We claim:

~~1. A nucleic acid construct for integration into a target genomic locus, wherein the nucleic acid construct is bidirectional and comprises:~~

~~(a) a first segment comprising a first coding sequence for a first retinoschisin protein or fragment thereof; and~~

~~(b) a second segment comprising a reverse complement of a second coding sequence for a second retinoschisin protein or fragment thereof.~~

~~2. The nucleic acid construct of claim 1, wherein the second segment is located 3' of the first segment.~~

~~3. The nucleic acid construct of claim 1 or 2, wherein the first retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof, the second retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof, or both the first retinoschisin protein or fragment thereof and the second retinoschisin protein or fragment thereof are a human retinoschisin protein or fragment thereof.~~

~~4. The nucleic acid construct of any one of claims 1-3, wherein the first coding sequence comprises, consists essentially of, or consists of complementary DNA (cDNA), the second coding sequence comprises, consists essentially of, or consists of cDNA, or both the first coding sequence and the second coding sequence comprise, consist essentially of, or consist of cDNA.~~

~~5. The nucleic acid construct of any one of claims 1-4, wherein the first coding sequence comprises, consists essentially of, or consists of exons 2-6 of human *RS1* or degenerate variants thereof, the second coding sequence comprises, consists essentially of, or consists of exons 2-6 of human *RS1* or degenerate variants thereof, or both the first coding sequence and the second coding sequence comprise, consist essentially of, or consist of exons 2-6 of human *RS1* or degenerate variants thereof.~~

~~6. The nucleic acid construct of any one of claims 1-5, wherein the first segment comprises a fragment or portion of the first intron of human *RS1* located 5' of the first coding sequence, and/or the second segment comprises a reverse complement of a fragment or~~

~~portion of the second intron of human *RS1* located 3' of the reverse complement of the second coding sequence.~~

~~7. The nucleic acid construct of any one of claims 1-6, wherein the first retinoschisin protein or fragment thereof is identical to the second retinoschisin protein or fragment thereof.~~

~~8. The nucleic acid construct of any one of claims 1-7, wherein the second coding sequence adopts a different codon usage from the codon usage of the first coding sequence.~~

~~9. The nucleic acid construct of any one of claims 1-8, wherein the second segment has at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% complementarity to the first segment.~~

~~10. The nucleic acid construct of any one of claims 1-9, wherein the second segment has less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, less than about 90%, less than about 95%, less than about 97%, or less than about 99% complementarity to the first segment.~~

~~11. The nucleic acid construct of any one of claims 1-10, wherein the reverse complement of the second coding sequence is:~~

~~(a) not substantially complementary to the first coding sequence;~~

~~(b) not substantially complementary to a fragment of the first coding sequence;~~

~~(c) highly complementary to the first coding sequence;~~

~~(d) highly complementary to the fragment of the first coding sequence;~~

~~(e) at least about 60%, at least about 70%, at least about 80%, or at least about 90% identical to the reverse complement of the first coding sequence;~~

(f) about 50% to about 80% identical to the reverse complement of the first coding sequence; or

(g) about 60% to about 100% identical to the reverse complement of the first coding sequence.

12. The nucleic acid construct of any one of claims 1-11, wherein the first segment is linked to the second segment by a linker.

13. The nucleic acid construct of claim 12, wherein the linker is about 5 to about 2000 nucleotides in length.

14. The nucleic acid construct of any one of claims 1-13, wherein the first segment comprises a first polyadenylation signal sequence located 3' of the first coding sequence, and the second segment comprises a reverse complement of a second polyadenylation signal sequence located 5' of the reverse complement of the second coding sequence.

15. The nucleic acid construct of claim 14, wherein the first polyadenylation signal sequence is different from the second polyadenylation signal sequence.

16. The nucleic acid construct of any one of claims 1-15, wherein the nucleic acid construct does not comprise a promoter that drives expression of the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof.

17. The nucleic acid construct of any one of claims 1-16, wherein the first segment comprises a first splice acceptor site located 5' of the first coding sequence, and the second segment comprises a reverse complement of a second splice acceptor site located 3' of the reverse complement of the second coding sequence.

18. The nucleic acid construct of claim 17, wherein the first splice acceptor site is from an *RS1* gene, the second splice acceptor site is from an *RS1* gene, or both the first splice acceptor site and the second splice acceptor site are from an *RS1* gene.

19. The nucleic acid construct of claim 18, wherein the first splice acceptor site is from intron 1 of human *RS1*, the second splice acceptor site is from intron 1 of human

~~*RS1*, or both the first acceptor site and the second splice acceptor site are from intron 1 of human *RS1*.~~

~~20. The nucleic acid construct of any one of claims 1-19, wherein the nucleic acid construct does not comprise a homology arm.~~

~~21. The nucleic acid construct of any one of claims 1-19, wherein the nucleic acid construct comprises homology arms.~~

~~22. The nucleic acid construct of any one of claims 1-21, wherein the nucleic acid construct is single-stranded.~~

~~23. The nucleic acid construct of any one of claims 1-21, wherein the nucleic acid construct is double-stranded.~~

~~24. The nucleic acid construct of any one of claims 1-23, wherein the nucleic acid construct comprises DNA.~~

~~25. The nucleic acid construct of any one of claims 1-24, wherein the first coding sequence is codon-optimized for expression in a host cell, the second coding sequence is codon-optimized for expression in the host cell, or both the first coding sequence and the second coding sequence are codon-optimized for expression in the host cell.~~

~~26. The nucleic acid construct of any one of claims 1-25, wherein the nucleic acid construct comprises one or more of the following terminal structures: hairpin, loop, inverted terminal repeat (ITR), or toroid.~~

~~27. The nucleic acid construct of claim 26, wherein the nucleic acid construct comprises ITRs.~~

~~28. The nucleic acid construct of any one of claims 1-27, wherein the first retinoschisin protein or fragment thereof and/or the second retinoschisin protein or fragment thereof comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at~~

least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 5.

