FcεRI found on basophils and mast cells, and thereby prevent the release of histamine and other anaphylactic factors resulting in the pathological condition.

**[0005]** Anaphylaxis has been reported to occur in patients after receiving anti-IgE antibodies, such as omalizumab (e.g., Xolair®). Anaphylaxis is an acute systemic (multi-system) and very severe type I hypersensitivity allergic reaction. It is caused by degranulation of mast cells and basophils and mediated by IgE. Through 2006, 124 of 57,269 (about 0.2%) asthma patients had anaphylaxis after omalizumab administration. While there are no reports of fatal anaphylaxis as a result of omalizumab, some cases have been serious, and potentially life-threatening. For this reason, the FDA recommends that patients receiving omalizumab be monitored in the physician's office for a period of time after omalizumab administration, and health care providers administering omalizumab should be prepared to manage anaphylaxis that can be life-threatening. Sixty percent of the cases reported (124) has been after the first two doses of omalizumab. Therefore, it is possible that the reaction is from pre-existing antibodies in patients that recognize an epitope on omalizumab, as opposed to an anti-drug reaction that develops after drug administration. As anaphylaxis is associated with antibody of the IgE isotype, there is a need to develop an assay for detecting and quantitating the amount of IgE in a patient that is specific to the therapeutic anti-IgE antibody to assess the risk of anaphylaxis preferably before such anti-IgE antibody treatment and identify high risk patients.

**[0006]** All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

## SUMMARY

**[0007]** Disclosed are methods for detecting an anti-drug antibody of IgE isotype that bind to a therapeutic anti-IgE antibody in a sample, comprising the steps of: a) contacting a sample that may contain the anti-drug antibody with a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to an IgE (such as human IgE) is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the IgE; and b) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0007a]** In one aspect, there is provided a method for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of:

(a) contacting a sample that may contain the anti-drug antibody with a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and

(b) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0008]** In some embodiments, the relative binding affinity of the mutant therapeutic antibody is about 7.5% or less, about 5% or less, about 2.5% or less, about 2.0% or less,

about 1.5% or less, about 1% or less, about 0.9% or less, about 0.8% or less, about 0.7% or less, about 0.5% or less, about 0.25% or less, about 0.1% or less of the relative binding affinity of the therapeutic anti-IgE antibody.

**[0009]** Disclosed are methods for detecting anti-drug antibodies of IgE isotype that bind to a therapeutic anti-IgE antibody in a sample, comprising the steps of: a) contacting a sample that may contain the anti-drug antibodies with a mutant therapeutic antibody having at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the potency of the mutant therapeutic antibody to an IgE (such as human IgE) is about 10% or less of the potency of the therapeutic anti-IgE antibody to the IgE; and b) detecting binding of the anti-drug antibodies to the mutant therapeutic antibody.

**[0009a]** In another aspect, there is provided a method for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of:

(a) contacting a sample that may contain the anti-drug antibody with a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, wherein the potency of the mutant therapeutic antibody to human IgE is 10% or less of the potency of the therapeutic anti-IgE antibody to said human IgE; and

(b) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0010]** In some embodiments, the potency of the mutant therapeutic antibody is about 7.5% or less, about 5% or less, about 2.5% or less, about 2.0% or less, about 1.5% or less, about 1% or less, about 0.9% or less, about 0.8% or less, about 0.7% or less, about 0.5% or less, about 0.25% or less, about 0.1% or less of the potency of the therapeutic anti-IgE antibody.

