CLAIMS

1. A composition comprising a Cas protein or a nucleic acid encoding the Cas protein and a guide RNA or a DNA encoding the guide RNA suitable 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 guide RNA target sequence includes or is proximate to a position corresponding to position 12666 of SEQ ID NO: 2 when the *HSD17B13* gene is optimally aligned with SEQ ID NO: 2, and

wherein the method comprises introducing the Cas protein or the nucleic acid encoding the Cas protein and the guide RNA or the DNA encoding the guide RNA into the cell, wherein the guide RNA forms a complex with the Cas protein and targets the guide RNA target sequence, and wherein the Cas protein cleaves the guide RNA target sequence to generate a targeted genetic modification in the *HSD17B13* gene.

2. The composition suitable for use according to claim 1, wherein the *HSD17B13* gene does not have a thymine 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.

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

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 226-239 and 264-268; and/or

(b) the guide RNA comprises a DNA-targeting segment comprising any one of SEQ ID NOS: 1629-1642 and 1648-1652; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 706-719; 936-949; 1166-1179, 1396-1409, 725-729, 955-959, 1185-1189, and 1415-1419.

4. The composition suitable for use according to any one of claims 1-3, wherein the guide RNA target sequence is within a region corresponding to exon 6 and/or intron

6 of SEQ ID NO: 2 or is within a region corresponding to intron 6 and/or exon 7 of SEQ ID NO: 2 when the *HSD17B13* gene is optimally aligned with SEQ ID NO: 2.

5. The composition suitable for use according to any one of claims 1-4, wherein the guide RNA target sequence is within 1000, 500, 400, 300, 200, 100, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 nucleotides of the position corresponding to position 12666 of SEQ ID NO: 2 when the *HSD17B13* gene is optimally aligned with SEQ ID NO: 2.

6. The composition suitable for use according to any one of claims 1-5, wherein the guide RNA target sequence includes the position corresponding to position 12666 of SEQ ID NO: 2 when the *HSD17B13* gene is optimally aligned with SEQ ID NO: 2.

7. The composition suitable for use according to any one of claims 1-6, 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 Cas protein and target the one or more additional guide RNA target sequences, and

wherein the Cas protein cleaves the one or more additional guide RNA target sequences.

8. The composition suitable for use according to any one of claims 1-7, wherein the method results in disruption of a donor splice site in intron 6 of the *HSD17B13* gene.

9. The composition suitable for use according to any one of claims 1-8, wherein the method results in loss of function of the *HSD17B13* gene.

10. The composition suitable for use according to any one of claims 1-9, wherein the targeted genetic modification is generated by repair of the cleaved guide RNA target sequence by non-homologous end-joining.

11. The composition suitable for use according to any one of claims 1-10, 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.

12. The composition suitable for use according to claim 11, wherein repair of the *HSD17B13* gene by the exogenous donor sequence occurs via non-homologous-end-joining-mediated insertion.

13. The composition suitable for use according to claim 11, wherein repair of the *HSD17B13* gene by the exogenous donor sequence occurs via homology-directed repair.

14. The composition suitable for use according to claim 13, wherein the exogenous donor sequence comprises a 5’ homology arm that hybridizes to a target sequence 5’ of the position corresponding to position 12666 of SEQ ID NO: 2 and a 3’ homology arm that hybridizes to a target sequence 3’ of the position corresponding to position 12666 of SEQ ID NO: 2, wherein the exogenous donor sequence recombines with the *HSD17B13* gene.

15. The composition suitable for use according to claim 14, wherein the exogenous donor sequence further comprises a nucleic acid insert flanked by the 5’ homology arm and the 3’ homology arm.

16. The composition suitable for use according to claim 15, 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.

17. The composition suitable for use according to any one of claims 11-16, wherein the exogenous donor sequence is between 50 nucleotides to 1 kb in length.

18. The composition suitable for use according to claim 17, wherein the exogenous donor sequence is between 80 nucleotides to 200 nucleotides in length.

19. The composition suitable for use according to any one of claims 11-18, wherein the exogenous donor sequence is a single-stranded oligodeoxynucleotide.

20. The composition suitable for use according to any one of claims 1-19, wherein the Cas protein is a Cas9 protein.

21. The composition suitable for use according to any one of claims 1-20, wherein the composition comprises the nucleic acid encoding the Cas protein.

22. The composition suitable for use according to claim 21, wherein the nucleic acid encoding the Cas protein comprises DNA.

23. The composition suitable for use according to claim 21, wherein the nucleic acid encoding the Cas protein comprises RNA.

24. The composition suitable for use according to any one of claims 1-23, wherein the composition comprises the guide RNA in the form of RNA.

25. The composition suitable for use according to any one of claims 1-23, wherein the composition comprises the DNA encoding the guide RNA.

26. The composition suitable for use according to any one of claims 1-25, wherein the Cas protein or the nucleic acid encoding the Cas protein and/or the guide RNA or the DNA encoding the guide RNA are in a lipid-nanoparticle.

27. The composition suitable for use according to any one of claims 1-25, wherein the nucleic acid encoding the Cas protein and/or the DNA encoding the guide RNA are in an adeno-associated virus vector.

28. The composition suitable for use according to any one of claims 1-27, wherein the guide RNA is a single-molecule guide RNA in which the crRNA portion is linked to the tracrRNA portion.

29. The composition suitable for use according to claim 28, wherein the guide RNA comprises the sequence set forth in SEQ ID NO: 1420, 256, 257, or 258.

30. The composition suitable for use according to any one of claims 1-27, wherein the crRNA portion and the tracrRNA portion are separate RNA molecules.

31. The composition suitable for use according to claim 30, 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.

32. The composition suitable for use according to any one of claims 1-31, wherein the guide RNA comprises a modification providing for modified or regulated stability.

33. The composition suitable for use according to any one of claims 1-32, wherein the cell is *ex vivo* or *in vivo*.

34. The composition suitable for use according to any one of claims 1-33, wherein the cell is a mouse cell, a rat cell or a human cell.

35. The composition suitable for use according to any one of claims 1-34, wherein the cell is a human liver cell, a mouse liver cell, a mouse pluripotent cell, or a rat pluripotent cell.

36. The composition suitable for use according to claim 35, wherein the cell is a human liver cell.

37. The composition suitable for use according to claim 36, wherein the cell is *in vivo*.

38. The composition suitable for use according to claim 37, wherein the Cas protein or a nucleic acid encoding the Cas protein and the guide RNA or a DNA encoding the guide RNA are introduced into a liver *in vivo*.

39. The composition suitable for use according to any one of claims 1-38, wherein the cell is a human cell, and wherein:

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 226-239; and/or

(b) the DNA-targeting segment comprises any one of SEQ ID NOS: 1629-1642; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 706-719; 936-949; 1166-1179, and 1396-1409.

40. The composition suitable for use according to any one of claims 1-35, wherein the cell is a mouse cell, and wherein:

(a) the guide RNA target sequence comprises any one of SEQ ID NOS: 264-268; and/or

(b) the DNA-targeting segment comprises any one of SEQ ID NOS: 1648-1652; and/or

(c) the guide RNA comprises any one of SEQ ID NOS: 725-729, 955-959, 1185-1189, and 1415-1419.