We claim:

1. A non-human animal comprising in its genome a humanized endogenous albumin locus in which a segment of the endogenous albumin locus has been deleted and replaced with a corresponding human albumin sequence.

2. The non-human animal of claim 1, wherein the humanized endogenous albumin locus encodes a protein comprising a human serum albumin peptide.

3. The non-human animal of claim 1 or 2, wherein the humanized endogenous albumin locus encodes a protein comprising a human albumin propeptide.

4. The non-human animal of any preceding claim, wherein the humanized endogenous albumin locus encodes a protein comprising a human albumin signal peptide.

5. The non-human animal of any preceding claim, wherein a region of the endogenous albumin locus comprising both coding sequence and non-coding sequence has been deleted and replaced with a corresponding human albumin sequence comprising both coding sequence and non-coding sequence.

6. The non-human animal of any preceding claim, wherein the humanized endogenous albumin locus comprises the endogenous albumin promoter, wherein the human albumin sequence is operably linked to the endogenous albumin promoter.

7. The non-human animal of any preceding claim, wherein at least one intron and at least one exon of the endogenous albumin locus have been deleted and replaced with the corresponding human albumin sequence.

8. The non-human animal of any preceding claim, wherein the entire albumin coding sequence of the endogenous albumin locus has been deleted and replaced with the corresponding human albumin sequence.

9. The non-human animal of claim 8, wherein the region of the endogenous albumin locus from the start codon to the stop codon has been deleted and replaced with the corresponding human albumin sequence.

10. The non-human animal of any preceding claim, wherein the humanized endogenous albumin locus comprises a human albumin 3' untranslated region.

11. The non-human animal of any preceding claim, wherein the endogenous albumin 5' untranslated region has not been deleted and replaced with the corresponding human albumin sequence.

12. The non-human animal of any preceding claim, wherein the region of the endogenous albumin locus from the start codon to the stop codon has been deleted and replaced with a human albumin sequence comprising the corresponding human albumin sequence and a human albumin 3' untranslated region, and

wherein the endogenous albumin 5' untranslated region has not been deleted and replaced with the corresponding human albumin sequence, and

wherein the endogenous albumin promoter has not been deleted and replaced with the corresponding human albumin sequence.

13. The non-human animal of any preceding claim, wherein:

(i) the human albumin sequence at the humanized endogenous albumin locus comprises a sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence set forth in SEQ ID NO: 35; or

(ii) the humanized endogenous albumin locus encodes a protein comprising a sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% identical to the sequence set forth in SEQ ID NO: 5;

(iii) the humanized endogenous albumin locus comprises a coding sequence comprising a sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence set forth in SEQ ID NO: 13; or

(iv) the humanized endogenous albumin locus comprises a sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the sequence set forth in SEQ ID NO: 17 or 18.

14. The non-human animal of any preceding claim, wherein the humanized endogenous albumin locus does not comprise a selection cassette or a reporter gene.

15. The non-human animal of any preceding claim, wherein the non-human animal is homozygous or heterozygous for the humanized endogenous albumin locus.

16. The non-human animal of any preceding claim, wherein the non-human animal comprises the humanized endogenous albumin locus in its germline.

17. The non-human animal of any preceding claim, wherein the non-human animal is a mammal.

18. The non-human animal of claim 17, wherein the non-human animal is a rat or a mouse.

19. The non-human animal of claim 18, wherein the non-human animal is ~~a~~ the mouse.

20. The non-human animal of any preceding claim, wherein the non-human animal is homozygous for the humanized endogenous albumin locus.

21. The non-human animal of any one of claims 1-19, wherein the non-human animal is heterozygous for the humanized endogenous albumin locus.

22. The non-human animal of any preceding claim, wherein the non-human animal comprises serum albumin levels of at least about 10 mg/mL.

23. The non-human animal of any preceding claim, wherein serum albumin levels in the non-human animal are at least as high as serum albumin levels in a control non-human animal comprising a wild type albumin locus.

24. The non-human animal of any preceding claim, wherein the non-human animal further comprises the coding sequence for an exogenous protein integrated into at least one allele of the humanized endogenous albumin locus in one or more cells of the non-human animal.