29. The nucleic acid construct of any one of claims 1-28, wherein the first coding sequence and/or the second coding sequence comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 8 or 9.

30. The nucleic acid construct of any one of claims 1-29, wherein the first coding sequence comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 8, and

wherein the second coding sequence comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 9.

31. The nucleic acid construct of any one of claims 1-30, wherein the nucleic acid construct comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 46 or 47.

32. The nucleic acid construct of any one of claims 1-31, wherein the second segment is located 3’ of the first segment,

wherein both the first retinoschisin protein or fragment thereof and the second retinoschisin protein or fragment thereof are a human retinoschisin protein or fragment thereof,

wherein the first retinoschisin protein or fragment thereof is identical to the second retinoschisin protein or fragment thereof,

~~wherein both the first coding sequence and the second coding sequence comprise complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,~~

~~wherein the second coding sequence adopts a different codon usage from the codon usage of the first coding sequence,~~

~~wherein the first segment comprises a first polyadenylation signal sequence located 3' of the first coding sequence, and the second segment comprises a reverse complement of a second polyadenylation signal sequence located 5' of the reverse complement of the second coding sequence,~~

~~wherein the first segment comprises a first splice acceptor site located 5' of the first coding sequence, and the second segment comprises a reverse complement of a second splice acceptor site located 3' of the reverse complement of the second coding sequence,~~

~~wherein the nucleic acid construct does not comprise a promoter that drives expression of the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof, and~~

~~wherein the nucleic acid construct does not comprise a homology arm.~~

~~33. A vector comprising the nucleic acid construct of any one of claims 1-32.~~

~~34. The vector of claim 33, wherein the vector is a viral vector.~~

~~35. The vector of claim 34, wherein the vector is an adeno-associated virus (AAV) vector.~~

~~36. The vector of claim 35, wherein the AAV comprises a single-stranded genome (ssAAV).~~

~~37. The vector of claim 35, wherein the AAV comprises a self-complementary genome (scAAV).~~

~~38. The vector of any one of claims 35-37, wherein the AAV is selected from the group consisting of: AAV2, AAV5, AAV8, or AAV7m8.~~

39. The vector of any one of claims 33-38, wherein the vector does not comprise a promoter that drives expression of the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof.

40. The vector of any one of claims 33-39, wherein the vector does not comprise a homology arm.

41. The vector of any one of claims 33-39, wherein the vector comprises homology arms.

42. A lipid nanoparticle comprising the nucleic acid construct of any one of claims 1-32.

43. A cell comprising the nucleic acid construct of any one of claims 1-32.

44. The cell of claim 43, wherein the cell is *in vitro*.

45. The cell of claim 43, wherein the cell is *in vivo*.

46. The cell of any one of claims 43-45, wherein the cell is a mammalian cell.

47. The cell of claim 46, wherein the cell is a human cell.

48. The cell of any one of claims 43-47, wherein the cell is a retinal cell.

49. The cell of any one of claims 43-48, wherein the cell expresses the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof.

50. The cell of any one of claims 43-49, wherein the nucleic acid construct is genomically integrated at the target genomic locus.

51. The cell of claim 50, wherein the target genomic locus is an endogenous *RS1* locus.

52. The cell of claim 50, wherein the nucleic acid construct is genomically integrated in intron 1 of the endogenous *RS1* locus.

53. The cell of claim 52, wherein endogenous *RS1* exon 1 splices into the first coding sequence or the second coding sequence of the nucleic acid construct.

54. The cell of claim 53, wherein the modified *RS1* locus comprising the genomically integrated nucleic acid construct encodes a protein comprising, consisting essentially of, or consisting of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 2 or 4.

55. The cell of any one of claims 51-54, wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site.

56. The cell of claim 55, wherein the integration of the nucleic acid construct into the endogenous *RS1* locus reduces or eliminates expression of the endogenous retinoschisin protein and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct.

57. The cell of any claim 55 or 56, wherein the endogenous *RS1* locus comprises a mutated *RS1* gene comprising a mutation that causes X-linked juvenile retinoschisis, and expression of the genomically integrated nucleic acid construct reduces or eliminates expression of the mutated *RS1* gene.

58. A nucleic acid construct for homology-independent targeted integration into a target genomic locus, wherein the nucleic acid construct comprises a coding sequence for a retinoschisin protein or fragment thereof flanked on each side by a nuclease target sequence for a nuclease agent.

