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(71) Applicant: **MITOCHON PHARMACEUTICALS LLC** [US/US]; 259 Radnor Chester Road, Suite 210, Radnor, PA 19087 (US).

(72) Inventors: **ALONSO, Robert**; 15 Winterberry Lane, North Hampton, NH 03862 (US). **GEISLER, John, Gerard**; 970 Cross Lane, Blue Bell, PA 19422 (US).

(74) Agents: **MCCULLEN, Sharon B.** et al.; Morgan Lewis & Bockius LLP, 1701 Market Street, Philadelphia, PA 19103 (US).

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(54) **Title**: INDUCED EXPRESSION OF BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) FOR TREATMENT OF NEUROMUSCULAR, NEURODEGENERATIVE, AUTOIMMUNE, DEVELOPMENTAL AND/OR METABOLIC DISEASES

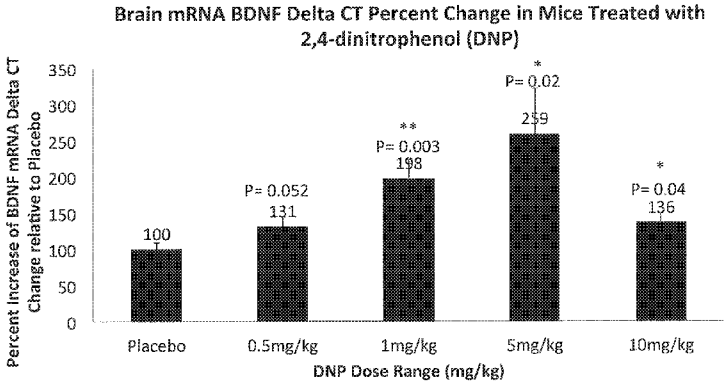


Figure 1

(57) **Abstract**: A method of treating a host of neuromuscular, neurodegenerative, developmental, autoimmune and metabolic diseases/disorders related to aging, such as traumatic injury, stroke, Huntington's disease, Epilepsy, Multiple Sclerosis (MS), Lupus, Type-1 and Type-2 diabetes, Maturity Onset Diabetes of the Young (MODY), myasthenia gravis (MG), rheumatoid arthritis (RA), Graves' disease, Guillain-Barre syndrome (GBS), metabolic syndrome, Muscular Dystrophy or Duchenne Muscular Dystrophy (DMD), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Friedreich's Ataxia, Batten Disease, Alzheimer's disease, optic neuritis, Leber's hereditary optic neuropathy (LHON), autism, Rett syndrome, Batten Disease, Angelman's Syndrome, Leigh disease, Fragile-X Syndrome, depression, Parkinson's disease, mitochondrial diseases, developmental disorders, metabolic disease disorders and/or autoimmune disorders by inducing endogenous BDNF expression with DNP treatment to protect from neuromuscular dysfunction/disorders and/or neurodegeneration and/or muscle wasting. DNP was administered to mice daily over a range of doses, and subsequently BDNF expression in the brain showed a dose dependent and non-linear increase in expression.

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# TITLE OF INVENTION

[001] Induced Expression of Brain Derived Neurotrophic Factor (BDNF) for Treatment of Neuromuscular, Neurodegenerative, Autoimmune, Developmental and/or Metabolic Diseases

## CROSS-REFERENCE TO RELATED APPLICATIONS

[002] This application claims priority to U.S. Provisional Application 62/106365, filed on January 22, 2015, which is expressly incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

[003] Brain-derived neurotrophic factor (BDNF) is one of several endogenous proteins that play key roles in neuronal development. BDNF influences nerve growth as a neurotrophin and/or as a myokine. Therefore there is a need for improved methods for inducing expression of BDNF. The present invention relates to the discovery that BDNF can be endogenously induced to increase expression by administration of DNP, and that there is a dose range between 0.001 mg/kg to less than 10 mg/kg that is useful in expression of BDNF and not harmful to the patient. Further, many approaches are underway to get BDNF across the blood brain barrier to treat a host of diseases. For example, these diseases include, but are not limited to, traumatic injury, stroke, Huntington's disease, Epilepsy, Multiple Sclerosis (MS), Lupus, Type-1 and Type-2 diabetes, Maturity Onset Diabetes of the Young (MODY), Myasthenia gravis (MG), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), metabolic syndrome, Duchenne Muscular Dystrophy (DMD), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Friedreich's Ataxia, Batten Disease, Alzheimer's disease, Optic neuritis, Leber's hereditary optic neuropathy (LHON), Autism, Rett syndrome, Batten Disease, Angelman's Syndrome, Leigh disease, Fragile-X Syndrome, Schizophrenia, Depression, Parkinson's disease and mitochondrial diseases. Treatment works by the process of reversing, slowing or preventing neuromuscular, neurodegenerative, autoimmune, developmental and/or metabolic disorders.

## FIELD OF THE INVENTION

[004] The present invention relates to methods of treatment of neuromuscular, neurodegenerative, autoimmune, developmental and/or metabolic disease and pharmaceutical compositions, including unit doses, for treatment of neuromuscular, neurodegenerative, autoimmune, developmental and/or metabolic disease. Specifically, the present invention relates to endogenously inducing the systemic organs of a person to increase expression of brain derived neurotrophin factor ("BDNF") via administering mitochondrial uncoupler (protonophore or ionophore) 2, 4-dinitrophenol ("DNP") or bipartite dinitrophenol isoforms (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-DNP) or mitochondrial uncouplers or weak acid's with a dissociable proton such as CCCP, FCCP, SF 6847, Flufenamic acid, PCP, TTFB, etc., to a patient in need thereof, using an effective dose of about 0.001mg/kg to 5 mg/kg, as well as the associated pharmaceutical composition of DNP and unit dose of DNP.

## BRIEF SUMMARY OF THE INVENTION

[005] In one embodiment, the present invention provides for a method of treating traumatic CNS injury, neurodegenerative disease, and/or autoimmune diseases, and/or developmental disorders, and/or metabolic disease by administrating DNP in the dose range of 0.01 mg/kg of body weight to less than 10 mg/kg of body weight to increase BDNF to attenuate disease progression or provide relief from symptoms. In certain embodiments, the invention provides a method of treatment for at least the following diseases: Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease (Adult-onset Huntington's, Juvenile Huntington's disease), Epilepsy (Cluster Seizures, Refractory Seizures, Atypical Absence Seizures, Atonic Seizures, Clonic Seizures, myoclonic seizures, tonic seizures, Tonic-Clonic Seizures, Simple Partial Seizures, Complex Partial Seizures, Secondary Generalized Seizures, Febrile Seizures, Nonepileptic Seizures, Gelastic and Dacrystic Seizures, and Absence Seizures), Multiple Sclerosis (MS) (relapse-remitting multiple sclerosis (RRMS), Secondary-progressive MS (SPMS), Primary-progressive MS (PPMS), and Progressive-relapsing MS (PRMS)), Lupus (Systemic Lupus Erythematosus (SLE), discoid (cutaneous), drug-induced lupus (dil) and neonatal lupus), Diabetes mellitus (Type-1 Diabetes, Type-2 Diabetes, Maturity

Onset Diabetes of the Young (MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODY10, MODY11)), Schizophrenia (Paranoid schizophrenia, Disorganized schizophrenia, Catatonic schizophrenia, Residual schizophrenia, Schizoaffective disorder), Myasthenia gravis (MG) (ocular myasthenia gravis, Congenital MG and generalized myasthenia gravis), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), Muscular Dystrophy (Duchenne Muscular Dystrophy (DMD), Becker, Myotonic, Congenital, Emery-Dreifuss, Facioscapulohumeral, Limb-girdle, Distal, and Oculopharyngeal), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Ataxia (Friedreich's Ataxia, Spinocerebellar ataxias 1 (SCA1), Spinocerebellar ataxias 2 (SCA2), Spinocerebellar ataxias 3 (SCA3), Spinocerebellar ataxias 6 (SCA6), Spinocerebellar ataxias 7 (SCA7), Spinocerebellar ataxias 11 (SCA11), Dentatorubral pallidolusyian atrophy (DRPLA) and Gluten ataxia), Batten Disease or neuronal ceroid lipofuscinoses (NCL) (infantile NCL (INCL), late infantile NCL (LINCL), juvenile NCL (JNCL) or adult NCL (ANCL)), Alzheimer's Disease (Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD)), Optic neuritis (ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD) (Asperger's Syndrome, Pervasive Developmental Disorders (PDDs), Childhood Disintegrative Disorder (CDD), and Autistic disorder), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression (Major Depression, Dysthymia, Postpartum Depression, Seasonal Affective Disorder, Atypical Depression, Psychotic Depression, Bipolar Disorder, Premenstrual Dysphoric Disorder, Situational Depression), Parkinson's disease (Idiopathic Parkinson's disease, Vascular parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Drug-induced Parkinsonism, Juvenile Parkinson's and atypical parkinsonism), mitochondrial diseases, developmental disorders, metabolic syndrome (increased blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol levels) and/or autoimmune disorders by inducing BDNF mRNA expression and protein levels with DNP treatment to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting.

**[006]** In another embodiment, the present invention relates to a composition of DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising an effective

dose of DNP, wherein the effective dose of the DNP is in the range of 0.001 mg/kg of body weight to 5 mg/kg of body weight.

**[007]** In yet another embodiment, the present invention relates to a pharmaceutical composition of DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is in the range of 0.1 mg to 300 mg.

**[008]** In yet another embodiment, the present invention relates to a method of treating neuromuscular or autoimmune or developmental or neurodegenerative or metabolic disorders, comprising receiving an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued to be received in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[009]** A fifth aspect of the present invention relates to a method of treating neuromuscular or autoimmune or developmental or metabolic or neurodegenerative disorders, comprising: providing instructions to administer an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is instructed to be received in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight.

## BRIEF DESCRIPTION OF THE FIGURES

**[0010]** The present invention will be better understood by examining the following figures which illustrate certain properties of the present invention wherein:

**[0011]** Fig. 1 depicts a chart showing that administration of DNP increases BDNF levels in the brain, in accordance with embodiments of the present invention.

**[0012]** Fig. 2a depicts the changes of BDNF protein levels by immunoblot from a mouse model of MS, Experimental Autoimmune encephalomyelitis.

**[0013]** Fig. 2b depicts the percent change of BDNF protein levels from a mouse model of MS based on an immunoblot study.

**[0014]** Fig. 2c depicts the effect of MP101 on progression of the phenotype in the MS model on clinical scores showing attenuation of disease progression.

**[0015]** Fig. 2d depicts a representative mouse spinal cord electron microscopy image at Day-16 (~peak of onset) for a mouse treated with 5 mg/kg of MP101 compared to placebo.

**[0016]** Fig. 3a depicts the results of a study involving Mecp2 mutant mice, a model of Rett Syndrome, after treatment with DNP at 6-weeks of age.

**[0017]** Fig. 3b depicts the results of a study involving Mecp2 mutant mice, a model of Rett Syndrome, after treatment with DNP at 12-weeks of age.

**[0018]** Fig. 4 depicts the results of a study involving Mecp2 mutant mice at 12-weeks of age after 1-month of oral gavage treatment, which shows an effect in the "clasping test" at 1 mg/kg DNP.

**[0019]** Figs. 5a, 5b and 5c depict the results of a study involving APP/PS1 mice at 4-months of age after 4-months treatment by oral gavage delivery with DNP in an Alzheimer's study

**[0020]** Fig. 6 depicts the results of a mouse study whereby mice were treated with DNP for 2-weeks at 1, 5 and 10 mg/kg by oral gavage and then provide a kanic acid injection into the brain to determine the impact on seizure time.

**[0021]** Fig. 7a depicts the results of a mouse study whereby mice were treated with DNP for 14 days to see the impact on protecting dopaminergic neuronal loss.

**[0022]** Fig. 7b depicts the results of another mouse study whereby mice were treated with DNP for 14 days to see the impact on protecting dopaminergic neuronal loss.

**[0023]** Fig. 8a depicts an MRI image of brain volume changes of wildtype (WT), mutant Huntington mice Vehicle (HD) with DNP treatment.

**[0024]** Fig. 8b depicts the quantitative brain volume loss in the cortex after DNP treatment.

**[0025]** Fig. 8c shows the quantitative brain volume loss in the striatum after DNP treatment.

[0026] Fig. 8d depicts the results of a mouse study showing that treatment with DNP preserves medium spiny neurons using biomarker DARPP32 at 26-weeks of age.

[0027] Fig. 8e depicts the results of a mouse study showing that treatment with DNP preserves general neuronal loss with biomarker to postsynaptic protein PSD95 levels in N171-82Q HD mice.

[0028] Fig. 8f depicts the results of a mouse study showing that treatment with DNP improves motor function in both the taper beam and balance beam after 17-weeks of treatment.

## DETAILED DESCRIPTION OF THE INVENTION

[0029] Hereinafter, the term "endogenous", unless otherwise defined, means growing or produced by growth from deep tissue, e.g. by growth from a person's brain. Alternatively, the term "endogenous", unless otherwise defined, means caused by factors inside the organism or system. Alternatively, the term "endogenous", unless otherwise defined, means produced or synthesized within the organism or system.

[0030] Hereinafter, unless otherwise defined, the term "muscle wasting" means atrophy of a person's muscle (e.g. diaphragm for breathing). Muscle atrophy is when muscles waste away. The main reason for muscle wasting is a lack of physical activity. This can happen when a disease or injury makes it difficult or impossible for you to move an arm or leg.

[0031] Hereinafter, unless otherwise defined, the terms "effective dose" or "effective relief" are measured objectively using one or more of the following quantitative assessments to achieve a validated assessment of the effectiveness of the dose or relief: ADS COG for Alzheimer's Disease; HDRS for Huntington's Disease; the Parkinson Rating Scale for Parkinson's Disease; the FSS and EDSS for Multiple Sclerosis; the ALSAQ for ALS; Stroke Assessment Scales of Stroke such as the NIH Stroke Scale or Barthel Index; Childhood Autism Rating Scale (CARS) for Autism; 6-minute walk test for Duchenne muscular dystrophy (DMD); and a seizure severity scale for seizures.

[0032] Hereinafter, unless otherwise defined, the term "about" means plus or minus 10% of the value referenced. For example, "about 1 mg/kg" means 0.9 mg/kg to 1.1 mg/kg.

**[0033]** Mitochondria uncouplers, e.g., 2, 4- dinitrophenol (DNP), may be advantageously administered as a therapeutic approach for neuroprotection in cases of traumatic CNS injury, neurodegenerative disease, autoimmune disease, developmental disorders, and metabolic disease. Mitochondria uncoupling can have a protective effect on brain cells by enhancing respiratory rates by mild uncoupling which leads to lower cellular stress due to a mechanism of action (MOA) of: 1) increasing oxygen ($O_2$) consumption, which prevents formation of superoxide radical anions ($O_2^-$) by decreasing $O_2$ tension in the microenvironment, 2) providing more oxidized levels of respiratory chain intermediates, such as in Complex I and III, known as a substantial source of reactive oxygen species (ROSs), 3) maintaining NADH levels lower, which prevents ROS formation by mitochondrial matrix flavoproteins and 4) lower membrane potential ($\Delta\Psi$), a condition which thermodynamically disfavors reverse of electron transfer from Complex II to I.

**[0034]** Further, neurite outgrowth may, in theory, be achieved with the use of uncouplers beyond the use for lowering ROSs. It is known that DNP can lower ROSs species with an acute single dose post-ischemia, and reduce infarct volume, however the benefits of improved outcome and recovery by repair can be accomplished with increasing expression of BDNF, requiring chronic treatment to induce sufficient levels of this neurotrophin. Infarct volume may therefore be further reduced from repair/growth of the damaged tissue by chronic DNP treatment.

**[0035]** In one embodiment, the present invention relates to the discovery that BDNF can be endogenously induced to increase expression with the treatment of DNP, and that there is a dose range of DNP that is effective and is not too high to be harmful, nor too low and provide no effect. The effectiveness of DNP in inducing BDNF does not increase linearly as the dose of DNP is increased. In one embodiment, we show that there is a DNP dose amount whereby the beneficial effect no longer increases, and, significantly, there is a dose amount whereby the beneficial effect of DNP actually decreases.

**[0036]** While not bound by theory, the mechanism of action for DNP is likely conversion of a non-genomic event into a genomic event. Mitochondrial uncouplers do not directly act upon a protein, but on a location, namely the mitochondrial matrix. The

mitochondrial matrix is a pH basic environment due to the pumping out of protons (hydrogen or $H^+$) through the cytochromes. Since mitochondrial uncouplers are weak acids with a dissociable proton, they are attracted to the basic environment of the mitochondrial matrix, where they travel as a cation and drop off a proton ($H^+$), then leave unprotonated back into the acidic environment of cytosol as an anion, to then get reprotonated back to a cation and start the cycle over again until metabolized and/or eliminated. This event lowers the mitochondrial membrane potential, which results in an increase in energy expenditure with the consumption of glucose and lipids in an attempt to re-establish the membrane potential. This effect is considered non-genomic, since DNP does not act directly through a protein or touch a protein, but just goes into a unique location within the cell of which happens to be the only location with a pH basic environment. It also lowers intra-mitochondria calcium. Adenylate cyclase, the enzyme that synthesizes 3'5'-cyclic monophosphate (cyclic AMP or cAMP), otherwise known as "second messenger", is highly sensitive to changes in calcium and magnesium and it has been shown that DNP up-regulates cAMP supplies. The cascade affect of up-regulating adenylate cyclase and producing more cAMP, then converts DNP's non-genomic effect, into a genomic effect, which changes expression of a host of genes, including increasing the transcription factor for BDNF, known as cAMP-responsive element-binding protein (CREB).