25. The non-human animal of claim 24, wherein the coding sequence for the exogenous protein is integrated into intron 1 of the at least one allele of the humanized endogenous albumin locus in the one or more cells of the non-human animal.

26. The non-human animal of any preceding claim, wherein the non-human animal further comprises an inactivated endogenous locus that is not the endogenous albumin locus.

27. The non-human animal of claim 26, wherein the non-human animal further comprises the coding sequence for an exogenous protein integrated into at least one allele of the humanized endogenous albumin locus in one or more cells of the non-human animal, wherein the exogenous protein replaces the function of the inactivated endogenous locus.

28. The non-human animal of claim 26 or 27, wherein the inactivated endogenous locus is an inactivated *F9* locus.

29. A non-human animal cell comprising in its genome a humanized endogenous albumin locus in which a segment of the endogenous albumin locus has been deleted and replaced with a corresponding human albumin sequence.

~~30. A non-human animal genome comprising a humanized endogenous albumin locus in which a segment of the endogenous albumin locus has been deleted and replaced with a corresponding human albumin sequence.~~

~~31. A humanized non-human animal albumin gene in which a segment of the non-human albumin gene has been deleted and replaced with a corresponding human albumin sequence.~~

~~32. A targeting vector for generating a humanized endogenous albumin locus in which a segment of the endogenous albumin locus has been deleted and replaced with a corresponding human albumin sequence, wherein the targeting vector comprises an insert nucleic acid comprising the corresponding human albumin sequence flanked by a 5' homology arm targeting a 5' target sequence at the endogenous albumin locus and a 3' homology arm targeting a 3' target sequence at the endogenous albumin locus.~~

~~33~~30. A method of assessing the activity of a human-albumin-targeting reagent *in vivo*, comprising:

(a) administering the human-albumin-targeting reagent to the non-human animal of any one of claims 1-28; and

(b) assessing the activity of the human-albumin-targeting reagent in the non-human animal.

~~34~~31. The method of claim ~~33~~30, wherein the administering comprises adeno-associated virus (AAV)-mediated delivery, lipid nanoparticle (LNP)-mediated delivery, or hydrodynamic delivery (HDD).

~~35~~32. The method of claim ~~34~~31, wherein the administering comprises LNP-mediated delivery.

~~36~~33. The method of claim ~~35~~32, wherein the LNP dose is between about 0.1 mg/kg and about 2 mg/kg.

~~37~~34. The method of claim ~~34~~31, wherein the administering comprises AAV8-mediated delivery.

~~38~~35. The method of any one of claims ~~33~~30-~~37~~34, wherein step (b) comprises isolating a liver from the non-human animal and assessing activity of the human-albumin-targeting reagent in the liver.

~~39~~36. The method of any one of claims ~~33~~30-~~38~~35, wherein the human-albumin-targeting reagent is a genome-editing agent, and the assessing comprises assessing modification of the humanized endogenous albumin locus.

~~40~~37. The method of claim ~~39~~36, wherein the assessing comprises measuring the frequency of insertions or deletions within the humanized endogenous albumin locus.

~~41~~38. The method of any one of claims ~~33~~30-~~40~~37, wherein the assessing comprises measuring expression of an albumin messenger RNA encoded by the humanized endogenous albumin locus.

~~42~~39. The method of any one of claims ~~33~~30-~~41~~38, wherein the assessing comprises measuring expression of an albumin protein encoded by the humanized endogenous albumin locus.

~~43~~40. The method of claim ~~42~~39, wherein assessing expression of the albumin protein comprises measuring serum levels of the albumin protein in the non-human animal or measuring expression of the albumin protein in the liver of the non-human animal.

~~44. The method of claim 42, wherein assessing expression of the albumin protein comprises measuring expression of the albumin protein in the liver of the non-human animal.~~

~~45~~41. The method of any one of claims ~~33~~30-~~43~~40, wherein the human-albumin-targeting reagent comprises a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent is designed to target a region of a human albumin gene.

