WHAT IS CLAIMED IS:

1. A method of modeling a disease associated with a genomic locus in a eukaryotic organism or a non-human organism comprising manipulation of a target sequence within a coding, non-coding or regulatory element of said genomic locus comprising delivering a non-naturally occurring or engineered composition comprising :

(A) - I. a CRISPR-Cas system RNA polynucleotide sequence, wherein the polynucleotide sequence comprises:

(a) a guide sequence capable of hybridizing to the target sequence,

(b) a tracr mate sequence, and

(c) a tracr sequence, and

II. a polynucleotide sequence encoding Cas9, optionally comprising at least one or more nuclear localization sequences,

wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence and the polynucleotide sequence encoding Cas9 is DNA or RNA,

or

(B) I. polynucleotides comprising:

(a) a guide sequence capable of hybridizing to the target sequence, and

(b) at least one or more tracr mate sequences,

II. a polynucleotide sequence encoding Cas9, and

III. a polynucleotide sequence comprising a tracr sequence,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence, and the polynucleotide sequence encoding Cas9 is DNA or RNA.

2. The method of claim 1, wherein the Cas9 is SaCas9.

3. The method of claim 1 or 2, wherein the polynucleotides encoding the sequence encoding Cas9, the guide sequence, tracr mate sequence or tracr sequence is/are RNA and are delivered via liposomes, nanoparticles, cell penetrating peptides, exosomes, microvesicles, or a gene-gun.

4. The method of any of claims 1 to 3, wherein the polynucleotides are comprised within a vector system comprising one or more vectors.

5. A method of modeling a disease associated with a genomic locus in a eukaryotic organism or a non-human organism comprising manipulation of a target sequence within a coding, non-coding or regulatory element of said genomic locus comprising delivering a non-naturally occurring or engineered composition comprising a viral vector system comprising one or more viral vectors operably encoding a composition for expression thereof, wherein the composition comprises:

(A) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to a CRISPR-Cas system RNA polynucleotide sequence, wherein the polynucleotide sequence comprises

(a) a guide sequence capable of hybridizing to the target sequence,

(b) a tracr mate sequence, and

(c) a tracr sequence, and

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9, optionally comprising at least one or more nuclear localization sequences,

wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

wherein components I and II are located on the same or different vectors of the system,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence,

or

(B) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to

(a) a guide sequence capable of hybridizing to the target sequence, and

(b) at least one or more tracr mate sequences,

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9, and

III. a third regulatory element operably linked to a tracr sequence,

wherein components I, II and III are located on the same or different vectors of the system, wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence; (2) the tracr mate sequence that is hybridized to the tracr sequence; and wherein the Cas9 is preferably SaCas9.

6. The method of claim 5, wherein one or more of the viral vectors are delivered via liposomes, nanoparticles, exosomes, microvesicles, or a gene-gun.

7. A method of treating or inhibiting a condition or a disease caused by one or more mutations in a genomic locus in a eukaryotic organism or a non-human organism comprising manipulation of a target sequence within a coding, non-coding or regulatory element of said genomic locus in a target sequence in a subject or a non-human subject in need thereof comprising modifying the subject or a non-human subject by manipulation of the target sequence and wherein the condition or disease is susceptible to treatment or inhibition by manipulation of the target sequence comprising providing treatment comprising:

delivering a non-naturally occurring or engineered composition comprising an AAV or lentivirus vector system, comprising one or more AAV or lentivirus vectors operably encoding a composition for expression thereof, wherein the target sequence is manipulated by the composition when expressed, wherein the composition comprises:

(A) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to a CRISPR-Cas system RNA polynucleotide sequence, wherein the polynucleotide sequence comprises

(a) a guide sequence capable of hybridizing to the target sequence in a eukaryotic cell,

(b) a tracr mate sequence, and

(c) a tracr sequence, and

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9 comprising at least one or more nuclear localization sequences,

wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

wherein components I and II are located on the same or different vectors of the system,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the arget sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence,

or

(B) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to

(a) a guide sequence capable of hybridizing to an target sequence in a eukaryotic cell, and

(b) at least one or more tracr mate sequences,

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9, and

III. a third regulatory element operably linked to a tracr sequence,

wherein components I, II and III are located on the same or different vectors of the system,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence,

wherein the CRISPR complex comprises Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence; and wherein the Cas9 is preferably SaCas9.