**[0037]** By way of example only, BDNF is lower in Huntington's Disease, and restoring BDNF to near normal levels is considered to be critical to attenuate disease onset. Therefore, treatment with DNP that effectively crosses the blood brain barrier and induces endogenous expression of BDNF is advantageous for treating diseases for which increased expression of BDNF will provide neuroprotection. Similarly, Rett Syndrome is considered a developmental disorder in young girls and is associated with lower levels of BDNF. Restoring levels back to near normal levels may prevent the stunting of head growth that appears around approximately 18 months of age as one marker of onset. For other diseases, such as multiple sclerosis (MS), the positive effects of BDNF have not been well studied, but we have shown in a model of MS that BDNF levels are elevated in the brain and striking axonal protection from the autoimmune disorder that destroys the myelin sheaths under chronic treatment of DNP. Others have shown that BDNF can

lower glucose levels in models of obesity and diabetes. Others have found that young, non-obese insulin resistant patients have low circulating levels of BDNF, which acts as a paracrine and may be a factor in the metabolic syndrome. Therefore, an elevated and sustained increase in BDNF may provide a broad effect in neurodegeneration, development, autoimmune, metabolic and neuromuscular disorders. In addition, an increase of BDNF in both central and/or peripheral compartments may be beneficial.

**[0038]** In addition to the brain, BDNF is also expressed in other muscle tissues and thought to act as a myokine to provide neuromuscular or muscle protection, in addition to protection from neurodegeneration.

**[0039]** Surprisingly, the dose range of about 0.001 to 5 mg/kg has been shown to be effective in treating muscular, neuromuscular, neurodegenerative, autoimmune, developmental and/or metabolic diseases, such as, for example, traumatic injury, stroke, Huntington's disease, Epilepsy, Multiple Sclerosis (MS), Lupus, Type-1 and Type-2 diabetes, MODY, metabolic syndrome, Duchenne Muscular Dystrophy (DMD), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Friedreich's Ataxia, Batten Disease, Alzheimer's disease, Optic neuritis, Autism, Rett syndrome, Batten Disease, Angelman's Syndrome, Fragile-X Syndrome, Schizophrenia, Depression, and Parkinson's disease. In one embodiment, the invention shows use of DNP in the effective dose range of about 0.01 to less than 10mg/kg to induce expression of BDNF in the brain of mammals, which avoid inducing too much BDNF to be harmful, or have no effect by inducing too little BDNF.

**[0040]** As described herein below, mitochondrial uncoupler DNP was tested in a range of doses in mice from 0.5 mg/kg of DNP to 10 mg/kg of DNP under oral chronic treatment to titrate the amount of drug in the brain required to induce increases of BDNF endogenously within the brain. It was discovered that DNP does in fact induce BDNF within the brain, but the highest dose of 10 mg/kg had a reduced level of BDNF compared with the next two lower doses. Therefore, it was discovered that there is a specific and limited dose range of DNP that is necessary to achieve statistically significant survival and behavioral benefit for a host of diseases that benefit from increased BDNF levels. In one embodiment, diseases and disorders of the systemic

organs and brain, islets of Langerhans, liver and brain may benefit from titrating the BDNF levels with a specific and limited DNP dose, such as, but not limited to, Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease (Adult-onset Huntington's, Juvenile Huntington's disease), Epilepsy (Cluster Seizures, Refractory Seizures, Atypical Absence Seizures, Atonic Seizures, Clonic Seizures, myoclonic seizures, tonic seizures, Tonic-Clonic Seizures, Simple Partial Seizures, Complex Partial Seizures, Secondary Generalized Seizures, Febrile Seizures, Nonepileptic Seizures, Gelastic and Dacrystic Seizures, and Absence Seizures), Multiple Sclerosis (MS) (relapse-remitting multiple sclerosis (RRMS), Secondary-progressive MS (SPMS), Primary-progressive MS (PPMS), and Progressive-relapsing MS (PRMS)), Lupus (Systemic Lupus Erythematosus (SLE), discoid (cutaneous), drug-induced lupus (dil) and neonatal lupus), Diabetes mellitus (Type-1 Diabetes, Type-2 Diabetes, Maturity Onset Diabetes of the Young (MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODY10, MODY11)), Schizophrenia (Paranoid schizophrenia, Disorganized schizophrenia, Catatonic schizophrenia, Residual schizophrenia, Schizoaffective disorder), Myasthenia gravis (MG) (ocular myasthenia gravis, Congenital MG and generalized myasthenia gravis), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), Muscular Dystrophy (Duchenne Muscular Dystrophy (DMD), Becker, Myotonic, Congenital, Emery-Dreifuss, Facioscapulohumeral, Limb-girdle, Distal, and Oculopharyngeal), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Ataxia (Friedreich's Ataxia, Spinocerebellar ataxias 1 (SCA1), Spinocerebellar ataxias 2 (SCA2), Spinocerebellar ataxias 3 (SCA3), Spinocerebellar ataxias 6 (SCA6), Spinocerebellar ataxias 7 (SCA7), Spinocerebellar ataxias 11 (SCA11), Dentatorubral pallidolusyian atrophy (DRPLA) and Gluten ataxia), Batten Disease or neuronal ceroid lipofuscinoses (NCL) (infantile NCL (INCL), late infantile NCL (LINCL), juvenile NCL (JNCL) or adult NCL (ANCL)), Alzheimer's Disease (Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD)), Optic neuritis (ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD) (Asperger's Syndrome, Pervasive Developmental Disorders (PDDs), Childhood Disintegrative Disorder (CDD), and Autistic disorder), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression (Major Depression,

Dysthymia, Postpartum Depression, Seasonal Affective Disorder, Atypical Depression, Psychotic Depression, Bipolar Disorder, Premenstrual Dysphoric Disorder, Situational Depression), Parkinson's disease (Idiopathic Parkinson's disease, Vascular parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Drug-induced Parkinsonism, Juvenile Parkinson's and atypical parkinsonism), mitochondrial diseases, developmental disorders, metabolic syndrome (increased blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol levels) and/or autoimmune disorders.

**[0041]** Wildtype C57BL/6J mice were treated with 2, 4-dinitrophenol for two weeks daily by oral gavage at 0.5, 1.0, 5.0, and 10.0 mg/kg DNP or placebo, N=8 per group. Brain tissue was used for semi quantitative polymerase chain reaction (PCR) to determine endogenous BDNF levels normalized to GapDH to determine delta-delta CT changes in mRNA. Data shows the delta-delta CT change for each dose level of DNP expressed as a percent change relative to the control group, which was given a placebo.

**[0042]** Fig. 1 shows that administration of DNP in Wildtype Mouse increases BDNF levels in the brain between 0.1 mg/kg DNP and 10 mg/kg DNP, and we have identified a bell-shaped curve such that at the higher dose of 10.0 mg/kg DNP, less BDNF is expressed. In one embodiment, a higher dose range of DNP may benefit patient populations that are in need of higher BDNF levels, such as Huntington's Disease, Rett Syndrome, Epilepsy, and Multiple Sclerosis (MS), and other forms of neurodegeneration and muscle or neuromuscular disorders, since BDNF is a myokine and can provide a positive benefit to muscle wasting.

**[0043]** Figure 2a shows the changes of BDNF protein levels by immunoblot from a mouse model of MS, Experimental Autoimmune Encephalomyelitis (EAE). The tissue was taken on Day 42 of the study during the recovery phase from the lumbal spinal cord of representative mice that were immunized on Day 1 with the MOG peptide, then treated with MP101 starting on Day 7 and stopping on Day 21. Intensity of the BDNF band increases from placebo, to 0.5 mg/kg, to 1 mg/kg, with a plateau effect at 5 mg/kg. Untreated animals are shown as naïve. The changes in BDNF levels are therefore 3-weeks post-treatment with DNP (aka MP101). DNP not only increases BDNF, but the effect of increasing BDNF has a lasting effect that is not obvious until now.

**[0044]** Figure 2b shows the percent changes of BDNF protein levels by immunoblot from a mouse model of MS, Experimental Autoimmune encephalomyelitis (EAE) 3-weeks post-treatment.

**[0045]** Figure 2c shows the effect of MP101 on progression of the phenotype in the MS model on clinical scores showing attenuation of disease progression.

**[0046]** Figure 2d shows a representative mouse spinal cord electron microscopy image at Day-16 (~peak of onset) of MP101 5 mg/kg treated mouse compared to placebo. The protective myelin sheaths surrounding the axons and axons are completely intact as compared to the placebo group.

**[0047]** Therefore, we have tested DNP to induce BDNF in the brain of wildtype model by mRNA changes and tested DNP to increase BDNF at the protein level with a demonstration of providing a protective effect in a model of MS, the Experimental Autoimmune Encephalomyelitis (EAE).

**[0048]** MP101 was tested in a model of Rett Syndrome using Mecp2 mutant mice. Rett Syndrome is a developmental disorder in young girls, with first symptoms starting at about 18-months of age, including reduced head growth. Figures 3a, 3b, 3c and 4 show the effects of treating these mutant mice with MP101 at 0.5, 1 mg/kg and 5 mg/kg by oral gavage.

**[0049]** In Figures 3a and 3b, Mecp2 mutant mice, a model of Rett Syndrome, were treated with MP101 (DNP) at 6-weeks of age and tested on their coordination to walk on a rotating cylinder (rotarod). Wildtype mice are used as a benchmark for general decline in behavior compared to Mecp2 mutant mice treated with Vehicle, 0.5mg/kg MP101, 1mg/kg MP101 and 5mg/kg MP101 by oral gavage. In Fig. 3a, the data shows that at 8-weeks of age, the mutant vehicle treated mice lost their ability to walk on the rotarod, whereas the wildtype mice and drug treated animals fall less and can handle higher speeds of rotation. In Fig. 3b, the data shows similar findings at Week-12 of age after 1-month of treatment.

**[0050]** In Figure 4, we show the results of Mecp2 mutant mice at 12-weeks of age and after 1-month of oral gavage treatment, which shows an effect in the "clasping test" at 1 mg/kg MP101.

**[0051]** In addition, Alzheimer's Disease, representing about 70% of all dementia cases, was evaluated using the APP/PS1 mice, which express the APPswe mutation and PS1deltaE9 mutation and develop relatively rapid Aβ pathology and cognitive deficits. At 4-months of age, the APP/PS1 mice were treated for 4-months by oral gavage delivery with MP101 (DNP) at 0.5, 1 and 5 mg/kg. Figs. 5a, 5b and 5c show that MP101 have improved cognition compared to Vehicle treated mice. The amount of time spent in the quadrant is an indicator of whether the mice remember the general location, with increased time indicating increased memory.

**[0052]** Figs 5a, 5b and 5c show that at all doses with DNP, the APP/PS1 mice improved in short term memory when tested on the Morris Water Maze for cognition in remembering where the hidden platform was, relative to vehicle which could not. Fig. 5a shows the distance traveled looking for the platform in the quadrant with the hidden platform, Fig. 5b shows the amount of time spent in the quadrant where the platform is hidden, and Fig. 5c shows the number of entries from the platform. The amount of time spent in the quadrant is an indicator of whether the subject remembers the general location.

**[0053]** DNP was also evaluated for a treatment of Epilepsy. The kanic acid model is an acute model of epilepsy caused by an injection in the right hippocampus of an analogue of glutamate (kanic acid) that over-stimulates the neurons causing death. Figure 6 shows the effect of treating wildtype mice for 14-days by oral gavage at 1, 5 and 10 mg/kg with MP101 (DNP), prior to injection of kanic acid to determine if DNP as a protective effect to the effects on over-stimulation and death by kanic acid.

**[0054]** Figure 6 shows that after 2-weeks of treatment with MP101 (DNP) at 1, 5 and 10 mg/kg by oral gavage and then a kanic acid injection into the brain of a mouse, there is a shortening of seizure time. DNP provided neural protection from over-stimulation caused by kanic acid relative to the Vehicle.

[0055] The merits of treating Parkinson's Disease with MP101 (DNP) was evaluated in wildtype mice and SIRT3 KO mice with 6-OHDA injections after two weeks of MP101 treatment. We examined the neuroprotective effects of varying MP-101 doses (0.5, 1, 5 mg/kg) against dopaminergic degeneration of nigrostriatal neurons induced by a single unilateral stereotaxic injection of neurotoxin 6-hydroxydopamine (6-OHDA) in the right striatum of the brain of 2-3 month old male C57Bl/6 mice or SIRT3 KO mice. SIRT3 KO is a model of a heightened sensitivity to glutamate-induced calcium overload and excitotoxicity, and oxidative and mitochondrial stress, therefore ideal for evaluating Parkinson's Disease, Huntington's Disease and temporal lobe epilepsy. Figure 7 shows that MP101 protected the dopaminergic neurons from the toxic effects of 6-OHDA.

[0056] Figs. 7a and 7b show the effects of DNP (MP101) treatment for 14-Days by oral gavage in protecting dopaminergic neuronal loss when the right striatum is injected with 6-OHDA after the last day. Fig. 7a show that when the mice are placed in a cylinder, the percent of left and right paw touches on the wall is improved in wildtype mice, and Fig. 7b shows that in the SIRT3 KO mice, which are more vulnerable to Parkinson's disease, there is improved motor coordination when treated with MP101 (DNP) and placed on a rotating cylinder (rotarod).

[0057] MP101 (DNP) was used in a mouse model of Huntington's Disease, the "Fragment Model" N171-82 HD mice, to determine its neuroprotective effects. The N171-82 HD mice were treated with MP101 at 0.5, 1 and 5 mg/kg by oral gavage daily for greater than 17-weeks. At the age of 26-weeks (17-weeks of treatment), the mice were tested for changes in behavioral, loss of brain volume, spiny neurons and general neurons. Figs 8a, 8b, 8c, 8d, 8e, and 8f show the effects of DNP (MP101 drug treatment).

[0058] Figs 8a-8f show the effects of MP101 in the Huntington's Disease model N171-82Q after 13-weeks (age 22 weeks) and/or 17-weeks (age 26-weeks) of treatment with DNP. Fig. 8a shows an MRI image of brain volume changes of wildtype (WT), mutant Huntington mice Vehicle (HD) and MP101 treated mice (HD-MP101). Fig. 8b shows the quantitative brain volume loss in the cortex. Fig. 8c shows the quantitative brain volume loss in the striatum. HD placebo (HD) shows loss in both Ctx and Str. MP-101 shows

minor loss in cortex and striatum. Fig. 8d shows that treatment with DNP preserves medium spiny neurons using biomarker DARPP32 at 26-weeks of age. Fig. 8e shows that treatment with DNP preserves general neuronal loss with biomarker to postsynaptic protein PSD95 levels in N171-82Q HD mice. Fig. 8f shows that treatment with DNP improves motor function in both the tapered beam and balance beam after 17-weeks of treatment.

**[0059]** In view of the foregoing, the present invention describes methods and formulations related to the effective use of DNP to increase BDNF to attenuate disease progression or provide remission of symptoms in certain diseases.

Method of Use

**[0060]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0061]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.001 mg/kg of body weight to about 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0062]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an

effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.01 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0063]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.01 mg/kg of body weight to about 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0064]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.01 mg/kg of body weight to 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0065]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.01 mg/kg of body

weight to about 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0066]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.005 mg/kg of body weight to 2 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0067]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.005 mg/kg of body weight to about 2 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0068]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.02 mg/kg of body weight to 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0069] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.02 mg/kg of body weight to about 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0070] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.02 mg/kg of body weight to 0.06 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0071] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.02 mg/kg of body weight to about 0.06 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0072] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned

diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.05 mg/kg of body weight to 0.09 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0073]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.05 mg/kg of body weight to about 0.09 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0074]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.2 mg/kg of body weight to 0.6 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0075]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the

effective dose of the DNP is continued in the dose range of about 0.2 mg/kg of body weight to about 0.6 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0076]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.5 mg/kg of body weight to 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0077]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.5 mg/kg of body weight to about 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0078]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.01 mg/kg of body weight to 0.1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0079] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.01 mg/kg of body weight to about 0.1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0080] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.01 mg/kg of body weight to 0.5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0081] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.01 mg/kg of body weight to about 0.5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

[0082] In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned

diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.05 mg/kg of body weight to 0.5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0083]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.05 mg/kg of body weight to about 0.5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0084]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.05 mg/kg of body weight to 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0085]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, autoimmune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the

effective dose of the DNP is continued in the dose range of about 0.05 mg/kg of body weight to about 0.9 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0086]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.02 mg/kg of body weight to 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0087]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging and any of the aforementioned diseases or conditions, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.02 mg/kg of body weight to about 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0088]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.01 mg/kg of body weight to 0.1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0089]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.01 mg/kg of body weight to about 0.1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0090]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.1 mg/kg of body weight to 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0091]** In one embodiment, a method of use of the invention may include a method of treating a neurodegenerative, neuromuscular, developmental, metabolic, auto-immune or mitochondrial disorder, including those related to aging, comprising administering to a patient in need of treatment an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 0.1 mg/kg of body weight to about 1 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0092]** In one embodiment, a method of use of the invention may include a method of treating neuromuscular or neurodegenerative disorder related to aging, comprising administering to a patient in need of treatment of a traumatic CNS injury or neurodegenerative disease an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 1 mg/kg

of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0093]** In one embodiment, a method of use of the invention may include a method of treating neuromuscular or neurodegenerative disorder related to aging, comprising administering to a patient in need of treatment of a traumatic CNS injury or neurodegenerative disease an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of about 1 mg/kg of body weight to about 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

**[0094]** In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described herein, is in the dose range of about 0.001 mg/kg of body weight to about 5 mg/kg of body weight, about 0.001 mg/kg of body weight to about 4 mg/kg of body weight, about 0.001 mg/kg of body weight to about 3 mg/kg of body weight, about 0.001 mg/kg of body weight to about 0.005 mg/kg of body weight, about 0.005 mg/kg of body weight to about .01 mg/kg of body weight, about 0.01 mg/kg of body weight to about 1 of body weight, about 0.01 mg/kg of body weight to about 0.1 of body weight, about 0.02 mg/kg of body weight to about 0.08 of body weight, about 0.025 mg/kg of body weight to about 0.06 of body weight, about 0.03 mg/kg of body weight to about 0.05 of body weight, about 0.05 mg/kg of body weight to about 0.1 of body weight, about 0.04 mg/kg of body weight to about 0.06 of body weight, about 0.06 mg/kg of body weight to about 0.09 of body weight, about 0.07 mg/kg of body weight to about 0.08 of body weight, about 0.09 mg/kg of body weight to about 0.11 of body weight, about 0.1 mg/kg of body weight to about 0.5 of body weight, about 0.2 mg/kg of body weight to about 0.4 of body weight, about 0.3 mg/kg of body weight to about 0.5 of body weight, about 0.4 mg/kg of body weight to about 0.6 of body weight, about 0.5 mg/kg of body weight to about 1 of body weight, about 0.6 mg/kg of body weight to about 0.9 of body weight, about 0.7 mg/kg of body weight to about 0.8 of body weight, about 0.8 mg/kg of body weight to about 1.2 mg/kg of body weight, about 1 mg/kg of body weight to about 5 mg/kg of body weight, or about 2 mg/kg of body weight to about 4 of body weight.

