METHODS AND COMPOSITIONS FOR MODULATING SPLICING AND TRANSLATION

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/838,010, filed April 24, 2019, which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 22, 2020, is named 47991-725_601_SL.txt and is 4,882,023 bytes in size.

BACKGROUND

[0003] Alternative splicing events in genes can lead to non-productive or less productive mRNA transcripts. Therapeutic agents that can target the alternative splicing events in genes can modulate the expression level of functional proteins in patients and/or inhibit aberrant protein expression. Such therapeutic agents can be used to treat a condition or disease caused by protein deficiency.

SUMMARY

[0003a] In one aspect, provided herein is a pharmaceutical composition comprising a therapeutic agent or a vector encoding the therapeutic agent, and a pharmaceutically acceptable excipient, wherein the therapeutic agent is configured to bind to a targeted portion of a pre-mRNA in a cell, wherein the pre-mRNA encodes a target peptide sequence and comprises an inefficient translation region, whereby splicing of the inefficient translation region from the pre-mRNA encoding the target peptide sequence is modulated, thereby modulating a level of a first processed mRNA that is devoid of the inefficient translation region and encodes a first protein comprising the target peptide sequence, and thereby modulating the expression of the target peptide sequence in the cell, wherein the first processed mRNA has a higher translation efficiency for producing the first protein comprising the target peptide sequence in the cell as compared to translation efficiency of a second processed mRNA for producing a second protein comprising the target peptide sequence, and wherein the second processed mRNA comprises the inefficient translation region.

[0003b] In one aspect, provided herein is the pharmaceutical composition as described herein for use in the treatment of a disease or condition in a subject in need thereof.

[0003c] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in manufacturing a medicament for the treatment of a disease or condition in a subject in need thereof, wherein the disease or the condition is selected from the group consisting of: Intellectual Disability; Colorectal Cancer; Bleeding Disorder, Platelet-Type, 15; Autosomal dominant macrothrombocytopenia; Hypertrophic Cardiomyopathy; Cardiomyopathy, Dilated, 1AA; cardiomyopathy, familial hypertrophic, 23, with or without ventricular noncompaction; Familial dilated cardiomyopathy; Charcot-Marie-Tooth Disease; Conduction disorder of the heart; Cardiomyopathy, Dilated; Alcohol Use Disorder; Alcohol abuse; Alcoholic Intoxication, Chronic; Alcohol Use Disorder; Alcohol abuse; Alcoholic Intoxication, Chronic; Schizophrenia; Bipolar Disorder; Alcoholic Intoxication, Chronic; Congenital Disorders of Glycosylation; Epileptic encephalopathy; Depressive disorder; Congenital disorder of glycosylation type 1H; pontocerebellar hypoplasia, type 9; epileptic encephalopathy; ataxias, hereditary; spastic paraplegia 63, autosomal recessive; Cerebellar Hypoplasia; Spastic Paraplegia, Hereditary; Nonketotic Hyperglycinemia; Hyperglycinemia, Transient Neonatal; Glycine encephalopathy; KBG syndrome; 16q24.3 microdeletion syndrome; Situs Inversus; Malignant neoplasm of breast; Maturity onset diabetes mellitus in young; Maturity-Onset Diabetes Of The Young, Type 14; Microcephaly; Polydactyly; Ciliopathies; Mental Depression; Seasonal Affective Disorder; Bipolar Disorder; Mood Disorders; Depressive disorder; Malignant neoplasm of breast; Cytopenia; Gastrointestinal Neoplasms; Depressive disorder; Prostate cancer, familial; Primary peritoneal carcinoma; ovarian cancer, familial, susceptibility to, 1; Breast Cancer, Familial Male; Malignant Neoplasms; Pancreatic Neoplasm; Breast Cancer, Familial; Neoplasm of uncertain or unknown behavior of breast; Ovarian Carcinoma; Adenocarcinoma of prostate; Neoplasm of uncertain or unknown behavior of ovary; Malignant neoplasm of pancreas; Pancreatic carcinoma; Malignant neoplasm of ovary; Congenital anemia; Hematologic Neoplasms; Breast adenocarcinoma; breast-ovarian cancer, familial, susceptibility to, 1; Pancreatic carcinoma, familial; Benign tumor of pancreas; Breast Carcinoma; breast cancer, familial, susceptibility to, 1; ovarian neoplasm; Hereditary Breast and Ovarian Cancer Syndrome; Mental Depression; Epithelial ovarian cancer; Malignant neoplasm of breast; Sporadic Breast Carcinoma; Breast-ovarian cancer, familial, 1; Pancreatic cancer, susceptibility to, 4; C8 deficiency, type II; ventricular tachycardia, catecholaminergic polymorphic, 4; ventricular tachycardia, catecholaminergic polymorphic, 1; Long QT Syndrome; Romano-Ward Syndrome; Long Qt Syndrome 14; peeling skin syndrome; peeling skin with leukonychia, acral punctate keratoses,