~~46~~42. The method of claim ~~45~~41, wherein the nuclease agent comprises a Cas protein and a guide RNA designed to target a guide RNA target sequence in the human albumin gene.

~~47~~43. The method of claim ~~46~~42, wherein the guide RNA target sequence is in intron 1 of the human albumin gene.

~~48~~44. The method of claim ~~46~~ 42 or ~~47~~43, wherein the Cas protein is a Cas9 protein.

~~49~~45. The method of any one of claims ~~33~~30-~~48~~44, wherein the human-albumin-targeting reagent comprises an exogenous donor nucleic acid, wherein the exogenous donor nucleic acid is designed to target the human albumin gene, and optionally wherein the exogenous donor nucleic acid is delivered via AAV.

~~50~~46. The method of claim ~~49~~45, wherein the exogenous donor nucleic acid is a single-stranded oligodeoxynucleotide (ssODN).

~~51~~47. The method of claim ~~49~~ 45 or ~~50~~46, wherein the exogenous donor nucleic acid does not comprise homology arms, or~~.~~

wherein the exogenous donor nucleic acid comprises an insert nucleic acid flanked by a 5’ homology arm targeting a 5’ target sequence at the humanized endogenous albumin locus and a 3’ homology arm targeting a 3’ target sequence at the humanized endogenous albumin locus.

~~52. The method of claim 49 or 50, wherein the exogenous donor nucleic acid comprises an insert nucleic acid flanked by a 5’ homology arm targeting a 5’ target sequence at~~

~~the humanized endogenous albumin locus and a 3' homology arm targeting a 3' target sequence at the humanized endogenous albumin locus.~~

~~53~~48. The method of claim ~~52~~47, wherein each of the 5' target sequence and the 3' target sequence comprises a segment of intron 1 of the human albumin gene.

~~54~~49. The method of any one of claims ~~49~~45-~~53~~48, wherein the exogenous donor nucleic acid encodes an exogenous protein.

~~55~~50. The method of claim ~~54~~49, wherein the protein encoded by a humanized endogenous albumin locus that has been targeted with the exogenous donor nucleic acid is a heterologous protein comprising a human albumin signal peptide fused to the exogenous protein.

~~56~~51. The method of claim ~~54~~ 49 or ~~55~~50, wherein the exogenous protein is a factor IX protein.

~~57~~52. The method of claim ~~56~~51, wherein the assessing comprises measuring serum levels of the factor IX protein in the non-human animal and/or comprises assessing activated partial thromboplastin time or performing a thrombin generation assay.

~~58~~53. The method of any one of claims ~~33~~30-~~57~~52, wherein the human-albumin-targeting reagent comprises (1) a nuclease agent designed to target a region of a human albumin gene and (2) an exogenous donor nucleic acid,

wherein the exogenous donor nucleic acid is designed to target the human albumin gene,

wherein the exogenous donor nucleic acid encodes an exogenous protein, and

wherein the protein encoded by a humanized endogenous albumin locus that has been targeted with the exogenous donor nucleic acid is a heterologous protein comprising a human albumin signal peptide fused to the exogenous protein.

~~59~~54. The method of any one of claims ~~54~~49-~~58~~53, wherein the assessing comprises measuring expression of a messenger RNA encoded by the exogenous donor nucleic acid.

~~60~~55. The method of claim ~~59~~54, wherein the assessing comprises an *in situ* hybridization assay to quantify expression of the messenger RNA encoded by the exogenous donor nucleic acid at single-cell resolution.

~~61~~56. The method of claim ~~59~~ 54 or ~~60~~55, wherein the assessing comprises measuring expression of the messenger RNA encoded by the exogenous donor nucleic acid in multiple lobes from the liver of the non-human animal.

~~62~~57. The method of any one of claims ~~54~~49-~~61~~56, wherein the assessing comprises measuring expression of the exogenous protein.

~~63~~58. The method of claim ~~62~~57, wherein assessing expression of the heterologous protein comprises measuring serum levels of the heterologous protein in the non-human animal or measuring expression of the heterologous protein in the liver of the non-human animal.