[0095] In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described herein, is in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight, 0.001 mg/kg of body weight to 4 mg/kg of body weight, 0.001 mg/kg of body weight to 3 mg/kg of body weight, 0.001 mg/kg of body weight to 0.005 mg/kg of body weight, 0.005 mg/kg of body weight to 0.01 mg/kg of body weight, 0.01 mg/kg of body weight to 1 of body weight, 0.01 mg/kg of body weight to 0.1 of body weight, 0.02 mg/kg of body weight to 0.08 of body weight, 0.025 mg/kg of body weight to 0.06 of body weight, 0.03 mg/kg of body weight to 0.05 of body weight, 0.05 mg/kg of body weight to 0.1 of body weight, 0.04 mg/kg of body weight to 0.06 of body weight, 0.06 mg/kg of body weight to 0.09 of body weight, 0.07 mg/kg of body weight to 0.08 of body weight, 0.09 mg/kg of body weight to 0.11 of body weight, 0.1 mg/kg of body weight to 0.5 of body weight, 0.2 mg/kg of body weight to 0.4 of body weight, 0.3 mg/kg of body weight to 0.5 of body weight, 0.4 mg/kg of body weight to 0.6 of body weight, 0.5 mg/kg of body weight to 1 of body weight, 0.6 mg/kg of body weight to 0.9 of body weight, 0.7 mg/kg of body weight to 0.8 of body weight, 0.8 mg/kg of body weight to 1.2 mg/kg of body weight, 1 mg/kg of body weight to 5 mg/kg of body weight, or 2 mg/kg of body weight to 4 of body weight.

[0096] In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described herein, is about 0.001 mg/kg, about 0.002 mg/kg, about 0.003 mg/kg, about 0.004 mg/kg, about 0.005 mg/kg, about 0.006 mg/kg, about 0.007 mg/kg, about 0.008 mg/kg, about 0.009 mg/kg, about 0.01 mg/kg, about 0.015 mg/kg, about 0.02 mg/kg, about 0.025 mg/kg, about 0.03 mg/kg, about 0.035 mg/kg, about 0.04 mg/kg, about 0.045 mg/kg, about 0.05 mg/kg, about 0.055 mg/kg, about 0.06 mg/kg, about 0.065 mg/kg, about 0.07 mg/kg, about 0.075 mg/kg, about 0.08 mg/kg, about 0.085 mg/kg, about 0.09 mg/kg, about 0.095 mg/kg, about 0.1 mg/kg, about 0.15 mg/kg, about 0.2 mg/kg, about 0.25 mg/kg, about 0.3 mg/kg, about 0.35 mg/kg, about 0.4 mg/kg, about 0.45 mg/kg, about 0.5 mg/kg, about 0.55 mg/kg, about 0.6 mg/kg, about 0.65 mg/kg, about 0.7 mg/kg, about 0.75 mg/kg, about 0.8 mg/kg, about 0.85 mg/kg, about 0.9 mg/kg, about 0.95 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg,

about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5.0 mg/kg.

**[0097]** In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described herein, is 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, 0.006 mg/kg, 0.007 mg/kg, 0.008 mg/kg, 0.009 mg/kg, 0.01 mg/kg, 0.015 mg/kg, 0.02 mg/kg, 0.025 mg/kg, 0.03 mg/kg, 0.035 mg/kg, 0.04 mg/kg, 0.045 mg/kg, 0.05 mg/kg, 0.055 mg/kg, 0.06 mg/kg, 0.065 mg/kg, 0.07 mg/kg, 0.075 mg/kg, 0.08 mg/kg, 0.085 mg/kg, 0.09 mg/kg, 0.095 mg/kg, about 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.35 mg/kg, 0.4 mg/kg, 0.45 mg/kg, 0.5 mg/kg, 0.55 mg/kg, 0.6 mg/kg, 0.65 mg/kg, 0.7 mg/kg, 0.75 mg/kg, 0.8 mg/kg, 0.85 mg/kg, 0.9 mg/kg, 0.95 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, or 5.0 mg/kg.

**[0098]** In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described herein, is about 10 mg/kg of body weight or less, about 5 mg/kg of body weight or less, about 4.5 mg/kg or less, about 4 mg/kg or less, about 3.5 mg/kg or less, about 3 mg/kg or less, about 2.5 mg/kg or less, about 2 mg/kg or less, about 1.5 mg/kg or less, about 1 mg/kg or less, about 0.95 mg/kg or less, about 0.9 mg/kg or less, about 0.85 mg/kg or less, about 0.8 mg/kg or less, about 0.75 mg/kg or less, about 0.7 mg/kg or less, about 0.65 mg/kg or less, about 0.6 mg/kg or less, about 0.55 mg/kg or less, about 0.5 mg/kg or less, about 0.45 mg/kg or less, about 0.4 mg/kg or less, about 0.35 mg/kg or less, about 0.3 mg/kg or less, about 0.25 mg/kg or less, about 0.2 mg/kg or less, about 0.15 mg/kg or less, about 0.1 mg/kg or less, about 0.09 mg/kg or less, about 0.08 mg/kg or less, about 0.07 mg/kg or less, about 0.06 mg/kg or less, about 0.05 mg/kg or less, about 0.04 mg/kg or less, about 0.03 mg/kg or less, about 0.02 mg/kg or less, about 0.01 mg/kg or less, or about 0.005 mg/kg or less. In all cases, the doses described herein are greater than zero mg/kg.

**[0099]** In an embodiment, administration of DNP, or a pharmaceutically acceptable salt thereof, in any form or combination as described herein, for any purpose as described

herein, is about 4 mg/kg or more, about 3.5 mg/kg or more, about 3 mg/kg or more, about 2.5 mg/kg or more, about 2 mg/kg or more, about 1.5 mg/kg or more, about 1 mg/kg or more, about 0.95 mg/kg or more, about 0.9 mg/kg or more, about 0.85 mg/kg or more, about 0.8 mg/kg or more, about 0.75 mg/kg or more, about 0.7 mg/kg or more, about 0.65 mg/kg or more, about 0.6 mg/kg or more, about 0.55 mg/kg or more, about 0.5 mg/kg or more, about 0.45 mg/kg or more, about 0.4 mg/kg or more, about 0.35 mg/kg or more, about 0.3 mg/kg or more, about 0.25 mg/kg or more, about 0.2 mg/kg or more, about 0.15 mg/kg or more, about 0.1 mg/kg or more, about 0.09 mg/kg or more, about 0.08 mg/kg or more, about 0.07 mg/kg or more, about 0.06 mg/kg or more, about 0.05 mg/kg or more, about 0.04 mg/kg or more, about 0.03 mg/kg or more, about 0.02 mg/kg or more, about 0.01 mg/kg or more, about 0.009 mg/kg or more, about 0.007 mg/kg or more, about 0.005 mg/kg or more, about 0.003 mg/kg or more, or about 0.001 mg/kg or more. In all cases, the doses described herein are less than 10 mg/kg.

**[00100]** In some examples, the effective dose is delivered orally. In some examples, the effective does is delivered intravenously. In some examples, the effective does is delivered intravenously by means of an intravenous drip along with saline. In some examples, the effective does is delivered intravenously by means of an intravenous drip along with other medicines, vitamins, fluids or nutrition. In some examples, the effective does is delivered subcutaneously. In some examples, the effective dose is delivered topically. In some examples, the effective dose is delivered transdermally. In some examples, the effective dose is combined with other necessary medicines, vitamins, fluids or nutrition.

**[00101]** In some examples, the effective dose is used to treat, prevent or alleviate any of the following diseases or conditions by inducing BDNF with DNP treatment: Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease (Adult-onset Huntington's, Juvenile Huntington's disease), Epilepsy (Cluster Seizures, Refractory Seizures, Atypical Absence Seizures, Atonic Seizures, Clonic Seizures, myoclonic seizures, tonic seizures, Tonic-Clonic Seizures, Simple Partial Seizures, Complex Partial Seizures, Secondary Generalized Seizures, Febrile Seizures, Nonepileptic Seizures, Gelastic and Dacrystic Seizures, and Absence Seizures), Multiple Sclerosis (MS) (relapse-remitting multiple sclerosis (RRMS), Secondary-progressive MS (SPMS), Primary-progressive MS

(PPMS), and Progressive-relapsing MS (PRMS)), Lupus (Systemic Lupus Erythematosus (SLE), discoid (cutaneous), drug-induced lupus (dil) and neonatal lupus), Diabetes mellitus (Type-1 Diabetes, Type-2 Diabetes, Maturity Onset Diabetes of the Young (MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODY10, MODY11)), Schizophrenia (Paranoid schizophrenia, Disorganized schizophrenia, Catatonic schizophrenia, Residual schizophrenia, Schizoaffective disorder), Myasthenia gravis (MG) (ocular myasthenia gravis, Congenital MG and generalized myasthenia gravis), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), Muscular Dystrophy (Duchenne Muscular Dystrophy (DMD), Becker, Myotonic, Congenital, Emery-Dreifuss, Facioscapulohumeral, Limb-girdle, Distal, and Oculopharyngeal), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Ataxia (Friedreich's Ataxia, Spinocerebellar ataxias 1 (SCA1), Spinocerebellar ataxias 2 (SCA2), Spinocerebellar ataxias 3 (SCA3), Spinocerebellar ataxias 6 (SCA6), Spinocerebellar ataxias 7 (SCA7), Spinocerebellar ataxias 11 (SCA11), Dentatorubral pallidolusyian atrophy (DRPLA) and Gluten ataxia), Batten Disease or neuronal ceroid lipofuscinoses (NCL) (infantile NCL (INCL), late infantile NCL (LINCL), juvenile NCL (JNCL) or adult NCL (ANCL)), Alzheimer's Disease (Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD)), Optic neuritis (ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD) (Asperger's Syndrome, Pervasive Developmental Disorders (PDDs), Childhood Disintegrative Disorder (CDD), and Autistic disorder), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression (Major Depression, Dysthymia, Postpartum Depression, Seasonal Affective Disorder, Atypical Depression, Psychotic Depression, Bipolar Disorder, Premenstrual Dysphoric Disorder, Situational Depression), Parkinson's disease (Idiopathic Parkinson's disease, Vascular parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Drug-induced Parkinsonism, Juvenile Parkinson's and atypical parkinsonism), mitochondrial diseases, developmental disorders, metabolic syndrome (increased blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol levels) and/or autoimmune disorders.

**[00102]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.005 mg/kg to 1.0 mg/kg. In some examples, the

effective dose used to treat, prevent or alleviate Huntington's disease is 0.01 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.01 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.02 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.02 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.025 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.025 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.03 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.035 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.035 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.035 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.035 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.035 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.045 mg/kg to 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.055 mg/kg to 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.055 mg/kg to 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.065 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.075 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.07 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.085 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.09 mg/kg to 0.2 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is 0.1 mg/kg to 0.3 mg/kg. In some examples, the

effective dose used to treat, prevent or alleviate Huntington's disease is 0.2 mg/kg to 0.4 mg/kg.

**[00103]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is about 0.005 mg/kg to about 1.0 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.01 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.01 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.02 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.02 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.025 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.025 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.03 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.035 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.035 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.035 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.035 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.035 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.045 mg/kg to about 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.055 mg/kg to about 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.055 mg/kg to about 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.065 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.075 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to

treat, prevent or alleviate Huntington's disease is about 0.07 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.085 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.09 mg/kg to about 0.2 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.1 mg/kg to about 0.3 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Huntington's disease is about 0.2 mg/kg to about 0.4 mg/kg.

**[00104]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.001 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.002 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.003 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.004 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.005 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.01 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.025 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.035 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.05 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.075 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.1 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.5 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.35 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the

symptoms of Huntington's disease is 0.25 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.075 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.05 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Huntington's disease is 0.01 mg/kg or less. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

**[00105]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is 0.01 mg/kg to 5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is 0.01 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is 0.05 mg/kg to 5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is 0.05 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.06 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.07 mg/kg to 0.9 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.075 mg/kg to 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.07 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.08 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.1 mg/kg to 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.3 mg/kg to 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.4 mg/kg to 0.7 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.7 mg/kg to 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.8 mg/kg to 1 mg/kg.

**[00106]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is about 0.05 mg/kg to about 5 mg/kg. In some

examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is about 0.01 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is about 0.05 mg/kg to about 5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Multiple Sclerosis (MS) is about 0.05 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.06 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.07 mg/kg to about 0.9 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.075 mg/kg to about 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.07 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.08 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.1 mg/kg to about 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.3 mg/kg to about 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.4 mg/kg to about 0.7 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.7 mg/kg to about 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is about 0.8 mg/kg to about 1 mg/kg.

**[00107]** In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 1.0 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.9 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.8 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.7 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.6 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.5 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.4 mg/kg or less. In some examples, the effective dose used to treat,

prevent or alleviate Multiple Sclerosis (MS) is 0.3 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.2 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.09 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.08 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.07 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.05 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.01 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.05 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.06 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.07 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.08 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.09 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.1 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.15 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.2 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.25 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.3 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.35 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.4 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.45 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.5 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.55 mg/kg or more. In some examples, the effective dose used to treat,

prevent or alleviate Multiple Sclerosis (MS) is 0.6 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.65 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.70 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.75 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.8 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 1.0 mg/kg or more. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

**[00108]** In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.05 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.5 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.6 mg/kg to 0.9 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.7 mg/kg to 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is about 0.5 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is about 0.6 mg/kg to about 0.9 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is about 0.7 mg/kg to about 0.8 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.1 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.4 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.5 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.6 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.7 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.8 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.9 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.8 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Epilepsy is 0.7 mg/kg or less. In some examples,

the effective dose used to treat, prevent or alleviate Epilepsy is 0.5 mg/kg or less. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

**[00109]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.005 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.02 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.01 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.02 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.025 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.025 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.03 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.035 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.035 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.035 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.035 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.035 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.045 mg/kg to 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.055 mg/kg to 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.055 mg/kg to 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.065 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.075 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.07 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.085 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is 0.09 mg/kg to 0.2 mg/kg.

[00110] In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is about 0.005 mg/kg to about 1.0 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.02 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.01 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.02 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.025 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.025 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.03 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.035 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.035 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.035 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.035 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.035 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.045 mg/kg to about 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.055 mg/kg to about 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.055 mg/kg to about 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.065 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.075 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.07 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.085 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Rett Syndrome is about 0.09 mg/kg to about 0.2 mg/kg.

**[00111]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.01 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.02 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.03 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.04 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.05 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.06 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.07 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.08 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.09 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.5 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.3 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.075 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.05 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Rett Syndrome is 0.01 mg/kg or less. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

**[00112]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is 0.01 mg/kg to 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is 0.01 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is 0.05 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.05 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or

alleviate Parkinson's Disease is 0.06 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.07 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.08 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.09 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.075 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.09 mg/kg to 0.2 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.1 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.2 mg/kg to 0.5 mg/kg.

**[00113]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is about 0.01 mg/kg to about 1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is about 0.01 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Parkinson's Disease is about 0.05 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.05 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.06 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.07 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.08 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.09 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.075 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.09 mg/kg to about 0.2 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.1 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is about 0.2 mg/kg to about 0.5 mg/kg.

[00114] In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 1.0 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.5 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.4 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.3 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.2 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.09 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.08 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.07 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.05 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.01 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.05 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.06 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.07 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.08 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.09 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.1 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.15 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.2 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.25 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.3 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Multiple Sclerosis (MS) is 0.35 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.4 mg/kg or more. In some examples, the effective dose used to treat, prevent or

alleviate Parkinson's Disease is 0.45 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate Parkinson's Disease is 0.5 mg/kg or more. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

**[00115]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is .005 mg/kg to 1.0 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.01 mg/kg to 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.02 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.025 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.025 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.03 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.035 mg/kg to 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.035 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.035 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.035 mg/kg to 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.035 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.045 mg/kg to 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.055 mg/kg to 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.055 mg/kg to 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.065 mg/kg to 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.075 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.07 mg/kg to 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.085 mg/kg to 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.09 mg/kg to 0.2 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.1 mg/kg to 0.3 mg/kg. In some

examples, the effective dose used to treat, prevent or alleviate Alzheimer's is 0.2 mg/kg to 0.4 mg/kg.

