We claim:

1. A non-human animal cell comprising a nucleic acid sequence encoding a heterologous Transferrin Receptor (TfR) protein or a portion thereof.

2. The non-human animal cell of claim 1, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises:

(i) a nucleic acid sequence comprising exon 2 of a human *TFRC* gene or a coding portion thereof;

(ii) a nucleic acid sequence comprising exon 3 of a human *TFRC* gene or a portion thereof;

(iii) a nucleic acid sequence comprising exon 4 of a human *TFRC* gene or a portion thereof;

(iv) a nucleic acid sequence comprising exon 5 of a human *TFRC* gene or a portion thereof;

(v) a nucleic acid sequence comprising exon 6 of a human *TFRC* gene or a portion thereof;

(vi) a nucleic acid sequence comprising exon 7 of a human *TFRC* gene or a portion thereof;

(vii) a nucleic acid sequence comprising exon 8 of a human *TFRC* gene or a portion thereof;

(viii) a nucleic acid sequence comprising exon 9 of a human *TFRC* gene or a portion thereof;

(ix) a nucleic acid sequence comprising exon 10 of a human *TFRC* gene or a portion thereof;

(x) a nucleic acid sequence comprising exon 11 of a human *TFRC* gene or a portion thereof;

(xi) a nucleic acid sequence comprising exon 12 of a human *TFRC* gene or a portion thereof;

(xii) a nucleic acid sequence comprising exon 13 of a human *TFRC* gene or a portion thereof;

(xiii) a nucleic acid sequence comprising exon 14 of a human *TFRC* gene or a portion thereof;

(xiv) a nucleic acid sequence comprising exon 15 of a human *TFRC* gene or a portion thereof;

(xv) a nucleic acid sequence comprising exon 16 of a human *TFRC* gene or a portion thereof;

(xvi) a nucleic acid sequence comprising exon 17 of a human *TFRC* gene or a portion thereof;

(xvii) a nucleic acid sequence comprising exon 18 of a human *TFRC* gene or a portion thereof;

(xviii) a nucleic acid sequence comprising exon 19 of a human *TFRC* gene or a coding portion thereof; or

(xix) any combination of (i)-(xviii).

3. The non-human animal cell of claim 1 or claim 2, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises:

(i) a nucleic acid sequence comprising exon 2 of a human *TFRC* gene or a coding portion thereof and intron 2 of a human *TFRC* gene or a portion thereof;

(ii) a nucleic acid sequence comprising exon 3 of a human *TFRC* gene or a portion thereof and intron 3 of a human *TFRC* gene or a portion thereof;

(iii) a nucleic acid sequence comprising exon 4 of a human *TFRC* gene or a portion thereof and intron 4 of a human *TFRC* gene or a portion thereof;

(iv) a nucleic acid sequence comprising exon 5 of a human *TFRC* gene or a portion thereof and intron 5 of a human *TFRC* gene or a portion thereof;

(v) a nucleic acid sequence comprising exon 6 of a human *TFRC* gene or a portion thereof and intron 6 of a human *TFRC* gene or a portion thereof;

(vi) a nucleic acid sequence comprising exon 7 of a human *TFRC* gene or a portion thereof and intron 7 of a human *TFRC* gene or a portion thereof;

(vii) a nucleic acid sequence comprising exon 8 of a human *TFRC* gene or a portion thereof and intron 8 of a human *TFRC* gene or a portion thereof;

(viii) a nucleic acid sequence comprising exon 9 of a human *TFRC* gene or a portion thereof and intron 9 of a human *TFRC* gene or a portion thereof;

(ix) a nucleic acid sequence comprising exon 10 of a human *TFRC* gene or a portion thereof and intron 10 of a human *TFRC* gene or a portion thereof;

(x) a nucleic acid sequence comprising exon 11 of a human *TFRC* gene or a portion thereof and intron 11 of a human *TFRC* gene or a portion thereof;

(xi) a nucleic acid sequence comprising exon 12 of a human *TFRC* gene or a portion thereof and intron 12 of a human *TFRC* gene or a portion thereof;

