CLAIMS

What is claimed is:

1. 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.

2. The method of claim 1, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is 5% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

3. The method of claim 1 or 2, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is 2.5% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

4. The method of any one of claims 1-3, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is 1 % or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

5. The method of any one of claims 1-4, wherein the relative binding affinity is measured by comparing the binding to the human IgE in an ELISA assay.

6. 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.

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

8. The method of claim 7, wherein 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 Asp at positions 30, 32, and 34 are substituted in the light chain.

9. The method of claim 8 , wherein 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.

10. The method of any one of claims 1-9, wherein the mutant therapeutic antibody is captured to a surface.

11. The method of claim 10, wherein the mutant therapeutic antibody is directly immobilized to the surface.

12. The method of claim 10, wherein the mutant therapeutic antibody is labeled and is captured to the surface through a capture agent that specifically binds to the label, wherein the capture agent is immobilized to the surface.

13. The method of claim 12, wherein the label is biotin and the capture agent is streptavidin.

14. The method of claim 12, wherein the label is digoxigenin and the capture agent is an anti-digoxigenin antibody.

15. The method of any one of claims 1-14, wherein the sample is contacted with the mutant therapeutic antibody that is captured to a surface.

16. The method of any one of claims 1-14, wherein the sample is contacted with the mutant therapeutic antibody before the mutant therapeutic antibody is captured to a surface.

17. The method of any one of claims 1-16, wherein the binding of the anti-drug antibodies to the mutant therapeutic antibody is detected with a detecting agent.

18. The method of claim 17, wherein the detecting agent is an FcεRIα polypeptide that binds to an Fc region of a human IgE.

19. The method of claim 18, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit.

20. The method of claim 19, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

21. The method of any one of claims 18-20, wherein the FcεRIα polypeptide is labeled.

22. The method of claim 21, wherein the label on the FcεRIα polypeptide is selected from the group consisting of biotin, digoxigenin, ruthenium, a radiologic label, a photoluminescent label, a chemiluminescent label, a fluorescent label, an electrochemiluminescent label, and an enzyme label.

23. The method of claim 21 or 22, wherein the label on the FcεRIα polypeptide is detected by a second detecting agent that specifically binds to the label on the FcεRIα polypeptide.

24. The method of any one of claims 1-6 and 10-23, wherein the therapeutic anti-IgE antibody is omalizumab.

25. The method of any one of claims 1-24, wherein the sample contains human serum or plasma.

26. The method of claim 25, wherein the serum or plasma contains the therapeutic antibody.

27. The method of claim 25, wherein the serum or plasma does not contain the therapeutic antibody.

28. The method of any one of claims 1-27, further comprising a step of comparing the binding of the anti-drug antibodies to the mutant therapeutic antibody detected in step b) to a reference.

29. The method of claim 28, wherein the reference is the detected binding between the mutant therapeutic antibody and a control antibody.

30. The method of claim 29, wherein the control antibody is a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity.

31. The method of claim 30, wherein 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.

32. A kit 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 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 human IgE;

(b) a detecting agent that binds to an Fc region of a human IgE; and

(c) a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody, wherein difference between relative binding affinities of the positive control antibody to the therapeutic anti-IgE antibody and to the mutant therapeutic antibody is less than 50%.

33. The kit of claim 32, wherein the detecting agent is an FcεRIα polypeptide comprising an extracellular domain of an FcεRIα subunit.

34. The kit of claim 33, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

35. The kit of claim 32-34, wherein 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.

36. A kit 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 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 human IgE;

(b) a detecting agent that binds to an Fc region of a human IgE; and

(c) a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody, wherein difference between relative binding affinities of the positive control antibody to the therapeutic anti-IgE antibody and to the mutant therapeutic antibody is less than 50%.

37. The kit of claim 36, wherein the detecting agent is an FcεRIα polypeptide comprising an extracellular domain of an FcεRIα subunit.

38. The kit of claim 37, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

39. The kit of claim 36-38, wherein 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.

40. 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.

41. The method of claim 40, wherein excess amount of FcεRIα polypeptide is contacted with the sample in step (a).

42. The method of claim 41, wherein at least 10-fold excess of FcεRIα polypeptide is contacted with the sample in step (a).

43. The method of any one of claims 40-42, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit.

44. The method of any one of claims 40-43, wherein the mutant therapeutic antibody is labeled and is captured to the surface by a capture agent that specifically binds to the label.

45. The method of claim 44, wherein the label is biotin and the surface is coated with streptavidin.

46. The method of any one of claims 40-45, wherein the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by a labeled anti-human IgE antibody.

47. The method of any one of claims 40-45, wherein 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.

48. A kit 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 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 human IgE;

(b) an FcεRIα polypeptide that binds to an Fc region of a human IgE; and

(c) a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody, wherein difference between relative binding affinities of the positive control antibody to the therapeutic anti-IgE antibody and to the mutant therapeutic antibody is less than 50%.