**[00116]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is about 0.005 mg/kg to about 1.0 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.01 mg/kg to about 0.5 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.02 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.025 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.025 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.03 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.035 mg/kg to about 0.4 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.035 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.035 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.035 mg/kg to about 0.08 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.035 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.045 mg/kg to about 0.055 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.055 mg/kg to about 0.085 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.055 mg/kg to about 0.065 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.065 mg/kg to about 0.075 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.075 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.07 mg/kg to about 0.09 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.085 mg/kg to about 0.1 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.09 mg/kg to about 0.2 mg/kg. In some examples, the effective

dose used to treat, prevent or alleviate Alzheimer's is about 0.1 mg/kg to about 0.3 mg/kg. In some examples, the effective dose used to treat, prevent or alleviate Alzheimer's is about 0.2 mg/kg to about 0.4 mg/kg.

**[00117]** In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.001 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.002 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.003 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.004 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.005 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.01 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.025 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.035 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.05 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.075 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.1 mg/kg or more. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.5 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.35 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.25 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.1 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.075 mg/kg or less. In some examples, the effective dose used to treat, prevent or alleviate the symptoms of Alzheimer's is 0.05 mg/kg or less. In all cases, the dose described herein is greater than zero mg/kg and less than 5 mg/kg.

[00118] In some examples, the invention is a method of treating any of these diseases, or of treating neuromuscular, neurodegenerative, autoimmune, developmental, metabolic, or any disorder related to aging, comprising administering to a patient in need of treatment of a traumatic CNS injury or neurodegenerative disease an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over a period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight to induce BDNF expression in brain. Indeed, the invention comprises administration of DNP, wherein the dose of DNP is useful to prevent harm in humans, as a means to avoid inducing too much BDNF, or have no effect by inducing too little BDNF. As is also apparent from the disclosures herein, the invention also comprises enhancing expression of BDNF, which provides protection from muscle wasting or muscle dysfunction, since BDNF is expressed not only in brain, but in muscle and may act as a myokine.

[00119] In some examples, the invention is a method of treating neuromuscular or neurodegenerative or autoimmune or developmental or metabolic disorders, comprising receiving an effective dose of DNP, or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is continued to be received in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms. In some examples, the invention is a method of treating neuromuscular or neurodegenerative or autoimmune or developmental or metabolic disorders, comprising providing instructions to administer an effective dose DNP, or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease, wherein the effective dose of the DNP is instructed to be received in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight.

[00120] In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of BDNF for up to three weeks after the last dose of DNP is received. In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of

BDNF for up to two weeks after the last dose of DNP is received. In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of BDNF for up to one week after the last dose of DNP is received. In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of BDNF for up to three days after the last dose of DNP is received. In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of BDNF for up to two days after the last dose of DNP is received. In some examples, the invention is a method of treating any of the diseases identified herein, whereby the effective dose of DNP has a lasting effect on sustaining elevated levels of BDNF for up to one day after the last dose of DNP is received.

**[00121]** In an embodiment, a dose encompassed herein may be administered as a composition based on the weight of the subject. In an embodiment, a dose may be administered per unit weight of the subject (e.g., mg of a composition described herein per kg weight of subject). In an embodiment, a dose encompassed herein may be administered as a composition based solely on the weight of the dose, without regard to the weight of the subject (e.g., mg of a composition described herein per dose administered to subject). In an embodiment, the dose is determined based on the weight of the active ingredients in the carrier. In another embodiment, the dose is determined based on the total weight of the active ingredients of the composition in the carrier. We are presuming in our dose range, that the average adult patient weights approximately 60 kg.

Composition

**[00122]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising an effective dose of DNP, wherein the effective dose of the DNP is in the range of 0.001 mg/kg of body weight to 5 mg/kg of body weight; 0.01 mg/kg to 1 mg/kg; 0.01 mg/kg to 0.1 mg/kg; 0.1 mg/kg to 0.5 mg/kg; or 1 mg/kg to 5 mg/kg. In some embodiments, the

pharmaceutical composition is an effective dose to induce BDNF expression to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting.

**[00123]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising an effective dose of DNP, wherein the effective dose of the DNP is in the range of about 0.001 mg/kg of body weight to about 5 mg/kg of body weight; about 0.01 mg/kg to about 1 mg/kg; about 0.01 mg/kg to about 0.1 mg/kg; about 0.1 mg/kg; about 0.1 mg/kg to about 0.5 mg/kg; about 0.5 mg/kg; about 1 mg/kg; about 1 mg/kg to about 5 mg/kg; about 5 mg/kg. In some embodiments, the pharmaceutical composition is an effective dose to induce BDNF expression to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting.

**[00124]** In some embodiments, the pharmaceutical composition is an immediate release formation. In some embodiments, the pharmaceutical composition is rapidly dissolving. In some embodiments, the pharmaceutical composition is a sustained release formation. In some embodiments, the pharmaceutical composition is a controlled release formation.

**[00125]** In other embodiments, as set forth in greater detail elsewhere herein, the dosage and dosing regimen for the active ingredients may be optimized based on the health and condition of the subject to be treated, as well as the desired outcome of the treatment.

Unit Dose

**[00126]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is in the range of about 0.1 mg to about 300 mg; wherein the unit dose is in the range of about 0.1 mg to about 1 mg; wherein the unit dose is in the range of about 1 mg to about 5 mg; wherein the unit dose is about 1 mg; wherein the unit dose is about 2 mg; wherein the unit dose is about 3 mg; wherein the unit dose is about 4 mg; wherein the unit dose is about 5 mg; wherein the unit dose is the range of about 5 mg to about 10 mg; wherein the unit dose is about 6 mg; wherein the unit dose is about 7 mg; wherein the unit dose is about 8 mg; wherein the unit dose is about 9 mg; wherein the unit dose is about 10 mg; wherein the unit dose is the range of about 10 mg to about 15 mg; wherein the unit dose is about 11 mg; wherein the unit dose is about 12 mg; wherein

the unit dose is about 13 mg; wherein the unit dose is about 14 mg; wherein the unit dose is about 15 mg; wherein the unit dose is the range of about 15 mg to about 20 mg; wherein the unit dose is about 16 mg; wherein the unit dose is about 17 mg; wherein the unit dose is about 18 mg; wherein the unit dose is about 19 mg; wherein the unit dose is about 20 mg; wherein the unit dose is the range of about 20 mg to about 30 mg; wherein the unit dose is about 25 mg; wherein the unit dose is about 30 mg; wherein the unit dose is the range of about 30 mg to about 40 mg; wherein the unit dose is about 35 mg; wherein the unit dose is about 40 mg; wherein the unit dose is the range of about 40 mg to about 50 mg; wherein the unit dose is about 45 mg; wherein the unit dose is about 50 mg; wherein the unit dose is the range of about 50 mg to about 100 mg; wherein the unit dose is about 75 mg; wherein the unit dose is about 100 mg; wherein the unit dose is the range of about 100 mg to about 200 mg; wherein the unit dose is about 150 mg; wherein the unit dose is about 200 mg; wherein the unit dose is the range of about 200 mg to about 300 mg; wherein the unit dose is about 200 mg; wherein the unit dose is about 250 mg; or wherein the unit dose is about 300 mg.

**[00127]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is in the range of 0.1 mg to 300 mg; wherein the unit dose is in the range of 0.1 mg to 1 mg; wherein the unit dose is in the range of 1 mg to 5 mg; wherein the unit dose is 1 mg; wherein the unit dose is 2 mg; wherein the unit dose is 3 mg; wherein the unit dose is 4 mg; wherein the unit dose is 5 mg; wherein the unit dose is the range of 5 mg to 10 mg; wherein the unit dose is 6 mg; wherein the unit dose is 7 mg; wherein the unit dose is 8 mg; wherein the unit dose is 9 mg; wherein the unit dose is 10 mg; wherein the unit dose is the range of 10 mg to 15 mg; wherein the unit dose is 11 mg; wherein the unit dose is 12 mg; wherein the unit dose is 13 mg; wherein the unit dose is 14 mg; wherein the unit dose is 15 mg; wherein the unit dose is the range of 15 mg to 20 mg; wherein the unit dose is 16 mg; wherein the unit dose is 17 mg; wherein the unit dose is 18 mg; wherein the unit dose is 19 mg; wherein the unit dose is 20 mg; wherein the unit dose is the range of 20 mg to 30 mg; wherein the unit dose is 25 mg; wherein the unit dose is 30 mg; wherein the unit dose is the range of 30 mg to 40 mg; wherein the unit dose is 35 mg; wherein the unit dose is 40 mg; wherein the unit dose is the range of 40

mg to 50 mg; wherein the unit dose is 45 mg; wherein the unit dose is 50 mg; wherein the unit dose is the range of 50 mg to 100 mg; wherein the unit dose is 75 mg; wherein the unit dose is 100 mg; wherein the unit dose is the range of 100 mg to 200 mg; wherein the unit dose is 150 mg; wherein the unit dose is 200 mg; wherein the unit dose is the range of 200 mg to 300 mg; wherein the unit dose is 200 mg; wherein the unit dose is 250 mg; or wherein the unit dose is 300 mg.

**[00128]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is in the range of 0.1 mg or more; wherein the unit dose is in the range of 0.5 mg or more; wherein the unit dose is in the range of 1 mg or more; wherein the unit dose is 5 mg or more; wherein the unit dose is 10 mg or more; wherein the unit dose is 15 mg or more; wherein the unit dose is 20 mg or more; wherein the unit dose is 30 mg or more; wherein the unit dose is 40 mg or more; wherein the unit dose is 50 mg or more; wherein the unit dose is 100 mg or more; wherein the unit dose is 150 mg or more; wherein the unit dose is 200 mg or more; or wherein the unit dose is 250 mg or more, but in all cases not greater than 300 mg.

**[00129]** In some embodiments, a pharmaceutical composition includes DNP, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is 0.25 mg or less, but in all cases greater than zero; wherein the unit dose is 0.5 mg or less; wherein the unit dose is 1 mg or less; wherein the unit dose is 5 mg or less; wherein the unit dose is 10 mg or less; wherein the unit dose is 15 mg or less; wherein the unit dose is 20 mg or less; wherein the unit dose is 30 mg or less; wherein the unit dose is 40 mg or less; wherein the unit dose is 50 mg or less; wherein the unit dose is 100 mg or less; wherein the unit dose is 150 mg or less; wherein the unit dose is 200 mg or less; wherein the unit dose is 250 mg or less; or wherein the unit dose is 300 mg or less.

**[00130]** In some embodiments, the unit dose is an immediate release formation. In some embodiments, the unit dose is an extended release formation. In some embodiments, the unit dose is a sustained release formation. In some embodiments, the unit dose is a controlled release formation. In some embodiments, the unit dose is an oral dosage form.

In some embodiments, the oral dosage form is a tablet. In some embodiments, the oral dosage form is a capsule. In some embodiments, the unit dose is a capsule with no filler. In some embodiments, the oral dosage form is rapidly dissolving.

**[00131]** In some embodiments, the unit dose is delivered intravenously. In some embodiments, the unit dose is delivered by means of an intravenous drip along with saline. In some embodiments, the unit dose is delivered by means of an intravenous drip along with saline, other medications, vitamins and/or nourishment. In some embodiments, the unit dose is delivered subcutaneously. In some embodiments, the unit dose is delivered topically. In some embodiments, the unit dose is delivered transdermally. In some embodiments, the unit dose is in the form of a patch.

**[00132]** In some embodiments, the unit dose is an effective amount to induce BDNF expression to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting. In some embodiments, the unit dose is a treatment for Huntington's disease. In some embodiments, the unit dose is a treatment for Multiple Sclerosis (MS). In some embodiments, the unit dose is a treatment for Epilepsy. In some embodiments, the unit dose is a treatment for Parkinson's Disease. In some embodiments, the unit dose is a treatment for Alzheimer's. In some embodiments, the unit dose is a treatment for Rhett Syndrome. In some embodiments, the unit dose is a treatment for, but not limited to, Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease (Adult-onset Huntington's, Juvenile Huntington's disease), Epilepsy (Cluster Seizures, Refractory Seizures, Atypical Absence Seizures, Atonic Seizures, Clonic Seizures, myoclonic seizures, tonic seizures, Tonic-Clonic Seizures, Simple Partial Seizures, Complex Partial Seizures, Secondary Generalized Seizures, Febrile Seizures, Nonepileptic Seizures, Gelastic and Dacrystic Seizures, and Absence Seizures), Multiple Sclerosis (MS) (relapse-remitting multiple sclerosis (RRMS), Secondary-progressive MS (SPMS), Primary-progressive MS (PPMS), and Progressive-relapsing MS (PRMS)), Lupus (Systemic Lupus Erythematosus (SLE), discoid (cutaneous), drug-induced lupus (dil) and neonatal lupus), Diabetes mellitus (Type-1 Diabetes, Type-2 Diabetes, Maturity onset diabetes of the young (MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODY10, MODY11)), Schizophrenia (Paranoid schizophrenia, Disorganized schizophrenia, Catatonic schizophrenia, Residual

schizophrenia, Schizoaffective disorder), Myasthenia gravis (MG) (ocular myasthenia gravis, Congenital MG and generalized myasthenia gravis), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), Muscular Dystrophy (Duchenne Muscular Dystrophy (DMD)), Becker, Myotonic, Congenital, Emery-Dreifuss, Facioscapulohumeral, Limb-girdle, Distal, and Oculopharyngeal), severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Ataxia (Friedreich's Ataxia, Spinocerebellar ataxias 1 (SCA1), Spinocerebellar ataxias 2 (SCA2), Spinocerebellar ataxias 3 (SCA3), Spinocerebellar ataxias 6 (SCA6), Spinocerebellar ataxias 7 (SCA7), Spinocerebellar ataxias 11 (SCA11), Dentatorubral pallidolusyian atrophy (DRPLA) and Gluten ataxia), Batten Disease or neuronal ceroid lipofuscinoses (NCL) (infantile NCL (INCL), late infantile NCL (LINCL), juvenile NCL (JNCL) or adult NCL (ANCL)), Alzheimer's Disease (Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD)), Optic neuritis (ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD) (Asperger's Syndrome, Pervasive Developmental Disorders (PDDs), Childhood Disintegrative Disorder (CDD), and Autistic disorder), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression (Major Depression, Dysthymia, Postpartum Depression, Seasonal Affective Disorder, Atypical Depression, Psychotic Depression, Bipolar Disorder, Premenstrual Dysphoric Disorder, Situational Depression), Parkinson's disease (Idiopathic Parkinson's disease, Vascular parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Drug-induced Parkinsonism, Juvenile Parkinson's and atypical parkinsonism), mitochondrial diseases, developmental disorders, metabolic syndrome (increased blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol levels) and/or autoimmune disorders.

**[00133]** The dose may be administered as a single daily dose, a twice-daily dose, three times daily, or more frequently. The dose may be administered three times weekly, twice weekly, once weekly, or less frequently. In an embodiment, administration frequency may be between 1 and 5 times a day. In another embodiment, administration frequency may be between 2 and 4 times a day. In another embodiment, administration frequency may be at least 3 times a day. In another embodiment, administration frequency may be twice a day. In another embodiment, administration frequency may be once a day. In

another embodiment, administration frequency may be less frequent than once a day. In other embodiments, administration frequency may be once every 2 days or once every 3 days or once every 4 days or once every 5 days or once every 6 days. In another embodiment, administration frequency may be once a week. In another embodiment, administration frequency may change with time, starting at a certain rate, such as once or twice a day, and then decreasing to less frequently, such as once every 2 days or once every 3 days, or once a week, after the first day of treatment. In another embodiment, administration frequency may change with time, starting at a certain rate, such as once or twice a day, and then decreasing to less frequently, such as once every 2 days or once every 3 days, or once a week, after the first two or three days of treatment. In another embodiment, administration frequency may change with time, starting at a certain rate, such as once or twice a day, and then decreasing to less frequently, such as once every 2 days or once every 3 days, or once a week, after the first week of treatment. In another embodiment, administration frequency may be on demand, as therapeutic treatment is required or desired.

**[00134]** Since the study in the EAE model for MS showed that after 2 weeks of DNP treatment, there is a statistically elevated level of BDNF protein 3-weeks post treatment (Fig. 2b), dose frequency could be chronic to raise BDNF protein levels, followed by infrequent doses or "drug holidays". Infrequent doses would be used as maintenance doses to keep BDNF at elevated levels. Therefore, after an initial period of higher frequency doses, frequency of doses could then be reduced to once every week, once every two weeks, once every three weeks or once a month.

**[00135]** It will be understood, based on the disclosure encompassed herein, how to determine whether a subject needs an additional and/or continued dose. It will also be understood that the selected dosing frequency may require an adjustment of the dosage of active ingredient. It will also be understood, based on the disclosure encompassed herein, that the selected dosage of active ingredient may require an adjustment of the dosing frequency. The disclosure encompassed herein, in combination with the skill in the art, will enable the skilled artisan to optimize both the dosage of the active ingredient and the frequency of administration of the active ingredient to treat a subject in need thereof.

[00136] The unit dose may also be adjusted based upon the size of the patient. The numbers provided herein are based upon a 60 kg patient. The same therapy could be provided for a smaller or larger sized patient, but reducing or increasing the dose size. By way of example only, a 20 kg child would need a much smaller dose.

Co-Administration of Compositions

[00137] In an embodiment, a composition described herein is administered in conjunction with one or more other medications or consumer products. Such other medications or consumer products may be administered or co-administered in forms and dosages as known in the art, or in the alternative, as has been described above for administration of active ingredients using the compositions described herein. By way of example only, for stroke patients, DNP may be administered along with Tissue plasminogen activator (tPA).