8. The method of any preceding claim, wherein the method is carried out *in vitro*, *ex vivo* or *in vivo*.

9. The method of any preceding claim including inducing expression.

10. The method of claim 1 wherein the condition or disease is an ocular disease.

11. The method of claim 10 where the ocular disease is retinitis pigmentosa or achromatopsia.

12. The method of any of claims 4 to 8 wherein the viral vector is an AAV or lentiviral vector.

13. A method of delivering the Cas9 of any preceding claim, comprising delivering to a cell mRNA encoding the Cas9.

14. The method of any one of claims 1 to 13, wherein the polynucleotide or sequence encoding the Cas9 is delivered to the cell by delivering mRNA encoding the Cas9 to the cell.

15. A method of preparing the AAV or lentivirus vector of claim 7 comprising transfecting plasmid(s) containing or consisting essentially of nucleic acid molecule(s) coding for the AAV or lentivirus into AAV-infected or lentivirus-infected cells, and supplying AAV AAV or lentivirus rep and/or cap and/or helper nucleic acid molecules obligatory for replication and packaging of the AAV or lentivirus.

16. A method of preparing an AAV or lentivirus vector for use in the method of claim 7, comprising transfecting plasmid(s) containing or consisting essentially of nucleic acid molecule(s) coding for the AAV or lentivirus into AAV-infected or lentivirus-infected cells, and supplying AAV AAV or lentivirus rep and/or cap and/or helper nucleic acid molecules obligatory for replication and packaging of the AAV or lentivirus.

17. The method of claim 15 or 16 wherein the AAV or lentivirus rep and/or cap obligatory for replication and packaging of the AAV or lentivirus are supplied by transfecting the cells with helper plasmid(s) or helper virus(es).

18. The method of claim 17 wherein the helper virus is a poxvirus, adenovirus, lentivirus, herpesvirus or baculovirus.

19. The method of claim 18 wherein the poxvirus is a vaccinia virus.

20. The method of any of claims 15 to 20 wherein the cells are mammalian cells.

21. The method of any of claims 15 to 20 wherein the cells are insect cells and the helper virus (where present) is baculovirus.

22. The method of any preceeding claim wherein the Cas9 is a wild type, truncated or a chimeric Cas9.

23. A composition as defined in any of claims 1-22 for use in medicine or in therapy.

24. A composition as defined in any of claims 1-22 for use in a method of modeling a disease associated with a genetic locus in a eukaryotic organism or a non-human organism comprising manipulation of a target sequence within a coding, non-coding or regulatory element of said genetic locus.

25. Use of a composition as defined in any of claims 1-24 in *ex vivo or in vivo* gene or genome editing.

26. Use of a composition as defined in any of claims 1-24 in the manufacture of a medicament for *in vitro*, *ex vivo or in vivo* gene or genome editing or for use in a method of modifying an organism or a non-human organism by manipulation of a target sequence in a genomic locus associated with a disease or in a method of treating or inhibiting a condition or diesease caused by one or more mutations in a genomic locus in a eukaryotic organism or a non-human organism.

27. A composition comprising:

(A) - I. a CRISPR-Cas system RNA polynucleotide sequence, wherein the polynucleotide sequence comprises:

(a) a guide sequence capable of hybridizing to a target sequence in a eukaryotic cell,

(b) a tracr mate sequence, and

(c) a tracr sequence, and

II. a polynucleotide sequence encoding Cas9, optionally comprising at least one or more nuclear localization sequences,

wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence and the polynucleotide sequence encoding SaCas9 is DNA or RNA,

or

(B) I. polynucleotides comprising:

(a) a guide sequence capable of hybridizing to an target sequence in a eukaryotic cell, and

(b) at least one or more tracr mate sequences,

II. a polynucleotide sequence encoding Cas9, and

III. a polynucleotide sequence comprising a tracr sequence,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and wherein the CRISPR complex comprises Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, (2) the tracr mate sequence that is hybridized to the tracr sequence, and the polynucleotide sequence encoding Cas9 is DNA or RNA; and the Cas9 is preferably SaCas9.

for use in medicine or therapy; or for use in a method of modifying an organism or a non-human organism by manipulation of a target sequence in a genomic locus associated with a disease or disorder; or for use in a method of treating or inhibiting a condition caused by one or more mutations in a genetic locus associated with a disease in a eukaryotic organism or a non-human organism.; or for use in *in vitro, ex vivo or in vivo* gene or genome editing.