cheilitis, and knuckle pads; erythrokeratoderma; palmoplantar keratosis; morbid obesity and spermatogenic failure; warburton anyane yeboa syndrome; mosaic variegated aneuploidy syndrome; Breast Cancer, Familial; Malignant neoplasm of ovary; Mitochondrial Diseases; Severe combined immunodeficiency with sensitivity to ionizing radiation; severe combined immunodeficiency, partial; Reticuloendotheliosis, familial, with eosinophilia; Omenn Syndrome; Athabaskan severe combined immunodeficiency; Severe Combined Immunodeficiency, Athabaskan-Type; Cocaine Abuse; Congenital anemia; Cytopenia; Neurodegeneration Due To Cerebral Folate Transport Deficiency; Megaloblastic Anemia due to Dihydrofolate Reductase Deficiency; Alcoholic Intoxication, Chronic; Bipolar Disorder; Unipolar Depression; Major Depressive Disorder; Schizophrenia and related disorders; Left ventricular noncompaction cardiomyopathy; Left ventricular noncompaction; Familial Meniere's disease; Charcot-Marie-Tooth Disease; noncompaction of left ventricular myocardium, familial isolated, autosomal dominant 1; Primary microcephaly; Microcephaly; Epileptic encephalopathy; Mental retardation, autosomal dominant 7; Colorectal Cancer; Depressive disorder; Mental Depression; Caudal Regression Syndrome; Arnold Chiari Malformation; Caudal dysplasia syndrome; Chiari malformation type II; Sacral Agenesis Syndrome; Sacral agenesis; Currarino triad; Spina bifida aperta of cervical spine; Neural tube defects; Polycystic Kidney, Autosomal Dominant; polycystic kidney disease 3, autosomal dominant; alcoholic intoxication, chronic; malignant neoplasm of breast; ataxias, hereditary; epilepsy, progressive myoclonic, 6; Epileptic encephalopathy; Lattice corneal dystrophy Type II; Meretoja syndrome; Malignant neoplasm of breast; Periodic Fever Syndrome; Familial Amyloid Polyneuropathy, Type IV; Cerebral Amyloid Angiopathy, Gsn-Related; Abnormality of the cornea; Amyloidosis, Finnish type; Primary microcephaly; cornelia de lange syndrome 5; radial club hand; cornelia de lange syndrome; wilson-turner x-linked mental retardation syndrome; congenital anemia; retinitis pigmentosa 79; charcot-marie-tooth disease; cytopenia; hemolytic anemia, nonspherocytic, due to hexokinase deficiency; neuropathy, hereditary motor and sensory, russe type; interferon gamma, receptor 1, deficiency; immunodeficiency 27a; immunodeficiency 27b; H. pylori infection, susceptibility to; Tuberculosis infection, protection against; Immunodeficiency 27A, mycobacteriosis, AR; Immunodeficiency 27B, mycobacteriosis, AD; Hepatitis B virus infection, susceptibility to; Tuberculosis, susceptibility to; Malignant neoplasm of breast; Lymphoma, Non-Hodgkin; immunodeficiency 15; Congenital myopathy; Arthrogryposis; Rhabdomyolysis; myopathy with exercise intolerance, Swedish type; Myopathy with lactic acidosis, hereditary; Charcot-Marie-Tooth disease, recessive intermediate B; Charcot-Marie-Tooth Disease; Deafness, Autosomal Recessive 89; Deafness, autosomal recessive 89; Dyslexia, susceptibility

to, 2; Joubert Syndrome 23; Polydactyly; Familial aplasia of the vermis; Joubert syndrome with Jeune asphyxiating thoracic dystrophy; Hydrocephalus; Ciliopathies; Short-rib thoracic dysplasia 14 with polydactyly; Retinitis Pigmentosa; Retinitis pigmentosa 69; Muscular Dystrophy, Limb-Girdle, Type 1B; Hypertrophic Cardiomyopathy; Left ventricular noncompaction; Osteogenesis Imperfecta; Charcot-Marie-Tooth Disease; Cardiomyopathy, Familial Idiopathic; Familial Partial Lipodystrophy, Type 1; Left ventricular noncompaction cardiomyopathy; Mandibuloacral dysostosis; Muscular Dystrophy, Congenital, Lmna-Related; Congenital myopathy; Arthrogryposis; Arrhythmogenic Right Ventricular Dysplasia; Muscular Dystrophies, Limb-Girdle; Malouf syndrome; Najjar syndrome; Charcot-Marie-Tooth disease, Type 2B1; Emery-Dreifuss Muscular Dystrophy 3; Lethal tight skin contracture syndrome; Familial Partial Lipodystrophy, Type 2; Conduction disorder of the heart; Cardiomyopathy, Dilated; Progeria Syndrome, Childhood-Onset; Atypical Werner syndrome; Congenital muscular dystrophy; Autosomal Recessive Emery-Dreifuss Muscular Dystrophy; Heart-hand syndrome, Slovenian type; Progeria; Autosomal Dominant Emery-Dreifuss Muscular Dystrophy; Cardiomyopathy, dilated, 1A; Mandibuloacral dysplasia; Muscular dystrophy, limb-girdle, type 1B; Emery-Dreifuss muscular dystrophy 2, AD; Malouf syndrome; Restrictive dermopathy, lethal; Emery-Dreifuss muscular dystrophy 3, AR; Heart-hand syndrome, Slovenian type; Charcot-Marie-Tooth disease, type 2B1; Hutchinson-Gilford progeria; Lipodystrophy, familial partial, type 2; Muscular dystrophy, congenital; Malignant neoplasm of breast; Deafness, Autosomal Recessive 63; Bardet-Biedl Syndrome; Polydactyly; Ciliopathies; Bardet-Biedl Syndrome 17; Major Affective Disorder 2; Bipolar Disorder; Epileptic encephalopathy; Rett Syndrome, Preserved Speech Variant; Lubs X-linked mental retardation syndrome; Encephalopathy, Neonatal Severe, Due To Mecp2 Mutations; Mental Retardation with Psychosis, Pyramidal Signs, and Macroorchidism; Mental Retardation, X-Linked, With Spasticity; Trisomy Xq28; Mental Retardation, X-Linked 16; Epileptic encephalopathy; Mental Retardation, X-Linked, Syndromic 13; Mental Retardation, X-Linked 1; Rett Syndrome, Atypical; Mental Retardation, X-Linked 79; Microcephaly; Ppm-X Syndrome; Rett Syndrome, Zappella Variant; Rett Syndrome; Autism susceptibility, X-linked 3; Benign neoplasm of adrenal gland; Retinitis Pigmentosa; Conventional (Clear Cell) Renal Cell Carcinoma; Squamous cell carcinoma of the head and neck; Malignant neoplasm of aortic body and other paraganglia; Retinitis Pigmentosa 38; Malignant Adrenal Medulla Neoplasm; Benign neoplasm of aortic body and other paraganglia; Primary microcephaly; Microcephaly 15, Primary, Autosomal Recessive; Autosomal Recessive Primary Microcephaly; Microcephaly; Leukemia, acute myeloid; Deafness, Autosomal Recessive 74; Cytopenia; Uridine 5-Prime Monophosphate Hydrolase Deficiency, Hemolytic

