We claim:

1. A non-human animal comprising in its genome a humanized endogenous *F12* locus in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence.

2. The non-human animal of claim 1, wherein the humanized endogenous *F12* locus encodes a protein comprising a human coagulation factor XII heavy chain.

3. The non-human animal of claim 1 or 2, wherein the humanized endogenous *F12* locus encodes a protein comprising a human coagulation factor XII light chain.

4. The non-human animal of any preceding claim, wherein the humanized endogenous *F12* locus encodes a protein comprising a human coagulation factor XII signal peptide.

5. The non-human animal of any preceding claim, wherein a region of the endogenous *F12* locus comprising both coding sequence and non-coding sequence has been deleted and replaced with a corresponding human *F12* sequence comprising both coding sequence and non-coding sequence.

6. The non-human animal of any preceding claim, wherein the humanized endogenous *F12* locus comprises the endogenous *F12* promoter, wherein the human *F12* sequence is operably linked to the endogenous *F12* promoter.

7. The non-human animal of any preceding claim, wherein at least one intron and at least one exon of the endogenous *F12* locus have been deleted and replaced with the corresponding human *F12* sequence.

8. The non-human animal of any preceding claim, wherein the entire *F12* coding sequence of the endogenous *F12* locus has been deleted and replaced with the corresponding human *F12* sequence.

9. The non-human animal of claim 8, wherein the region of the endogenous *F12* locus from the start codon to the stop codon has been deleted and replaced with the corresponding human *F12* sequence.

10. The non-human animal of any preceding claim, wherein the endogenous *F12* 3' untranslated region has not been deleted and replaced with the corresponding human *F12* sequence.

11. The non-human animal of any preceding claim, wherein the endogenous *F12* 5' untranslated region has not been deleted and replaced with the corresponding human *F12* sequence.

12. The non-human animal of any preceding claim, wherein the region of the endogenous *F12* locus from the start codon to the stop codon has been deleted and replaced with the corresponding human *F12* sequence, and

wherein the endogenous *F12* promoter has not been deleted and replaced with the corresponding human *F12* sequence.

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

(i) the human *F12* sequence at the humanized endogenous *F12* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 31 or 32; and/or

(ii) the humanized endogenous *F12* locus encodes a protein comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 5 or 46; and/or

(iii) the humanized endogenous *F12* locus comprises a coding sequence comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 13 or 48; and/or

(iv) the humanized endogenous *F12* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 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 *F12* locus comprises a selection cassette or a reporter gene within an intron of the corresponding human *F12* sequence, or wherein the humanized endogenous *F12* 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 for the humanized endogenous *F12* locus.

16. The non-human animal of any preceding claim, wherein the non-human animal comprises the humanized endogenous *F12* 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 the mouse.

20. The non-human animal of any preceding claim, wherein the non-human animal expresses a short human coagulation factor XII isoform in the brain.

21. The non-human animal of claim 20, wherein:

(i) the short human coagulation factor XII isoform is encoded by an *F12* mRNA detected by probes against exons 11-14 of human *F12* but not by probes against exons 1-6 of human *F12*; and/or

(ii) the short human coagulation factor XII isoform is $FXII_{297-596}$; and/or

(iii) the short human coagulation factor XII isoform is expressed in neurons in the brain; and/or

(iv) the short human coagulation factor XII isoform can be activated by plasma kallikrein and converts pro-HGF to active HGF.

22. The non-human animal of any preceding claim, wherein the non-human animal has an activated partial thromboplastin time (aPTT) that is not significantly different from an aPTT in a corresponding wild type non-human animal and/or wherein the non-human animal has a prothrombin time (PT) that is not significantly different from a PT in the corresponding wild type non-human animal.

23. The non-human animal of any preceding claim, wherein the non-human animal has human coagulation factor XII plasma levels of at least about 5 μg/mL.

24. A non-human animal cell comprising in its genome a humanized endogenous *F12* locus in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence.

25. A non-human animal genome comprising a humanized endogenous *F12* locus in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence.

26. A targeting vector for generating a humanized endogenous *F12* locus in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence, wherein the targeting vector comprises an insert nucleic acid comprising the corresponding human *F12* sequence flanked by a 5' homology arm targeting a 5' target sequence at the endogenous *F12* locus and a 3' homology arm targeting a 3' target sequence at the endogenous *F12* locus.

27. A humanized non-human animal *F12* gene in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence.

28. A method of assessing the activity of a human-coagulation-factor-XII-targeting reagent *in vivo*, comprising:

(a) administering the human-coagulation-factor-XII-targeting reagent to the non-human animal of any one of claims 1-23; and

(b) assessing the activity of the human-coagulation-factor-XII-targeting reagent in the non-human animal.

29. The method of claim 28, wherein the administering comprises adeno-associated virus (AAV)-mediated delivery, lipid nanoparticle (LNP)-mediated delivery, hydrodynamic delivery (HDD), or injection.

30. The method of claim 28 or 29, wherein step (b) comprises isolating plasma from the non-human animal and assessing activity of the human-coagulation-factor-XII-targeting reagent in the plasma.