59. The nucleic acid construct of claim 58, wherein the nuclease target sequence in the nucleic acid construct is identical to a nuclease target sequence for integration into the target genomic locus, wherein the nuclease target sequence in the target genomic locus is destroyed if the nucleic acid construct is inserted in the correct orientation but is reformed if the nucleic acid construct is inserted into the target genomic locus in the opposite orientation.

60. A nucleic acid construct for homologous recombination with a target genomic locus, wherein the nucleic acid construct comprises a coding sequence for a retinoschisin protein or fragment thereof flanked by homology arms on each side, optionally wherein the coding sequence and homology arms are further flanked on each side by a nuclease target sequence for a nuclease agent, and optionally wherein each homology arm is between about 25 nucleotides and about 2.5 kb in length.

61. The nucleic acid construct of any one of claims 58-60, wherein the retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof.

62. The nucleic acid construct of any one of claims 58-61, wherein the coding sequence for the retinoschisin protein or fragment thereof comprises, consists essentially of, or consists of complementary DNA (cDNA).

63. The nucleic acid construct of any one of claims 58-62, wherein the coding sequence for the retinoschisin protein or fragment thereof comprises, consists essentially of, or consists of exons 2-6 of human *RS1* or degenerate variants thereof.

64. The nucleic acid construct of any one of claims 58-63, wherein the nucleic acid construct comprises a fragment or portion of the first intron of human *RS1* located 5' of the coding sequence.

65. The nucleic acid construct of any one of claims 58-64, wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof.

66. The nucleic acid construct of any one of claims 58-65, wherein the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence.

67. The nucleic acid construct of any one of claims 58-66, wherein the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence.

68. The nucleic acid construct of claim 67, wherein the splice acceptor site is from an *RS1* gene.

~~69. The nucleic acid construct of claim 68, wherein the splice acceptor site is from intron 1 of human *RS1*.~~

~~70. The nucleic acid construct of any one of claims 58-69, wherein the nucleic acid construct is single-stranded.~~

~~71. The nucleic acid construct of any one of claims 58-69, wherein the nucleic acid construct is double-stranded.~~

~~72. The nucleic acid construct of any one of claims 58-71, wherein the nucleic acid construct comprises DNA.~~

~~73. The nucleic acid construct of any one of claims 58-72, wherein the coding sequence is codon-optimized for expression in a host cell.~~

~~74. The nucleic acid construct of any one of claims 58-73, wherein the construct comprises one or more of the following terminal structures: hairpin, loop, inverted terminal repeat (ITR), or toroid.~~

~~75. The nucleic acid construct of claim 74, wherein the region of the nucleic acid construct comprising the coding sequence and the nuclease target sequences is flanked by ITRs.~~

~~76. The nucleic acid construct of any one of claims 58-75, wherein the nuclease agent is a Cas protein and a guide RNA, and the nuclease target sequence is a guide RNA target sequence.~~

~~77. The nucleic acid construct of claim 76, wherein the guide RNA target sequence is an inverted guide RNA target sequence.~~

~~78. The nucleic acid construct of claim 76 or 77 wherein the Cas protein is Cas9.~~

~~79. The nucleic acid construct of any one of claims 58-78, wherein the retinoschisin protein or fragment thereof comprises, consists essentially of, or consists of a~~

~~sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 5.~~

~~80. The nucleic acid construct of any one of claims 58-79, wherein the coding sequence for the retinoschisin protein or fragment thereof comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 8 or 9.~~

~~81. The nucleic acid construct of any one of claims 58-80, wherein the nucleic acid construct comprises, consists essentially of, or consists of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 45.~~

~~82. The nucleic acid construct of any one of claims 58, 59, and 61-81, wherein the nucleic acid construct is the nucleic acid construct for homology-independent targeted integration into the target genomic locus,~~

~~wherein the retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof,~~

~~wherein the coding sequence for the retinoschisin protein or fragment thereof comprises complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,~~

~~wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof,~~

~~wherein the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence,~~

~~wherein the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence, and~~

~~wherein the nuclease target sequence in the nucleic acid construct is identical to a nuclease target sequence for integration into the target genomic locus, wherein the nuclease~~

~~target sequence in the target genomic locus is destroyed if the nucleic acid construct is inserted in the correct orientation but is reformed if the nucleic acid construct is inserted into the target genomic locus in the opposite orientation.~~

~~83. The nucleic acid construct of any one of claims 60-81, wherein the nucleic acid construct is the nucleic acid construct for homologous recombination with the target genomic locus,~~

~~wherein the retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof,~~

~~wherein the coding sequence for the retinoschisin protein or fragment thereof comprises complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,~~

~~wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof,~~

~~wherein the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence,~~

~~wherein the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence, and~~

~~wherein each homology arm is between about 25 nucleotides and about 2.5 kb in length.~~

~~84. A vector comprising the nucleic acid construct of any one of claims 58-83.~~

~~85. The vector of claim 84, wherein the vector is a viral vector.~~

~~86. The vector of claim 85, wherein the vector is an adeno-associated virus (AAV) vector.~~

~~87. The vector of claim 86, wherein the AAV comprises a single-stranded genome (ssAAV).~~

~~88. The vector of claim 86, wherein the AAV comprises a self-complementary genome (scAAV).~~

89. The vector of any one of claims 86-88, wherein the AAV is selected from the group consisting of: AAV2, AAV5, AAV8, or AAV7m8.