Anemia due to; Congenital anemia; NUT midline carcinoma; Malignant neoplasm of breast; Deafness, Autosomal Recessive; Deafness, Autosomal Recessive 9; Auditory Neuropathy, Nonsyndromic Recessive; Auditory neuropathy, autosomal recessive, 1; Malignant neoplasm of breast; Breast Carcinoma; Neoplasm of uncertain or unknown behavior of breast; Breast adenocarcinoma; Ketotic hypoglycemia; Rhabdomyolysis; Glycogen Storage Disease IXB; Phosphorylase kinase deficiency of liver and muscle, autosomal recessive; Congenital anemia; Congenital Disorders of Glycosylation; Cytopenia; Epileptic encephalopathy; Paroxysmal nocturnal hemoglobinuria; Paroxysmal Nocturnal Hemoglobinuria 1; West Syndrome; Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2; Congenital anemia; Congenital Disorders of Glycosylation; Cytopenia; Epileptic encephalopathy; Paroxysmal nocturnal hemoglobinuria; Paroxysmal Nocturnal Hemoglobinuria 1; West Syndrome; Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2; Bruck Syndrome 2; Osteogenesis Imperfecta; Bruck Syndrome 1; Arthrogryposis; Bruck Syndrome; Cutaneous Melanoma; Melanoma; Parkinson Disease 2, Autosomal Recessive Juvenile; Parkinson Disease; Young Onset Parkinson Disease; Parkinson Disease, Late-Onset; Leprosy, Susceptibility To; Adenocarcinoma, Ovarian, Somatic; Adenocarcinoma Of Lung, Somatic; Primary Microcephaly; Neurodevelopmental Disorder With Microcephaly, Hypotonia, And Variable Brain Anomalies; Myocardial infarcation, susceptibility to; Pure Gonadal Dysgenesis, 46, XX; Ovarian dysgenesis 3; Insulin resistance, susceptibility to; Leukodystrophy; Epileptic encephalopathy; Adams-Oliver Syndrome 3; Adams Oliver syndrome; Mood Disorders; Congenital anemia; Hematologic Neoplasms; Anemia, Diamond-Blackfan; Cytopenia; Aase Smith syndrome 2; Radial club hand; Precursor T-Cell Lymphoblastic Leukemia-Lymphoma; Diamond-Blackfan anemia 6; Hereditary non-polyposis colorectal cancer syndrome; Familial Colorectal Cancer Type X; Hereditary Nonpolyposis Colorectal Cancer; Hereditary Nonpolyposis Colorectal Neoplasms; Thyroid Hormone Metabolism, Abnormal; Thyroid Hormone Resistance Syndrome; Bipolar Disorder; Disturbance in mood; Combined Oxidative Phosphorylation Deficiency 28; Coffin-Siris Syndrome 5; Coffin-Siris syndrome; Meningioma; Meningiomas, Multiple; Meningioma, familial, susceptibility to; Primary microcephaly; Congenital anemia; Osteogenesis Imperfecta; Cytopenia; Epileptic encephalopathy; Radial club hand; Cornelia De Lange Syndrome; Growth Deficiency and Mental Retardation with Facial Dysmorphism; Congenital muscular hypertrophy-cerebral syndrome; Cornelia de Lange syndrome 2; Infiltrating duct carcinoma of female breast; Colorectal Cancer; Neurofibromatosis 1; Neurofibromatosis, Type 1-Like Syndrome; Legius syndrome; Shwachman syndrome; Glioblastoma Multiforme; Ovarian Serous Adenocarcinoma; Polynesian Bronchiectasis; Kartagener Syndrome; Polyhydramnios,

Megalencephaly, And Symptomatic Epilepsy; Hydrocephalus; Epileptic encephalopathy; Oligodontia; Hypodontia; Orofacial cleft 10; Malignant neoplasm of urinary bladder; Acute Promyelocytic Leukemia; Adenocarcinoma of large intestine; Bladder Neoplasm; Epileptic encephalopathy; Neoplasm of uncertain or unknown behavior of bladder; Mental Retardation, Autosomal Dominant 41; Benign neoplasm of bladder; Lymphoma, Non-Hodgkin; Carcinoma in situ of bladder; Central nervous system lymphoma; Carcinoma of bladder; Plantar Lipomatosis, Unusual Facies, and Developmental Delay; Pierpont syndrome; X-linked Adrenal Hypoplasia; Depressive Symptoms; Familial dilated cardiomyopathy; Familial Glucocorticoid Deficiency Type 1; Conduction disorder of the heart; Cardiomyopathy, Dilated; Angelman Syndrome; Epileptic encephalopathy; Microcephaly; Duplication 15q11-q13 Syndrome; Leukodystrophy, Hypomyelinating, 6; Chromosome 10p12-p11 Deletion Syndrome; Colorectal Cancer; Desanto-Shinawi Syndrome; Ataxias, Hereditary; Cerebellar Ataxia, Mental Retardation, And Dysequilibrium Syndrome 2; Hydrocephalus; Cerebellar Hypoplasia; Dysequilibrium Syndrome; OPTIC ATROPHY 11; Polynesian Bronchiectasis; Ciliary Dyskinesia, Primary, 22; Kartagener Syndrome; and Ciliopathies.