**[0011]** Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the mutant therapeutic antibody comprises one, two, three, four, five, or six amino acid mutations in CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody. In some embodiments, the therapeutic anti-IgE antibody is omalizumab, and the mutant therapeutic antibody comprises one, two, or three amino acid mutations in the first CDR of the light chain of omalizumab. In some embodiments, the therapeutic anti-IgE antibody is omalizumab, and the mutant therapeutic antibody comprises an amino acid substitution at position 34 (Asp) in the light chain (SEQ ID NO:1) of omalizumab. In some embodiments, the mutant therapeutic antibody comprises the heavy chain amino acid sequence of SEQ ID NO:2 and the light chain amino acid sequence of SEQ ID NO:1, wherein amino acids at positions 30 (Asp) and 34 (Asp) or positions 32 (Asp) and 34 (Asp) in the light chain are substituted. In some embodiments, the mutant therapeutic antibody comprises the heavy chain amino acid sequence of SEQ ID NO:2 and the light chain amino acid sequence of SEQ ID NO:1, wherein amino acid D (Asp) at positions 30, 32, and 34 are substituted in the light chain. In some embodiments, amino acid Asp is substituted with Ala. In some embodiments, the mutant therapeutic antibody comprises the heavy chain amino acid sequence of SEQ ID NO:2 and the light chain amino acid sequence of SEQ ID NO:1 with amino acid substitutions of Asp to Ala at positions 30, 32, and 34 in the light chain. In some embodiments, the therapeutic anti-IgE antibody is omalizumab, and the mutant therapeutic antibody comprises one, two, or three amino acid mutations in the third CDR of the heavy

mutant therapeutic antibody is detected by a HRP conjugated anti-digoxigenin antibody. In some embodiments, the FcεRIα polypeptide is labeled with ruthenium, and the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by an electrochemiluminescence assay.

**[0015]** In some embodiments, the sample contains human serum or plasma. In some embodiments, the sample contains the therapeutic anti-IgE antibody. In some embodiments, the sample does not contain the therapeutic anti-IgE antibody. In some embodiments, the serum or plasma contains omalizumab. In other embodiments, the serum or plasma does not contain omalizumab.

**[0016]** In some embodiments, the methods further comprise a step of comparing the binding of the anti-drug antibodies to the mutant therapeutic antibody to a reference. In some embodiments, the reference is the detected binding between the mutant therapeutic antibody and a control antibody. In some embodiments, the control antibody is a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity. In some embodiments, the positive control antibody comprises a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO:8. In some embodiments, the positive control antibody further comprises the heavy chain and light chain constant regions from a human IgE.

**[0017]** Disclosed are kits for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample comprising (a) a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to an IgE (such as human IgE) is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the IgE; and b) a detecting agent that binds to an Fc region of an IgE. Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the detecting agent is an FcεRIα polypeptide. Any of the FcεRIα polypeptides provided herein may be included in the kit. In some embodiments, the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit. In some embodiments, the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region. In some embodiments, the FcεRIα polypeptide is labeled (such as labeled by biotin, digoxigenin, ruthenium, etc.). In some embodiments, the kit further comprises streptavidin-HRP or Amdex SA-HRP. In some embodiments, the kit further comprises HRP-conjugated anti-digoxigenin antibody for detecting digoxigenin labeled

FcεRIα polypeptide. In some embodiments, the kit further comprises a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity. In some embodiments, the positive control antibody comprises a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO:8. In some embodiments, the positive control antibody further comprises the heavy chain and light chain constant regions from a human IgE.

**[0017a]** In another aspect, there is provided a method for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of:

(a) contacting a sample that may contain the anti-drug antibody with (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE, wherein the mutant therapeutic antibody comprises one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE;

(b) capturing the mutant therapeutic antibody to a surface; and

(c) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0018]** Disclosed are kits for detecting anti-drug antibodies of IgE isotype that bind to a therapeutic anti-IgE antibody in a sample comprising a) a mutant therapeutic antibody having at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the potency of the mutant therapeutic antibody to an IgE (such as human IgE) is about 10% or less of the potency of the therapeutic anti-IgE antibody to the IgE; and b) a detecting agent that binds to an Fc region of an IgE. Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the detecting agent is an FcεRIα polypeptide. Any of the FcεRIα polypeptides provided herein may be included in the kit. In some embodiments, the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit. In some embodiments, the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region. In some embodiments, the FcεRIα polypeptide is labeled (such as labeled by biotin, digoxigenin, ruthenium, etc.). In some embodiments, the kit further comprises streptavidin-HRP or Amdex SA-HRP. In some embodiments, the kit further comprises HRP-conjugated anti-digoxigenin antibody for detecting digoxigenin labeled FcεRIα polypeptide. In some embodiments, the kit further comprises a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity. In some embodiments, the positive control antibody comprises a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO:8. In some embodiments, the positive control antibody further comprises the heavy chain and light chain constant regions from a human IgE.