31. The method of any one of claims 28-30, wherein step (b) comprises assessing the activity of the human-coagulation-factor-XII-targeting reagent in the liver or the brain of the non-human animal.

32. The method of any one of claims 28-31, wherein step (b) comprises assessing coagulation or thrombin generation.

33. The method of any one of claims 28-32, wherein step (b) comprises assessing HGF-Met signaling.

34. The method of any one of claims 28-33, wherein step (b) comprises measuring expression of an *F12* messenger RNA encoded by the humanized endogenous *F12* locus or measuring expression of a coagulation factor XII protein encoded by the humanized endogenous coagulation factor XII locus.

35. The method of any one of claims 28-34, wherein the human-coagulation-factor-XII-targeting reagent is a genome-editing agent, and step (b) comprises assessing modification of the humanized endogenous *F12* locus.

36. The method of claim 35, wherein step (b) comprises measuring the frequency of insertions or deletions within the humanized endogenous *F12* locus.

37. The method of any one of claims 28-36, wherein the human-coagulation-factor-XII-targeting reagent comprises a nuclease agent designed to target a region of a human *F12* gene.

38. The method of claim 37, wherein the nuclease agent comprises a Cas protein and a guide RNA designed to target a guide RNA target sequence in the human *F12* gene.

39. The method of claim 38, wherein the Cas protein is a Cas9 protein.

40. The method of any one of claims 28-39, wherein the human-coagulation-factor-XII-targeting reagent comprises an exogenous donor nucleic acid, wherein the exogenous donor nucleic acid is designed to target the human *F12* gene, and optionally wherein the exogenous donor nucleic acid is delivered via AAV.

41. The method of any one of claims 28-34, wherein the human-coagulation-factor-XII-targeting reagent is an RNAi agent, an antisense oligonucleotide, an antigen-binding protein, or a small molecule.

42. A method of optimizing the activity of a human-coagulation-factor-XII-targeting reagent *in vivo*, comprising:

(I) performing the method of any one of claims 28-41 a first time in a first non-human animal comprising in its genome a humanized endogenous *F12* 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 *F12* locus; and

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

43. The method of claim 42, wherein the changed variable in step (II) is:

(i) the delivery method of introducing the human-coagulation-factor-XII-targeting reagent into the non-human animal;

(ii) the route of administration of introducing the human-coagulation-factor-XII-targeting reagent into the non-human animal;

(iii) the concentration or amount of the human-coagulation-factor-XII-targeting reagent introduced into the non-human animal;

(iv) the form of the human-coagulation-factor-XII-targeting reagent introduced into the non-human animal; or

(v) the human-coagulation-factor-XII-targeting reagent introduced into the non-human animal.

44. A method of making the non-human animal of any one of claims 1-23, comprising:

(a) introducing into a non-human animal host embryo a genetically modified non-human animal embryonic stem (ES) cell comprising in its genome a humanized endogenous *F12* locus in which a segment of the endogenous *F12* locus has been deleted and replaced with a corresponding human *F12* sequence; and

(b) gestating the non-human animal host embryo in a non-human animal surrogate mother, wherein the non-human animal surrogate mother produces an F0 progeny genetically modified non-human animal comprising the humanized endogenous *F12* locus.

45. A method of making the non-human animal of any one of claims 1-23, comprising:

(a) introducing into a non-human animal embryonic stem (ES) cell a targeting vector comprising a nucleic acid insert comprising the human *F12* sequence flanked by a 5' homology arm corresponding to a 5' target sequence in the endogenous *F12* locus and a 3' homology arm corresponding to a 3' target sequence in the endogenous *F12* locus,

wherein the targeting vector recombines with the endogenous *F12* locus to produce a genetically modified non-human ES cell comprising in its genome the humanized endogenous *F12* locus comprising the human *F12* 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 non-human animal surrogate mother, wherein the non-human animal surrogate mother produces an F0 progeny genetically modified non-human animal comprising in its genome the humanized endogenous *F12* locus comprising the human *F12* sequence.

46. A method of making the non-human animal of any one of claims 1-23, comprising:

(a) introducing into a non-human animal one-cell stage embryo a targeting vector comprising a nucleic acid insert comprising the human *F12* sequence flanked by a 5' homology arm corresponding to a 5' target sequence in the endogenous *F12* locus and a 3' homology arm corresponding to a 3' target sequence in the endogenous *F12* locus,

wherein the targeting vector recombines with the endogenous *F12* locus to produce a genetically modified non-human one-cell stage embryo comprising in its genome the humanized endogenous *F12* locus comprising the human *F12* sequence;

(b) gestating the genetically modified non-human animal one-cell stage embryo in a non-human animal surrogate mother to produce a genetically modified F0 generation non-human animal comprising in its genome the humanized endogenous *F12* locus comprising the human *F12* sequence.

47. A method of assessing expression of a short *F12* mRNA isoform in a biological sample, comprising:

(a) detecting and quantifying RNA transcripts using primers and/or probes against one or more of exons 9-14 of an *F12* gene; and

(b) detecting and quantifying RNA transcripts using primers and/or probes against one or more of exons 1-6 of the *F12* gene

wherein the short isoform is detected by primers and/or probes against exons 9-14 but not by primers and/or probes against exons 1-6.