[0003d] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in manufacturing a medicament for the treatment of a disease or condition in a subject in need thereof, wherein the disease or the condition is caused by a deficient amount or activity of a functional target protein, and wherein the first protein comprising the target peptide sequence is at least partially functionally equivalent to the functional target protein.

[0004] Disclosed herein, in some examples, is a method of modulating expression of a target peptide sequence by a cell having a pre-mRNA that encodes the target peptide sequence and comprises an inefficient translation region, the method comprising contacting the cell with a therapeutic agent that binds to a targeted region of the pre-mRNA encoding the target peptide sequence, whereby splicing of the inefficient translation region from the pre-mRNA encoding the target peptide sequence is modulated, thereby modulating a level of a first processed mRNA that is devoid of the inefficient translation region and encodes a first protein comprising the target peptide sequence, and thereby modulating the expression of the target peptide sequence in the cell, wherein the first processed mRNA has a higher translation efficiency for producing the first protein comprising the target peptide sequence in the cell as compared to translation efficiency of a second processed mRNA for producing a second protein comprising the target peptide sequence, and wherein the second processed mRNA comprises the inefficient translation region.

[0005] Disclosed herein, in some examples, is a method of treating a disease or a condition in a subject in need thereof by modulating expression of a target peptide sequence in a cell of the

subject, the cell having a pre-mRNA that encodes the target peptide sequence and comprises an inefficient translation region, the method comprising: contacting the cell of the subject with a therapeutic agent that modulates splicing of the inefficient translation region from the pre-mRNA encoding the target peptide sequence, wherein the therapeutic agent binds to a targeted region of the pre-mRNA, whereby splicing of the inefficient translation region from the pre-mRNA is modulated, thereby modulating a level of a first processed mRNA that is devoid of the inefficient translation region and encodes a first protein comprising the target peptide sequence, and thereby modulating expression of the target peptide sequence in the cell of the subject, wherein the first processed mRNA has a higher translation efficiency for producing the first protein comprising the target peptide sequence in the cell as compared to translation efficiency of a second processed mRNA for producing a second protein comprising the target peptide sequence, and wherein the second processed mRNA comprises the inefficient translation region.

[0006] In some cases, the second processed mRNA is otherwise identical to the first processed mRNA but comprises the inefficient translation region. In some cases, the pre-mRNA encoding the target peptide sequence comprises a first start codon, a second start codon, and a premature termination codon (PTC) located downstream of the first start codon and upstream of the second start codon, and wherein the inefficient translation region comprises the premature termination codon (PTC) and the second start codon. In some cases, the inefficient translation region comprises a region that encodes a proline-rich peptide sequence.

[0007] Disclosed herein, in some examples, is a method of modulating expression of a target peptide sequence by a cell having a pre-mRNA that encodes the target peptide sequence and comprises a first start codon, a second start codon, and a premature termination codon (PTC) located downstream of the first start codon and upstream of the second start codon, the method comprising contacting the cell with a therapeutic agent that binds to a targeted portion of the pre-mRNA encoding the target peptide sequence, whereby splicing of the PTC and the second start codon from the pre-mRNA is modulated, thereby modulating a level of a first processed mRNA that is devoid of the PTC and the second start codon and encodes a first protein comprising the target peptide sequence, and thereby modulating the expression of the target peptide sequence in the cell.

[0008] Disclosed herein, in some examples, is a method of treating a disease or a condition in a subject in need thereof by modulating expression of a target peptide sequence in a cell of the subject, the cell having a pre-mRNA that encodes the target peptide sequence and comprises a first start codon, a second start codon, and a premature termination codon (PTC) located downstream of the first start codon and upstream of the second start codon, the method

oligonucleotide, and wherein the therapeutic agent consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.

[0028] In some cases, the method further comprises assessing mRNA level encoding the target peptide sequence or expression level of the target peptide sequence.

[0029] In some cases, the subject is a human. In some cases, the subject is a non-human animal. In some cases, the subject is a fetus, an embryo, or a child. In some cases, the cell or the cells is *ex vivo*, or in a tissue, or organ *ex vivo*.

[0030] In some cases, the therapeutic agent is administered to the subject by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.

[0031] Disclosed herein, in some examples, is a therapeutic agent for use in the method disclosed herein.

[0032] Disclosed herein, in some examples, is a pharmaceutical composition comprising the therapeutic agent described herein and a pharmaceutically acceptable excipient.

[0033] Disclosed herein, in some examples, is a method of treating a subject in need thereof, comprising administering the pharmaceutical composition described herein by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection to the subject.

INCORPORATION BY REFERENCE

[0034] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a therapeutic agent or a vector encoding the therapeutic agent, and a pharmaceutically acceptable excipient,

wherein the therapeutic agent is configured to bind to a targeted portion of a pre-mRNA in a cell, wherein the pre-mRNA encodes a target peptide sequence and comprises an inefficient translation region, whereby splicing of the inefficient translation region from the pre-mRNA encoding the target peptide sequence is modulated, thereby modulating a level of a first processed mRNA that is devoid of the inefficient translation region and encodes a first protein comprising the target peptide sequence, and thereby modulating the expression of the target peptide sequence in the cell, wherein the first processed mRNA has a higher translation efficiency for producing the first protein comprising the target peptide sequence in the cell as compared to translation efficiency of a second processed mRNA for producing a second protein comprising the target peptide sequence, and wherein the second processed mRNA comprises the inefficient translation region.

2. The pharmaceutical composition of claim 1, wherein the pre-mRNA encoding the target peptide sequence comprises a first start codon, a second start codon, and a premature termination codon (PTC) located downstream of the first start codon and upstream of the second start codon, and wherein the inefficient translation region comprises the premature termination codon (PTC) and the second start codon.

3. The pharmaceutical composition of claim 1, wherein the inefficient translation region comprises a region that encodes a proline-rich peptide sequence.