[00138] For Diabetes Mellitus, DNP may be administered along with insulin (Humulin N, Novolin N) or other biologics as an injectable, or as an oral tablet with Metformin (Glucophage, Glumetza, others), sulfonylureas (glyburide (DiaBeta, Glynase), glipizide (Glucotrol) and glimepiride (Amaryl), etc.), Meglitinides (epaglinide (Prandin) and nateglinide (Starlix)), Thiazolidinediones (Rosiglitazone (Avandia) and pioglitazone (Actos)), DPP-4 inhibitors (sitagliptin (Januvia), saxagliptin (Onglyza) and linagliptin (Tradjenta)), GLP-1 receptor agonists ((Byetta) and liraglutide (Victoza)), SGLT2 inhibitors (canagliflozin (Invokana) and/or dapagliflozin (Farxiga)).

[00139] For Huntington's Disease, DNP may be administered with Tetrabenazine (Xenazine), Antipsychotic drugs, such as haloperidol (Haldol), or others like amantadine, levetiracetam (Keppra) and/or clonazepam (Klonopin).

[00140] For Parkinson's Disease, DNP may be administered with Carbidopa-levodopa (Rytary, Sinemet), Dopamine agonists such as pramipexole (Mirapex), ropinirole (Requip) and rotigotine (given as a patch, Neupro), a short-acting injectable dopamine agonist, apomorphine (Apokyn), MAO-B inhibitors (Eldepryl, Zelapar), or Catechol-O-methyltransferase (COMT) inhibitors (Entacapone (Comtan), Tolcapone (Tasmar),etc.), Anticholinergics (benztropine (Cogentin), trihexyphenidyl), and/or Amantadine.

**[00141]** For Alzheimer's Disease, DNP may be administered with Cholinesterase inhibitors (donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon)), and/or Memantine (Namenda).

**[00142]** For Depression, DNP may be administered with selective serotonin reuptake inhibitors (SSRIs) (luoxetine (Prozac), paroxetine (Paxil, Pexeva), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro)), Norepinephrine-dopamine reuptake inhibitors (NDRIs). Bupropion (Wellbutrin, Aplenzin, Forfivo XL), atypical antidepressants (Trazodone, mirtazapine (Remeron), vortioxetine (Brintellix), vilazodone (Viibryd), etc.), and/or tricyclic antidepressants (imipramine (Tofranil), nortriptyline (Pamelor), Monoamine oxidase inhibitors (MAOIs) tranylcypromine (Parnate), phenelzine (Nardil), isocarboxazid (Marplan), etc.).

**[00143]** For Schizophrenia, DNP may also be administered along with Atypical antipsychotics (Aripiprazole (Abilify), Asenapine (Saphris), Clozapine (Clozaril), Iloperidone (Fanapt), etc.), Conventional, or typical, and/or antipsychotics (Chlorpromazine, Fluphenazine, Haloperidol (Haldol), Perphenazine, etc.).

**[00144]** For MS, DNP may be administered along with Corticosteroids (prednisone, intravenous methylprednisolone), Beta interferons, Glatiramer acetate (Copaxone), Dimethyl fumarate (Tecfidera), Fingolimod (Gilenya), Teriflunomide (Aubagio), Natalizumab (Tysabri), Alemtuzumab (Lemtrada), and/or Mitoxantrone, etc.

**[00145]** For epilepsy, DNP may be administered along with Carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, sodium valproate, tiagabine, topiramate, vigabatrin, and/or zonisamide, etc.

**[00146]** For Traumatic Brain Injury (TBI), DNP may be administered along with Diuretics, anti-seizure drugs, and/or Coma-inducing drugs.

**[00147]** For Lupus, DNP may be administered along with Nonsteroidal anti-inflammatory drugs (NSAIDs) (naproxen sodium (Aleve) and ibuprofen (Advil, Motrin IB, others)), Antimalarial drugs such as hydroxychloroquine (Plaquenil), Corticosteroids (Prednisone,

etc.), and/or Immunosuppressants (azathioprine (Imuran, Azasan), mycophenolate (CellCept), leflunomide (Arava), methotrexate (Trexall), etc.).

**[00148]** For Prader Willi Syndrome, DNP may be administered along with Human growth hormone (HGH), and/or sex hormone treatment (testosterone for males or estrogen and progesterone for females), etc..

**[00149]** For Graves' disease, DNP may be administered along with Anti-thyroid medications (propylthiouracil and methimazole (Tapazole)), and/or Beta blockers (Propranolol (Inderal), Atenolol (Tenormin), Metoprolol (Lopressor, Toprol-XL), Nadolol (Corgard)).

**[00150]** For Muscular Dystrophy, DNP may be administered along with Corticosteroids, such as prednisone and/or Heart medications, such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers.

**[00151]** DNP may also be administered along with pain relief medication, vitamins, nutrition, hydration fluids, or other medication.

**[00152]** The term "co-administration" or "combination therapy" is used to describe a therapy in which at least two compositions, which may include one or more product compositions as described herein, are used to treat, address, or affect a skin condition or another disorder as described herein at the same time. In an embodiment, at least two compositions in effective amounts are used to treat, address, or affect a skin condition or another disorder as described herein at the same time. In another embodiment, at least two active ingredients, the combination of which comprises an effective amount, are used to treat, address, or affect a skin condition or another disorder as described herein at the same time. In an embodiment, the result of treatment with the at least two compositions may be additive of the treatment results obtained using each composition separately, either directly additive, or additive to a degree lesser than the results obtained with the two compositions separately. In an embodiment, the result of treatment with the at least two compositions may be synergistic, to varying degrees. In an embodiment, the result of treatment with the at least two compositions may be greater than the treatment results obtained using each composition separately. In an aspect, the result of treatment for at least two active ingredients is less than that obtained with the active ingredients

separately, while the other active ingredients in the composition are about the same as the results of treatment obtained separately. In an aspect, the result of treatment for all active ingredients in the composition is less than that obtained with the active ingredients separately.

**[00153]** Although the term co-administration encompasses the administration of two compositions to the patient at the same time, it is not necessary that the compositions be administered to the patient at the same time, although effective amounts of the individual active ingredients delivered by the compositions will be present in the patient at the same time.

**[00154]** A product composition described herein may advantageously be administered in combination with at least one other therapeutic agent to provide improved treatment of a skin condition or another disorder. The combinations, uses and methods of treatment of the invention may also provide advantages in treatment of patients or consumers who fail to respond adequately to other known treatments. In an embodiment, a product composition described herein may be administered to a patient already undergoing treatment with at least one other skin care composition, to provide improved treatment of any combination of conditions described herein. In an embodiment, a product composition set forth herein is co-administered with one or more lotions, foams, or creams.

**[00155]** It will further be understood by the skilled artisan that, in addition to the above embodiments of dosage and dosing regimens, both the dosage and the dosing regimen will be considered and each adjusted, as necessary, in view of the condition of the subject being treated.

**[00156]** It will be appreciated by those skilled in the art that changes could be made to the exemplary embodiments shown and described above without departing from the broad inventive concepts thereof. It is understood, therefore, that this invention is not limited to the exemplary embodiments shown and described, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the claims. For example, specific features of the exemplary embodiments may or may not be

part of the claimed invention and various features of the disclosed embodiments may be combined.

**[00157]** Unless specifically set forth herein, the terms "a", "an" and "the" are not limited to one element but instead should be read as meaning "at least one".

**[00158]** It is to be understood that at least some of the figures and descriptions of the invention have been simplified to focus on elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that those of ordinary skill in the art will appreciate may also comprise a portion of the invention. However, because such elements are well known in the art, and because they do not necessarily facilitate a better understanding of the invention, a description of such elements is not provided herein.

**[00159]** Further, to the extent that the methods of the present invention do not rely on the particular order of steps set forth herein, the particular order of the steps should not be construed as limitation on the claims. Any claims directed to the methods of the present invention should not be limited to the performance of their steps in the order written, and one skilled in the art can readily appreciate that the steps may be varied and still remain within the spirit and scope of the present invention.

We claim:

1. A method of treating neuromuscular, autoimmune, neurodegenerative, developmental or metabolic disorders comprising:

administering to a patient in need of treatment of a traumatic CNS injury or neurodegenerative disease an effective dose of 2,4-dinitrophenol (DNP), or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease,

wherein the effective dose of the 2,4-dinitrophenol (DNP) is continued in the dose range of 0.001 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

2. The method of claim 1, wherein the effective dose is in the range of about 1.0 mg/kg of body weight to about 5 mg/kg of body weight.

3. The method of claim 1, wherein the effective dose is in the range of about 0.1 mg/kg of body weight to about 1.0 mg/kg of body weight.

4. The method of claim 1, wherein the effective dose is in the range of 0.01 mg/kg of body weight to about 0.1 mg/kg of body weight.

5. The method of claim 1, wherein the effective dose is in the range of about 0.1 mg/kg of body weight to about 0.5 mg/kg of body weight.

6. The method of claim 1, wherein the effective dose is in the range of about 0.5 mg/kg of body weight to about 1.0 mg/kg of body weight.

7. The method of claim 1, wherein the effective dose is about 1.0 mg/kg of body weight.

8. The method according to any of claims 1-7, wherein the effective dose is delivered orally or intravenously.

9. The method according to any of claims 1-7, wherein the effective dose is delivered orally.

10. The method according to any of claims 1-7, wherein the effective does is delivered intravenously.

11. The method according to any of claims 1-7, wherein the disease is selected from the group consisting of Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease, Epilepsy, Multiple Sclerosis (MS) (relapse-remitting multiple sclerosis (RRMS), Secondary-progressive MS (SPMS), Primary-progressive MS (PPMS), and Progressive-relapsing MS (PRMS)), Lupus, Diabetes, Schizophrenia, Myasthenia gravis (MG), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS), Muscular Dystrophy, severe burns, aging, Amyotrophic Lateral Sclerosis (ALS), Ataxia, Batten Disease or neuronal ceroid lipofuscinoses (NCL), Alzheimer's Disease, Optic neuritis

(ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression, Parkinson's disease, mitochondrial diseases, developmental disorders, metabolic syndrome and/or autoimmune disorders.

12. The method according to any of claims 1-10, wherein the disease is Huntington's disease.

13. The method according to any of claims 1-10, wherein the disease is Multiple Sclerosis (MS) (MS).

14. The method according to any of claims 1-10, wherein the disease is Epilepsy.

15. The method according to any of claims 1-10, wherein the disease is Parkinson's Disease.

16. The method according to any of claims 1-10, wherein the dose of DNP is useful to prevent harm in humans, as a means to avoid inducing too much BDNF, or have no effect by inducing too little BDNF.

17. The method according to any of claims 1-10, wherein enhancing expression of BDNF provides protection from muscle wasting or muscle dysfunction.

18. A pharmaceutical composition of 2,4-dinitrophenol (DNP), or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising an effective dose of 2,4-dinitrophenol (DNP), wherein the effective dose of the 2,4-dinitrophenol (DNP) is in the range of 0.001 mg/kg of body weight to 5 mg/kg of body weight.

19. The pharmaceutical composition of claim 18 in the range of about 0.001 mg/kg to about .01 mg/kg.

20. The pharmaceutical composition of claim 18 in the range of about 0.01 mg/kg to about .1 mg/kg.

21. The pharmaceutical composition of claim 18 in the range of about 0.1 mg/kg to about 1 mg/kg.

22. The pharmaceutical composition of claim 18 in the range of about 1 mg/kg to about 5 mg/kg.

23. The pharmaceutical composition according to any of claims 18-22, comprising an immediate release formation.

24. The pharmaceutical composition according to any of claims 18-22, comprising a controlled release formation.

25. The pharmaceutical composition according to any of claims 18-22, comprising a sustained release formation.

26. The pharmaceutical composition according to any of claims 18-22, wherein the composition is an effective dose to induce BDNF expression to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting.

27. A pharmaceutical composition of 2,4-dinitrophenol (DNP), or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprising a unit dose, wherein the unit dose is in the range of about .1 mg to about 300 mg.

28. The pharmaceutical composition of claim 27 wherein the unit dose is in the range of about 0.1 mg to about 1 mg.

29. The pharmaceutical composition of claim 27 wherein the unit dose is 1 mg.

30. The pharmaceutical composition of claim 27 wherein the unit dose is in the range of about 1 mg to about 5 mg.

31. The pharmaceutical composition of claim 27 wherein the unit dose is in the range of about 5 mg to about 10 mg.

32. The pharmaceutical composition of claim 27 wherein the unit dose is 5 mg.

33. The pharmaceutical composition of claim 27 wherein the unit dose is 10 mg.

34. The pharmaceutical composition of claim 27 wherein the unit dose is 15 mg.

35. The pharmaceutical composition of claim 27 wherein the unit dose is 20 mg.

36. The pharmaceutical composition of claim 27 wherein the unit dose is 30 mg.

37. The pharmaceutical composition of claim 27 wherein the unit dose is 40 mg.

38. The pharmaceutical composition of claim 27 wherein the unit dose is 50 mg.

39. The pharmaceutical composition of claim 27 wherein the unit dose is 75 mg.

40. The pharmaceutical composition of claim 27 wherein the unit dose is 100 mg.

41. The pharmaceutical composition of claim 27 wherein the unit dose is 150 mg.

42. The pharmaceutical composition of claim 27 wherein the unit dose is 200 mg.

43. The pharmaceutical composition of claim 27 wherein the unit dose is 250 mg.

44. The pharmaceutical composition of claim 27 wherein the unit dose is 300 mg.

45. The pharmaceutical composition according to any of claims 27-44, comprising an immediate release formation.

46. The pharmaceutical according to any of claims 27-44, comprising a controlled release formation.

47. The pharmaceutical composition according to any of claims 27-44, comprising a sustained release formation.

48. The pharmaceutical composition according to any of claims 27-44, comprising an oral dosage form.

49. The pharmaceutical composition according to any of claims 27-44, wherein the oral dosage form comprises a tablet.

50. The pharmaceutical composition according to any of claims 27-44, wherein the oral dosage form comprises a capsule.

51. The pharmaceutical composition according to any of claims 27-44, wherein the oral dosage form is rapidly dissolving.

52. The pharmaceutical composition according to any of claims 27-44, wherein the composition is delivered intravenously.

53. The pharmaceutical composition according to any of claims 27-44, wherein the composition is delivered subcutaneously.

54. The pharmaceutical composition according to any of claims 27-44, wherein the composition is delivered transdermally.

55. The pharmaceutical composition according to any of claims 27-44, wherein the composition is an effective unit dose to induce BDNF expression to reverse, slow or prevent neuromuscular and/or neurodegeneration and/or muscle wasting.

56. The pharmaceutical composition according to any of claims 27-44, comprising a treatment for Huntington's disease.

57. The pharmaceutical composition according to any of claims 27-44, comprising a treatment for Multiple Sclerosis (MS).

58. The pharmaceutical composition according to any of claims 27-44, comprising a treatment for Traumatic Brain Injury (TBI), Ischemic stroke, Huntington's disease, Epilepsy, Multiple Sclerosis (MS), Lupus, Diabetes, Schizophrenia, Myasthenia gravis (MG), rheumatoid arthritis (RA), Graves' disease, Guillain–Barré syndrome (GBS),

Muscular Dystrophy, Duchenne Muscular Dystrophy (DMD), severe burns, Amyotrophic Lateral Sclerosis (ALS), Ataxia, Batten Disease or neuronal ceroid lipofuscinoses (NCL), Alzheimer's Disease, Optic neuritis (ON), Leber's hereditary optic neuropathy (LHON), Autism Spectrum Disorders (ASD), Rett syndrome, Angelman's Syndrome, Leigh disease, Prader Willi Syndrome, Fragile-X Syndrome, Depression, Parkinson's disease, mitochondrial diseases, developmental disorders, metabolic syndrome and/or autoimmune disorders.

59. A method of treating neuromuscular, neurodegenerative, autoimmune, developmental or metabolic disorders, comprising:

receiving an effective dose of 2,4-dinitrophenol (DNP), or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease,

wherein the effective dose of the 2,4-dinitrophenol (DNP) is continued to be received in the dose range of 0.01 mg/kg of body weight to 5 mg/kg of body weight to increase BDNF to attenuate disease progression or provide remission of symptoms.

60. A method of treating neuromuscular neurodegenerative, autoimmune, developmental or metabolic disorders, comprising:

providing instructions to administer an effective dose of 2,4-dinitrophenol (DNP), or a pharmaceutically acceptable salt thereof, over period sufficiently long to achieve remission of the symptoms of the disease,

wherein the effective dose of the 2,4-dinitrophenol (DNP) is instructed to be received in the dose range of 0.01 mg/kg of body weight to 5 mg/kg of body weight.

