CLAIMS

1. Use of a composition comprising a CRISPR-Cas system comprising:

a Cas9 comprising at least one nuclear localization sequence, a guide sequence capable of hybridizing to a hepatic target sequence expressed in liver and associated with a gene involved in a liver disease or disorder, a tracr mate sequence and a tracr sequence, or

one or more polynucleotides encoding the CRISPR-Cas system

in the preparation of a medicament for treating a liver disease or disorder in an organism.

2. Use according to Claim 1, in which expression of a gene product is altered by the CRISPR-Cas system in liver, thereby producing a phenotypic change.

3. Use according to Claim 1 or 2, in which the composition is to be delivered to liver cells in an organism.

4. Use according to Claim 1, 2 or 3, in which the medicament is for treating or inhibiting a condition caused by a defect in the hepatic target sequence expressed in liver.

5. Use according to Claim 1, in which the composition comprises one or more viral vectors comprising:

(a) a first regulatory element operably linked to a polynucleotide sequence encoding the guide sequence, the tracr mate sequence, and the tracr sequence, and

(b) a second regulatory element operably linked to a polynucleotide sequence encoding the Cas9 comprising at least one nuclear localization sequence,

in which components (a) and (b) are located on same or different vectors.

6. Use according to Claim 1, in which the composition comprises:

(a) a polynucleotide sequence comprising, from 5’ to 3’, the guide sequence, the tracr mate sequence, and the tracr sequence, and

(b) a polynucleotide sequence encoding the Cas9 and at least one nuclear localization sequence, in which the tracr mate sequence is capable of hybridizing to the tracr sequence, in which the guide sequence is capable of directing sequence-specific binding

of a CRISPR complex comprising the Cas9 to the target sequence, and in which the polynucleotide sequence encoding the Cas9 is DNA or RNA.

7. Use according to Claim 1, in which the composition comprises:

(a) a polynucleotide sequence comprising the guide sequence and the tracr mate sequence,

(b) a polynucleotide sequence encoding the Cas9 and at least one nuclear localization sequence, and

(c) a polynucleotide sequence comprising the tracr sequence,

in which the tracr mate sequence is capable of hybridizing to the tracr sequence, in which the guide sequence is capable of directing sequence-specific binding of a CRISPR complex comprising the Cas9 to the target sequence, and in which the polynucleotide sequence encoding a Cas9 is DNA or RNA.

8. Use according to any preceding claim, in which expression of two or more hepatic gene products is altered.

9. Use according to any of Claims 1 to 6, in which the guide sequence is fused to the tracr mate sequence and the tracr sequence.

10. Use according to any one Claims 1 to 7, in which the polynucleotide sequence encoding the Cas9 is codon optimized for expression in the organism.

11. Use according to any of Claims 1 to 7, in which the organism is a mammal.

12. Use according to any of Claims 1 to 7, in which the Cas9 is *S. pyogenes* or *S. aureus* Cas9.

13. Use according Claim 5, in which the one or more viral vectors is an AAV or lentiviral vector.

14. Use according to Claim 13, in which the viral vector is an AAV2/8 vector.

15. Use according to any of Claims 5, 6, or 7, in which (a) and (b) are located on the same viral vector.

16. Use according to Claim 15, in which the viral vector is an AAV vector and the Cas9 is *S. aureus* Cas9.

17. Use according to any of Claims 1 to 7, in which the hepatic target sequence comprises a polynucleotide sequence encoding proprotein convertase subtilisin kexin 9 (PCSK9), Alpha-1 Antitrypsin (A1AT), SERPINA1, Hmgcr, Apolipoprotein B (ApoB), or low density lipoprotein receptor (LDL-R).

18. Use according to any of Claims 1 to 7, in which the polynucleotide sequence encoding the Cas9 is operably linked to a liver-specific promoter.

19. Use according to any of Claims 1 to 7, in which the polynucleotide sequence encoding the Cas9 is operably linked to a TBG promoter.

20. Use according to any of Claims 1 to 7, in which the liver disease or disorder is AAT deficiency.

21. Use according to any of Claims 1 to 7, in which one or more deficient genotypes are corrected.

22. Use according to any of Claims 1 to 7, in which the CRISPR-Cas system is to be delivered as RNA polynucleotides using a stable nucleic acid-lipid particle (SNALP).

23. Use according to any of Claims 1 to 7, in which the CRISPRCas system is to be delivered using a AAV2/8 vector.