90. The vector of any one of claims 84-89, wherein the vector does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof.

91. The vector of any one of claims 84-90, wherein the vector does not comprise a homology arm.

92. A lipid nanoparticle comprising the nucleic acid construct of any one of claims 58-83.

93. A cell comprising the nucleic acid construct of any one of claims 58-83.

94. The cell of claim 93, wherein the cell is *in vitro*.

95. The cell of claim 93, wherein the cell is *in vivo*.

96. The cell of any one of claims 93-95, wherein the cell is a mammalian cell.

97. The cell of claim 96, wherein the cell is a human cell.

98. The cell of any one of claims 93-97, wherein the cell is a retinal cell.

99. The cell of any one of claims 93-98, wherein the cell expresses the retinoschisin protein or fragment thereof.

100. The cell of any one of claims 93-99, wherein the nucleic acid construct is genomically integrated at the target genomic locus.

101. The cell of claim 100, wherein the target genomic locus is an endogenous *RS1* locus.

102. The cell of claim 100, wherein the nucleic acid construct is genomically integrated in intron 1 of the endogenous *RS1* locus.

~~103. The cell of claim 102, wherein endogenous *RS1* exon 1 splices into the coding sequence for the retinoschisin protein or fragment thereof in the nucleic acid construct.~~

~~104. The cell of claim 103, wherein the modified *RS1* locus comprising the genomically integrated nucleic acid construct encodes a protein comprising, consisting essentially of, or consisting of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 2 or 4.~~

~~105. The cell of any one of claims 101-104, wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site.~~

~~106. The cell of claim 105, wherein the integration of the nucleic acid construct into the endogenous *RS1* locus reduces or eliminates expression of the endogenous retinoschisin protein and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct.~~

~~107. The cell of any claim 105 or 106, wherein the endogenous *RS1* locus comprises a mutated *RS1* gene comprising a mutation that causes X-linked juvenile retinoschisis, and expression of the genomically integrated nucleic acid construct reduces or eliminates expression of the mutated *RS1* gene.~~

~~108~~1. A composition for use in expressing retinoschisin in a cell or for use in integrating a coding sequence for a retinoschisin protein or fragment thereof into a target genomic locus in a cell, comprising:

(a) a nucleic acid construct comprising the coding sequence for the retinoschisin protein or fragment thereof for integration into the target genomic locus; and

(b) a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent targets a nuclease target sequence in the target genomic locus,

wherein the target genomic locus is in an endogenous *RS1* locus,

wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site,

wherein the integration of the nucleic acid construct into the endogenous *RS1* locus in the cell reduces or eliminates expression of the endogenous retinoschisin protein and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct, and

wherein the coding sequence comprises exons 2-6 of human *RS1* or degenerate variants thereof.

2. The composition for use of claim 1, wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof.

3. The composition for use of claim 1 or 2, wherein:

(I) the nucleic acid construct comprises a fragment or portion of the first intron of human *RS1* located 5' of the coding sequence; and/or

(II) the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence; and/or

(III) the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence, optionally wherein the splice acceptor site is from intron 1 of human *RS1*.

4. The composition for use of any one of claims 1-3, wherein the nucleic acid construct is for homology-independent targeted integration into a target genomic locus, wherein the nucleic acid construct comprises the coding sequence for a retinoschisin protein or fragment thereof flanked on each side by a nuclease target sequence for a nuclease agent.

~~109. A composition for use in expressing retinoschisin in a cell or for use in integrating a coding sequence for a retinoschisin protein or fragment thereof into a target genomic locus in a cell, comprising:~~

~~(a) the nucleic acid construct of any one of claims 58-83; and~~

~~(b) a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent targets a nuclease target sequence in the target genomic locus.~~

~~1105~~. The composition for use of claim ~~1094~~, wherein the nuclease target sequence in the target genomic locus is identical to the nuclease target sequence in the nucleic acid construct, and ~~.~~

~~111. The composition of claim 110,~~ wherein the nuclease target sequence in the target genomic locus is destroyed if the nucleic acid construct is inserted in the correct orientation but is reformed if the nucleic acid construct is inserted into the target genomic locus in the opposite orientation.

6. The composition for use of claim 4 or 5, wherein the coding sequence for the retinoschisin protein or fragment thereof comprises complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,

wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof,

wherein the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence,

wherein the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence, and

wherein the nuclease target sequence in the nucleic acid construct is identical to a nuclease target sequence for integration into the target genomic locus, wherein the nuclease target sequence in the target genomic locus is destroyed if the nucleic acid construct is inserted in the correct orientation but is reformed if the nucleic acid construct is inserted into the target genomic locus in the opposite orientation.

7. The composition for use of any one of claims 1-3, wherein the nucleic acid construct is for homologous recombination with a target genomic locus, wherein the nucleic acid construct comprises the coding sequence for a retinoschisin protein or fragment thereof flanked by homology arms on each side, optionally wherein the coding sequence and homology arms are further flanked on each side by a nuclease target sequence for a nuclease agent, and optionally wherein each homology arm is between about 25 nucleotides and about 2.5 kb in length.

