We claim:

1. A composition comprising one or more vectors comprising a nucleic acid encoding amyloid-beta precursor protein and a nucleic acid encoding presenilin-1.

2. The composition of claim 1, wherein:

(I) the amyloid-beta precursor protein is an APP695 amyloid-beta precursor protein isoform; and/or

(II) the amyloid-beta precursor protein comprises one or more mutations associated with familial Alzheimer's disease, optionally wherein the amyloid-beta precursor protein comprises three mutations associated with familial Alzheimer's disease.

3. The composition of claim 1 or 2, wherein the amyloid-beta precursor protein comprises K670N/M671L, E693G, and I716F mutations with reference to a human APP770 isoform or K595N/M596L, E618G, and I641F mutations with reference to a human APP695 isoform.

4. The composition of any preceding claim, wherein the amyloid-beta precursor protein comprises the sequence set forth in SEQ ID NO: 1 or the sequence set forth in SEQ ID NO: 2.

5. The composition of any preceding claim, wherein the presenilin-1 comprises one or more mutations associated with familial Alzheimer's disease, optionally wherein the presenilin-1 comprises two mutations associated with familial Alzheimer's disease.

6. The composition of any preceding claim, wherein the presenilin-1 comprises the following mutations: M146L and L286V.

7. The composition of any preceding claim, wherein the presenilin-1 comprises the sequence set forth in SEQ ID NO: 3 or the sequence set forth in SEQ ID NO: 4.

8. The composition of any preceding claim, wherein the amyloid-beta precursor protein comprises K670N/M671L, E693G, and I716F mutations with reference to a human APP770 isoform or K595N/M596L, E618G, and I641F mutations with reference to a human APP695 isoform, and

wherein the presenilin-1 comprises the following mutations: M146L and L286V.

9. The composition of any preceding claim, wherein:

(I) the amyloid-beta precursor protein comprises the sequence set forth in SEQ ID NO: 1, and the presenilin-1 comprises the sequence set forth in SEQ ID NO: 3; or

(II) the nucleic acid encoding the amyloid-beta precursor protein comprises the sequence set forth in SEQ ID NO: 2, and the nucleic acid encoding the presenilin-1 comprises the sequence set forth in SEQ ID NO: 4.

10. The composition of any preceding claim, wherein the nucleic acid encoding the amyloid-beta precursor protein is operably linked to a promoter, and wherein the nucleic acid encoding the presenilin-1 is operably linked to a promoter, optionally:

wherein the promoter operably linked to the nucleic acid encoding the amyloid-beta precursor protein is a neuron-specific promoter, optionally wherein the promoter is a synapsin-1 promoter, and optionally wherein the promoter is a human synapsin-1 promoter, and

wherein the promoter operably linked to the nucleic acid encoding the presenilin-1 is a neuron-specific promoter, optionally wherein the promoter is a synapsin-1 promoter, and optionally wherein the promoter is a human synapsin-1 promoter.

11. The composition of any preceding claim, wherein the one or more vectors comprise one or more viral vectors, optionally wherein the one or more vectors comprise one or more adeno-associated virus (AAV) vectors, optionally wherein the one or more AAV vectors comprise one or more recombinant AAV9 vectors.

12. The composition of any preceding claim, wherein the amyloid-beta precursor protein comprises K670N/M671L, E693G, and I716F mutations with reference to a human APP770 isoform or K595N/M596L, E618G, and I641F mutations with reference to a

human APP695 isoform, optionally wherein the amyloid-beta precursor protein comprises the sequence set forth in SEQ ID NO: 1,

wherein the presenilin-1 comprises the following mutations: M146L and L286V, optionally wherein the presenilin-1 comprises the sequence set forth in SEQ ID NO: 3,

wherein the nucleic acid encoding the amyloid-beta precursor protein is operably linked to a neuron-specific promoter, optionally wherein the promoter is a human synapsin-1 promoter,

wherein the nucleic acid encoding the presenilin-1 is operably linked to a neuron-specific promoter, optionally wherein the promoter is a human synapsin-1 promoter, and

wherein the one or more vectors comprise one or more adeno-associated virus (AAV) vectors, optionally wherein the one or more AAV vectors comprise one or more recombinant AAV9 vectors.

13. The composition of any preceding claim, wherein the one or more vectors comprise a first vector comprising the nucleic acid encoding the amyloid-beta precursor protein and a second vector comprising the nucleic acid encoding the presenilin-1.

14. The composition of any one of claims 1-12, wherein the one or more vectors comprise a single vector comprising the nucleic acid encoding the amyloid-beta precursor protein and the nucleic acid encoding the presenilin-1.