4. The pharmaceutical composition of claim 1, wherein the target peptide sequence has at least 100 amino acids.

5. The pharmaceutical composition of claim 1, wherein at least a portion of the targeted region of the pre-mRNA is upstream or downstream of the inefficient translation region.

6. The pharmaceutical composition of claim 1, wherein at least a portion of the targeted region of the pre-mRNA is within the inefficient translation region.

7. The pharmaceutical composition of claim 1, wherein the first processed mRNA and the second processed mRNA are both splicing products of the pre-mRNA in the cell.

8. The pharmaceutical composition of claim 2, wherein the second processed mRNA comprises a sequence of the first processed mRNA, the PTC, and the second start codon.

9. The pharmaceutical composition of claim 8, wherein the first protein comprising the target peptide sequence is translated starting from the first start codon on the first processed mRNA, and the second protein is translated starting from the second start codon on the second processed mRNA.
10. The pharmaceutical composition of claim 1, wherein exclusion of the inefficient translation region from the pre-mRNA encoding the target peptide sequence is increased.
11. The pharmaceutical composition of claim 1, wherein the therapeutic agent increases the level of the first processed mRNA encoding the target peptide sequence in the cell.
12. The pharmaceutical composition of claim 1, wherein the therapeutic agent increases the level of the target peptide sequence in the cell.
13. The pharmaceutical composition of claim 1, wherein the target peptide sequence is a portion of a full length protein.
14. The pharmaceutical composition of claim 1, wherein the target peptide sequence produced is a fully functional protein.
15. The pharmaceutical composition of claim 1, wherein the target peptide sequence is an N-terminal portion of a full length protein.
16. The pharmaceutical composition of claim 15, wherein the target peptide sequence is encoded by a portion of the pre-mRNA upstream of the inefficient translation region.
17. The pharmaceutical composition of claim 1, wherein the inefficient translation region is in a 3' untranslated region (3' UTR) of the second processed mRNA.
18. The pharmaceutical composition of claim 1, wherein the target peptide sequence is a C-terminal portion of a full length protein.
19. The pharmaceutical composition of claim 18, wherein the target peptide sequence is encoded by a portion of the pre-mRNA downstream of the inefficient translation region.
20. The pharmaceutical composition of claim 1, wherein the pre-mRNA is an MeCP2 pre-mRNA.
21. The pharmaceutical composition of claim 20, wherein the pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to anyone selected from the group consisting of SEQ ID NOs: 2-27.
22. The pharmaceutical composition of claim 20, wherein the target peptide sequence is translated from a sequence selected from the group consisting of SEQ ID NOs: 32-34.
23. The pharmaceutical composition of claim 20, wherein the therapeutic agent binds to a targeted region of a MeCP2 pre-mRNA, wherein the targeted region is within a sequence selected from the group consisting of SEQ ID NOs: 28-31.

24. The pharmaceutical composition of claim 20, wherein the first processed mRNA encodes a protein having at least 80% sequence identity to SEQ ID NO: 8204 or 8205.

25. The pharmaceutical composition of claim 20, wherein the therapeutic agent decreases a level of a second processed mRNA encoding a protein having at least 80% sequence identity to SEQ ID NO: 440 or 441.

26. The pharmaceutical composition of claim 20, wherein the therapeutic agent decreases level of e2 isoform of MeCP2 protein and increases level of e1 isoform of MeCP2 protein in the cell.

27. The pharmaceutical composition of claim 20, wherein the targeted region of the pre-mRNA

(a) comprises at least 10 contiguous nucleobases of SEQ ID NO: 238 or 239;

(b) is within a sequence between a pair of genomic sites selected from the group consisting of GRCh38/hg38: chrX 154092307 and GRCh38/hg38: chrX 154092184;

(c) is at least 50 nucleotides downstream of genomic site GRCh38/hg38: chrX 154092184;

(d) is at most 1500 nucleotides downstream of genomic site GRCh38/hg38: chrX 154092184;

(e) is at least 50 nucleotides upstream of genomic site GRCh38/hg38: chrX 154092307; or

(f) is at most 1500 nucleotides upstream of genomic site GRCh38/hg38: chrX 154092307.

28. The pharmaceutical composition of claim 20, wherein the therapeutic agent is an antisense oligomer that has a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 35-129 and 4548-4611.

29. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an antisense oligomer (ASO) complementary to the targeted region of the pre-mRNA.

30. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an ASO that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted region of the pre-mRNA encoding the target peptide sequence.

31. The pharmaceutical composition of claim 1, wherein the therapeutic agent is a small molecule.

32. The pharmaceutical composition of claim 1, comprising the vector encoding the therapeutic agent.

33. The pharmaceutical composition of claim 32, wherein the vector is a viral vector.

34. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an antisense oligomer, and wherein the therapeutic agent comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.

35. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an antisense oligomer, and wherein the therapeutic agent comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.

36. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an antisense oligomer, and wherein the therapeutic agent comprises at least one modified sugar moiety.

37. The pharmaceutical composition of claim 36, wherein each sugar moiety is a modified sugar moiety.

38. The pharmaceutical composition of claim 1, wherein the therapeutic agent is an antisense oligomer, and wherein the therapeutic agent consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.

