Claims

1. A guide RNA comprising:

    a. a guide sequence comprising at least 95%, 90%, or 85% identical to a sequence selected from SEQ ID NOs: 15, 8, and 41;

    b. a guide sequence comprising at least 17, 18, 19, or 20 contiguous nucleotides of a sequence selected from SEQ ID NOs: 15, 8, and 41; or

    c. a guide sequence selected from SEQ ID NOs: 15, 8, and 41.

2. The guide RNA of claim 1, further comprising the nucleotide sequence of SEQ ID NO: 202.

3. The guide RNA of claim 1, wherein the guide RNA further comprises a nucleotide sequence selected from SEQ ID NO: 170, 171, 172, and 173 wherein the sequence of SEQ ID NO: 170, 171, 172, or 173 is 3' of the guide sequence.

4. The guide RNA of any one of claims 1-3, wherein the guide RNA further comprises a 3' tail.

5. The guide RNA of any one of claims 1-4, wherein the guide RNA comprises at least one modification.

6. The guide RNA of claim 5, wherein the modification comprises a 5' end modification.

7. The guide RNA of claim 5 or 6, wherein the modification comprises a 3' end modification.

8. The guide RNA of any one of claims 1-7, wherein the guide RNA comprises a modification in a hairpin region.

9. The guide RNA of any one of claims 1-8, wherein the modification comprises a 2'-O-methyl (2'-O-Me) modified nucleotide.

10. The guide RNA of any one of claims 1-9, wherein the modification comprises a phosphorothioate (PS) bond between nucleotides.

11. The guide RNA of any one of claims 1-10, wherein the modification comprises a 2'-fluor (2'F) modified nucleotide.

12. The guide RNA of any one of claims 1 or 3-11, further comprising the nucleotide sequence of SEQ ID NO: 171.

13. The guide RNA of claim 12, modified according to the pattern of nucleotide sequence of SEQ ID NO: 405.

14. The guide RNA of any one of claims 1 or 3-11, further comprising the nucleotide sequence of SEQ ID NO: 173.

15. The guide RNA of claim 14, modified according to the pattern of SEQ ID NO: 248-255 or 450.

16. The guide RNA of any one of claims 12-15, wherein the guide sequence is SEQ ID NO: 15.

17. The guide RNA of any one of claims 12-15, wherein the guide sequence is SEQ ID NO: 8.

18. The guide RNA of any one of claims 12-15, wherein the guide sequence is SEQ ID NO: 41.

19. The guide RNA of any one of claims 1 or 4-11, wherein the guide RNA is modified according to the pattern of SEQ ID NO: 300, wherein the N's are collectively the guide sequence of claim 1.

20. The guide RNA of claim 16, wherein each N in SEQ ID NO: 300 is any natural or non-natural nucleotide.

21. The guide RNA of claim 19, wherein the guide sequence is SEQ ID NO: 15 and the guide RNA is modified according to mG*mG*mA* UUGCGUAUGGGACACAA GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCC GUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUm CmGmGmUmGmCmU*mU*mU*mU, wherein "mA," "mC," "mU," or "mG" denote a nucleotide that has been modified with 2'-O-Me, a * denotes a phosphorothioate bond, and an N is a natural nucleotide.

22. The guide RNA of claim 19, wherein the guide sequence is SEQ ID NO: 8 and the guide RNA is modified according to mU*mA*mC*CCGGGAGUUGACUUUGG GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCC GUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUm CmGmGmUmGmCmU*mU*mU*mU, wherein "mA," "mC," "mU," or "mG" denote a nucleotide that has been modified with 2'-O-Me, a * denotes a phosphorothioate bond, and N is a natural nucleotide.

23. The guide RNA of claim 19, wherein the guide sequence is SEQ ID NO: 41 and the guide RNA is modified according to mU*mA*mU*UAUCAAAUCACAUUACC

GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCC GUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUm CmGmGmUmGmCmU*mU*mU*mU, wherein "mA," "mC," "mU," or "mG" denote a nucleotide that has been modified with 2'-O-Me, a * denotes a phosphorothioate bond, and N is a natural nucleotide.

24. A composition comprising a guide RNA of any one of claims 1-23.

25. A composition of claim 24, further comprising an RNA-guided DNA binding agent or nucleic acid encoding an RNA-guided DNA binding agent.

26. The composition of claim 25, wherein the nucleic acid encoding an RNA-guided DNA binding agent comprises an mRNA comprising an open reading frame (ORF) encoding an RNA guided DNA binding agent.

27. The composition of claim 25 or 26, wherein the RNA-guided DNA binding agent is Cas9.

28. The composition of claim 27, wherein the Cas9 is S. pyogenes Cas9.

29. The composition of claim 27, wherein the ORF encoding a Cas9 comprises an ORF from an mRNA of SEQ ID NOs: 501-516.

30. The composition of any one of claims 26-29, wherein the ORF is a modified ORF.

31. The composition of any one of claims 24-30, further comprising a pharmaceutical excipient.

32. The composition of any one of claims 24-31, wherein the guide RNA is associated with a lipid nanoparticle (LNP).

33. The composition of claim 32, wherein the LNP comprises an ionizable lipid.

34. The composition of claim 33, wherein the ionizable lipid is (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate.

35. The composition of any one of claims 32-34, wherein the LNP comprises (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate, DSPC, cholesterol, and PEG2k-DMG.

36. A pharmaceutical composition comprising a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35.

37. A pharmaceutical composition comprising a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35 for use in inducing a double stranded break or a single stranded break within a KLKB1 gene in a cell or reducing expression of KLKB1 in a cell.

38. The pharmaceutical composition for use of claim 37, for reducing expression of the KLKB1 gene in a cell or subject.

39. A pharmaceutical composition comprising a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35 for use in treating a subject having hereditary angioedema (HAE).

40. The pharmaceutical composition for use of claim 39, comprising reducing the frequency and/or severity of HAE attacks.

41. A pharmaceutical composition comprising a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35 for use in treating or preventing angioedema associated with HAE, bradykinin production and accumulation, bradykinin-induced swelling, angioedema obstruction of the airway, or asphyxiation.

42. A pharmaceutical composition comprising a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35 for use in reducing total plasma kallikrein activity or reducing prekallikrein and/or kallikrein levels in a subject.

43. The pharmaceutical composition for use of claim 42, wherein the total plasma kallikrein activity is reduced by more than 60%.

44. Use of a guide RNA of any one of claims 1-23 or composition of any one of claims 24-35 in the manufacture of a medicament for:

a) inducing a double stranded break or a single stranded break within a KLKB1 gene in a cell or reducing expression of KLKB1 in a cell;

b) inducing a double stranded break or a single stranded break within a KLKB1 gene in a cell or reducing expression of KLKB1 in a cell, wherein the cell is in a subject;

c) treating a subject having hereditary angioedema (HAE);

d) treating a subject having hereditary angioedema (HAE), wherein the frequency and/or severity of HAE attacks is reduced;

e) treating or preventing angioedema associated with HAE, bradykinin production and accumulation, bradykinin-induced swelling, angioedema obstruction of the airway, or asphyxiation;

f) reducing total plasma kallikrein activity in a subject; or

g) reducing total plasma kallikrein activity in a subject, wherein the total plasma kallikrein activity is reduced by more than 60% in the subject.