CLAIMS

1. Use of a non-naturally occurring nuclease system comprising one or more vectors comprising:

i) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule in a cell of a subject, wherein the target sequence comprises a mutation resulting in an R135 mutation in rhodopsin; and

ii) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

in the manufacture of a medicament for administration to a retinal area for the treatment of a retinal degeneration in a subject in need thereof, wherein components (i) and (ii) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or two strands of the DNA molecule to alter expression of the rhodopsin comprising an R135 mutation.

2. An *in vitro* method of altering expression of rhodopsin comprising an R135 mutation in a photoreceptor cell, wherein the cell comprises a DNA molecule encoding the rhodopsin comprising the R135 mutation, the method comprising introducing into the cell a non-naturally occurring nuclease system comprising one or more vectors comprising:

a) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of the DNA molecule, wherein the target sequence comprises a mutation resulting in an R135 mutation in rhodopsin; and

b) a regulatory element operable in the cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

wherein components (a) and (b) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves the DNA molecule to alter expression of the rhodopsin comprising the R135 mutation.

3. The use of claim 1 or the method of claim 2, wherein the system is CRISPR.

4. The use of claim 1 or the method of claim 2, wherein the system is packaged into a single adeno-associated virus (AAV) particle.

5. The use of claim 1 or the method of claim 2, wherein the system inactivates the rhodopsin comprising the R135 mutation.

6. The use of claim 1 or the method of claim 2, wherein the nuclease system excises the mutation resulting in an R135 mutation in rhodopsin.

7. The use of claim 1 or the method of claim 2, wherein the promoter is a bidirectional promoter.

8. The use or method of claim 7, wherein the bidirectional promoter is H1.

9. The use or method of claim 8, wherein the H1 promoter comprises:

a) control elements that provide for transcription in one direction of the at least one nucleotide sequence encoding the gRNA; and

b) control elements that provide for transcription in the opposite direction of the nucleotide sequence encoding the genome-targeted nuclease.

10. The use of claim 1 or the method of claim 2, wherein the genome-targeted nuclease is Cas9 protein.

11. The use or method of claim 10, wherein the Cas9 protein is codon optimized for expression in the cell.

12. The use or method of claim 7 or claim 8, wherein the promoter is operably linked to at least one, two, three, four, five, six, seven, eight, nine, or ten gRNA.

13. The use of claim 1, wherein the retinal area is the retina.

14. The use or method of claim 1 or claim 2, wherein the mutation at R135 is selected from the group consisting of R135G, R135W, R135L.

15. The use or method of any one of claims 1-14, wherein the target sequence is selected from the group consisting of the nucleotide sequences set forth in SEQ ID NO: 115-126, or combinations thereof.

16. The use of claim 1 or the method of claim 2, wherein the gRNA sequence is selected from the group consisting of the nucleotide sequences set forth in SEQ ID NO: 131-142, or combinations thereof.

17. A non-naturally occurring nuclease system comprising one or more vectors comprising:

i) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule in a cell of a

subject, wherein the target sequence comprises a mutation resulting in an R135 mutation in rhodopsin and wherein the DNA molecule encodes rhodopsin comprising the R135 mutation; and

ii) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

for use in a retinal area for the treatment of a retinal degeneration in a subject in need thereof, wherein components (i) and (ii) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or two strands of the DNA molecule to alter expression of the rhodopsin comprising the R135 mutation.

18. The system of claim 17, wherein the system is CRISPR.

19. The system of claim 17, wherein the system is packaged into a single adeno-associated virus (AAV) particle.

20. The system of claim 17, wherein the system inactivates the rhodopsin comprising the R135 mutation.

21. The system of claim 17, wherein the nuclease system excises the mutation resulting in an R135 mutation in rhodopsin.

22. The system of claim 17, wherein the promoter is a bidirectional promoter.

23. The system of claim 22, wherein the bidirectional promoter is H1.

24. The system of claim 23, wherein the H1 promoter comprises:

a) control elements that provide for transcription in one direction of the at least one nucleotide sequence encoding the gRNA; and

b) control elements that provide for transcription in the opposite direction of the nucleotide sequence encoding the genome-targeted nuclease.

25. The system of claim 17, wherein the genome-targeted nuclease is Cas9 protein.

26. The system of claim 25, wherein the Cas9 protein is codon optimized for expression in the cell.

27. The system of claim 17, wherein the promoter is operably linked to at least one, two, three, four, five, six, seven, eight, nine, or ten gRNA.

28. The system of claim 17, wherein the retinal area is the retina.