8. The composition for use of claim 7, wherein the retinoschisin protein or fragment thereof is a human retinoschisin protein or fragment thereof,

wherein the coding sequence for the retinoschisin protein or fragment thereof comprises complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,

wherein the nucleic acid construct does not comprise a promoter that drives expression of the retinoschisin protein or fragment thereof,

wherein the nucleic acid construct comprises a polyadenylation signal sequence located 3' of the coding sequence,

wherein the nucleic acid construct comprises a splice acceptor site located 5' of the coding sequence, and

wherein each homology arm is between about 25 nucleotides and about 2.5 kb in length.

9. The composition for use of any one of claims 1-3, wherein the nucleic acid construct is bidirectional and comprises:

(a) a first segment comprising a first coding sequence for a first retinoschisin protein or fragment thereof; and

(b) a second segment comprising a reverse complement of a second coding sequence for a second retinoschisin protein or fragment thereof.

10. The composition for use of claim 9, wherein the nucleic acid construct does not comprise a homology arm.

11. The composition for use of claim 9 or 10, wherein the first retinoschisin protein or fragment thereof is identical to the second retinoschisin protein or fragment thereof, and wherein the second coding sequence adopts a different codon usage from the codon usage of the first coding sequence.

12. The composition for use of any one of claims 9-11, wherein the second segment is located 3' of the first segment,

wherein both the first retinoschisin protein or fragment thereof and the second retinoschisin protein or fragment thereof are a human retinoschisin protein or fragment thereof,

wherein the first retinoschisin protein or fragment thereof is identical to the second retinoschisin protein or fragment thereof,

wherein both the first coding sequence and the second coding sequence comprise complementary DNA (cDNA) comprising exons 2-6 of human *RS1* or degenerate variants thereof,

wherein the second coding sequence adopts a different codon usage from the codon usage of the first coding sequence,

wherein the first segment comprises a first polyadenylation signal sequence located 3' of the first coding sequence, and the second segment comprises a reverse complement of a second polyadenylation signal sequence located 5' of the reverse complement of the second coding sequence,

wherein the first segment comprises a first splice acceptor site located 5' of the first coding sequence, and the second segment comprises a reverse complement of a second splice acceptor site located 3' of the reverse complement of the second coding sequence,

wherein the nucleic acid construct does not comprise a promoter that drives expression of the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof, and

wherein the nucleic acid construct does not comprise a homology arm.

~~112. A composition for use in expressing retinoschisin in a cell or for use in integrating a coding sequence for a retinoschisin protein or fragment thereof into a target genomic locus in a cell, comprising:~~

~~(a) the nucleic acid construct of any one of claims 1-32; and~~

~~(b) a nuclease agent or a nucleic acid encoding the nuclease agent, wherein the nuclease agent targets a nuclease target sequence in the target genomic locus.~~

~~113. The composition of any one of claims 108-112, wherein the target genomic locus is in an *RS1* gene.~~

~~114~~13. The composition for use of ~~claim 113~~any one of claims 1-12, wherein the nuclease target sequence in the target genomic locus is in the first intron in the *RS1* gene at the endogenous *RS1* locus.

~~115. The composition of claim 113 or 114, wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site.~~

~~116. The composition of claim 115, wherein the integration of the nucleic acid construct into the endogenous *RS1* locus in the cell reduces or eliminates expression of the endogenous retinoschisin protein and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct.~~

~~117~~14. The composition for use of any one of claims ~~108-116~~1-13, wherein the nucleic acid construct is in a viral vector, optionally ~~.~~

~~118. The composition of claim 117,~~ wherein the viral vector is an adeno-associated virus (AAV) viral vector, and optionally ~~.~~

~~119. The vector of claim 118,~~ wherein the AAV is selected from the group consisting of: AAV2, AAV5, AAV8, or AAV7m8.

~~120~~15. The composition for use of any one of claims ~~108-119~~1-14, wherein the nuclease agent is a Cas protein and a guide RNA, and the nuclease target sequence is a guide RNA target sequence.

16. The composition for use of claim 15, wherein the Cas protein is a Cas9 protein.

17. The composition for use of claim 15 or 16, wherein:

(I) the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid comprises a DNA encoding the Cas protein, and wherein the composition comprises the DNA encoding the guide RNA, and optionally wherein the DNA encoding the Cas protein and the DNA encoding the guide RNA are in one or more viral vectors; or

(II) the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid comprises a messenger RNA encoding the Cas protein, wherein the composition comprises the guide RNA in the form of RNA, and optionally wherein the

composition comprises the guide RNA in the form of RNA, and wherein the guide RNA and the messenger RNA encoding the Cas protein are in a lipid nanoparticle.

18. The composition for use of any one of claims 1-17, wherein the endogenous *RS1* locus comprises a mutated *RS1* gene comprising a mutation that causes X-linked juvenile retinoschisis.

19. The composition for use of any one of claims 1-18, wherein the cell is a human cell, optionally wherein the cell is a retinal cell.

20. The composition for use of any one of claims 1-19, wherein the cell is *in vivo* in an animal.

21. The composition for use of claim 20, wherein integration of the nucleic acid construct results in retinal structural restoration.