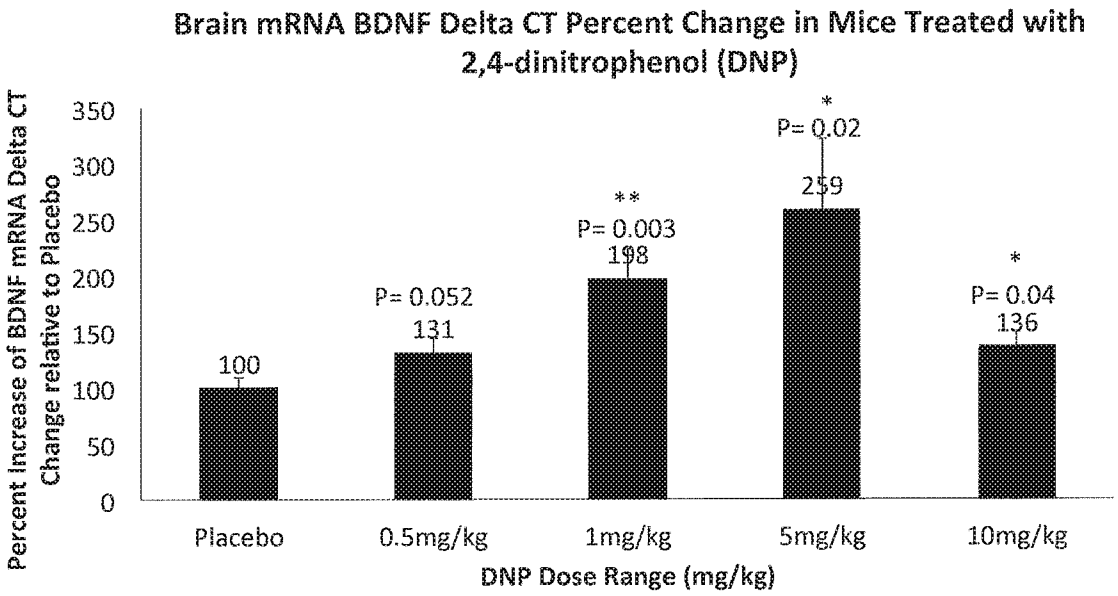

Brain mRNA BDNF Delta CT Percent Change in Mice Treated with 2,4-dinitrophenol (DNP)
Percent Increase of BDNF mRNA Delta CT Change relative to Placebo
350
300
250
200
150
100
50
0
100
P= 0.052
131
**
P= 0.003
198
*
P= 0.02
259
*
P= 0.04
136
Placebo
0.5mg/kg
1mg/kg
5mg/kg
10mg/kg
DNP Dose Range (mg/kg)

Figure 1

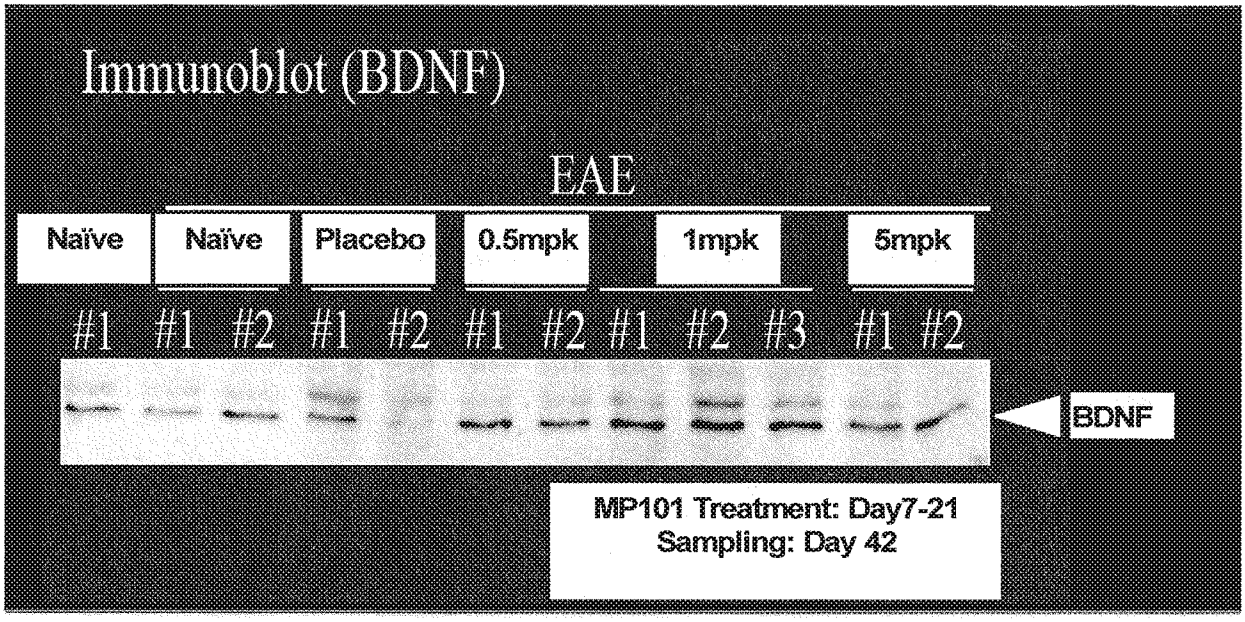



Figure 2a

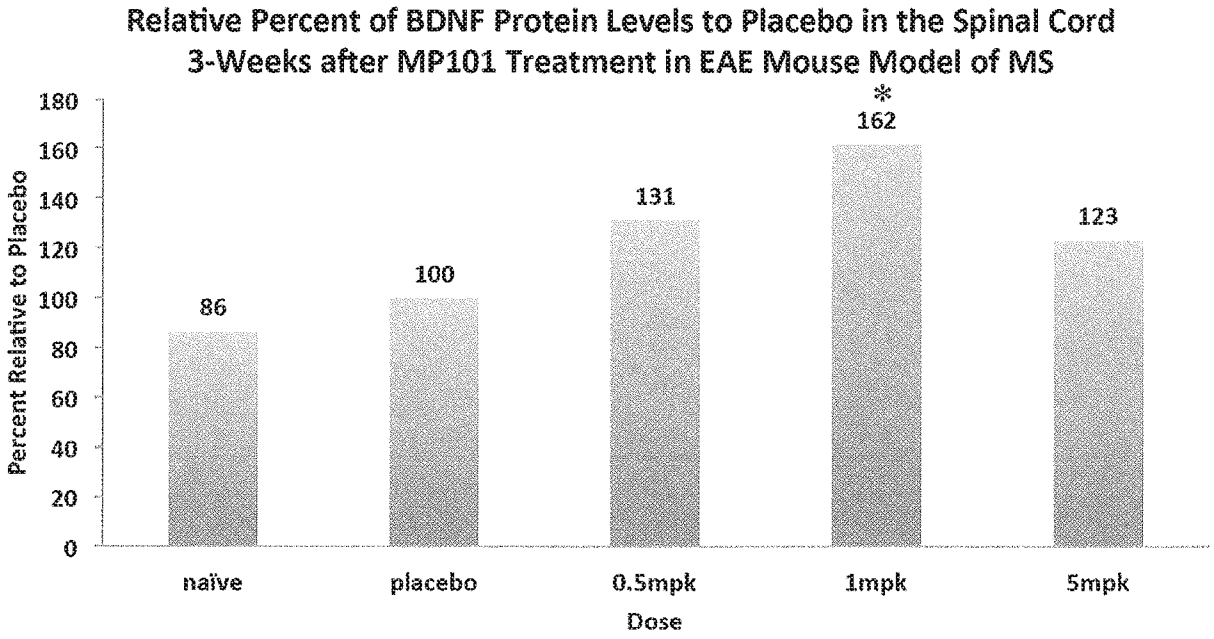



Figure 2b

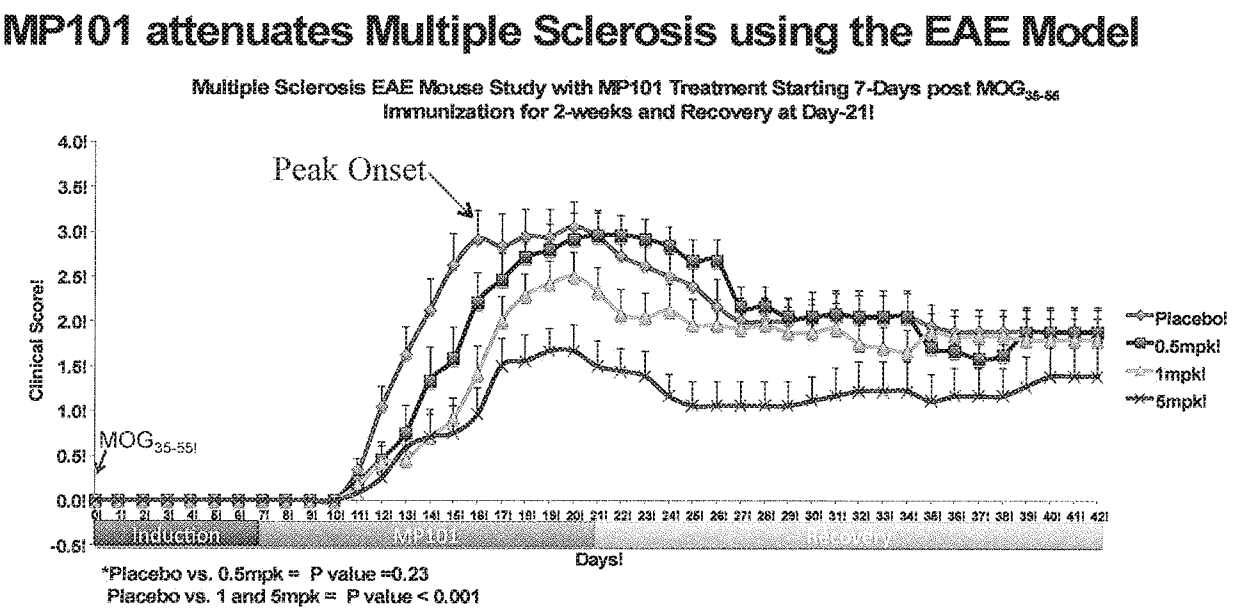



Figure 2c

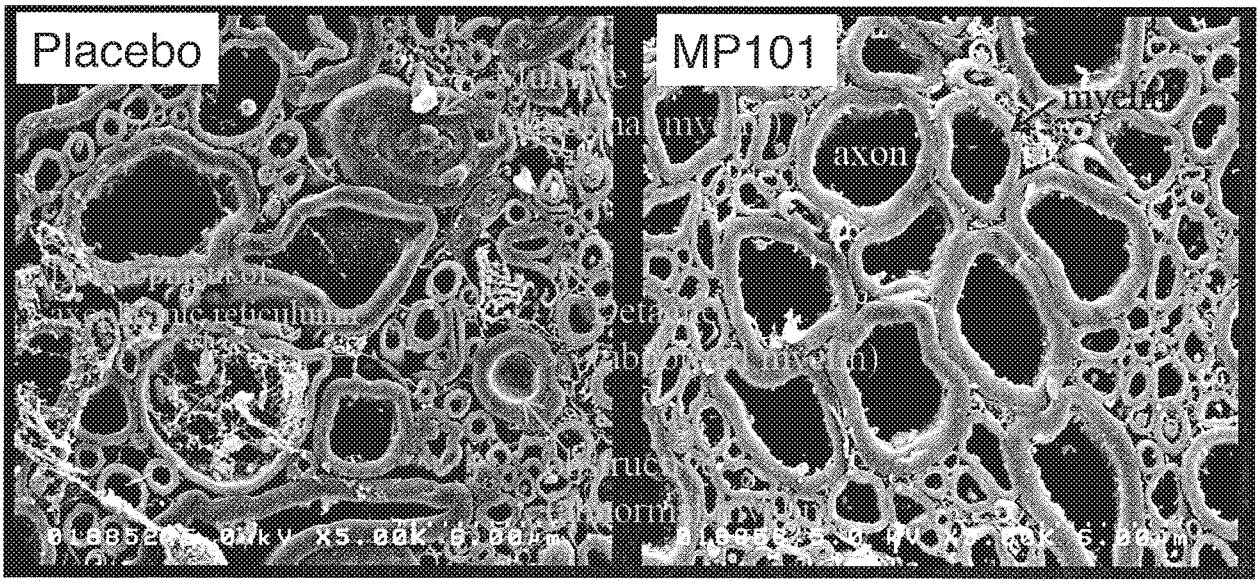



Figure 2d

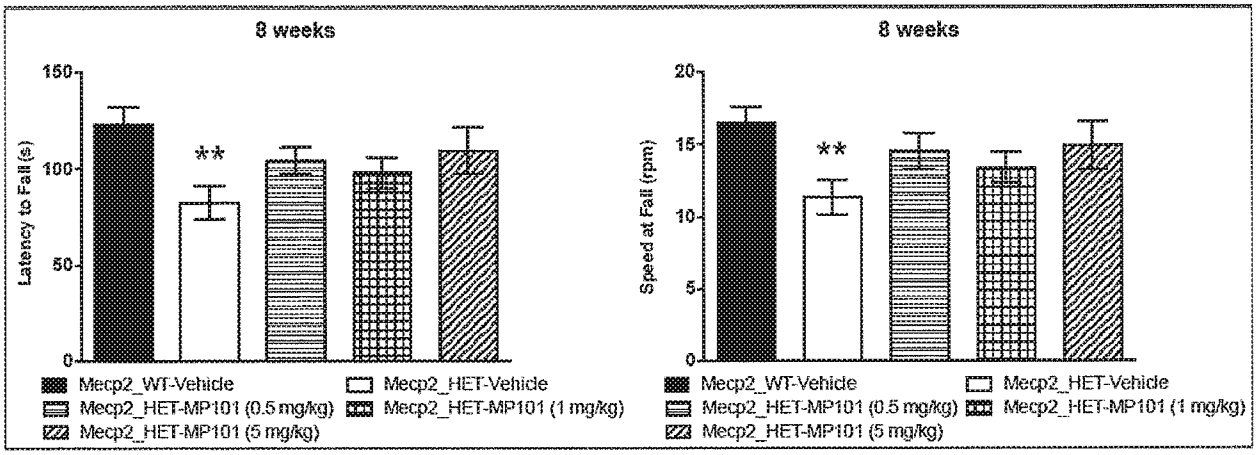



Figure 3a

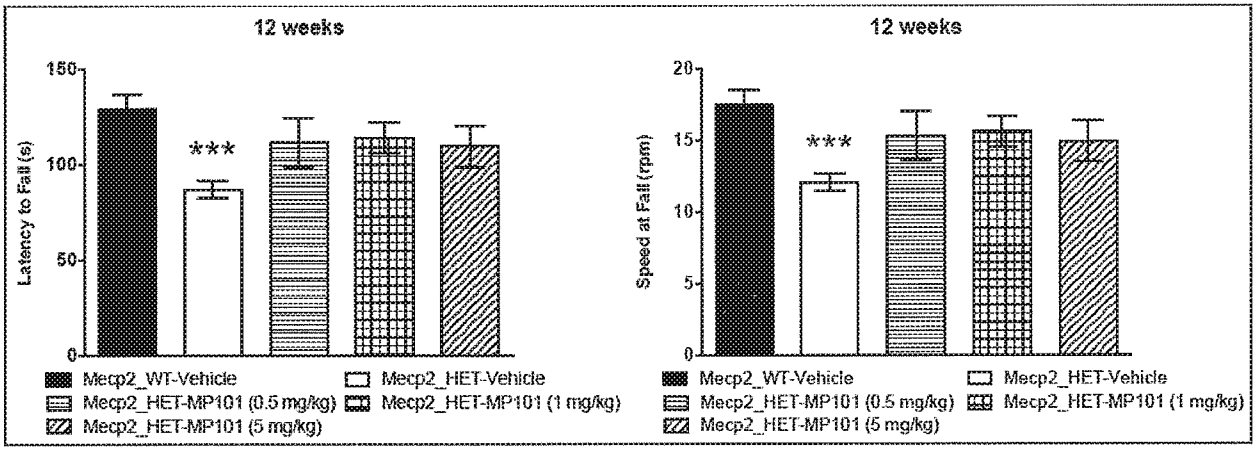
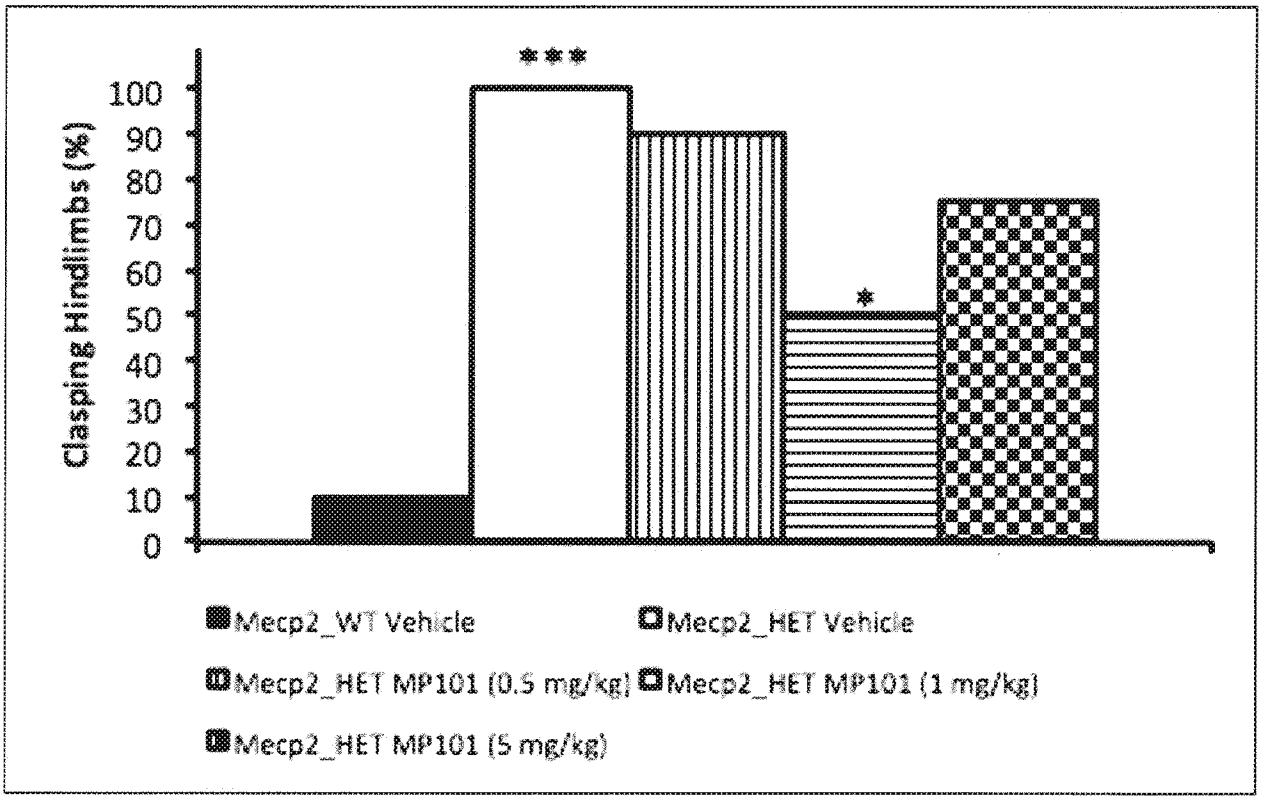