15. A cell comprising the composition of any preceding claim, wherein:

(I) the cell is a mammalian cell, optionally wherein the cell is a non-human primate cell or a rodent cell, optionally wherein the rodent cell is a mouse cell or a rat cell, and optionally wherein the cell is the mouse cell; and/or

(II) the cell is a neuron.

16. The cell of claim 15, wherein the cell comprises a human microtubule-associated protein tau coding sequence comprising a tauopathy-associated mutation, wherein the microtubule-associated protein tau is expressed, optionally wherein the human microtubule-

associated protein tau coding sequence is genomically integrated, and optionally wherein the tauopathy-associated mutation is a P301S mutation.

17. The cell of claim 15 or 16, wherein:

(I) the cell comprises a humanized *APOE* genomic locus, optionally wherein a human apolipoprotein E4 protein is expressed from the humanized *APOE* genomic locus;

(II) the cell comprises a humanized *MAPT* genomic locus, optionally wherein a human microtubule-associated protein tau protein is expressed from the humanized *MAPT* genomic locus;

(III) the cell comprises a humanized *APP* genomic locus, optionally wherein a chimeric non-human animal/human amyloid-beta precursor protein comprising K670N/M671L mutations with reference to a human APP770 isoform or K595N/M596L mutations with reference to a human APP695 isoform is expressed from the humanized *APP* genomic locus; or

(IV) any combination thereof.

18. The cell of claim 17, wherein the cell comprises the humanized *APOE* genomic locus, the humanized *MAPT* genomic locus, and the humanized *APP* genomic locus.

19. A non-human animal comprising the composition of any one of claims 1-14, wherein the non-human animal is a mammal, optionally wherein the non-human animal is a non-human primate or a rodent, optionally wherein the rodent is a mouse or a rat, and optionally wherein the non-human animal is the mouse.

20. The non-human animal of claim 19, wherein the non-human animal comprises the composition in the brain, optionally wherein the non-human animal comprises the composition in a plurality of neurons in the brain.

21. The non-human animal of claim 19 or 20, wherein:

(a) the non-human animal comprises a human microtubule-associated protein tau coding sequence comprising a tauopathy-associated mutation, wherein the microtubule-associated protein tau is expressed, optionally wherein the human microtubule-associated protein

tau coding sequence is genomically integrated, and optionally wherein the tauopathy-associated mutation is a P301S mutation; and/or

(b) (I) the non-human animal comprises a humanized *APOE* genomic locus, optionally wherein a human apolipoprotein E4 protein is expressed from the humanized *APOE* genomic locus;

(II) the non-human animal comprises a humanized *MAPT* genomic locus, optionally wherein a human microtubule-associated protein tau is expressed from the humanized *MAPT* genomic locus;

(III) the non-human animal comprises a humanized *APP* genomic locus, optionally wherein a chimeric non-human animal/human amyloid-beta precursor protein comprising K670N/M671L mutations with reference to a human APP770 isoform or K595N/M596L mutations with reference to a human APP695 isoform is expressed from the humanized *APP* genomic locus; or

(IV) any combination thereof,

optionally wherein the non-human animal comprises the humanized *APOE* genomic locus, the humanized *MAPT* genomic locus, and the humanized *APP* genomic locus.

22. The non-human animal of any one of claims 19-21, wherein:

(I) the non-human animal has one or more Alzheimer's disease phenotypes; and/or

(II) the non-human animal has one or more or all of the following: Aβ plaque pathology; loss of synapses; gliosis; and dystrophic neurites around Aβ plaques; and/or

(III) the non-human animal has one or more or all of the following: tau aggregates in dystrophic neurites surrounding Aβ plaques (NP-tau); neurofibrillary tangles (NFTs); and increased phosphorylated tau in the somatodendritic compartment of neurons; and/or

(IV) the non-human animal has co-deposition of ApoE protein in Aβ plaques.

23. A method of modeling Alzheimer's disease in a non-human animal, wherein the composition of any one of claims 1-14 is to be administered to the non-human animal.

24. A method of making the non-human animal of any one of claims 19-22, wherein the composition is to be administered to a non-human animal.

25. A method of assessing a therapeutic candidate for the treatment of Alzheimer's disease, comprising:

(a) administering a candidate agent to the non-human animal of any one of claims 19-22;

(b) performing one or more assays to determine if the candidate agent has an effect on an Alzheimer's disease phenotype; and

(c) identifying the candidate agent that ameliorates the Alzheimer's disease phenotype as a therapeutic candidate.

26. A method of assessing a therapeutic candidate for the prevention of Alzheimer's disease, comprising:

(a) administering a candidate agent to a non-human animal;

(b) administering the composition of any one of claims 1-14 to the non-human animal;

(c) performing one or more assays to determine if the candidate agent has an effect on an Alzheimer's disease phenotype; and

(d) identifying the candidate agent that prevents the Alzheimer's disease phenotype as a therapeutic candidate.