28. The composition of claim 27, wherein the polynucleotides are comprised within a vector system comprising one or more vectors.

29. The method, use or composition of any of the preceding claims, wherein the CRISPR-Cas system RNA is a chimeric RNA (chiRNA).

30. The method, use or composition of any of the preceding claims, wherein the CRISPR-Cas system is a multiplexed SaCas9 enzyme system further comprising multiple chimeras and/or multiple multiguide sequences and a single tracr sequence.

31. The method, use or composition according any of the preceding claims, wherein theCas9 is a nuclease directing cleavage of both strands at the location of the target sequence.

32. The method, use or composition according to any of the preceding claims, wherein the Cas9 comprises one or more mutations.

33. The method, use or composition according to claim 32, wherein the Cas9 comprises one or more mutations D10A, E762A, H840A, N854A, N863A or D986A.

34. The method, use or composition according to claim 32 wherein the one or more mutations is in a RuvC1 domain of the Cas9.

35. The method, use or composition according to claim 30, wherein the Cas9 is a nickase directing cleavage at the location of the target sequence.

36. The method, use or composition according to claim 35, wherein the nickase is a double nickase.

37. The method, use or composition according to any preceding claim further comprising at least two or more NLS.

38. The method, use or composition according to any preceding claim, wherein the SaCas9 has one or more mutations in a catalytic domain, wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and wherein the enzyme further comprises a functional domain.

39. The method, use or composition according to claim 38, wherein the functional domain is a transcriptional activation domain.

40. The method, use or composition according to claim 39, wherein the transcriptional activation domain is VP64.

41. A therapeutic genome editing method for treating or inhibiting a condition or a disease caused by one or more mutations in a genomic locus in a eukaryotic organism or a non-human organism comprising manipulation of a target sequence within a coding, non-coding or regulatory element of said genomic locus in a target sequence in a subject or a non-human subject in need thereof comprising modifying the subject or a non-human subject by manipulation of the target sequence and wherein the condition or disease is susceptible to treatment or inhibition by manipulation of the target sequence comprising providing treatment comprising:

delivering a non-naturally occurring or engineered composition comprising an AAV or lentivirus vector system, comprising one or more AAV or lentivirus vectors operably encoding a composition for expression thereof, wherein the target sequence is manipulated by the composition when expressed, wherein the composition comprises:

(A) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to a CRISPR-Cas system RNA polynucleotide sequence, wherein the polynucleotide sequence comprises

(a) a guide sequence capable of hybridizing to the target sequence in a eukaryotic cell,

(b) a tracr mate sequence, and

(c) a tracr sequence, and

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9 comprising at least one or more nuclear localization sequences,

wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

wherein components I and II are located on the same or different vectors of the system,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises the Cas9 complexed with (1) the guide sequence that is hybridized to the arget sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence,

or

(B) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising

I. a first regulatory element operably linked to

(a) a guide sequence capable of hybridizing to an target sequence in a eukaryotic cell, and

(b) at least one or more tracr mate sequences,

II. a second regulatory element operably linked to an enzyme-coding sequence encoding Cas9, and

III. a third regulatory element operably linked to a tracr sequence,

wherein components I, II and III are located on the same or different vectors of the system,

wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, and

wherein the CRISPR complex comprises Cas9 complexed with (1) the guide sequence that is hybridized to the target sequence, (2) the tracr mate sequence that is hybridized to the tracr; and the Cas9 is preferably SaCas9.