**[0019]** Disclosed are methods for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of: (a) contacting a sample that may contain the anti-drug antibody with (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE, wherein the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant

therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; (b) capturing the mutant therapeutic antibody to a surface; and (c) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0020]** In some embodiments, excess amount of FcεRIα polypeptide is contacted with the sample in step (a). In some embodiments, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, or at least about 10-fold excess of FcεRIα polypeptide is contacted with the sample in step (a). Any of the FcεRIα polypeptides provided herein may be used. In some embodiments, the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit. The FcεRIα polypeptide may be labeled or not labeled.

**[0021]** Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the mutant therapeutic antibody is labeled and is captured to the surface by a capture agent that specifically binds to the label. In some embodiments, the label is biotin and the surface is coated with streptavidin. In some embodiments, the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by a labeled anti-human IgE antibody. In some embodiments, the FcεRIα polypeptide is labeled and the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by a detecting agent that specifically binds to the label on the FcεRIα polypeptide. In some embodiments, the FcεRIα polypeptide is labeled with digoxigenin, and the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by a HRP conjugated anti-digoxigenin antibody. In some embodiments, the FcεRIα polypeptide is labeled with ruthenium, and the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by an electrochemiluminescence assay.

**[0022]** Disclosed are kits for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample comprising: (a) a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to human IgE; and (b) an FcεRIα polypeptide that binds to an Fc region of a human IgE. Any of the mutant therapeutic antibodies provided herein may be used. Any of the FcεRIα polypeptide described herein may be used. In some embodiments, excess amount of FcεRIα polypeptide is provided in the kit. In some embodiments, the FcεRIα polypeptide is labeled. In some embodiments, the kit further comprises a detecting agent that specifically

binds to the label on the FcεRIα polypeptide. In some embodiments, the kit further comprises an anti-human IgE antibody. In some embodiments, the anti-human IgE antibody is labeled.

**[0023]** Disclosed are methods for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of: (a) preincubating a sample that may contain the anti-drug antibody with excess amount of an FcεRIα polypeptide that binds to an Fc region of a human IgE; (b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to a human IgE is reduced as compared to the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (c) detecting binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody.

**[0023a]** In another aspect, there is provided a method for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, comprising the steps of:

(a) preincubating a sample that may contain the anti-drug antibody with excess amount of an FcεRIα polypeptide that binds to an Fc region of a human IgE;

(b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and

(c) detecting binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody.

**[0024]** Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE.

**[0025]** In some embodiments, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, or at least about 10-fold excess of FcεRIα polypeptide is preincubated with the sample in step (a). Any of the FcεRIα polypeptides provided herein may be used.

**[0026]** In some embodiments, the therapeutic anti-IgE antibody or the mutant therapeutic antibody is captured to a surface before or after incubating with the sample in step (b). In some embodiments, the therapeutic anti-IgE antibody or the mutant therapeutic antibody is directly immobilized to a surface before incubating with the sample in step (b).

**[0027]** In some embodiments, the therapeutic anti-IgE antibody or the mutant therapeutic antibody is labeled and is captured to the surface through an immobilized capture agent that specifically binds to the label. In some embodiments, the therapeutic anti-IgE antibody or the mutant therapeutic antibody is labeled with biotin and is captured to a streptavidin coated surface.

**[0028]** In some embodiments, the binding of the anti-drug antibody to the therapeutic antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-human IgE antibody. In some embodiments, the FcεRIα polypeptide is labeled, and the binding of the

anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by detecting the label. In some embodiments, the FcεRIα polypeptide is labeled with digoxigenin, and the binding of the anti-drug antibody to the therapeutic antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-digoxigenin antibody. In some embodiments, the FcεRIα polypeptide is labeled with ruthenium, and the binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by an electrochemiluminescence assay.