39. The pharmaceutical composition of claim 1, wherein the target peptide sequence is a portion of a protein selected from the group consisting of: MECP2, ACIN1, ACTN1, ACTN2, ADH4, AKR1C3, ALDH1A2, ALG8, AMPD2, AMT, ANKRD11, ANKS3, APOL4, APPL1, ARCN1, ARMC8, ARNTL, BOC, BRCA1, C8B, CALM1, CALM3, CASP5, CAST, CEP19, CEP57, CHEK1, CIB2, COX4I1, DCLRE1C, DECR1, DHFR, DKK2, DLG2, DOK2, DPF3, DTNA, DYRK1A, FOLH1, FUZ, GANAB, GEMIN4, GGA3, GOSR2, GPM6A, GRB10, GSN, HDAC8, HIVEP1, HK1, IFNGR1, IKBKB, ISCU, KARS, KIAA0319, KIAA0586, KIZ, KLK6, LMNA, LMNTD1, LRRC7, LRTOMT, LZTFL1, MAGI2, MERTK, MFSD2A, MLF1, MOB1B, MSRB3, NR1I3, NT5C3A, NUTM1, OTOF, PDCD4, PDPK1, PHKB, PIGA, PLOD2, POLR2F, PPP6C, PRKN, PRUNE1, PSMA6, PSMC3IP, PTPN1, RAB11B, RBPJ, RNPS1, RPL5, RPS20, SECISBP2, SELENBP1, SEPT11, SIRT2, SLC25A26, SMARCE1, SMC1A, SMG1, SPACA7, SPRED1, SRP54, SRPK2, STK36, STRADA, SUMO1, TBL1XR1, TLR8, TXNRD2, UBE3A, UFM1, WAC, WDR81, YME1L1, and ZMYND10.

40. The pharmaceutical composition of claim 1 for use in the treatment of a disease or condition in a subject in need thereof.

41. Use of the pharmaceutical composition of claim 1 in manufacturing a medicament for the treatment of a disease or condition in a subject in need thereof, wherein the disease or the condition is selected from the group consisting of: Intellectual Disability; Colorectal Cancer; Bleeding Disorder, Platelet-Type, 15; Autosomal dominant macrothrombocytopenia; Hypertrophic Cardiomyopathy; Cardiomyopathy, Dilated, 1AA; cardiomyopathy, familial hypertrophic, 23, with or without ventricular noncompaction; Familial dilated cardiomyopathy; Charcot-Marie-Tooth Disease; Conduction disorder of the heart; Cardiomyopathy, Dilated; Alcohol Use Disorder; Alcohol abuse; Alcoholic Intoxication, Chronic; Alcohol Use Disorder; Alcohol abuse; Alcoholic Intoxication, Chronic; Schizophrenia; Bipolar Disorder; Alcoholic Intoxication, Chronic; Congenital Disorders of Glycosylation; Epileptic encephalopathy; Depressive disorder; Congenital disorder of glycosylation type 1H; pontocerebellar hypoplasia, type 9; epileptic encephalopathy; ataxias, hereditary; spastic paraplegia 63, autosomal recessive; Cerebellar Hypoplasia; Spastic Paraplegia, Hereditary; Nonketotic Hyperglycinemia; Hyperglycinemia, Transient Neonatal; Glycine encephalopathy; KBG syndrome; 16q24.3 microdeletion syndrome; Situs Inversus; Malignant neoplasm of breast; Maturity onset diabetes mellitus in young; Maturity-Onset Diabetes Of The Young, Type 14; Microcephaly; Polydactyly; Ciliopathies; Mental Depression; Seasonal Affective Disorder; Bipolar Disorder; Mood Disorders; Depressive disorder; Malignant neoplasm of breast; Cytopenia; Gastrointestinal Neoplasms; Depressive disorder; Prostate cancer, familial; Primary peritoneal carcinoma; ovarian cancer, familial, susceptibility to, 1; Breast Cancer, Familial Male; Malignant Neoplasms; Pancreatic Neoplasm; Breast Cancer, Familial; Neoplasm of uncertain or unknown behavior of breast; Ovarian Carcinoma; Adenocarcinoma of prostate; Neoplasm of uncertain or unknown behavior of ovary; Malignant neoplasm of pancreas; Pancreatic carcinoma; Malignant neoplasm of ovary; Congenital anemia; Hematologic Neoplasms; Breast adenocarcinoma; breast-ovarian cancer, familial, susceptibility to, 1; Pancreatic carcinoma, familial; Benign tumor of pancreas; Breast Carcinoma; breast cancer, familial, susceptibility to, 1; ovarian neoplasm; Hereditary Breast and Ovarian Cancer Syndrome; Mental Depression; Epithelial ovarian cancer; Malignant neoplasm of breast; Sporadic Breast Carcinoma; Breast-ovarian cancer, familial, 1; Pancreatic cancer, susceptibility to, 4; C8 deficiency, type II; ventricular tachycardia, catecholaminergic polymorphic, 4; ventricular tachycardia, catecholaminergic polymorphic, 1; Long QT Syndrome; Romano-Ward Syndrome; Long Qt Syndrome 14; peeling skin syndrome; peeling skin with leukonychia, acral punctate keratoses, cheilitis, and knuckle pads; erythrokeratoderma; palmoplantar keratosis; morbid obesity and