~~64. The method of claim 62, wherein assessing expression of the heterologous protein comprises measuring expression in the liver of the non-human animal.~~

~~65~~59. A method of optimizing the activity of a human-albumin-targeting reagent *in vivo*, comprising:

(I) performing the method of any one of claims ~~33~~30-~~64~~ 58 a first time in a first non-human animal comprising in its genome a humanized endogenous albumin locus;

(II) changing a variable and performing the method of step (I) a second time with the changed variable in a second non-human animal comprising in its genome a humanized endogenous albumin locus; and

(III) comparing the activity of the human-albumin-targeting reagent in step (I) with the activity of the human-albumin-targeting reagent in step (II), and selecting the method resulting in the higher activity.

60. The method of claim 59, wherein:

(i) the changed variable in step (II) is the delivery method of introducing the human-albumin-targeting reagent into the non-human animal, optionally wherein the administering comprises LNP-mediated delivery, and the changed variable in step (II) is the LNP formulation;

(ii) the changed variable in step (II) is the route of administration of introducing the human-albumin-targeting reagent into the non-human animal;

(iii) the changed variable in step (II) is the concentration or amount of the human-albumin-targeting reagent introduced into the non-human animal;

(iv) the changed variable in step (II) is the form of the human-albumin-targeting reagent introduced into the non-human animal;

(v) the changed variable in step (II) is the human-albumin-targeting reagent introduced into the non-human animal;

(vi) the human-albumin-targeting reagent comprises a Cas protein or a nucleic acid encoding the Cas protein and a guide RNA or a DNA encoding the guide RNA, wherein the guide RNA is designed to target a guide RNA target sequence in a human albumin gene, and:

(A) wherein the changed variable in step (II) is the guide RNA sequence or the guide RNA target sequence;

(B) wherein the human-albumin-targeting reagent comprises a messenger RNA (mRNA) encoding the Cas protein and the guide RNA, and the changed variable in step (II) is the ratio of Cas mRNA to guide RNA;

(C) wherein the changed variable in step (II) is guide RNA modifications; or

(vii) the human-albumin-targeting reagent comprises an exogenous donor nucleic acid, and:

(A) wherein the changed variable in step (II) is the form of the exogenous donor nucleic acid;

(B) wherein the exogenous donor nucleic acid comprises an insert nucleic acid flanked by a 5' homology arm targeting a 5' target sequence at the humanized endogenous albumin locus and a 3' homology arm targeting a 3' target sequence at the humanized endogenous albumin locus, and the changed variable in step (II) is the sequence or length of the 5' homology arm and/or the sequence or length of the 3' homology arm.

~~66. The method of claim 65, wherein the changed variable in step (II) is the delivery method of introducing the human-albumin-targeting reagent into the non-human animal.~~

~~67. The method of claim 66, wherein the administering comprises LNP-mediated delivery, and the changed variable in step (II) is the LNP formulation.~~

~~68. The method of claim 65, wherein the changed variable in step (II) is the route of administration of introducing the human-albumin-targeting reagent into the non-human animal.~~

~~69. The method of claim 65, wherein the changed variable in step (II) is the concentration or amount of the human-albumin-targeting reagent introduced into the non-human animal.~~

~~70. The method of claim 65, wherein the changed variable in step (II) is the form of the human-albumin-targeting reagent introduced into the non-human animal.~~

~~71. The method of claim 65, wherein the changed variable in step (II) is the human-albumin-targeting reagent introduced into the non-human animal.~~

~~72. The method of claim 65, wherein the human-albumin-targeting reagent comprises a Cas protein or a nucleic acid encoding the Cas protein and a guide RNA or a DNA encoding the guide RNA, wherein the guide RNA is designed to target a guide RNA target sequence in a human albumin gene.~~

~~73. The method of claim 72, wherein the changed variable in step (II) is the guide RNA sequence or the guide RNA target sequence.~~

74. The method of claim 72, wherein the human-albumin-targeting reagent comprises a messenger RNA (mRNA) encoding the Cas protein and the guide RNA, and the changed variable in step (II) is the ratio of Cas mRNA to guide RNA.

