CLAIMS:

1. A humanized immunodeficient mouse comprising:
(a) human cells selected from human hematopoietic stem cells (HSCs) and human peripheral blood mononuclear cells (PBMCs); and
(b) a human patient-derived xenograft (PDX) from a tumor,
wherein the mouse lacks functional mouse immune cells, and
wherein the human cells and the PDX are non-HLA matched.

2. The mouse of claim 1, wherein the human cells are HSCs.

3. The mouse of claim 1, wherein the human cells are PBMCs.

4. The mouse of claim 1, wherein the tumor is a cancer select from an ovarian cancer, a lung cancer, a bladder cancer, a lymphoma, a breast cancer, a brain cancer, a pancreatic cancer, a prostate cancer, a colon cancer, a colorectal cancer, an endometrial cancer, a gastric/GIST cancer, a hepatocellular cancer, a kidney/renal cancer, a skin cancer, a soft tissue carcinoma, a sarcoma, and a cancer cell line.

5. The mouse of claim 1, wherein the mouse immune cells are selected from mouse T cells and mouse B cells.

6. The mouse of claim 1, wherein the mouse is homozygous for a *scid* mutation.

7. The mouse of claim 1, wherein the mouse is homozygous or hemizygous for an IL-2 receptor gamma chain deficiency.

8. The mouse of claim 6, wherein the mouse is homozygous or hemizygous for an IL-2 receptor gamma chain deficiency.

9. The mouse of claim 1, wherein the mouse has a non-obese diabetic (NOD) *scid* gamma genetic background.

10. The mouse of claim 1, further comprising transgenes encoding human interleukin-3 (IL-3), human granulocyte/macrophage-stimulating factor (GM-CSF), and/or human Steel factor (SF).

11. The mouse of claim 1, further comprising human liver and/or human thymus fragments.

12. A method of generating the humanized immunodeficient mouse of claim 1, comprising:
(a) introducing into an immunodeficient mouse the human cells selected from hematopoietic stem cells (HSCs) and human peripheral blood mononuclear cells (PBMCs); and
(b) introducing into the immunodeficient mouse the human PDX from a tumor.

13. A method comprising:
(a) administering one or more agent(s) to the humanized immunodeficient mouse of claim 1, wherein the mouse has a PDX tumor; and
(b) assessing effectiveness of the one or more agent(s) for treating the PDX tumor.

14. The method of claim 13, wherein the one or more agent(s) is an anti-cancer agent.

15. The method of claim 13, wherein the one or more agent(s) is selected from: a small molecules, proteins, peptides, nucleic acids, carbohydrates, oligosaccharides, lipids, and combinations thereof.

16. The method of claim 13, wherein the one or more agent(s) is selected from: an antibody or antigen-binding fragment thereof, bi-specific T-cell engager, a genetically engineered lymphocyte that expresses chimeric antigen receptor (CAR), a tumor infiltrating lymphocyte (TIL), and a vaccine.

17. The method of claim 13, wherein the administering comprises administering two or more agents, and the method further comprises comparing effectiveness of the two or more agents for treating the tumor.

18. The method of claim 17, further comprising rank ordering the two or more agents based on effectiveness of the two or more agents for treating the tumor.

19. A humanized immunodeficient non-obese diabetic (NOD) *scid* gamma mouse comprising:
(a) human cells selected from human hematopoietic stem cells (HSCs) and human peripheral blood mononuclear cells (PBMCs); and
(b) a human patient-derived xenograft (PDX) from a tumor,
wherein the mouse lacks functional mouse T cells and B cells, and
wherein the human cells and the PDX are non-HLA matched.

20. The mouse of claim 19, wherein the human cells are HSCs.

21. The mouse of claim 19, wherein the human cells are PBMCs.

22. The mouse of claim 19, wherein the tumor is a cancer select from an ovarian cancer, a lung cancer, a bladder cancer, a lymphoma, a breast cancer, a brain cancer, a pancreatic cancer, a prostate cancer, a colon cancer, a colorectal cancer, an endometrial cancer, a gastric/GIST cancer, a hepatocellular cancer, a kidney/renal cancer, a skin cancer, a soft tissue carcinoma, a sarcoma, and a cancer cell line.

23. The mouse of claim 19, further comprising transgenes encoding human interleukin-3 (IL-3), human granulocyte/macrophage-stimulating factor (GM-CSF), and/or human Steel factor (SF).

24. The mouse of claim 19, further comprising human liver and/or human thymus fragments.

25. A method of generating the humanized immunodeficient mouse of claim 19, comprising:
(a) introducing into an immunodeficient mouse the human cells selected from hematopoietic stem cells (HSCs) and human peripheral blood mononuclear cells (PBMCs); and
(b) introducing into the immunodeficient mouse the human PDX from a tumor.

26. A method comprising:

(a) administering one or more agent(s) to the humanized immunodeficient mouse of claim 19, wherein the mouse has a PDX tumor; and

(b) assessing effectiveness of the one or more agent(s) for treating the PDX tumor.

27. The method of claim 26, wherein the one or more agent(s) is an anti-cancer agent.

28. The method of claim 26, wherein the one or more agent(s) is selected from: a small molecules, proteins, peptides, nucleic acids, carbohydrates, oligosaccharides, lipids, and combinations thereof.

29. The method of claim 26, wherein the one or more agent(s) is selected from: an antibody or antigen-binding fragment thereof, bi-specific T-cell engager, a genetically engineered lymphocyte that expresses chimeric antigen receptor (CAR), a tumor infiltrating lymphocyte (TIL), and a vaccine.

30. The method of claim 26, wherein the administering comprises administering two or more agents, and the method further comprises comparing effectiveness of the two or more agents for treating the tumor.

31. The method of claim 30, further comprising rank ordering the two or more agents based on effectiveness of the two or more agents for treating the tumor.