spermatogenic failure; warburton anyane yeboa syndrome; mosaic variegated aneuploidy syndrome; Breast Cancer, Familial; Malignant neoplasm of ovary; Mitochondrial Diseases; Severe combined immunodeficiency with sensitivity to ionizing radiation; severe combined immunodeficiency, partial; Reticuloendotheliosis, familial, with eosinophilia; Omenn Syndrome; Athabaskan severe combined immunodeficiency; Severe Combined Immunodeficiency, Athabaskan-Type; Cocaine Abuse; Congenital anemia; Cytopenia; Neurodegeneration Due To Cerebral Folate Transport Deficiency; Megaloblastic Anemia due to Dihydrofolate Reductase Deficiency; Alcoholic Intoxication, Chronic; Bipolar Disorder; Unipolar Depression; Major Depressive Disorder; Schizophrenia and related disorders; Left ventricular noncompaction cardiomyopathy; Left ventricular noncompaction; Familial Meniere's disease; Charcot-Marie-Tooth Disease; noncompaction of left ventricular myocardium, familial isolated, autosomal dominant 1; Primary microcephaly; Microcephaly; Epileptic encephalopathy; Mental retardation, autosomal dominant 7; Colorectal Cancer; Depressive disorder; Mental Depression; Caudal Regression Syndrome; Arnold Chiari Malformation; Caudal dysplasia syndrome; Chiari malformation type II; Sacral Agenesis Syndrome; Sacral agenesis; Currarino triad; Spina bifida aperta of cervical spine; Neural tube defects; Polycystic Kidney, Autosomal Dominant; polycystic kidney disease 3, autosomal dominant; alcoholic intoxication, chronic; malignant neoplasm of breast; ataxias, hereditary; epilepsy, progressive myoclonic, 6; Epileptic encephalopathy; Lattice corneal dystrophy Type II; Meretoja syndrome; Malignant neoplasm of breast; Periodic Fever Syndrome; Familial Amyloid Polyneuropathy, Type IV; Cerebral Amyloid Angiopathy, Gsn-Related; Abnormality of the cornea; Amyloidosis, Finnish type; Primary microcephaly; cornelia de lange syndrome 5; radial club hand; cornelia de lange syndrome; wilson-turner x-linked mental retardation syndrome; congenital anemia; retinitis pigmentosa 79; charcot-marie-tooth disease; cytopenia; hemolytic anemia, nonspherocytic, due to hexokinase deficiency; neuropathy, hereditary motor and sensory, russe type; interferon gamma, receptor 1, deficiency; immunodeficiency 27a; immunodeficiency 27b; H. pylori infection, susceptibility to; Tuberculosis infection, protection against; Immunodeficiency 27A, mycobacteriosis, AR; Immunodeficiency 27B, mycobacteriosis, AD; Hepatitis B virus infection, susceptibility to; Tuberculosis, susceptibility to; Malignant neoplasm of breast; Lymphoma, Non-Hodgkin; immunodeficiency 15; Congenital myopathy; Arthrogryposis; Rhabdomyolysis; myopathy with exercise intolerance, Swedish type; Myopathy with lactic acidosis, hereditary; Charcot-Marie-Tooth disease, recessive intermediate B; Charcot-Marie-Tooth Disease; Deafness, Autosomal Recessive 89; Deafness, autosomal recessive 89; Dyslexia,

susceptibility to, 2; Joubert Syndrome 23; Polydactyly; Familial aplasia of the vermis; Joubert syndrome with Jeune asphyxiating thoracic dystrophy; Hydrocephalus; Ciliopathies; Short-rib thoracic dysplasia 14 with polydactyly; Retinitis Pigmentosa; Retinitis pigmentosa 69; Muscular Dystrophy, Limb-Girdle, Type 1B; Hypertrophic Cardiomyopathy; Left ventricular noncompaction; Osteogenesis Imperfecta; Charcot-Marie-Tooth Disease; Cardiomyopathy, Familial Idiopathic; Familial Partial Lipodystrophy, Type 1; Left ventricular noncompaction cardiomyopathy; Mandibuloacral dysostosis; Muscular Dystrophy, Congenital, Lmna-Related; Congenital myopathy; Arthrogryposis; Arrhythmogenic Right Ventricular Dysplasia; Muscular Dystrophies, Limb-Girdle; Malouf syndrome; Najjar syndrome; Charcot-Marie-Tooth disease, Type 2B1; Emery-Dreifuss Muscular Dystrophy 3; Lethal tight skin contracture syndrome; Familial Partial Lipodystrophy, Type 2; Conduction disorder of the heart; Cardiomyopathy, Dilated; Progeria Syndrome, Childhood-Onset; Atypical Werner syndrome; Congenital muscular dystrophy; Autosomal Recessive Emery-Dreifuss Muscular Dystrophy; Heart-hand syndrome, Slovenian type; Progeria; Autosomal Dominant Emery-Dreifuss Muscular Dystrophy; Cardiomyopathy, dilated, 1A; Mandibuloacral dysplasia; Muscular dystrophy, limb-girdle, type 1B; Emery-Dreifuss muscular dystrophy 2, AD; Malouf syndrome; Restrictive dermopathy, lethal; Emery-Dreifuss muscular dystrophy 3, AR; Heart-hand syndrome, Slovenian type; Charcot-Marie-Tooth disease, type 2B1; Hutchinson-Gilford progeria; Lipodystrophy, familial partial, type 2; Muscular dystrophy, congenital; Malignant neoplasm of breast; Deafness, Autosomal Recessive 63; Bardet-Biedl Syndrome; Polydactyly; Ciliopathies; Bardet-Biedl Syndrome 17; Major Affective Disorder 2; Bipolar Disorder; Epileptic encephalopathy; Rett Syndrome, Preserved Speech Variant; Lubs X-linked mental retardation syndrome; Encephalopathy, Neonatal Severe, Due To Mecp2 Mutations; Mental Retardation with Psychosis, Pyramidal Signs, and Macroorchidism; Mental Retardation, X-Linked, With Spasticity; Trisomy Xq28; Mental Retardation, X-Linked 16; Epileptic encephalopathy; Mental Retardation, X-Linked, Syndromic 13; Mental Retardation, X-Linked 1; Rett Syndrome, Atypical; Mental Retardation, X-Linked 79; Microcephaly; Ppm-X Syndrome; Rett Syndrome, Zappella Variant; Rett Syndrome; Autism susceptibility, X-linked 3; Benign neoplasm of adrenal gland; Retinitis Pigmentosa; Conventional (Clear Cell) Renal Cell Carcinoma; Squamous cell carcinoma of the head and neck; Malignant neoplasm of aortic body and other paraganglia; Retinitis Pigmentosa 38; Malignant Adrenal Medulla Neoplasm; Benign neoplasm of aortic body and other paraganglia; Primary microcephaly; Microcephaly 15, Primary, Autosomal Recessive; Autosomal Recessive Primary