(xii) a nucleic acid sequence comprising exon 13 of a human *TFRC* gene or a portion thereof and intron 13 of a human *TFRC* gene or a portion thereof;

(xiii) a nucleic acid sequence comprising exon 14 of a human *TFRC* gene or a portion thereof and intron 14 of a human *TFRC* gene or a portion thereof;

(xiv) a nucleic acid sequence comprising exon 15 of a human *TFRC* gene or a portion thereof and intron 15 of a human *TFRC* gene or a portion thereof;

(xv) a nucleic acid sequence comprising exon 16 of a human *TFRC* gene or a portion thereof and intron 16 of a human *TFRC* gene or a portion thereof;

(xvi) a nucleic acid sequence comprising exon 17 of a human *TFRC* gene or a portion thereof and intron 17 of a human *TFRC* gene or a portion thereof;

(xvii) a nucleic acid sequence comprising exon 18 of a human *TFRC* gene or a portion thereof and intron 18 of a human *TFRC* gene or a portion thereof;

(xviii) a nucleic acid sequence comprising exon 19 of a human *TFRC* gene or a coding portion thereof; or

(xix) any combination of (i)-(xviii).

4. The non-human animal cell of any one of claims 1-0, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises of a nucleic acid sequence selected from the group consisting of a nucleic acid sequence set forth as SEQ ID NO:5, a nucleic acid sequence set forth as SEQ ID NO:6, a nucleic acid sequence set forth as SEQ ID NO:9, and a nucleic acid sequence set forth as SEQ ID NO:10.

5. The non-human animal cell of any one of claims 1-0, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof is at an endogenous *Tfrc* locus.

6. The non-human animal cell of any one of claims 1-0, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof replaces an orthologous endogenous nucleic acid sequence encoding an endogenous TfR protein or a portion thereof.

7. The non-human animal cell of any one of claims 1-6, wherein the non-human animal cell, comprises an endogenous *Tfrc* locus, and wherein the endogenous *Tfrc* locus comprises an endogenous *Tfrc* gene comprising a heterozygous or homozygous replacement of an endogenous nucleic acid sequence encoding an endogenous TfR protein or a portion thereof with the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof,

wherein the endogenous nucleic acid sequence encoding the endogenous TfR protein or the portion thereof and the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof are orthologous.

8. The non-human animal cell of any one of claims 1-7, wherein the heterologous TfR protein or the portion thereof comprises an amino acid sequence of a human TfR protein or a portion thereof.

9. The non-human animal cell of any one of claims 1-0, wherein the heterologous TfR protein or the portion thereof comprises:

(i) an amino acid sequence set forth as SEQ ID NO:4;

(ii) an amino acid sequence set forth as SEQ ID NO:25;

(iii) an amino acid sequence set forth as SEQ ID NO:26;

(iv) an amino acid sequence set forth as SEQ ID NO:27;

(v) an amino acid sequence set forth as SEQ ID NO:28; or

(vi) any combination of (i)-(v).

10. The non-human animal cell of any one of claims 1-0, wherein the heterologous TfR protein or the portion thereof comprises an amino acid sequence set forth as SEQ ID NO: 25.

11. The non-human animal cell of any one of claims 1-0, wherein the non-human animal cell is a mammalian cell.

12. The non-human animal cell of any one of claims 1-0, wherein the non-human animal cell is a rodent cell.

13. The non-human animal cell of any one of claims 1-0, wherein the non-human animal cell is a rat cell or a mouse cell.

14. The non-human animal cell of any one of claims 1-0, wherein the heterologous TfR protein is a full-length human TfR protein, and

wherein the full-length human TfR protein is expressed on the cell surface of the non-human animal cell.

15. The non-human animal cell of any one of claims 1-0, wherein the non-human animal cell is a non-human animal cell identified in Table 1, and

wherein the heterologous TfR protein or the portion thereof is expressed on the cell surface of the non-human animal cell identified in Table 1.

16. The non-human animal cell of any one of claims 1-13, wherein the non-human animal cell is a non-human animal cell that does not express the heterologous TfR protein or the portion thereof on the cell surface of the non-human animal cell.