75. The method of claim 72, wherein the changed variable in step (II) is guide RNA modifications.

76. The method of claim 65, wherein the human-albumin-targeting reagent comprises an exogenous donor nucleic acid.

77. The method of claim 76, wherein the changed variable in step (II) is the form of the exogenous donor nucleic acid.

78. The method of claim 76, wherein the exogenous donor nucleic acid comprises an insert nucleic acid flanked by a 5' homology arm targeting a 5' target sequence at the humanized endogenous albumin locus and a 3' homology arm targeting a 3' target sequence at the humanized endogenous albumin locus, and the changed variable in step (II) is the sequence or length of the 5' homology arm and/or the sequence or length of the 3' homology arm.

79. A method of making the non-human animal of any one of claims 1-28, comprising:

(a) introducing into a non-human animal embryonic stem (ES) cell:

(i) a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent targets a target sequence in the endogenous albumin locus; and

(ii) a targeting vector comprising a nucleic acid insert comprising the human albumin sequence flanked by a 5' homology arm corresponding to a 5' target sequence in the endogenous albumin locus and a 3' homology arm corresponding to a 3' target sequence in the endogenous albumin locus,

wherein the targeting vector recombines with the endogenous albumin locus to produce a genetically modified non-human ES cell comprising in its genome the humanized endogenous albumin locus comprising the human albumin sequence;

(b) introducing the genetically modified non-human ES cell into a non-human animal host embryo; and

(c) gestating the non-human animal host embryo in a surrogate mother, wherein the surrogate mother produces an F0 progeny genetically modified non-human animal comprising in its genome the humanized endogenous albumin locus comprising the human albumin sequence.

80. The method of claim 79, wherein the targeting vector is a large targeting vector at least 10 kb in length or in which the sum total of the 5' and 3' homology arms is at least 10 kb in length.

81. A method of making the non-human animal of any one of claims 1-28, comprising:

(a) introducing into a non-human animal one-cell stage embryo:

(i) a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent targets a target sequence in the endogenous albumin locus; and

(ii) a targeting vector comprising a nucleic acid insert comprising the human albumin sequence flanked by a 5' homology arm corresponding to a 5' target sequence in the endogenous albumin locus and a 3' homology arm corresponding to a 3' target sequence in the endogenous albumin locus,

wherein the targeting vector recombines with the endogenous albumin locus to produce a genetically modified non-human one-cell stage embryo comprising in its genome the humanized endogenous albumin locus comprising the human albumin sequence;

(b) gestating the genetically modified non-human animal one-cell stage embryo in a surrogate mother to produce a genetically modified F0 generation non-human animal comprising in its genome the humanized endogenous albumin locus comprising the human albumin sequence.

82. The method of any one of claims 79-81, wherein the nuclease agent comprises a Cas protein and a guide RNA.

83. The method of claim 82, wherein the Cas protein is a Cas9 protein.

~~84. The method of claim 82, wherein step (a) further comprises introducing a second guide RNA that targets a second target sequence within the endogenous albumin locus.~~

~~85. The method of any one of claims 79-84, wherein the non-human animal is a mouse or a rat.~~

~~86. The method of claim 85, wherein the non-human animal is a mouse.~~

~~87~~61. A method of making the non-human animal of any one of claims 1-28, comprising:

(I) (a) modifying the genome of a pluripotent non-human animal cell to comprise the humanized endogenous albumin locus;

(b) identifying or selecting the genetically modified pluripotent non-human animal cell comprising the humanized endogenous albumin locus;

(c) introducing the genetically modified pluripotent non-human animal cell into a non-human animal host embryo; and

(d) gestating the non-human animal host embryo in a non-human animal surrogate mother; or

(II) (a) modifying the genome of a non-human animal one-cell stage embryo to comprise the humanized endogenous albumin locus;

(b) selecting the genetically modified non-human animal one-cell stage embryo comprising the humanized endogenous albumin locus; and

(c) gestating the genetically modified non-human animal one-cell stage embryo in a non-human animal surrogate mother.