**[0029]** Disclosed are kits for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample comprising: (a) the therapeutic anti-IgE antibody or a mutant therapeutic antibody thereof, wherein the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is reduced as compared to the relative binding affinity of the therapeutic anti-IgE antibody to human IgE; and (b) an FcεRIα polypeptide that binds to an Fc region of a human IgE. Any of the mutant therapeutic antibodies provided herein may be used. In some embodiments, the kit further comprises an anti-human IgE antibody. In some embodiments, the anti-human IgE antibody is labeled. Any of the FcεRIα polypeptide provided herein may be used. In some embodiments, the FcεRIα polypeptide is labeled. In some embodiments, the kit further comprises a detecting agent that specifically binds to the label on the FcεRIα polypeptide.

**[0030]** Disclosed are methods of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of: (a) contacting a sample from the patient with a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0030a]** In another aspect, there is provided a method of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of:

(a) contacting a sample from the patient with a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and

(b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody indicate the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0031]** Disclosed are methods of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of: (a) contacting a sample from the patient with a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, wherein the potency of the mutant therapeutic antibody to human IgE is about 10% or less of the potency of the

therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0031a]** In another aspect, there is provided a method of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of:

(a) contacting a sample from the patient with a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, wherein the potency of the mutant therapeutic antibody to human IgE is 10% or less of the potency of the therapeutic anti-IgE antibody to said human IgE; and

(b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0032]** Disclosed are methods of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of: (a) contacting a sample from a patient with (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE, wherein the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; (b) capturing the mutant therapeutic antibody to a surface; and (c) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0032a]** In another aspect, there is provided a method of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of:

(a) contacting a sample from a patient with (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE, wherein the mutant therapeutic antibody comprises one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE;

(b) capturing the mutant therapeutic antibody to a surface; and

(c) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0033]** Disclosed are methods of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of: (a) preincubating a sample from a patient with excess amount of an FcεRIα polypeptide that binds to an Fc region of a human IgE; (b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is reduced as compared to the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (c) detecting binding of an anti-drug antibody of IgE isotype to the therapeutic anti-IgE antibody or the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0033a]** In another aspect, there is provided a method of identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, comprising the steps of:

(a) preincubating a sample from a patient with excess amount of an FcεRIα polypeptide that binds to an Fc region of a human IgE;

(b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising one, two, three, four, five, or six amino acid mutations in the CDR sequences of the heavy and/or light chain of the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and

(c) detecting binding of an anti-drug antibody of IgE isotype to the therapeutic anti-IgE antibody or the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0034]** Disclosed are methods of treating a patient having an IgE-mediated disorder, comprising the steps of: (a) determining the level of an anti-drug antibody of IgE isotype to a therapeutic anti-IgE antibody in a sample from the patient; (b) administering an effective amount of the therapeutic anti-IgE antibody to the patient if the level of the anti-drug antibody in the sample do not indicate that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody. The level of the anti-drug antibody may be determined by any of the methods provided herein.

**[0035]** Disclosed are uses of a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody in the preparation of a kit for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, wherein the detection comprises the steps of: (a) contacting a sample that may contain the anti-drug antibody with the mutant therapeutic antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0036]** Disclosed are uses of a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody in the preparation of a kit for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, wherein the detection comprises the steps of: (a) contacting a sample that may contain the anti-drug antibody with the mutant therapeutic antibody, wherein the potency of the mutant therapeutic antibody to human IgE is about 10% or less of the potency of the therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0037]** Disclosed are uses of (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE in the preparation of a kit for detecting an anti-drug antibody of IgE isotype that binds to a therapeutic anti-IgE antibody in a sample, wherein the detection comprises the steps of: (a) contacting a sample that may contain the anti-drug antibody with (i) the mutant therapeutic antibody and (ii) the FcεRIα polypeptide, wherein the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; (b) capturing the mutant therapeutic antibody to a surface; and (c) detecting binding of the anti-drug antibody to the mutant therapeutic antibody.