Figure 3b

Figure 4


***
*
Clasping Hindlimbs (%)
100
90
80
70
60
50
40
30
20
10
0
Mecp2_WT Vehicle
Mecp2_HET Vehicle
Mecp2_HET MP101 (0.5 mg/kg)
Mecp2_HET MP101 (1 mg/kg)
Mecp2_HET MP101 (5 mg/kg)

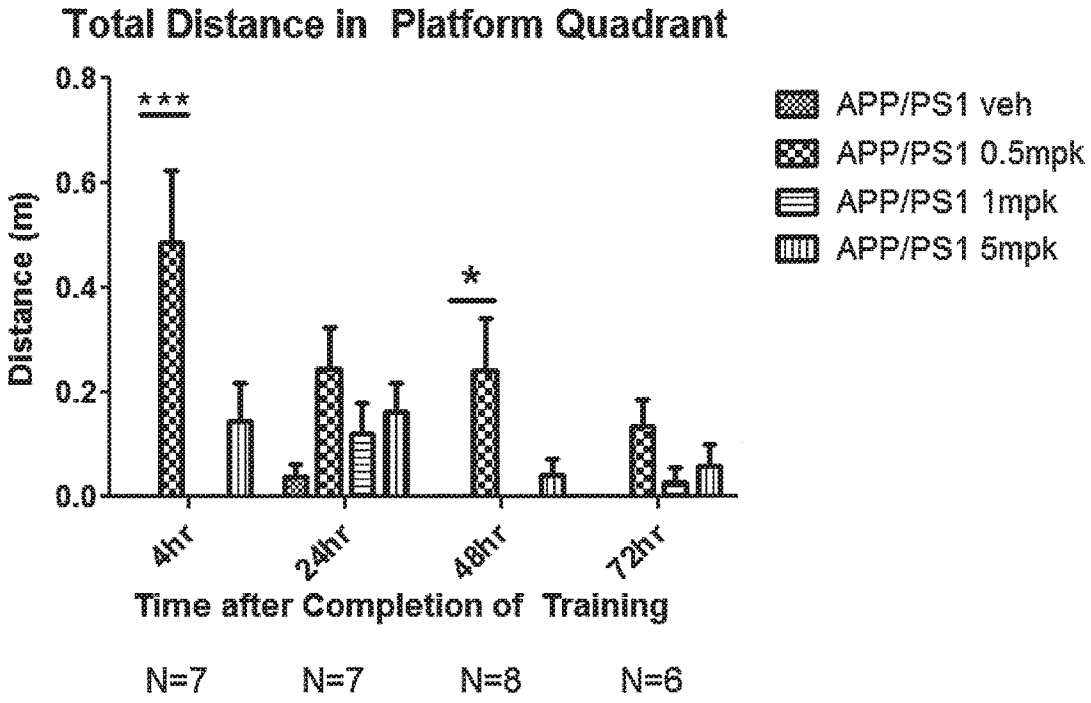



Figure 5a

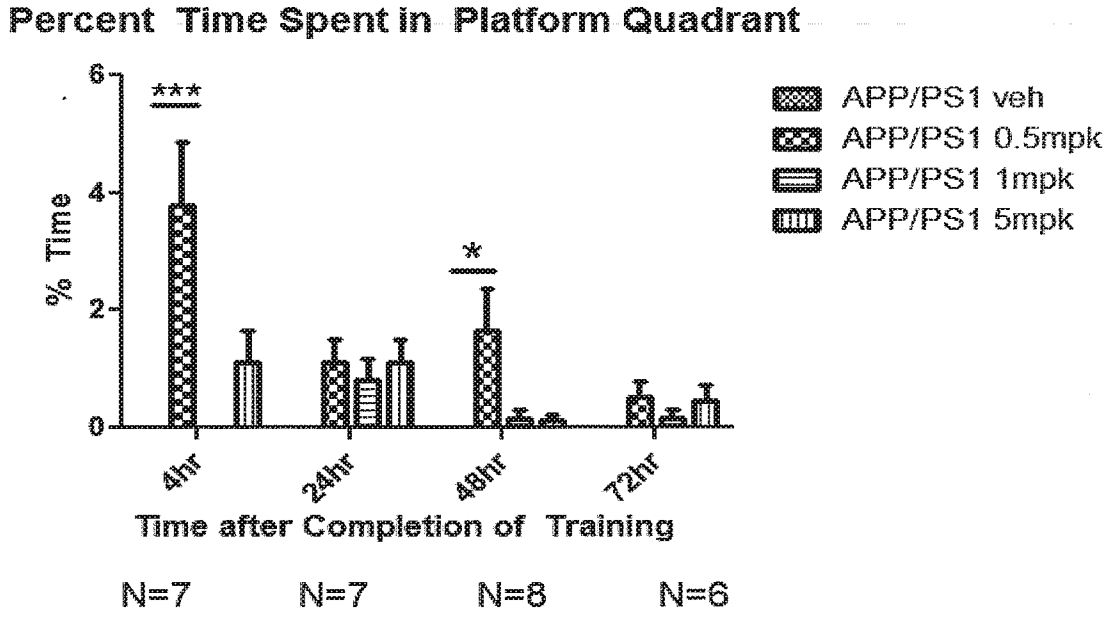



Figure 5b

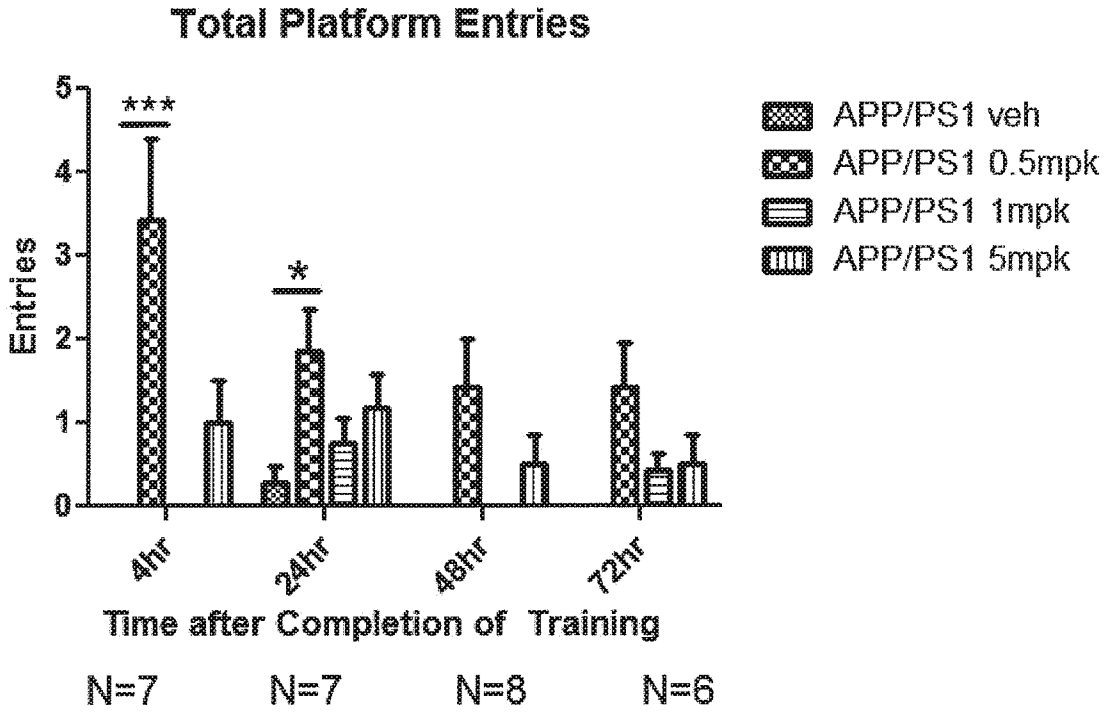

Total Platform Entries
Entries
0
1
2
3
4
5
***
*
4hr
24hr
48hr
72hr
Time after Completion of Training
N=7
N=7
N=8
N=6
APP/PS1 veh
APP/PS1 0.5mpk
APP/PS1 1mpk
APP/PS1 5mpk

Figure 5c

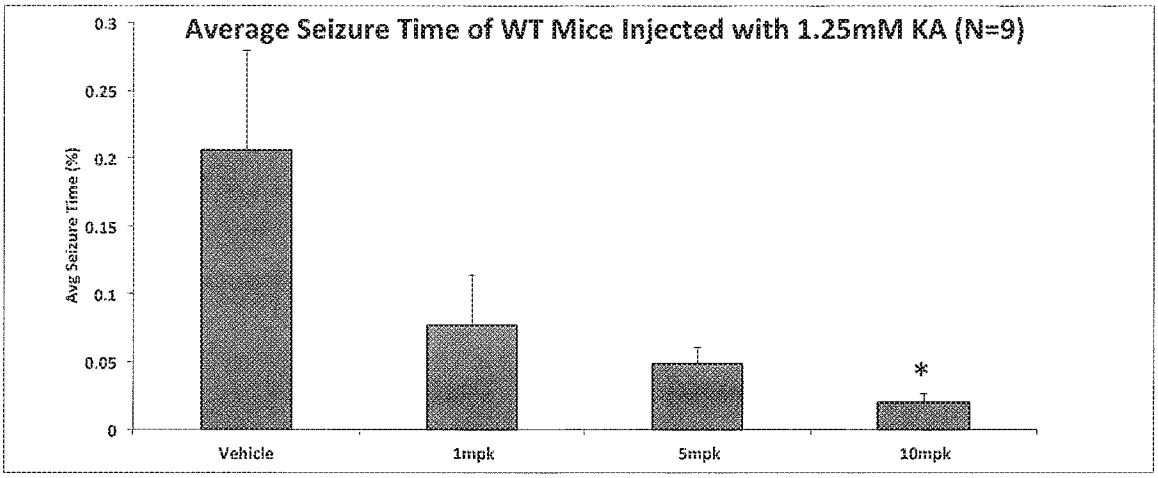

Average Seizure Time of WT Mice Injected with 1.25mM KA (N=9)
Avg Seizure Time (%)
0.3
0.25
0.2
0.15
0.1
0.05
0
*
Vehicle
1mpk
5mpk
10mpk

