

CLAIMS:

1. A system for use in treating a genetic disorder, the system comprising:
 - (a) a gene editing vector comprising a nucleic acid sequence encoding a nuclease that targets the PCSK9 gene; and
 - (b) a donor vector comprising a transgene cassette comprising a nucleic acid sequence encoding a transgene and regulatory sequences that direct expression of the transgene in the target cell, the donor vector further comprising homology-directed recombination (HDR) arms 5' and 3' to the transgene cassette, wherein the transgene is not PCSK9.
2. The system according to claim 1, further comprising regulatory sequences that direct expression of the nuclease in a target cell comprising a PCSK9 gene
3. The system according to claim 1 or claim 2, wherein the nuclease targets PCSK9 exon 7.
4. The system according to any one of claims 1 to 3, wherein the nuclease is a meganuclease specific for PCSK9.
5. The system according to claim 4, wherein the meganuclease is the ARCUS meganuclease.
6. The system according to any one of claims 1 to 5, wherein the transgene is ornithine transcarbamylase (OTC), phenylalanine hydroxylase (PAH), argininosuccinic acid synthetase (ASS1), or low-density lipoprotein receptor (LDLR).
7. The system according to any one of claims 1 to 6, wherein at least one of the donor vector and gene editing vector is an adeno-associated viral (AAV) vector, and the AAV vector comprises AAV 5' inverted terminal repeats (ITRs) and AAV 3' ITRs.

8. The system according to claim 7, wherein the ratio of gene editing AAV vector of (a) to donor AAV vector of (b) is such that donor AAV vector of (b) is in excess of gene editing vector of (a).
9. A system for use in treating a genetic disorder, the system comprising:
- (a) a gene editing AAV comprising an AAV capsid and a first vector genome comprising a 5' ITR, a sequence encoding a meganuclease that targets PCSK9 under control of regulatory sequences that direct expression of the meganuclease in a target cell comprising a PCSK9 gene, and a 3' ITR; and
 - (b) a donor AAV vector comprising an AAV capsid and a second vector genome comprising: a 5' ITR, a 5' homology directed recombination (HDR) arm, a transgene and regulatory sequences that direct expression of the transgene in the target cell, a 3' HDR arm, and a 3' ITR,
- wherein the transgene is not PCSK9.
10. The system according to claim 9, wherein the gene editing AAV vector of (a) and the donor AAV vector of (b) have the same AAV capsid.
11. The system according to claim 10, wherein the AAV capsid is selected from AAV8, AAV9, rh10, AAV6.2, AAV3B, hu37, rh79, and rh64.
12. The system according to any one of claims 2 to 11, wherein the nuclease is under the control of a tissue-specific promoter.
13. The system according to any one of claims 2 to 11, wherein the nuclease is under the control of a constitutive promoter.
14. The system according to claim 12, wherein the nuclease is under the control of a liver-specific promoter, optionally a human thyroxin-binding globulin (TBG) promoter, or hybrid liver promoter (HLP).
15. Use of the system according to any one of claims 1 to 14, in the preparation of a medicament for treating a disorder in humans wherein parts (a) and (b) of the system are to be co-

administered.

16. Use of:

(a) a gene editing AAV vector comprising a sequence encoding a nuclease and regulatory sequences that direct expression of the nuclease in a target cell comprising a PCSK9 gene; and

(b) a donor AAV vector comprising a transgene and regulatory sequences that direct expression of the transgene in the target cell, the donor vector further comprising homology-directed recombination (HDR) arms 5' and 3' to the transgene cassette; in the preparation of a medicament for the treatment of a liver metabolic disorder in a neonate subject, wherein the gene editing AAV vector and the donor AAV vector are to be co-administered.

17. The use according to claim 16, wherein the gene editing AAV vector of (a) and the donor vector of (b) are delivered simultaneously via the same route.

18. The use according to claim 16 or claim 17, wherein the gene editing AAV vector of (a) is suspended in a vehicle for injection at a concentration of 2×10^{11} GC/mL to 2×10^{12} GC/mL.

19. The use according to claim 16 or claim 17, wherein the gene editing AAV vector of (a) is suspended in a vehicle for injection at a concentration of 2×10^{12} GC/mL to 1×10^{13} GC/mL.

20. The use according to any one of claims 16 to 19, wherein the liver metabolic disorder is ornithine transcarbamylase deficiency.

21. The use according to any one of claims 16 to 19, wherein the liver metabolic disorder is ornithine transcarbamylase deficiency (OTC), familial hypercholesteremia (FH), citrullinemia type I (CTLN1) or phenylketonuria (PKU).