We claim:

1. A ~~non-human animal~~mouse 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,

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,

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 mouse expresses a short human coagulation factor XII isoform in the brain, 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 $FXII_{297-596}$.

~~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.~~

62. The non-human animal of any preceding claimmouse of claim 1, 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.

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

(I) the endogenous *F12* 3' untranslated region has not been deleted and replaced with the corresponding human *F12* sequence.; and/or

11. The non-human animal of any preceding claim, wherein (II) 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.

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

(iI) 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~~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~~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~~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~~5. The mouse ~~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~~6. The mouse ~~non-human animal~~ of any preceding claim, wherein the mouse~~non-human animal~~ is homozygous for the humanized endogenous *F12* locus.

~~16~~7. The mouse ~~non-human animal~~ of any preceding claim, wherein the mouse ~~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~~8. The mouse ~~non-human animal~~ of any preceding claim, wherein the mouse ~~non-human animal~~ has an activated partial thromboplastin time (aPTT) that is not significantly different from an aPTT in a corresponding wild type mouse ~~non-human animal~~ and/or wherein the mouse ~~non-human animal~~ has a prothrombin time (PT) that is not significantly different from a PT in the corresponding wild type mouse~~non-human animal~~.

~~23~~9. The mouse ~~non-human animal~~ of any preceding claim, wherein the mouse~~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~~10. 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 mouse ~~non-human animal~~ of any one of claims 1-~~23~~9; and

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

~~29~~11. The method of claim ~~28~~10, wherein the administering comprises adeno-associated virus (AAV)-mediated delivery, lipid nanoparticle (LNP)-mediated delivery, hydrodynamic delivery (HDD), or injection.

~~30~~12. The method of claim ~~28~~ 10 or ~~29~~11, wherein:

(I) step (b) comprises isolating plasma from the mouse ~~non-human animal~~ and assessing activity of the human-coagulation-factor-XII-targeting reagent in the plasma~~.~~; and/or

~~31. The method of any one of claims 28-30, wherein~~

(II) step (b) comprises assessing the activity of the human-coagulation-factor-XII-targeting reagent in the liver or the brain of the mouse~~non-human animal.~~; and/or

~~32. The method of any one of claims 28-31, wherein~~

(III) step (b) comprises assessing coagulation or thrombin generation~~.~~; and/or

~~33. The method of any one of claims 28-32, wherein~~

(IV) step (b) comprises assessing HGF-Met signaling~~.~~; and/or

~~34. The method of any one of claims 28-33, wherein~~

(V) step (b) comprises measuring expression of an *F12* messenger RNA encoded by the humanized endogenous *F12* locus; and/or

(VI) step (b) comprises measuring expression of a coagulation factor XII protein encoded by the humanized endogenous coagulation factor XII locus~~.~~; and/or

~~35. The method of any one of claims 28-34, wherein~~

(VII) the human-coagulation-factor-XII-targeting reagent is a genome-editing agent, and step (b) comprises assessing modification of the humanized endogenous *F12* locus~~.~~, optionally

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

~~37~~13. The method of any one of claims ~~28-36~~10-12, wherein:

(I) the human-coagulation-factor-XII-targeting reagent comprises a nuclease agent designed to target a region of a human *F12* gene~~.~~, optionally

~~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~~.~~, and optionally

~~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~~

(II) 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~~

(III) the human-coagulation-factor-XII-targeting reagent is an RNAi agent~~,~~ or an antisense oligonucleotide~~,~~;

(IV) the human-coagulation-factor-XII-targeting reagent is an antigen-binding protein~~,~~; or

(V) the human-coagulation-factor-XII-targeting reagent is a small molecule.

~~42~~14. 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~~10-13 a first time in a first mouse ~~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 mouse ~~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~~15. The method of claim ~~42~~14, wherein the changed variable in step (II) is:

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

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

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

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

(v) the human-coagulation-factor-XII-targeting reagent introduced into the mouse~~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.