

Claims

We claim:

1. A polynucleotide comprising a microRNA sponge cassette, wherein the microRNA sponge cassette comprises one or more nucleotide sequences that target one or more miRNA of interest.
2. The polynucleotide of claim 1, wherein one or more nucleotide sequences that target the microRNA of interest is a tandem multiplexes of perfectly or imperfectly complementary sequences to the microRNA of interest.
3. The polynucleotide of claim 1, wherein one or more nucleotide sequences that target the microRNA of interest is at least at least 85% complementary to the mature microRNA of interest sequence, at least 90% complementary to the mature microRNA of interest sequence, at least 95% complementary to the mature microRNA of interest sequence, at least 96% complementary to the mature microRNA of interest sequence, at least 97% complementary to the mature microRNA of interest sequence, at least 98% complementary to the mature microRNA of interest sequence or at least 99% complementary to the mature microRNA of interest sequence.
4. The polynucleotide of any one of claims 1-3, wherein the microRNA sponge cassette comprises at least 2 or more nucleotide sequences that target one or more miRNA of interest, at least 3 or more nucleotide sequences that target one or more miRNA of interest, at least 4 or more nucleotide sequences that target one or more miRNA of interest or at least 2 or more nucleotide sequences that target one or more miRNA of interest.
5. The polynucleotide of any one of claims 1-4, wherein the microRNA sponge cassette comprises 2, 4, 6, or 8 repeats of a nucleotide sequences that target the microRNA of interest.
6. The polynucleotide of any one of claims 1-5, wherein the microRNA sponge cassette comprises one or more nucleotide sequences that target miR106a.
7. The polynucleotide of any one of claims 1-6, wherein the nucleotide sequence that targets miRNA of interest comprises the nucleotide sequence of SEQ ID NO: 1 or 2.

8. The polynucleotide of any one of claims 1-7, wherein the microRNA sponge cassette comprises the nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8.
9. A recombinant AAV (rAAV) having a genome comprising the polynucleotide sequence of any one of claims 1-11.
10. The rAAV of claim 9, wherein the genome comprises the U6 or H1 promoter.
11. The rAAV of claim 9 or 10, wherein the genome further comprises a stuffer sequence.
12. The rAAV of claim 11, wherein the stuffer sequence comprises the nucleotide sequence of SEQ ID NO: 11.
13. The rAAV of anyone of claims 9-12, wherein the genome comprises nucleotides 980 to 3131 of the nucleotide sequences of SEQ ID NO: 21.
14. The rAAV of anyone of claims 9-13, wherein the vector is a serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVRH10, AAVRH74, AAV11, AAV12, AAV13, Anc80, or AAV7m8 or their derivatives.
15. A rAAV particle comprising the rAAV of any one of claims 9-14.
16. A composition comprising a polynucleotide of any one of claims 1-8, a rAAV of any one of claims 9-14, or a rAAV particle of claim 15.
17. A method of treating Rett syndrome comprising administering a therapeutically effective amount of the rAAV of any one of claims 9-14, a rAAV particle of claim 15, or the composition of claim 16.
18. A method of activating expression of a X-linked gene comprising administering a therapeutically effective amount of the a rAAV of any one of claims 9-14, a rAAV particle of claim 15, or the composition of claim 16.
19. The method of claim 18, wherein the X-linked gene is Methyl CpG binding protein 2 (*MECP2*).

20. A method of treating a X-linked disorder comprising administering a therapeutically effective amount of the rAAV of any one of claims 9-14, a rAAV particle of claim 15, or the composition of claim 16.
21. The method of claim 20, wherein the X-linked disorder is rett syndrome, hemophilia A, hemophilia B, Dent's disease 1, Dent's disease 2, DDX3X syndrome, Albinism-deafness syndrome, Aldrich syndrome, Alport syndrome, Anaemia (hereditary hypochromic), Anemia, (sideroblastic with ataxia), Cataract, Charcot-Marie-Tooth, Color blindness, Diabetes (insipidus, nephrogenic), Dyskeratosis congenita, Ectodermal dysplasia, Faciogenital dysplasia, Fabry disease, Glucose-6-phosphate dehydrogenase deficiency, Glycogen storage disease type VIII, Gonadal dysgenesis, Testicular feminization syndrome, Addison's disease with cerebral sclerosis, Adrenal hypoplasia, Granulomatous disease, siderius X-linked mental retardation syndrome, Agammaglobulinaemia Bruton type, Choroidoretinal degeneration, Choroidaemia, Albinism (ocular), fragile X syndrome, Epileptic encephalopathy (early infantile 2), Hydrocephalus (aqueduct stenosis), Hypophosphataemic rickets, Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency), incontinentia pigmenti, Kallmann syndrome, paroxysmal nocturnal hemoglobinuria, Spinal muscular atrophy 2, Spastic paraplegia, Keratosis follicularis spinulosa, Lowe (oculocerebrorenal) syndrome, Menkes syndrome, Renpenning Syndrome, Mental retardation, Coffin-Lowry syndrome, Microphthalmia (Lenz syndrome), Muscular dystrophy (Becker, Duchenne and Emery—Dreifuss types), Myotubular myopathy, Night blindness, Norrie's disease (pseudoglioma), Nystagmus, Orofaciodigital syndrome, Ornithine transcarbamylase deficiency (type I hyperammonaemia), Phosphoglycerate kinase deficiency, Phosphoribosylpyrophosphate synthetase deficiency, Retinitis pigmentosa, Retinoschisis, Muscular atrophy/Dihydrotestosterone receptor deficiency, Spinal muscular atrophy, Spondyloepiphyseal dysplasia tarda, Thrombocytopenia, Thyroxine-binding globulin, McLeod syndrome.
22. Use of a therapeutically effective amount of the a rAAV of any one of claims 9-14, an rAAV particle of claim 15, or the composition of claim 16, for the preparation of a medicament for treating Rett Syndrome.
23. Use of a therapeutically effective amount of the a rAAV of any one of claims 9-14, an rAAV particle of claim 15, or the composition of claim 16, for the preparation of a medicament for activating expression of a X-linked gene.

