CLAIMS

1. A composition comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein and a guide RNA or a DNA encoding the guide RNA for use in a method of modifying an *HSD17B13* gene in a cell,

wherein the guide RNA comprises a CRISPR RNA (crRNA) portion and a trans-activating CRISPR RNA (tracrRNA) portion and targets a guide RNA target sequence within the *HSD17B13* gene,

wherein the method comprises introducing the Cas9 protein or the nucleic acid encoding the Cas9 protein and the guide RNA or the DNA encoding the guide RNA into the cell,

wherein the guide RNA forms a complex with the Cas9 protein and targets the guide RNA target sequence, and

wherein the Cas9 protein cleaves the guide RNA target sequence to generate a targeted genetic modification in the *HSD17B13* gene,

wherein the method results in loss of function of the *HSD17B13* gene, and

wherein the cell is a liver cell.

2. The composition for use according to claim 1, wherein:

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 20-239 and 259-268; and/or

(b) the guide RNA comprises a DNA-targeting segment comprising any one of SEQ ID NOS: 1423-1652; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 500-1419.

3. The composition for use according to claim 2, wherein the cell is a human cell, and wherein:

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 20-239; and/or

(b) the DNA-targeting segment comprises any one of SEQ ID NOS: 1423-1642; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 500-719, 730-949, 960-1179, and 1190-1409.

4. The composition for use according to claim 2, wherein the cell is a mouse cell, and wherein:

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 259-268; and/or

(b) the DNA-targeting segment comprises any one of SEQ ID NOS: 1643-1652; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 720-729, 950-959, 1180-1189, and 1410-1419.

5. The composition for use according to any one of claims 1-4, further comprising one or more additional guide RNAs or one or more DNAs encoding the one or more additional guide RNAs, wherein the one or more additional guide RNAs target one or more additional guide RNA target sequences within the *HSD17B13* gene, and

wherein the method further comprises introducing the one or more additional guide RNAs or the one or more DNAs encoding the one or more additional guide RNAs into the cell, wherein the one or more additional guide RNAs form one or more complexes with the Cas9 protein and target the one or more additional guide RNA target sequences.

6. The composition for use according to any one of claims 1-5, wherein the targeted genetic modification is generated by repair of the cleaved guide RNA target sequence by non-homologous end-joining.

7. The composition for use according to any one of claims 1-6, further comprising an exogenous donor sequence,

wherein the method further comprises introducing into the cell the exogenous donor sequence, wherein the exogenous donor sequence recombines with a target genomic locus in the *HSD17B13* gene to generate the targeted genetic modification.

8. The composition for use according to claim 7, wherein repair of the *HSD17B13* gene by the exogenous donor sequence occurs via non-homologous-end-joining-mediated insertion.

9. The composition for use according to claim 7, wherein repair of the *HSD17B13* gene by the exogenous donor sequence occurs via homology-directed repair.

10. The composition for use according to claim 9, wherein the exogenous

donor sequence comprises a 5’ homology arm that hybridizes to a 5’ target sequence within the *HSD17B13* gene and a 3’ homology arm that hybridizes to a 3’ target sequence within the *HSD17B13* gene, wherein the exogenous donor sequence recombines with the *HSD17B13* gene.

11. The composition for use according to claim 10, wherein the exogenous donor sequence further comprises a nucleic acid insert flanked by the 5’ homology arm and the 3’ homology arm.

12. The composition for use according to claim 11, wherein the nucleic acid insert comprises a thymine, and wherein upon recombination of the exogenous donor sequence with the *HSD17B13* gene, the thymine is inserted between nucleotides corresponding to positions 12665 and 12666 of SEQ ID NO: 1 when the *HSD17B13* gene is optimally aligned with SEQ ID NO: 1.

13. The composition for use according to any one of claims 7-12, wherein the exogenous donor sequence is between 50 nucleotides to 1 kb in length.

14. The composition for use according to claim 13, wherein the exogenous donor sequence is between 80 nucleotides to 200 nucleotides in length.

15. The composition for use according to any one of claims 7-14, wherein the exogenous donor sequence is a single-stranded oligodeoxynucleotide.

16. The composition for use according to any one of claims 1-15, wherein the composition comprises the nucleic acid encoding the Cas9 protein.

17. The composition for use according to claim 16, wherein the nucleic acid encoding the Cas9 protein comprises DNA.

18. The composition for use according to claim 16, wherein the nucleic acid encoding the Cas9 protein comprises RNA.

19. The composition for use according to any one of claims 1-18, wherein the composition comprises the guide RNA in the form of RNA.

20. The composition for use according to any one of claims 1-18, wherein the composition comprises the DNA encoding the guide RNA.

21. The composition for use according to any one of claims 1-20, wherein the Cas9 protein or the nucleic acid encoding the Cas9 protein and/or the guide RNA or the DNA encoding the guide RNA are in a lipid nanoparticle.

22. The composition for use according to any one of claims 1-20, wherein the nucleic acid encoding the Cas9 protein and/or the DNA encoding the guide RNA are in an adeno-associated virus vector.

23. The composition for use according to any one of claims 1-22, wherein the guide RNA is a single-molecule guide RNA in which the crRNA portion is linked to the tracrRNA portion.

24. The composition for use according to claim 23, wherein the guide RNA comprises the sequence set forth in SEQ ID NO: 1420, 256, 257, or 258.

25. The composition for use according to any one of claims 1-22, wherein the crRNA portion and the tracrRNA portion are separate RNA molecules.

26. The composition for use according to claim 25, wherein the crRNA portion comprises the sequence set forth in SEQ ID NO: 1421 and/or the tracrRNA portion comprises the sequence set forth in SEQ ID NO: 1422.

27. The composition for use according to any one of claims 1-26, wherein the guide RNA comprises a modification providing for modified or regulated stability.

28. The composition for use according to any one of claims 1-27, wherein the cell is *in vivo*.

29. The composition for use according to any one of claims 1-28, wherein the cell is a human liver cell or a mouse liver cell.

30. The composition for use according to claim 29, wherein the cell is the human liver cell.

31. The composition for use according to claim 30, wherein the human liver cell is *in vivo*.

32. The composition for use according to claim 31, wherein the Cas9 protein or a nucleic acid encoding the Cas9 protein and the guide RNA or a DNA encoding the guide RNA are introduced into a liver *in vivo*.

33. The composition for use according to claim 31, wherein the human liver cell is in a subject having or susceptible to developing a chronic liver disease.

34. The composition for use according to claim 33, wherein the chronic liver disease is fatty liver disease, nonalcoholic fatty liver disease, alcoholic fatty liver disease, cirrhosis, or hepatocellular carcinoma.