49. The kit of claim 48, further comprising an anti-human IgE antibody.

50. The kit of claim 49, wherein the anti-human IgE antibody is labeled.

51. The kit of any one of claims 48-50, wherein the FcεRIα polypeptide is labeled.

52. The kit of any one of claims 48-51, further comprising a detecting agent that specifically binds to the label on the FcεRIα polypeptide.

53. 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.

54. The method of claim 53, wherein at least 10-fold excess of FcεRIα polypeptide is preincubated with the sample in step (a).

55. The method of any one of claims 53 or 54, wherein 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).

56. The method of any one of claims 53-55, wherein the therapeutic anti-IgE antibody or the mutant therapeutic antibody is directly immobilized to a surface before incubating with the sample in step (b).

57. The method of any one of claims 53-55, wherein 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.

58. The method of claim 57, wherein the therapeutic anti-IgE antibody or the mutant therapeutic antibody is labeled with biotin and is captured to a streptavidin coated surface.

59. The method of any one of claims 53-58, wherein the binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-human IgE antibody.

60. The method of any one of claims 53-58, wherein 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.

61. The method of claim 60, wherein the FcεRIα polypeptide is labeled with digoxigenin, and the binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-digoxigenin antibody.

62. The method of claim 60, wherein 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 via electrochemiluminescence.

63. 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.

64. 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.

65. 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.

66. 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.

67. Use of a therapeutic anti-IgE antibody in the manufacture of a medicament for treating an IgE-mediated disorder in a patient, wherein the level of an anti-drug antibody of IgE isotype to a therapeutic anti-IgE antibody that has been determined according to the method of any one of claims 63-66 does not indicate that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

CLAIMS

What is claimed is:

1. 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 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 the anti-drug antibody to the mutant therapeutic antibody.

2. The method of claim 1, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is about 5% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

3. The method of claim 1 or 2, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is about 2.5% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

4. The method of any one of claims 1-3, wherein the relative binding affinity of the mutant therapeutic antibody to the human IgE is about 1% or less of the relative binding affinity of the therapeutic anti-IgE antibody to the human IgE.

5. The method of any one of claims 1-4, wherein the relative binding affinity is measured by comparing the binding to the human IgE in an ELISA assay.

6. 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 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 the anti-drug antibody to the mutant therapeutic antibody.

7. The method of any one of claims 1-6, 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.

8. The method of any one of claims 1-7, wherein 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.

9. The method of claim 8, wherein 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 Asp at positions 30, 32, and 34 are substituted in the light chain.

10. The method of claim 9, wherein 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.

11. The method of any one of claims 1-10, wherein the mutant therapeutic antibody is captured to a surface.

12. The method of claim 11, wherein the mutant therapeutic antibody is directly immobilized to the surface.

13. The method of claim 11, wherein the mutant therapeutic antibody is labeled and is captured to the surface through a capture agent that specifically binds to the label, wherein the capture agent is immobilized to the surface.

14. The method of claim 13, wherein the label is biotin and the capture agent is streptavidin.

15. The method of claim 13, wherein the label is digoxigenin and the capture agent is an anti-digoxigenin antibody.

16. The method of any one of claims 1-15, wherein the sample is contacted with the mutant therapeutic antibody that is captured to a surface.

17. The method of any one of claims 1-15, wherein the sample is contacted with the mutant therapeutic antibody before the mutant therapeutic antibody is captured to a surface.

18. The method of any one of claims 1-17, wherein the binding of the anti-drug antibodies to the mutant therapeutic antibody is detected with a detecting agent.

19. The method of claim 18, wherein the detecting agent is an FcεRIα polypeptide that binds to an Fc region of a human IgE.

20. The method of claim 19, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit.

21. The method of claim 20, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

22. The method of any one of claims 19-21, wherein the FcεRIα polypeptide is labeled.

23. The method of claim 22, wherein the label on the FcεRIα polypeptide is selected from the group consisting of biotin, digoxigenin, ruthenium, a radiologic label, a photoluminescent label, a chemiluminescent label, a fluorescent label, an electrochemiluminescent label, and an enzyme label.

24. The method of claim 22 or 23, wherein the label on the FcεRIα polypeptide is detected by a second detecting agent that specifically binds to the label on the FcεRIα polypeptide.

25. The method of any one of claims 1-7 and 11-24, wherein the therapeutic anti-IgE antibody is omalizumab.

26. The method of any one of claims 1-25, wherein the sample contains human serum or plasma.

27. The method of claim 26, wherein the serum or plasma contains the therapeutic antibody.

28. The method of claim 26, wherein the serum or plasma does not contain the therapeutic antibody.

29. The method of any one of claims 1-28, further comprising a step of comparing the binding of the anti-drug antibodies to the mutant therapeutic antibody detected in step b) to a reference.

