b) the patient has been identified as having a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the agent is for use in combination with a T_H2 pathway inhibitor; or

(c) the IgE⁺ B cell depleting antibody is an anti-M1' domain antibody.

50. An agent selected from an IgE antagonist or an FcεR antagonist for use in a method of treating a patient having a mast cell-mediated inflammatory disease, wherein

(i) the genotype of the patient has been determined to comprise an active tryptase allele count that is below a reference active tryptase allele count; or

(ii) a sample from the patient has been determined to have an expression level of tryptase that is below a reference level of tryptase, optionally wherein the patient has been determined to have a level of a Type 2 biomarker in a sample from the patient that is at or above a reference level of the Type 2 biomarker, and the IgE antagonist or FcεR antagonist is for use in combination with an additional TH2 pathway inhibitor, further optionally wherein the FcεR antagonist is a BTK inhibitor, further optionally wherein the BTK inhibitor is GDC-0853, acalabrutinib, GS-4059, spebrutinib, BGB-3111, or HM71224.