**[0038]** Disclosed are uses of (i) a therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE in the preparation of a kit for detecting an anti-drug antibody of IgE isotype that binds to the therapeutic anti-IgE antibody in a sample, wherein the detection comprises the steps of: (a) preincubating a sample that may contain the anti-drug antibody with excess

amount of the FcεRIα polypeptide; (b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or the mutant therapeutic antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is reduced as compared to the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (c) detecting binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody.

**[0039]** Disclosed are uses of a mutant therapeutic antibody comprising at least one amino acid mutation from a therapeutic anti-IgE antibody in the preparation of a kit for identifying a patient having a risk of anaphylactic reaction to the therapeutic anti-IgE antibody, wherein the identifying comprises the steps of: (a) contacting a sample from the patient with the mutant therapeutic antibody, wherein the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody indicate the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0040]** Disclosed are uses of a mutant therapeutic antibody comprising at least one amino acid mutation from a therapeutic anti-IgE antibody in the preparation of a kit for identifying a patient having a risk of anaphylactic reaction to the therapeutic anti-IgE antibody, wherein the identifying comprises the steps of: (a) contacting a sample from the patient with the mutant therapeutic antibody, wherein the potency of the mutant therapeutic antibody to human IgE is about 10% or less of the potency of the therapeutic anti-IgE antibody to said human IgE; and (b) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0041]** Disclosed are uses of (i) a mutant therapeutic antibody and (ii) an FcεRIα polypeptide that binds to an Fc region of a human IgE in the preparation of a kit for identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, wherein the identifying comprises the steps of: (a) contacting a sample from a patient with (i) the mutant therapeutic antibody and (ii) the FcεRIα polypeptide, wherein the mutant therapeutic antibody comprises at least one amino acid mutation from the therapeutic anti-IgE antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is about 10% or less of the relative binding affinity of the therapeutic anti-IgE

antibody to said human IgE; (b) capturing the mutant therapeutic antibody to a surface; and (c) detecting binding of an anti-drug antibody of IgE isotype to the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0042]** Disclosed are uses of (i) an FcεRIα polypeptide that binds to an Fc region of a human IgE and (ii) a therapeutic anti-IgE antibody or a mutant therapeutic antibody comprising at least one amino acid mutation from the therapeutic anti-IgE antibody in the preparation of a kit for identifying a patient having a risk of anaphylactic reaction to a therapeutic anti-IgE antibody, wherein the identifying comprises the steps of: (a) preincubating a sample from a patient with excess amount of the FcεRIα polypeptide; (b) incubating the preincubated sample from step (a) with the therapeutic anti-IgE antibody or the mutant therapeutic antibody, and the relative binding affinity of the mutant therapeutic antibody to human IgE is reduced as compared to the relative binding affinity of the therapeutic anti-IgE antibody to said human IgE; and (c) detecting binding of an anti-drug antibody of IgE isotype to the therapeutic anti-IgE antibody or the mutant therapeutic antibody, wherein the presence and/or the level of the anti-drug antibody in the sample indicates that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0043]** Disclosed are compositions comprising a therapeutic anti-IgE antibody for treating a patient having an IgE-mediated disorder, wherein the level of an anti-drug antibody of IgE isotype to the therapeutic anti-IgE antibody in a sample from the patient has been determined and the level of the anti-drug antibody in the sample does not indicate that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody. Disclosed is a therapeutic anti-IgE antibody for treating a patient having an IgE-mediated disorder, wherein the level of an anti-drug antibody of IgE isotype to the therapeutic anti-IgE antibody in a sample from the patient has been determined and the level of the anti-drug antibody in the sample does not indicate that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

**[0044]** It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure. These and other aspects of the disclosure will become apparent to one of skill in the art.