30. The method of claim 29, wherein the reference is the detected binding between the mutant therapeutic antibody and a control antibody.

31. The method of claim 30, wherein the control antibody is a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity.

32. The method of claim 31, wherein 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.

33. A kit 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) a detecting agent that binds to an Fc region of a human IgE.

34. The kit of claim 33, wherein the detecting agent is an FcεRIα polypeptide comprising an extracellular domain of an FcεRIα subunit.

35. The kit of claim 34, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

36. The kit of any one of claims 33-35, further comprising a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity.

37. The kit of claim 36, wherein 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.

38. A kit 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 potency of the mutant therapeutic antibody to human IgE is about 10% or less of the potency of the therapeutic anti-IgE antibody to human IgE; and

(b) a detecting agent that binds to an Fc region of a human IgE.

39. The kit of claim 38, wherein the detecting agent is an FcεRIα polypeptide comprising an extracellular domain of an FcεRIα subunit.

40. The kit of claim 39, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit fused to an IgG constant region.

41. The kit of any one of claims 38-40, further comprising a positive control antibody that binds both the therapeutic anti-IgE antibody and the mutant therapeutic antibody with similar affinity.

42. The kit of claim 41, wherein 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.

43. 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 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.

44. The method of claim 43, wherein excess amount of FcεRIα polypeptide is contacted with the sample in step (a).

45. The method of claim 44, wherein at least about 10-fold excess of FcεRIα polypeptide is contacted with the sample in step (a).

46. The method of any one of claims 43-45, wherein the FcεRIα polypeptide comprises an extracellular domain of an FcεRIα subunit.

47. The method of any one of claims 43-46, wherein the mutant therapeutic antibody is labeled and is captured to the surface by a capture agent that specifically binds to the label.

48. The method of claim 47, wherein the label is biotin and the surface is coated with streptavidin.

49. The method of any one of claims 43-48, wherein the binding of the anti-drug antibody to the mutant therapeutic antibody is detected by a labeled anti-human IgE antibody.

50. The method of any one of claims 43-48, wherein 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.

51. A kit 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.

52. The kit of claim 51, further comprising an anti-human IgE antibody.

53. The kit of claim 52, wherein the anti-human IgE antibody is labeled.

54. The kit of any one of claims 51-53, wherein the FcεRIα polypeptide is labeled.

55. The kit of any one of claims 51-54, further comprising a detecting agent that specifically binds to the label on the FcεRIα polypeptide.

56. 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 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 the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody.

57. The method of claim 56, 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.

58. The method of claim 56 or 57, wherein at least about 10-fold excess of FcεRIα polypeptide is preincubated with the sample in step (a).

59. The method of any one of claims 56-58, wherein 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).

60. The method of any one of claims 56-59, wherein the therapeutic anti-IgE antibody or the mutant therapeutic antibody is directly immobilized to a surface before incubating with the sample in step (b).

61. The method of any one of claims 56-59, wherein 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.

62. The method of claim 61, wherein the therapeutic anti-IgE antibody or the mutant therapeutic antibody is labeled with biotin and is captured to a streptavidin coated surface.

63. The method of any one of claims 56-62, wherein the binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-human IgE antibody.

64. The method of any one of claims 56-62, wherein 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.

65. The method of claim 64, wherein the FcεRIα polypeptide is labeled with digoxigenin, and the binding of the anti-drug antibody to the therapeutic anti-IgE antibody or the mutant therapeutic antibody is detected by a HRP conjugated anti-digoxigenin antibody.

66. The method of claim 64, wherein 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 via electrochemiluminescence.

67. A kit 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.

68. The kit of claim 67, further comprising an anti-human IgE antibody.

69. The kit of claim 68, wherein the anti-human IgE antibody is labeled.

70. The kit of any one of claims 67-69, wherein the FcεRIα polypeptide is labeled.

71. The kit of claim 70, further comprising a detecting agent that specifically binds to the label on the FcεRIα polypeptide.

72. 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 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 indicate the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

73. 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 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.

74. 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 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.

75. 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 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.

76. Use of a therapeutic anti-IgE antibody in the manufacture of a medicament fortreating an IgE-mediated disorder in a patient, wherein

the level of an anti-drug antibody of IgE isotype to a therapeutic anti-IgE antibody that has been determined in a sample from the patientdoes not indicate that the patient has a risk of anaphylactic reaction to the therapeutic anti-IgE antibody.

77. The use of claim 76, wherein the level of the anti-drug antibody in the sample is determined by a method comprising the steps:

(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.

78. The use of claim 76, wherein the level of the anti-drug antibody in the sample is determined by a method comprising the steps:

(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.

79. The use of claim 76, wherein the level of the anti-drug antibody in the sample is determined by a method comprising the steps:

(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.

80. The use of claim 76, wherein the level of the anti-drug antibody in the sample is determined by a method comprising the steps:

(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.