~~121. A composition comprising a guide RNA or a DNA encoding the guide RNA, wherein the guide RNA comprises a DNA-targeting segment that targets a guide RNA target sequence in an *RS1* gene, and wherein the guide RNA binds to a Cas protein and targets the Cas protein to the guide RNA target sequence in the *RS1* gene.~~

~~122. The composition of claim 121, wherein the composition further comprises the Cas protein or a nucleic acid encoding the Cas protein.~~

~~123. The composition of claim 120 or 122, wherein the Cas protein is a Cas9 protein.~~

~~124. The composition of claim 123, wherein the Cas protein is derived from a *Streptococcus pyogenes* Cas9 protein.~~

~~125. The composition of any one of claims 120 and 122-124, wherein the composition comprises the Cas protein in the form of a protein.~~

~~126. The composition of any one of claims 120 and 122-124, wherein the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid~~

~~comprises a DNA encoding the Cas protein, optionally wherein the composition comprises the DNA encoding the guide RNA.~~

~~127. The composition of claim 126, wherein the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid comprises a DNA encoding the Cas protein, wherein the composition comprises the DNA encoding the guide RNA, and wherein the DNA encoding the Cas protein and the DNA encoding the guide RNA are in one or more viral vectors.~~

~~128. The composition of claim 127, wherein the one or more viral vectors are adeno-associated virus (AAV) viral vectors.~~

~~129. The composition of claim 128, wherein the AAV is selected from the group consisting of: AAV2, AAV5, AAV8, or AAV7m8.~~

~~130. The composition of any one of claims 120 and 122-124, wherein the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid comprises a messenger RNA encoding the Cas protein, optionally wherein the composition comprises the guide RNA in the form of RNA.~~

~~131. The composition of any one of claims 120 and 122-124, wherein the composition comprises the nucleic acid encoding the Cas protein, wherein the nucleic acid comprises a messenger RNA encoding the Cas protein, wherein the composition comprises the guide RNA in the form of RNA, and wherein the guide RNA and the messenger RNA encoding the Cas protein are in a lipid nanoparticle.~~

~~132. The composition of claim 131, wherein the messenger RNA encoding the Cas protein comprises at least one modification.~~

~~133. The composition of claim 132, wherein the messenger RNA encoding the Cas protein is modified to comprise a modified uridine at one or more or all uridine positions.~~

~~134. The composition of claim 133, wherein the modified uridine is pseudouridine.~~

135. The composition of claim 133 or 134, wherein the messenger RNA encoding the Cas protein is fully substituted with pseudouridine.

136. The composition of any one of claims 132-135, wherein the messenger RNA encoding the Cas protein comprises a 5' cap.

137. The composition of any one of claims 132-136, wherein the messenger RNA encoding the Cas protein comprises a poly(A) tail.

138. The composition of any one of claims 130-137, wherein the messenger RNA encoding the Cas protein comprises the sequence set forth in SEQ ID NO: 6243 or 6245.

139. The composition of any one of claims 120 and 122-138, wherein the nucleic acid encoding the Cas protein is codon-optimized for expression in a mammalian cell or a human cell.

140. The composition of any one of claims 120 and 122-139, wherein the Cas protein comprises the sequence set forth in SEQ ID NO: 27, 6242, or 6246.

141. The composition of any one of claims 120-140, wherein the guide RNA target sequence is in an intron of the *RS1* gene.

142. The composition of claim 141, wherein the intron is the first intron of the *RS1* gene.

143. The composition of any one of claims 120-142, wherein the *RS1* gene is a human *RS1* gene.

144. The composition of any one of claims 120-143, wherein the DNA-targeting segment comprises:

(a) at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 3148-6241;

(b) at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 3148-4989;

(c) at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 3148-3151, 3154-3186, 3188-3247, and 3249-4351;

(d) at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304; or

(e) at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 4990-6241.

145. The composition of any one of claims 120-144, wherein the DNA-targeting segment is:

(a) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 3148-6241;

(b) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 3148-4989;

(c) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 3148-3151, 3154-3186, 3188-3247, and 3249-4351;

(d) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304; or

(e) at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 4990-6241.

146. The composition of any one of claims 120-145, wherein the DNA-targeting segment comprises, consists essentially of, or consists of the sequence set forth in:

(a) any one of SEQ ID NOS: 3148-6241;

(b) any one of SEQ ID NOS: 3148-4989;

(c) any one of SEQ ID NOS: 3148-3151, 3154-3186, 3188-3247, and 3249-4351;

(d) any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304; or

(e) any one of SEQ ID NOS: 4990-6241.

147. The composition of any one of claims 120-146, wherein the DNA-targeting segment comprises at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides of the sequence set forth in any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304.

148. The composition of any one of claims 120-147, wherein the DNA-targeting segment is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence set forth in any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304.

149. The composition of any one of claims 120-148, wherein the DNA-targeting segment comprises, consists essentially of, or consist of the sequence set forth in any one of SEQ ID NOS: 3150, 3151, 3159, 3675, 4297, and 4304.

150. The composition of any one of claims 120-149, wherein the composition comprises the guide RNA in the form of RNA.

151. The composition of any one of claims 120-149, wherein the composition comprises the DNA encoding the guide RNA.

152. The composition of any one of claims 120-150, wherein the guide RNA comprises at least one modification.

153. The composition of claim 152, wherein the at least one modification comprises a 2'-O-methyl-modified nucleotide.

154. The composition of claim 152 or 153, wherein the at least one modification comprise a phosphorothioate bond between nucleotides.