17. The non-human animal cell of any one of claims 1-13 and 16, wherein the non-human animal cell does not express the heterologous TfR protein or the portion thereof on the cell surface, and wherein the non-human animal cell is not a cell identified in Table 1.

18. The non-human animal cell of any one of claims 1-13 and 16-17, wherein the non-human animal cell does not express the heterologous TfR protein or the portion thereof on the cell surface, and wherein the non-human animal cell is a pluripotent cell.

19. The non-human animal cell of any one of claims 1-13 and 16-18, wherein the non-human animal cell does not express the heterologous TfR protein or the portion thereof on the cell surface, and wherein the non-human animal cell is an embryonic stem cell.

20. The non-human animal cell of any one of claims 1-13 and 16-18, wherein the non-human animal cell does not express the heterologous TfR protein or the portion thereof on the cell surface, and wherein the non-human animal cell is a germ cell.

21. The non-human animal cell of any one of claims 1-20, wherein the non-human animal cell is a mouse cell.

22. The non-human animal cell of any one of claims 1-20, wherein the non-human animal cell is a mouse cell and wherein the nucleic acid sequence encoding a heterologous TfR protein or the portion thereof comprises a nucleic acid sequence set forth as SEQ ID NO:9 or SEQ ID NO:10.

23. A non-human animal comprising a nucleic acid sequence encoding a heterologous transferrin receptor (TfR) protein or a portion thereof.

24. The non-human animal of claim 23, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises:

(i) a nucleic acid sequence comprising exon 2 of a human *TFRC* gene or a coding portion thereof;

(ii) a nucleic acid sequence comprising exon 3 of a human *TFRC* gene or a portion thereof;

(iii) a nucleic acid sequence comprising exon 4 of a human *TFRC* gene or a portion thereof;

(iv) a nucleic acid sequence comprising exon 5 of a human *TFRC* gene or a portion thereof;

(v) a nucleic acid sequence comprising exon 6 of a human *TFRC* gene or a portion thereof;

(vi) a nucleic acid sequence comprising exon 7 of a human *TFRC* gene or a portion thereof;

(vii) a nucleic acid sequence comprising exon 8 of a human *TFRC* gene or a portion thereof;

(viii) a nucleic acid sequence comprising exon 9 of a human *TFRC* gene or a portion thereof;

(ix) a nucleic acid sequence comprising exon 10 of a human *TFRC* gene or a portion thereof;

(x) a nucleic acid sequence comprising exon 11 of a human *TFRC* gene or a portion thereof;

(xi) a nucleic acid sequence comprising exon 12 of a human *TFRC* gene or a portion thereof;

(xii) a nucleic acid sequence comprising exon 13 of a human *TFRC* gene or a portion thereof;

(xiii) a nucleic acid sequence comprising exon 14 of a human *TFRC* gene or a portion thereof;

(xiv) a nucleic acid sequence comprising exon 15 of a human *TFRC* gene or a portion thereof;

(xv) a nucleic acid sequence comprising exon 16 of a human *TFRC* gene or a portion thereof;

(xvi) a nucleic acid sequence comprising exon 17 of a human *TFRC* gene or a portion thereof;

(xvii) a nucleic acid sequence comprising exon 18 of a human *TFRC* gene or a portion thereof;

(xviii) a nucleic acid sequence comprising exon 19 of a human *TFRC* gene or a coding portion thereof; or

(xix) any combination of (i)-(xviii).

25. The non-human animal of claim 23 or claim 24, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises:

(i) a nucleic acid sequence comprising exon 2 of a human *TFRC* gene or a coding portion thereof and intron 2 of a human *TFRC* gene or a portion thereof;

(ii) a nucleic acid sequence comprising exon 3 of a human *TFRC* gene or a portion thereof and intron 3 of a human *TFRC* gene or a portion thereof;

(iii) a nucleic acid sequence comprising exon 4 of a human *TFRC* gene or a portion thereof and intron 4 of a human *TFRC* gene or a portion thereof;

(iv) a nucleic acid sequence comprising exon 5 of a human *TFRC* gene or a portion thereof and intron 5 of a human *TFRC* gene or a portion thereof;

(v) a nucleic acid sequence comprising exon 6 of a human *TFRC* gene or a portion thereof and intron 6 of a human *TFRC* gene or a portion thereof;