42. The method of claim 41, wherein the condition or disease is retinitis pigentosa or achromatopsia.

43. The method of claim 41, wherein the AAV is AAV1, AAV2, AAV5, AAV7, AAV8, AAV DJ or any combination thereof.

44. A method of individualized or personalized treatment of a genetic disease in a subject in need of such treatment comprising:

(a) introducing multiple mutations *ex vivo* in a tissue, organ or a cell line comprising SaCas9-expressing eukaryotic cell(s), or *in vivo* in a transgenic non-human mammal having cells that express SaCas9, comprising delivering to cell(s) of the tissue, organ, cell or mammal the vector as herein-discussed, wherein the specific mutations or precise sequence substitutions are or have been correlated to the genetic disease;

(b) testing treatment(s) for the genetic disease on the cells to which the vector has been delivered that have the specific mutations or precise sequence substitutions correlated to the genetic disease; and

(c) treating the subject based on results from the testing of treatment(s) of step (b).

45. The method of claim 44, wherein the genetic disease is an ocular disease.

46. The method of claim 45, wherein the ocular disease is retinitis pigmentosa or achromatopsia.

CLAIMS

1. Use of a composition for the manufacture of a medicament for treating an ocular genetic disease by localized administration to a subject's eye, in which the composition comprises a CRISPR-Cas system comprising:

A. a polynucleotide encoding a CRISPR-Cas system guide comprising: (a) a guide sequence capable of hybridizing to an ocular genetic disease target sequence, (b) a tracr mate sequence, and (c) a tracr sequence, in which (a), (b), and (c) are arranged in a 5' to 3' orientation; and

B. a polynucleotide encoding a Cas9;

in which each of A and B are formulated for delivery together in a delivery vehicle, the vehicle being an adeno-associated viral (AAV) vector, in which the AAV is AAV1, AAV2, or AAV5; and capable, when administered together to the subject's eye, of forming a CRISPR-Cas complex comprising the Cas9 and the CRISPR-Cas system guide.

2. Use according to Claim 1, in which the CRISPR-Cas system guide is a chimeric RNA (chiRNA).

3. Use according to Claim 1 or 2, in which the ocular genetic disease is a retinal disease.

4. Use according to Claim 3, in which the retinal disease is a hereditary disease.

5. Use according to any preceding claim, in which the Cas9 is a nuclease directing cleavage of both DNA strands at the location of the target sequence, or in which the Cas9 is a nickase directing cleavage of one DNA strand at the location of the target sequence.

6. Use according to any preceding claim, in which the Cas9 is complexed with the CRISPRCas system guide.

7. Use according to Claim 6, in which the tracr mate sequence hybridizes to the tracr sequence, and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence.

8. Use according to any preceding claim, in which the ocular genetic disease is selected from Stargardt disease, Bardet-Biedl Syndrome, Best disease, blue cone monochromacy,

choroidermia, cone-rod dystrophy, congenital stationary night blindness, enhanced S-cone syndrome, juvenile X-linked retinoschisis, Leber congenital amaurosis (LCA), Malattia leventinesse, Norrie disease or X-linked familial exudative vitreoretinopathy, Pattern dystrophy, Sorsby dystrophy, Usher syndrome, retinitis pigmentosa, achromatopsia or macular dystrophies or macular degeneration, and age-related macular degeneration.

9. Use according to Claim 8, in which the ocular genetic disease is Leber congenital amaurosis (LCA), Usher syndrome, or retinitis pigmentosa.

10. Use according to any preceding claim, in which the Cas9 is a *Streptococcus pyogenes* Cas9 (SpCas9), a *Staphylococcus aureus* Cas9 (SaCas9), or a *Streptococcus thermophilus* Cas9 (StCas9).

11. Use according to any preceding claim, in which the CRISPR-Cas system is a multiplexed system comprising two or more CRISPR-Cas system guides with different guide sequences.

12. Use according to any preceding claim, in which the Cas9 comprises one or more nuclear localization sequences.

13. Use according to any preceding claim, in which the Cas9 comprises one or more mutations, and in which the Cas9 is fused to a heterologous protein domain.

14. Use according to any preceding claim, in which the composition further comprises a recombination template.

15. Use according to any preceding claim, in which the composition is formulated for subretinal injection.