155. The composition of any one of claims 152-154, wherein the at least one modification comprise a modification at one or more of the first five nucleotides at the 5' end of the guide RNA.

156. The composition of any one of claims 152-155, wherein the at least one modification comprises a modification at one or more of the last five nucleotides at the 3’ end of the guide RNA.

157. The composition of any one of claims 152-156, wherein the at least one modification comprises phosphorothioate bonds between the first four nucleotides at the 5’ end of the guide RNA.

158. The composition of any one of claims 152-157, wherein the at least one modification comprises phosphorothioate bonds between the last four nucleotides at the 3’ end of the guide RNA.

159. The composition of any one of claims 152-158, wherein the at least one modification comprises 2’-O-methyl-modified nucleotides at the first three nucleotides at the 5’ end of the guide RNA.

160. The composition of any one of claims 152-159, wherein the at least one modification comprises 2’-O-methyl-modified nucleotides at the last three nucleotides at the 3’ end of the guide RNA.

161. The composition of any one of claims 152-160, wherein the at least one modification comprises: (i) phosphorothioate bonds between the first four nucleotides at the 5’ end of the guide RNA; (ii) phosphorothioate bonds between the last four nucleotides at the 3’ end of the guide RNA; (iii) 2’-O-methyl-modified nucleotides at the first three nucleotides at the 5’ end of the guide RNA; and (iv) 2’-O-methyl-modified nucleotides at the last three nucleotides at the 3’ end of the guide RNA.

162. The composition of any one of claims 152-161, wherein the guide RNA comprises the modified nucleotides of SEQ ID NO: 44.

163. The composition of any one of claims 120-162, wherein the guide RNA is a single guide RNA (sgRNA).

~~164. The composition of claim 163, wherein the guide RNA comprises, consists essentially of, or consists of the sequence set forth in any one of SEQ ID NOS: 33-39 and 53.~~

~~165. The composition of any one of claims 120-161, wherein the guide RNA is a dual guide RNA (dgRNA) comprising two separate RNA molecules comprising a CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA).~~

~~166. The composition of claim 165, wherein the crRNA comprises the sequence set forth in any one of SEQ ID NOS: 29 and 52.~~

~~167. The composition of claim 165 or 166, wherein the tracrRNA comprises the sequence set forth in any one of SEQ ID NOS: 30-32.~~

~~168. The composition of any one of claims 120-167, wherein the composition is associated with a lipid nanoparticle, optionally wherein the composition comprises the guide RNA.~~

~~169. The composition of any one of claims 120-167, wherein the DNA encoding the guide RNA is in a viral vector.~~

~~170. The composition of claim 169, wherein the viral vector is an adeno-associated virus (AAV) viral vector.~~

~~171. The vector of claim 170, wherein the AAV is selected from the group consisting of: AAV2, AAV5, AAV8, or AAV7m8.~~

~~172. The composition of any one of claims 120-171, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable carrier.~~

~~173. The composition of any one of claims 120-172, further comprising a second guide RNA or a DNA encoding the second guide RNA, wherein the second guide RNA comprises a DNA-targeting segment that targets a second guide RNA target sequence in the *RS1* gene, and wherein the second guide RNA binds to the Cas protein and targets the Cas protein to the second guide RNA target sequence in the *RS1* gene.~~

~~174. A cell comprising the composition of any one of claims 108-173.~~

~~175. A cell comprising the composition of any one of claims 108-120 and 123-173.~~

~~176. The cell of claim 175, wherein the cell is *in vitro*.~~

~~177. The cell of claim 175, wherein the cell is *in vivo*.~~

~~178. The cell of any one of claims 175-177, wherein the cell is a mammalian cell.~~

~~179. The cell of claim 178, wherein the cell is a human cell.~~

~~180. The cell of any one of claims 175-179, wherein the cell is a retinal cell.~~

~~181. The cell of any one of claims 175-180, wherein the cell expresses the first retinoschisin protein or fragment thereof or the second retinoschisin protein or fragment thereof.~~

~~182. The cell of any one of claims 175-181, wherein the nucleic acid construct is genomically integrated at the target genomic locus.~~

~~183. The cell of claim 182, wherein the target genomic locus is an endogenous *RS1* locus.~~

~~184. The cell of claim 182, wherein the nucleic acid construct is genomically integrated in intron 1 of the endogenous *RS1* locus.~~

~~185. The cell of claim 184, wherein endogenous *RS1* exon 1 splices into the first coding sequence or the second coding sequence of the nucleic acid construct.~~

~~186. The cell of claim 185, wherein the modified *RS1* locus comprising the genomically integrated nucleic acid construct encodes a protein comprising, consisting essentially of, or consisting of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 2 or 4.~~

~~187. The cell of any one of claims 183-186, wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site.~~

~~188. The cell of claim 187, wherein the integration of the nucleic acid construct into the endogenous *RS1* locus reduces or eliminates expression of the endogenous retinoschisin protein and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct.~~

