We claim:

1. A mouse comprising a genetic modification, wherein the genetic modification comprises a replacement of endogenous low affinity FcγR genes with at least two low affinity human FcγR genes placed at the endogenous mouse low affinity FcγR gene locus, and wherein the mouse comprises a functional FcR γ-chain.

2. The mouse of claim 1, wherein the at least two low affinity human FcγR genes are selected from FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA and FcγRIIIB.

3. The mouse of claim 1, wherein the at least two low affinity human FcγR genes are FcγRIIA and FcγRIIIA.

4. The mouse of claim 3, wherein the human FcγRIIIA is expressed on NK cells of the mouse.

5. The mouse of claim 1, wherein the at least two low affinity human FcγR genes are FcγRIIB, FcγRIIC, and FcγRIIIB.

6. The mouse of claim 3, wherein the FcγRIIA and FcγRIIIA genes comprise allelic variants or polymorphisms.

7. The mouse of claim 5, wherein the mouse comprises human low affinity FcγR allelic variants, and the allelic variants are selected from the group consisting of (a) FcγRIIA allelic variant 131H, (b) FcγRIIIA allelic variant 158V, (c) FcγRIIB allelic variant 232I, (d) FcγRIIIB allelic variant characterized by a neutrophil antigen 2 (NA2) allele, and, (e) a combination thereof.

8. A genetically modified mouse, wherein the genetic modification comprises a replacement of endogenous mouse genes encoding FcγRIIB, FcγRIII, and FcγRIV α-subunits with a gene encoding a human FcγRIIIA α-subunit, wherein the mouse expresses a human FcγRIIIA protein associated with an endogenous mouse FcR γ-subunit, wherein the human FcγRIIIA protein is expressed on the surface of a mouse NK cell.

9. The genetically modified mouse of claim 8, wherein mouse NK cell is a circulating NK cell in the blood of the mouse, and the FcγRIIIA protein expressed on

the surface of the mouse NK cell binds an immunoadhesin or an antibody that comprises a human Fc or a modified human Fc, wherein the immunoadhesin or antibody specifically binds a target cell in the mouse, and binding of the immunoadhesin or the antibody to the FcγRIIIA of the NK cell mediates NK cell killing of the target cell.

10. The genetically modified mouse of claim 9, wherein the target cell is infected with a human pathogen, and the immunoadhesin or antibody specifically binds an epitope of the human pathogen.

11. The genetically modified mouse of claim 9, wherein the target cell is a tumor cell, and the immunoadhesin or antibody specifically binds an epitope of the tumor cell.

12. A method for measuring therapeutic-dependent cell killing, comprising:
(a) administering to a genetically modified mouse a therapeutic agent that specifically binds a target cell that is not an NK cell in the mouse, wherein the therapeutic agent comprises a human Fc;
(b) measuring a level of NK-mediated target cell killing in the mouse or in a tissue sample of the mouse; and,
(c) determining the amount of target cell killing that is mediated by the therapeutic agent, thereby measuring therapeutic-dependent cell killing;
wherein the genetic modification comprises a deletion of a gene encoding the α-subunit of mouse FcγRIIB, a deletion of a gene encoding the α-subunit of mouse FcγRIII, and a deletion of a gene encoding the α-subunit of mouse FcγRIV, and wherein the mouse comprises a gene encoding an α-subunit of a human FcγRIIIA at the endogenous mouse α-subunit locus and wherein the mouse expresses a functional FcR γ-chain subunit.

13. The method of claim 12, wherein the mouse further comprises at the endogenous mouse α-subunit locus a gene encoding a human FcγR α-subunit selected from an an FcγRIIA α-subunit , FcγRIIB α-subunit, an FcγRIIC α-subunit, an FcγRIIIB α-subunit, and a combination thereof.

14. The method of claim 12, wherein the target cell is a human pathogen, and the therapeutic specifically binds an epitope of the human pathogen.

15. The method of claim 12, wherein the target cell is a mouse cell infected by a human pathogen, and the therapeutic specifically binds an epitope of the human pathogen.

16. The method of claim 12, wherein the target cell is a human cell infected by a human pathogen, and the therapeutic specifically binds an epitope of the human pathogen.

17. The method of claim 12, wherein the target cell is a human tumor cell, and the therapeutic specifically binds an epitope of the human tumor cell.

18. The method of claim 12, wherein the tissue sample is a blood sample.

19. The method of claim 12, wherein the therapeutic is an antibody.

20. The method of claim 17, wherein the antibody is a human antibody.

We claim:

1. A transgenic mouse whose genome comprises at least two low affinity human FcγR α-chain genes that replace the endogenous mouse low affinity FcγR α-chain genes, wherein the mouse comprises a functional endogenous FcR γ-chain and functionally expresses the at least two low affinity human FcγR α-chain genes.

2. The transgenic mouse of claim 1, wherein the at least two low affinity human FcγR α-chain genes are selected from the group consisting of a human FcγRIIA α-chain gene, a human FcγRIIB α-chain gene, a human FcγRIIC α-chain gene, a human FcγRIIIA α-chain gene and a human FcγRIIIB α-chain gene.

3. The transgenic mouse of claim 1, wherein the at least two low affinity human FcγR genes are a human FcγRIIA α-chain gene and a human FcγRIIIA α-chain gene.

4. The transgenic mouse of claim 3, wherein the human FcγRIIIA α-chain protein is expressed on NK cells of the mouse.

5. The transgenic mouse of claim 1, wherein the genome of the mouse comprises a human FcγRIIB α-chain gene, a human FcγRIIC α-chain gene, and a human FcγRIIIB α-chain gene.

6. A transgenic mouse whose genome comprises a human FcγRIIIA α-chain gene that replaces the endogenous mouse FcγRIIB, FcγRIII, and FcγRIV α-chain genes, wherein the mouse functionally expresses the human FcγRIIIA α-chain gene on the surface of a mouse NK cell with a mouse FcR γ-chain.

7. A method of screening an agent comprising an Fc region of a human antibody comprising:
(a) administering an agent comprising an Fc region of a human antibody to the transgenic mouse of claim 1, wherein the agent binds to a target cell in the mouse;

(b) measuring antibody-dependent cell-mediated cytotoxicity (ADCC) of natural killer (NK) cells against the target cell; and,

c) comparing the amount of ADCC in step b) to a control, wherein increased target cell killing indicates the agent has increased ability to mediate ADCC.

8. The method of claim 7, wherein the transgenic mouse comprises
(a) a human FcγRIIA α-chain gene and a human FcγRIIIA α-chain gene that replace the endogenous FcγRIIB, FcγRIII, and FcγRIV α-chain genes; or

(b) a human FcγRIIA α-chain gene, a human FcγRIIB α-chain gene, a human FcγRIIC α-chain gene, a human FcγRIIIA α-chain gene and a human FcγRIIIB α-chain gene that replace the endogenous FcγRIIB, FcγRIII, and FcγRIV α-chain genes.

9. The method of claim 7, wherein the target cell is a tumor cell and the agent binds an epitope of the tumor cell.

10. The method of claim 7, wherein the target cell is a mouse cell infected by a human pathogen and the agent binds an epitope of the human pathogen.

11. The method of claim 7, wherein the target cell is a human cell infected by a human pathogen and the agent binds an epitope of the human pathogen.

12. The method of claim 7, wherein the target cell is a human tumor cell and the agent binds an epitope of the human tumor cell.

13. The method of claim 7, wherein the ADCC of NK cells against the target cell is measured in a blood sample of the mouse.

14. The method of claim 7, wherein the agent is an antibody.

15. The method of claim 14, wherein the antibody is a human antibody.