Microcephaly; Microcephaly; Leukemia, acute myeloid; Deafness, Autosomal Recessive 74; Cytopenia; Uridine 5-Prime Monophosphate Hydrolase Deficiency, Hemolytic Anemia due to; Congenital anemia; NUT midline carcinoma; Malignant neoplasm of breast; Deafness, Autosomal Recessive; Deafness, Autosomal Recessive 9; Auditory Neuropathy, Nonsyndromic Recessive; Auditory neuropathy, autosomal recessive, 1; Malignant neoplasm of breast; Breast Carcinoma; Neoplasm of uncertain or unknown behavior of breast; Breast adenocarcinoma; Ketotic hypoglycemia; Rhabdomyolysis; Glycogen Storage Disease IXB; Phosphorylase kinase deficiency of liver and muscle, autosomal recessive; Congenital anemia; Congenital Disorders of Glycosylation; Cytopenia; Epileptic encephalopathy; Paroxysmal nocturnal hemoglobinuria; Paroxysmal Nocturnal Hemoglobinuria 1; West Syndrome; Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2; Congenital anemia; Congenital Disorders of Glycosylation; Cytopenia; Epileptic encephalopathy; Paroxysmal nocturnal hemoglobinuria; Paroxysmal Nocturnal Hemoglobinuria 1; West Syndrome; Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome 2; Bruck Syndrome 2; Osteogenesis Imperfecta; Bruck Syndrome 1; Arthrogryposis; Bruck Syndrome; Cutaneous Melanoma; Melanoma; Parkinson Disease 2, Autosomal Recessive Juvenile; Parkinson Disease; Young Onset Parkinson Disease; Parkinson Disease, Late-Onset; Leprosy, Susceptibility To; Adenocarcinoma, Ovarian, Somatic; Adenocarcinoma Of Lung, Somatic; Primary Microcephaly; Neurodevelopmental Disorder With Microcephaly, Hypotonia, And Variable Brain Anomalies; Myocardial infarcation, susceptibility to; Pure Gonadal Dysgenesis, 46, XX; Ovarian dysgenesis 3; Insulin resistance, susceptibility to; Leukodystrophy; Epileptic encephalopathy; Adams-Oliver Syndrome 3; Adams Oliver syndrome; Mood Disorders; Congenital anemia; Hematologic Neoplasms; Anemia, Diamond-Blackfan; Cytopenia; Aase Smith syndrome 2; Radial club hand; Precursor T-Cell Lymphoblastic Leukemia-Lymphoma; Diamond-Blackfan anemia 6; Hereditary non-polyposis colorectal cancer syndrome; Familial Colorectal Cancer Type X; Hereditary Nonpolyposis Colorectal Cancer; Hereditary Nonpolyposis Colorectal Neoplasms; Thyroid Hormone Metabolism, Abnormal; Thyroid Hormone Resistance Syndrome; Bipolar Disorder; Disturbance in mood; Combined Oxidative Phosphorylation Deficiency 28; Coffin-Siris Syndrome 5; Coffin-Siris syndrome; Meningioma; Meningiomas, Multiple; Meningioma, familial, susceptibility to; Primary microcephaly; Congenital anemia; Osteogenesis Imperfecta; Cytopenia; Epileptic encephalopathy; Radial club hand; Cornelia De Lange Syndrome; Growth Deficiency and Mental Retardation with Facial Dysmorphism; Congenital muscular hypertrophy-cerebral syndrome; Cornelia de Lange

syndrome 2; Infiltrating duct carcinoma of female breast; Colorectal Cancer; Neurofibromatosis 1; Neurofibromatosis, Type 1-Like Syndrome; Legius syndrome; Shwachman syndrome; Glioblastoma Multiforme; Ovarian Serous Adenocarcinoma; Polynesian Bronchiectasis; Kartagener Syndrome; Polyhydramnios, Megalencephaly, And Symptomatic Epilepsy; Hydrocephalus; Epileptic encephalopathy; Oligodontia; Hypodontia; Orofacial cleft 10; Malignant neoplasm of urinary bladder; Acute Promyelocytic Leukemia; Adenocarcinoma of large intestine; Bladder Neoplasm; Epileptic encephalopathy; Neoplasm of uncertain or unknown behavior of bladder; Mental Retardation, Autosomal Dominant 41; Benign neoplasm of bladder; Lymphoma, Non-Hodgkin; Carcinoma in situ of bladder; Central nervous system lymphoma; Carcinoma of bladder; Plantar Lipomatosis, Unusual Facies, and Developmental Delay; Pierpont syndrome; X-linked Adrenal Hypoplasia; Depressive Symptoms; Familial dilated cardiomyopathy; Familial Glucocorticoid Deficiency Type 1; Conduction disorder of the heart; Cardiomyopathy, Dilated; Angelman Syndrome; Epileptic encephalopathy; Microcephaly; Duplication 15q11-q13 Syndrome; Leukodystrophy, Hypomyelinating, 6; Chromosome 10p12-p11 Deletion Syndrome; Colorectal Cancer; Desanto-Shinawi Syndrome; Ataxias, Hereditary; Cerebellar Ataxia, Mental Retardation, And Dysequilibrium Syndrome 2; Hydrocephalus; Cerebellar Hypoplasia; Dysequilibrium Syndrome; OPTIC ATROPHY 11; Polynesian Bronchiectasis; Ciliary Dyskinesia, Primary, 22; Kartagener Syndrome; and Ciliopathies.

42. Use of the pharmaceutical composition of claim 1 in manufacturing a medicament for the treatment of a disease or condition in a subject in need thereof, wherein the disease or the condition is caused by a deficient amount or activity of a functional target protein, and wherein the first protein comprising the target peptide sequence is at least partially functionally equivalent to the functional target protein.

43. The use according to claim 41 or 42, wherein the pharmaceutical composition is to be administered to the subject by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.