(vi) a nucleic acid sequence comprising exon 7 of a human *TFRC* gene or a portion thereof and intron 7 of a human *TFRC* gene or a portion thereof;

(vii) a nucleic acid sequence comprising exon 8 of a human *TFRC* gene or a portion thereof and intron 8 of a human *TFRC* gene or a portion thereof;

(viii) a nucleic acid sequence comprising exon 9 of a human *TFRC* gene or a portion thereof and intron 9 of a human *TFRC* gene or a portion thereof;

(ix) a nucleic acid sequence comprising exon 10 of a human *TFRC* gene or a portion thereof and intron 10 of a human *TFRC* gene or a portion thereof;

(x) a nucleic acid sequence comprising exon 11 of a human *TFRC* gene or a portion thereof and intron 11 of a human *TFRC* gene or a portion thereof;

(xi) a nucleic acid sequence comprising exon 12 of a human *TFRC* gene or a portion thereof and intron 12 of a human *TFRC* gene or a portion thereof;

(xii) a nucleic acid sequence comprising exon 13 of a human *TFRC* gene or a portion thereof and intron 13 of a human *TFRC* gene or a portion thereof;

(xiii) a nucleic acid sequence comprising exon 14 of a human *TFRC* gene or a portion thereof and intron 14 of a human *TFRC* gene or a portion thereof;

(xiv) a nucleic acid sequence comprising exon 15 of a human *TFRC* gene or a portion thereof and intron 15 of a human *TFRC* gene or a portion thereof;

(xv) a nucleic acid sequence comprising exon 16 of a human *TFRC* gene or a portion thereof and intron 16 of a human *TFRC* gene or a portion thereof;

(xvi) a nucleic acid sequence comprising exon 17 of a human *TFRC* gene or a portion thereof and intron 17 of a human *TFRC* gene or a portion thereof;

(xvii) a nucleic acid sequence comprising exon 18 of a human *TFRC* gene or a portion thereof and intron 18 of a human *TFRC* gene or a portion thereof;

(xviii) a nucleic acid sequence comprising exon 19 of a human *TFRC* gene or a coding portion thereof; or

(xix) any combination of (i)-(xviii).

26. The non-human animal of any one of claims 23-25, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof comprises a nucleic acid sequence selected from the group consisting of a nucleic acid sequence set forth as SEQ ID NO:5, a nucleic acid sequence set forth as SEQ ID NO:6, a nucleic acid sequence set forth as SEQ ID NO:9, and a nucleic acid sequence set forth as SEQ ID NO:10.

27. The non-human animal of any one of claims 23-26, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof is at an endogenous *Tfrc* locus.

28. The non-human animal of any one of claims 23-27, wherein the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof replaces an orthologous endogenous nucleic acid sequence encoding an endogenous TfR protein or a portion thereof.

29. The non-human animal of any one of claims 23-28, wherein the non-human animal, comprises an endogenous *Tfrc* locus, and wherein the endogenous *Tfrc* locus comprises an endogenous *Tfrc* gene comprising a heterozygous or homozygous replacement of an endogenous nucleic acid sequence encoding an endogenous TfR protein or a portion thereof with the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof,

wherein the endogenous nucleic acid sequence encoding the endogenous TfR protein or the portion thereof and the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof are orthologous.

30. The non-human animal of any one of claims 23-29, wherein the heterologous TfR protein or the portion thereof comprises an amino acid sequence of a human TfR protein or a portion thereof.

31. The non-human animal of any one of claims 23-30, wherein the heterologous TfR protein or the portion thereof comprises:

(i) an amino acid sequence set forth as SEQ ID NO:4;

(ii) an amino acid sequence set forth as SEQ ID NO:25;

(iii) an amino acid sequence set forth as SEQ ID NO:26;

(iv) an amino acid sequence set forth as SEQ ID NO:27;

(v) an amino acid sequence set forth as SEQ ID NO:28; or

(vi) any combination of (i)-(v).

32. The non-human animal of any one of claims 23-31, wherein the heterologous TfR protein or the portion thereof comprises an amino acid sequence set forth as SEQ ID NO:25.