~~189. The cell of any claim 187 or 188, wherein the endogenous *RS1* locus comprises a mutated *RS1* gene comprising a mutation that causes X-linked juvenile retinoschisis, and expression of the genomically integrated nucleic acid construct reduces or eliminates expression of the mutated *RS1* gene.~~

~~190. A method of integrating a coding sequence for a retinoschisin protein or fragment thereof into a target genomic locus and expressing the retinoschisin protein or fragment thereof in a cell, comprising administering the composition of any one of claims 108-120 and 123-173 to the cell, wherein the coding sequence is integrated into the target genomic locus and the retinoschisin protein or fragment thereof is expressed in the cell.~~

~~191. The method of claim 190, wherein the cell is a mammalian cell.~~

~~192. The method of claim 191, wherein the cell is a human cell.~~

~~193. The method of any one of claims 190-192, wherein the cell is a retinal cell.~~

~~194. The method of any one of claims 190-193, wherein the cell is *in vitro*.~~

~~195. The method of any one of claims 190-193, wherein the cell is *in vivo*.~~

~~196. The method of claim 195, wherein the cell is a retinal cell, and the administering comprises subretinal injection or intravitreal injection.~~

~~197. A method of treating a subject with X-linked juvenile retinoschisis, comprising administering the composition of any one of claims 108-120 and 123-173 to the subject, wherein the nucleic acid construct is integrated into and expressed from the target genomic locus in one or more retinal cells of the subject, and wherein a therapeutically effective level of retinoschisin expression is achieved in the subject.~~

~~198. The method of claim 197, wherein the subject is a human.~~

~~199. The method of claim 197 or 198, wherein the subject has an endogenous *RS1* gene comprising at least one mutation associated with or that causes X-linked juvenile retinoschisis.~~

~~200. The method of claim 199, wherein the mutation is a R141C mutation.~~

~~201. The method of any one of claims 197-200, wherein the administering comprises subretinal injection or intravitreal injection.~~

~~202. The method of any one of claims 197-201, wherein integration of the nucleic acid construct results in retinal structural restoration.~~

~~203. The method of any one of claims 190-202, wherein the nucleic acid construct and the nuclease agent or the nucleic acid encoding the nuclease agent are administered in different delivery vehicles.~~

~~204. The method of any one of claims 190-202, wherein the nucleic acid construct and the nuclease agent or the nucleic acid encoding the nuclease agent are administered in the same delivery vehicle.~~

~~205. The method of any one of claims 190-204, wherein the nucleic acid construct and the nuclease agent or the nucleic acid encoding the nuclease agent are administered simultaneously.~~

~~206. The method of any one of claims 190-203, wherein the nucleic acid construct and the nuclease agent or the nucleic acid encoding the nuclease agent are administered sequentially in any order.~~

~~207. The method of claim 206, wherein the nucleic acid construct is administered prior to the nuclease agent or the nucleic acid encoding the nuclease agent.~~

~~208. The method of claim 206, wherein the nucleic acid construct is administered subsequent to the nuclease agent or the nucleic acid encoding the nuclease agent.~~

~~209. The method of claim 207 or 208, wherein the time between the sequential administration is about 2 hours to about 48 hours.~~

~~210. The method of any one of claims 190-209, wherein the target genomic locus is in an endogenous *RS1* gene.~~

~~211. The method of claim 210, wherein the nuclease target sequence in the target genomic locus is in the first intron in the endogenous *RS1* gene.~~

~~212. The method of claim 211, wherein the nucleic acid construct is genomically integrated in intron 1 of the endogenous *RS1* locus, and wherein endogenous *RS1* exon 1 splices into the coding sequence for the retinoschisin protein or fragment thereof in the nucleic acid construct.~~

~~213. The method of claim 212, wherein the modified *RS1* locus comprising the genomically integrated nucleic acid construct encodes a protein comprising, consisting essentially of, or consisting of a sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to SEQ ID NO: 2 or 4.~~

~~214. The method of any one of claims 210-213, wherein integration of the nucleic acid construct into the endogenous *RS1* locus prevents transcription of the endogenous *RS1* gene downstream of the integration site.~~

~~215. The method of claim 214, wherein the integration of the nucleic acid construct into the endogenous *RS1* locus reduces or eliminates expression of the endogenous retinoschisin protein from the endogenous *RS1* locus and replaces it with expression of the retinoschisin protein or fragment thereof encoded by the nucleic acid construct.~~

~~216. A method of modifying an *RS1* gene in a cell, comprising administering the composition of any one of claims 122-173 to the cell, wherein the guide RNA binds to the Cas protein and targets the Cas protein to the guide RNA target sequence in the *RS1* gene, and the Cas protein cleaves the guide RNA target sequence.~~

~~217. The method of claim 216, wherein the cell is a mammalian cell.~~

~~218. The method of claim 217, wherein the cell is a human cell.~~

~~219. The method of any one of claims 216-218, wherein the cell is a retinal cell.~~

~~220. The method of any one of claims 216-219, wherein the cell is *in vitro*.~~

~~221. The method of any one of claims 216-219, wherein the cell is *in vivo*.~~

~~222. The method of claim 221, wherein the cell is a retinal cell, and the administering comprises subretinal injection or intravitreal injection.~~

~~223. The method of any one of claims 216-222, wherein the guide RNA target sequence is in the first intron in the *RS1* gene.~~