24. The use of claim 23, wherein the X-linked gene is Methyl CpG binding protein 2 (*MECP2*).
25. Use of a therapeutically effective amount of the a rAAV of any one of claims 9-14, an rAAV particle of claim 15, or the composition of claim 16, for the preparation of a medicament for the treatment of a X-linked disorder.
26. The use of claim 25, wherein the X-linked disorder is rett syndrome, hemophilia A, hemophilia B, Dent's disease 1, Dent's disease 2, DDX3X syndrome, Albinism-deafness syndrome, Aldrich syndrome, Alport syndrome, Anaemia (hereditary hypochromic), Anemia, (sideroblastic with ataxia), Cataract, Charcot-Marie-Tooth, Color blindness, Diabetes (insipidus, nephrogenic), Dyskeratosis congenita, Ectodermal dysplasia, Faciogenital dysplasia, Fabry disease, Glucose-6-phosphate dehydrogenase deficiency, Glycogen storage disease type VIII, Gonadal dysgenesis, Testicular feminization syndrome, Addison's disease with cerebral sclerosis, Adrenal hypoplasia, Granulomatous disease, siderius X-linked mental retardation syndrome, Agammaglobulinaemia Bruton type, Choroidoretinal degeneration, Choroidaemia, Albinism (ocular), fragile X syndrome, Epileptic encephalopathy (early infantile 2), Hydrocephalus (aqueduct stenosis), Hypophosphataemic rickets, Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency), incontinentia pigmenti, Kallmann syndrome, paroxysmal nocturnal hemoglobinuria, Spinal muscular atrophy 2, Spastic paraplegia, Keratosis follicularis spinulosa, Lowe (oculocerebrorenal) syndrome, Menkes syndrome, Renpenning Syndrome, Mental retardation, Coffin-Lowry syndrome, Microphthalmia (Lenz syndrome), Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types), Myotubular myopathy, Night blindness, Norrie's disease (pseudoglioma), Nystagmus, Orofaciodigital syndrome, Ornithine transcarbamylase deficiency (type I hyperammonaemia), Phosphoglycerate kinase deficiency, Phosphoribosylpyrophosphate synthetase deficiency, Retinitis pigmentosa, Retinoschisis, Muscular atrophy/Dihydrotestosterone receptor deficiency, Spinal muscular atrophy, Spondyloepiphyseal dysplasia tarda, Thrombocytopenia, Thyroxine-binding globulin, McLeod syndrome.
27. A composition comprising a therapeutically effective amount of the rAAV of any one of claims 9-14, the rAAV particle of claim 15, or the composition of claim 16 for treating Rett Syndrome.

28. A composition comprising a therapeutically effective amount of the rAAV of any one of claims 9-14, the rAAV particle of claim 15, or the composition of claim 16 for activating expression of a X-linked gene.

29. The composition of claim 28, wherein the X-linked gene is Methyl CpG binding protein 2 (*MECP2*).

30. A composition comprising a therapeutically effective amount of the rAAV of any one of claims 9-14, the rAAV particle of claim 15, or the composition of claim 16 for treating a X-linked disorder.

31. The composition of claim 30, wherein the X-linked disorder is rett syndrome, hemophilia A, hemophilia B, Dent's disease 1, Dent's disease 2, DDX3X syndrome, Albinism-deafness syndrome, Aldrich syndrome, Alport syndrome, Anaemia (hereditary hypochromic), Anemia, (sideroblastic with ataxia), Cataract, Charcot-Marie-Tooth, Color blindness, Diabetes (insipidus, nephrogenic), Dyskeratosis congenita, Ectodermal dysplasia, Faciogenital dysplasia, Fabry disease, Glucose-6-phosphate dehydrogenase deficiency, Glycogen storage disease type VIII, Gonadal dysgenesis, Testicular feminization syndrome, Addison's disease with cerebral sclerosis, Adrenal hypoplasia, Granulomatous disease, siderius X-linked mental retardation syndrome, Agammaglobulinaemia Bruton type, Choroidoretinal degeneration, Choroidaemia, Albinism (ocular), fragile X syndrome, Epileptic encephalopathy (early infantile 2), Hydrocephalus (aqueduct stenosis), Hypophosphataemic rickets, Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency), incontinentia pigmenti, Kallmann syndrome, paroxysmal nocturnal hemoglobinuria, Spinal muscular atrophy 2, Spastic paraplegia, Keratosis follicularis spinulosa, Lowe (oculocerebrorenal) syndrome, Menkes syndrome, Renpenning Syndrome, Mental retardation, Coffin-Lowry syndrome, Microphthalmia (Lenz syndrome), Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types), Myotubular myopathy, Night blindness, Norrie's disease (pseudoglioma), Nystagmus, Orofaciodigital syndrome, Ornithine transcarbamylase deficiency (type I hyperammonaemia), Phosphoglycerate kinase deficiency, Phosphoribosylpyrophosphate synthetase deficiency, Retinitis pigmentosa, Retinoschisis, Muscular atrophy/Dihydrotestosterone receptor deficiency, Spinal muscular atrophy, Spondyloepiphyseal dysplasia tarda, Thrombocytopenia, Thyroxine-binding globulin, McLeod syndrome.