33. The non-human animal of any one of claims 23-32, wherein the non-human animal is a mammal.

34. The non-human animal of any one of claims 23-33, wherein the non-human animal is a rodent.

35. The non-human animal of any one of claims 23-34, wherein the non-human animal is rat or a mouse.

36. The non-human animal of any one of claims 23-35, wherein the non-human animal comprises a non-human animal cell identified in Table 1 that expresses the heterologous TfR protein or the portion thereof on the cell surface.

37. The non-human animal of any one of claims 23-36, wherein the non-human animal comprises a non-human animal blood brain barrier endothelial cell that expresses the heterologous TfR protein or the portion thereof on the cell surface.

38. The non-human animal of any one of claims 23-37, wherein the heterologous TfR protein comprises a full-length human TfR protein, and

wherein the non-human animal comprises a non-human animal cell identified in Table 1 that expresses the full-length human TfR protein on the cell surface.

39. The non-human animal of any one of claims 23-38, wherein the non-human animal comprises a non-human animal cell that does not express the heterologous TfR protein or the portion thereof on the cell surface.

40. The non-human animal of any one of claims 0-39, wherein the non-human animal comprises a non-human animal germ cell that does not express the heterologous TfR protein or the portion thereof.

41. The non-human animal of any one of claims 23-40, wherein the non-human animal is a mouse.

42. A non-human animal genome or a non-human animal cell nucleus, wherein the non-human animal genome or the non-human animal cell nucleus comprises a nucleic acid sequence encoding a heterologous transferrin receptor (TfR) protein or a portion thereof.

43. A chimeric nucleic acid molecule, comprising a nucleic acid sequence of a modified non-human animal *Tfrc* gene that (a) encodes a TfR protein and (b) comprises a replacement of a sequence encoding the TfR protein or a portion thereof with a homologous sequence encoding a heterologous TfR protein or a portion thereof,

wherein the chimeric nucleic acid molecule encodes a functional TfR protein.

44. A method of making the non-human animal cell of any one of claims 1-22, comprising inserting the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof into the genome of the non-human animal cell.

45. A method of making the non-human animal of any one of claims 23-41, comprising:

inserting the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof into a genome of a non-human animal embryonic stem (ES) cell to form a modified non-human animal ES cell comprising the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof in the genome of the non-human animal ES cell;

introducing the modified non-human animal ES cell into host embryo cells *in vitro*; and

gestating, in a non-human surrogate mother animal, the host embryo cells comprising the modified non-human animal ES cell, wherein, after the gestating, the non-human surrogate mother animal births a non-human animal progeny comprising a germ cell comprising the nucleic acid sequence encoding the heterologous TfR protein or the portion thereof.

46. The non-human animal of any one of claims 0-0, or the non-human animal made according to the method of claim 45, comprising a binding protein that binds the heterologous TfR protein, wherein the non-human animal expresses the heterologous TfR protein or an extracellular domain thereof on a surface of a cell.

47. The non-human animal of claim 46, wherein the heterologous TfR protein is a human TfR protein.

48. The non-human animal of claim 46 or claim 47, wherein the non-human animal is a mouse.

49. A non-human animal, a non-human animal cell, or a non-human animal genome comprising a knockout mutation of an endogenous α-glucosidase (*Gaa*) gene.

50. The non-human animal, the non-human animal cell, or the non-human animal genome of claim 49, further comprising a nucleic acid encoding a heterologous TfR protein or a portion thereof.

51. A non-human animal model for testing an anti-human-TfR binding protein, comprising:
a non-human animal according to any one of claims 23-41 and 50, and
an anti-human-TfR binding protein that binds human TfR.

52. The non-human animal model of claim 51, wherein the anti-human-TfR binding protein is fused to a therapeutic agent.

53. The non-human animal model of claim 52, wherein the therapeutic agent is α-glucosidase.

54. A method of making a *Gaa* knockout non-human animal comprising modifying an endogenous *Gaa* gene at an endogenous *Gaa* locus of a non-human animal to comprise a knockout mutation of the *Gaa* gene.

55. A non-human animal, non-human animal cell, or non-human animal genome made according to any method described herein.