Figure 6

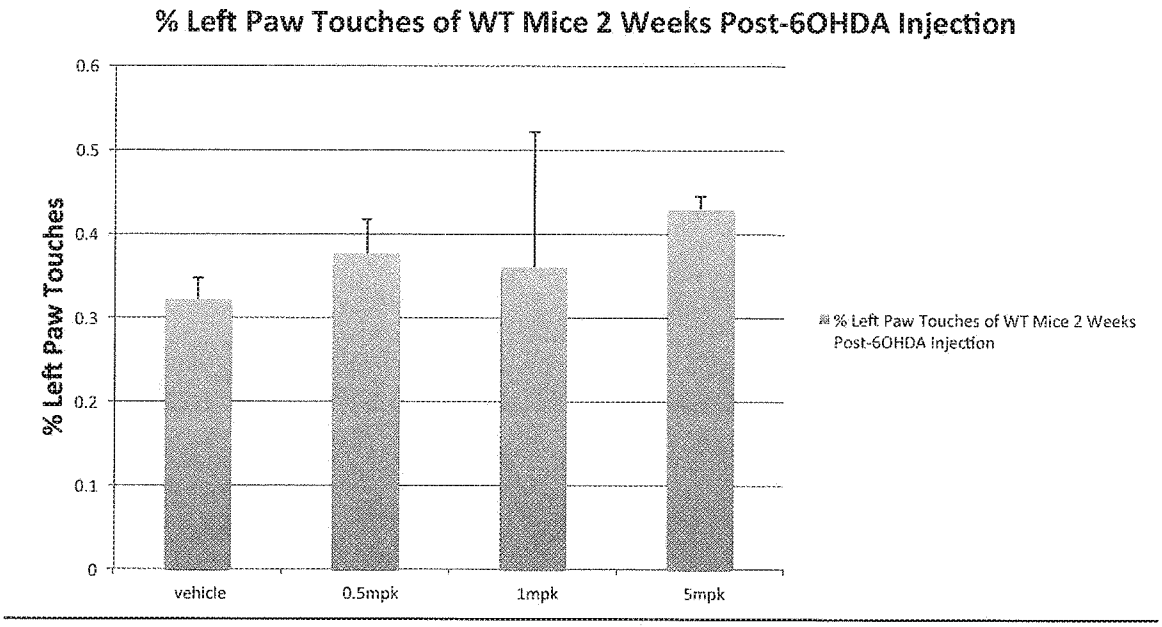



Figure 7a

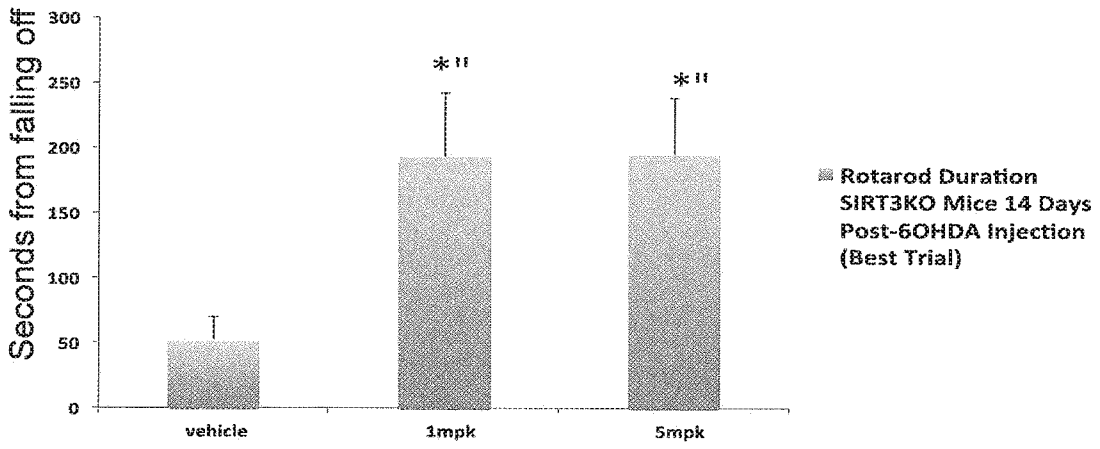



Figure 7b

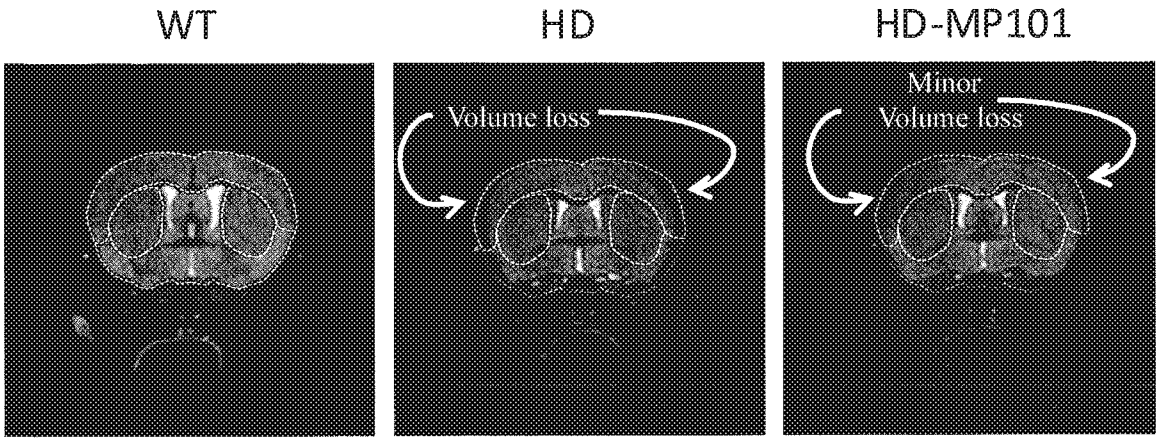



Figure 8a

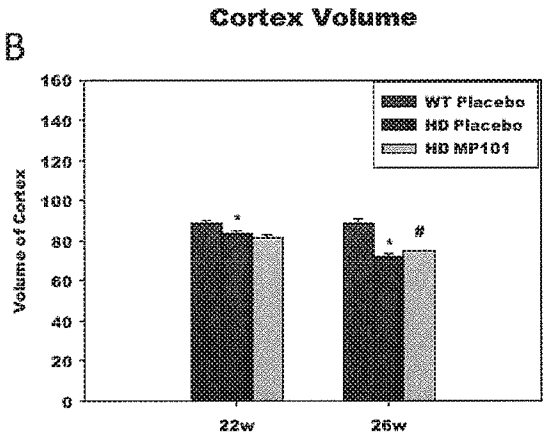



Figure 8b

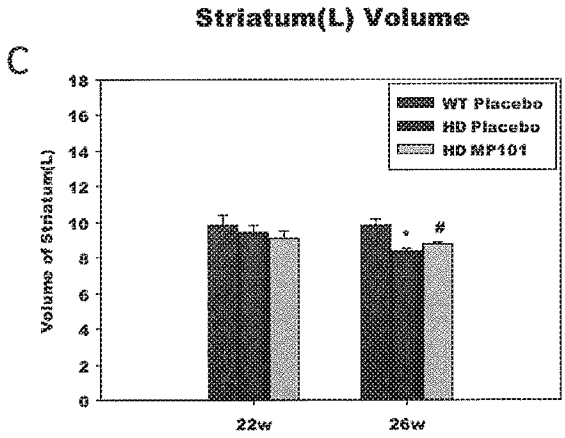



Figure 8c

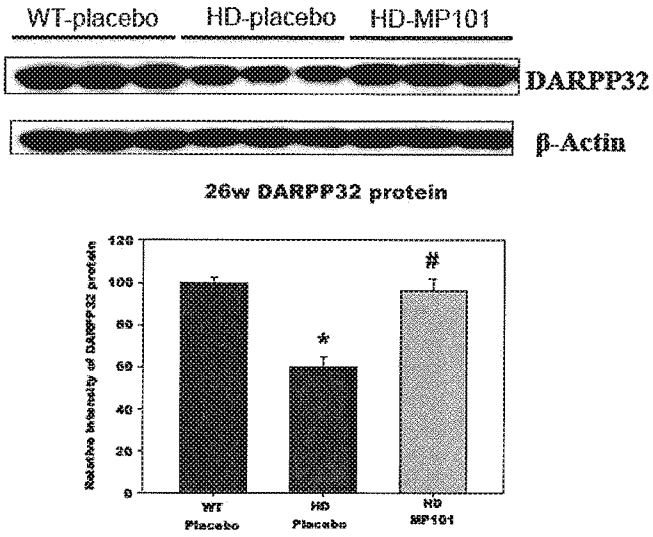



Figure 8d

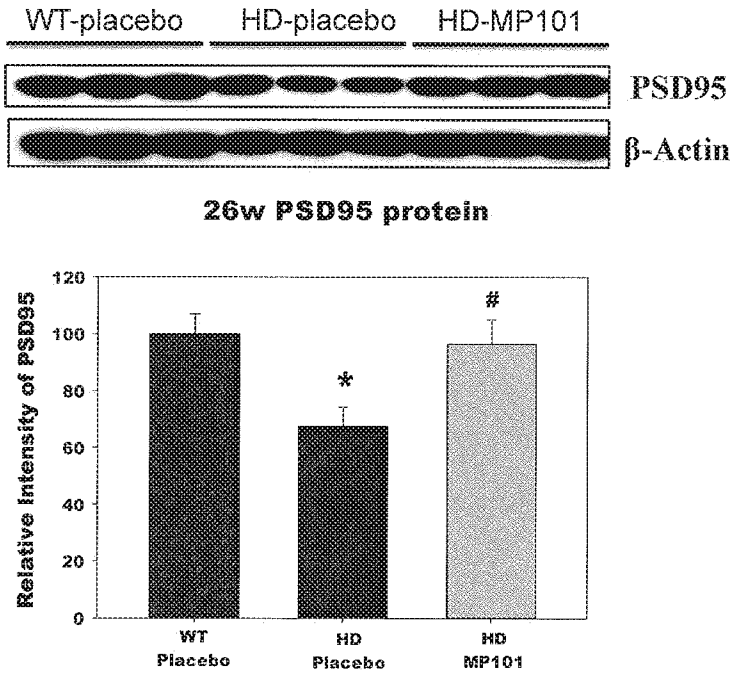
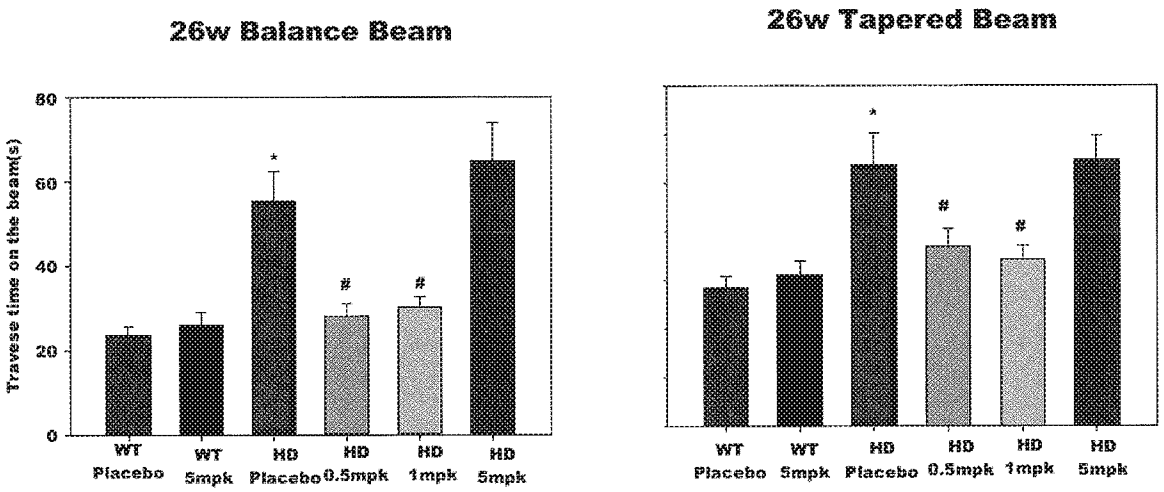



Figure 8e




The values are the mean and SEM. one-way ANOVA tests were used. n=14-16.
*$p$<0.005 versus the WT Placebo group; #$p$<0.005 versus the HD Placebo group

Figure 8f

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/014312

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/06 A61P25/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | FERNANDA DE FELICE ET AL: "Novel neuroprotective, neuritogenic and anti-amyloidogenic properties of 2,4-dinitrophenol: The gentle face of Janus", IUBMB LIFE, vol. 58, no. 4, 1 April 2006 (2006-04-01), pages 185-191, XP55257117, GB ISSN: 1521-6543, DOI: 10.1080/15216540600702198 | 18,22, 23,27, 40,45, 48,50, 51,59,60 |
| Y | the whole document | 1-60 |

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-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 March 2016 | 30/03/2016 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Steendijk, Martin |

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | RODRIGO F. MADEIRO DA COSTA ET AL: "2,4-Dinitrophenol Blocks Neurodegeneration and Preserves Sciatic Nerve Function after Trauma", JOURNAL OF NEUROTRAUMA., vol. 27, no. 5, 1 May 2010 (2010-05-01), pages 829-841, XP55256920, US ISSN: 0897-7151, DOI: 10.1089/neu.2009.1189 | 18-20, 23,26, 59,60 |
| Y | abstract | 1-60 |
| | ----- | |
| X | DE FELICE FERNANDA G ET AL: "Inhibition of Alzheimer's disease beta-amyloid aggregation, neurotoxicity, and in vivo deposition by nitrophenols: Implications for Alzheimer's therapy", THE FASEB JOURNAL, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, US, vol. 15, no. 7, 1 May 2001 (2001-05-01), pages 1297-1299, XP007908887, ISSN: 0892-6638 | 18-20, 23,26, 59,60 |
| Y | abstract see also under discussion | 1-60 |
| | ----- | |
| X | Urushitani ET AL: "N-Methyl-D-Aspartate Receptor-Mediated Mitochondrial Ca Overload in Acute Excitotoxic Motor Neuron Death: A Mechanism Distinct From Chronic Neurotoxicity After Ca 2? Influx", J. Neurosci. Res, 1 January 2001 (2001-01-01), pages 377-387, XP55257256, Retrieved from the Internet: URL:http://onlinelibrary.wiley.com//doi/10.1002/1097-4547%2820010301%2963:5%3C377::AID-JNR1032%3E3.0.CO;2-%23/pdf | 18-20, 23,26 |
| Y | page 383, left-hand column | 1-60 |
| | ----- | |
| X | JIGNESH D. PANDYA ET AL: "Post-Injury Administration of Mitochondrial Uncouplers Increases Tissue Sparing and Improves Behavioral Outcome following Traumatic Brain Injury in Rodents", JOURNAL OF NEUROTRAUMA., vol. 24, no. 5, 1 May 2007 (2007-05-01), pages 798-811, XP55257245, US ISSN: 0897-7151, DOI: 10.1089/neu.2006.3673 | 18,22, 23,26, 27,30, 45,55, 58-60 |
| Y | abstract | 1-60 |
| | ----- | |
| | -/-- | |

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | YING JIN ET AL: "The Mitochondrial Uncoupling Agent 2,4-Dinitrophenol Improves Mitochondrial Function, Attenuates Oxidative Damage, and Increases White Matter Sparing in the Contused Spinal Cord", JOURNAL OF NEUROTRAUMA., vol. 21, no. 10, 1 October 2004 (2004-10-01), pages 1396-1404, XP55257246, US ISSN: 0897-7151, DOI: 10.1089/neu.2004.21.1396 | 18,22, 23,26, 27,30, 45,55, 58-60 |
| Y | abstract | 1-60 |
| | ----- | |
| X | AMIT S. KORDE ET AL: "The mitochondrial uncoupler 2,4-dinitrophenol attenuates tissue damage and improves mitochondrial homeostasis following transient focal cerebral ischemia", JOURNAL OF NEUROCHEMISTRY, vol. 94, no. 6, 1 September 2005 (2005-09-01), pages 1676-1684, XP55257230, NEW YORK, NY, US ISSN: 0022-3042, DOI: 10.1111/j.1471-4159.2005.03328.x | 18,22, 23,26, 27,30, 45,55, 58-60 |
| Y | abstract | 1-60 |
| | ----- | |
| Y | Liu: "Integrative adaptive responses to mild mitochondrial uncoupling emphasize arc/arg3.1 signaling and tsc2-associated mtor inhibition", Society for Neuroscience Abstract Viewer and Itinerary Planner, 1 January 2012 (2012-01-01), XP55257185, Retrieved from the Internet: URL:http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2964&sKey=b0ba5ade-cd5e-4863-96b4-827c50e05ccd&cKey=589d7ce9-2ce9-41c2-8bce-7d8cb3231a24&mKey=70007181-01c9-4de9-a0a2-eebfa14cd9f1 [retrieved on 2016-03-10] the whole document | 1-60 |
| | ----- | |
| | -/-- | |

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CAMILLE C. CALDEIRA DA SILVA ET AL: "Mild mitochondrial uncoupling in mice affects energy metabolism, redox balance and longevity", AGING CELL, vol. 7, no. 4, 1 August 2008 (2008-08-01), pages 552-560, XP55257324, GB ISSN: 1474-9718, DOI: 10.1111/j.1474-9726.2008.00407.x page 557, left-hand column | 18-21, 23,26, 59,60 |
| X,P | WO 2015/031756 A1 (UNIV YALE [US]) 5 March 2015 (2015-03-05) pages 31-36; claims | 1-11, 16-55, 58-60 |
| Y,P | DONG LIU ET AL: "The mitochondrial uncoupler DNP triggers brain cell mTOR signaling network reprogramming and CREB pathway up-regulation", JOURNAL OF NEUROCHEMISTRY, vol. 134, no. 4, 19 June 2015 (2015-06-19) , pages 677-692, XP55256922, NEW YORK, NY, US ISSN: 0022-3042, DOI: 10.1111/jnc.13176 abstract | 1-60 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/014312

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2015031756 A1 | 05-03-2015 | NONE | |

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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(43)申请公布日 2017.11.28

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(30)优先权数据
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2017.09.21

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PCT/US2016/014312 2016.01.21

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(71)申请人 米托充制药公司
地址 美国宾夕法尼亚州

(72)发明人 R.阿龙索 J.G.盖斯勒

(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 李志强 万雪松

(51)Int.Cl.
*A61K 31/06*(2006.01)
*A61P 25/00*(2006.01)
*A61P 25/14*(2006.01)
*A61P 25/08*(2006.01)
*A61P 3/10*(2006.01)
*A61P 25/18*(2006.01)
*A61P 21/04*(2006.01)
*A61P 19/02*(2006.01)
*A61P 21/00*(2006.01)
*A61P 25/28*(2006.01)
*A61P 17/02*(2006.01)
*A61P 27/02*(2006.01)
*A61P 25/24*(2006.01)
*A61P 25/16*(2006.01)
*A61P 3/00*(2006.01)
*A61P 37/02*(2006.01)
*A61P 17/00*(2006.01)

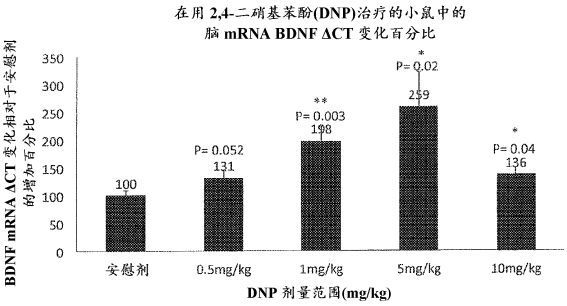
权利要求书3页 说明书30页 附图9页

(54)发明名称

# 用于治疗神经肌肉、神经变性、自身免疫、发育和/或代谢疾病的脑源性神经营养因子(BDNF)的诱导表达

(57)摘要

通过用DNP治疗来诱导内源的BDNF表达以保护免于神经肌肉功能障碍/病症和/或神经变性和/或肌肉萎缩,治疗涉及衰老的神经肌肉、神经变性、发育、自身免疫和代谢疾病/病症的宿主的方法,所述疾病/病症例如创伤性损伤、中风、亨廷顿病、癫痫、多发性硬化(MS)、狼疮、1型和2型糖尿病、青春晚期糖尿病(MODY)、重症肌无力(MG)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、代谢综合征、肌营养不良或杜兴肌营养不良(DMD)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、弗里德赖希共济失调、巴藤病、阿尔茨海默病、视神经炎、莱伯遗传性视神经病(LHON)、自闭症、Rett综合征、巴藤病、Angelman综合征、利氏病、脆性-X综合征、抑郁症、帕金森病、线粒体疾病、发育障碍、代谢疾病障碍和/或自身免疫性病症。每日将一定剂量范围内的DNP给予小鼠,和随后脑中的BDNF表达显示表达的剂量依赖性和非线性增加。




CN 107405315 A

1.一种治疗神经肌肉、自身免疫、神经变性、发育或代谢病症的方法，包括：

在足够长以实现疾病的症状减轻的时间内，给予需要治疗创伤性CNS损伤或神经变性疾病的患者有效剂量的2,4-二硝基苯酚(DNP)或其药学上可接受的盐，

其中2,4-二硝基苯酚(DNP)的有效剂量在0.001 mg/kg体重至5 mg/kg体重的剂量范围内持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

2．权利要求1的方法，其中有效剂量的范围为约1.0 mg/kg体重至约5 mg/kg体重。

3．权利要求1的方法，其中有效剂量的范围为约0.1 mg/kg体重至约1.0 mg/kg体重。

4．权利要求1的方法，其中有效剂量的范围为0.01 mg/kg体重至约0.1 mg/kg体重。

5．权利要求1的方法，其中有效剂量的范围为约0.1 mg/kg体重至约0.5 mg/kg体重。

6．权利要求1的方法，其中有效剂量的范围为约0.5 mg/kg体重至约1.0 mg/kg体重。

7．权利要求1的方法，其中有效剂量为约1.0 mg/kg体重。

8.权利要求1-7中任一项的方法，其中有效剂量经口服或静脉内递送。

9.权利要求1-7中任一项的方法，其中有效剂量经口服递送。

10.权利要求1-7中任一项的方法，其中有效剂量经静脉内递送。

11．权利要求1-7中任一项的方法，其中所述疾病选自创伤性脑损伤(TBI)、缺血性中风、亨廷顿病、癫痫、多发性硬化(MS) (复发-缓解性多发性硬化(RRMS)、继发性-进行性MS(SPMS)、原发性-进行性MS (PPMS)和进行性-复发性MS (PRMS))、狼疮、糖尿病、精神分裂症、重症肌无力(MG)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、共济失调、巴藤病或神经元蜡样脂褐质沉积症(NCL)、阿尔茨海默病、视神经炎(ON)、莱伯遗传性视神经病(LHON)、自闭症谱系障碍(ASD)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症、帕金森病、线粒体疾病、发育障碍、代谢综合征和/或自身免疫性病症。

12.权利要求1-10中任一项的方法，其中所述疾病是亨廷顿病。

13．权利要求1-10中任一项的方法，其中所述疾病是多发性硬化(MS) (MS)。

14.权利要求1-10中任一项的方法，其中所述疾病是癫痫。

15.权利要求1-10中任一项的方法，其中所述疾病是帕金森病。

16.权利要求1-10中任一项的方法，其中DNP的剂量以避免诱导太多的BDNF或因诱导太少的BDNF而没有效果的方式，用于防止人的损害。

17.权利要求1-10中任一项的方法，其中提高BDNF的表达提供保护免于肌肉萎缩或肌肉功能障碍。

18．2,4-二硝基苯酚(DNP)或其药学上可接受的盐、溶剂合物或水合物的药物组合物，其包含有效剂量的2,4-二硝基苯酚(DNP)，其中2,4-二硝基苯酚(DNP)的有效剂量范围为0.001 mg/kg体重至5 mg/kg体重。

19．权利要求18的药物组合物，范围为约0.001 mg/kg至约.01 mg/kg。

20．权利要求18的药物组合物，范围为约0.01 mg/kg至约.1 mg/kg。

21．权利要求18的药物组合物，范围为约0.1 mg/kg至约1 mg/kg。

22．权利要求18的药物组合物，范围为约1 mg/kg至约5 mg/kg。

23.权利要求18-22中任一项的药物组合物，包含立即释放制剂。

24.权利要求18-22中任一项的药物组合物，包含控制释放制剂。

25.权利要求18-22中任一项的药物组合物,包含持续释放制剂。

26.权利要求18-22中任一项的药物组合物,其中所述组合物是诱导BDNF表达以逆转、减慢或防止神经肌肉和/或神经变性和/或肌肉萎缩的有效剂量。

27. 2,4-二硝基苯酚(DNP)或其药学上可接受的盐、溶剂合物或水合物的药物组合物,其包含单位剂量,其中所述单位剂量的范围为约.1 mg至约300 mg。

28. 权利要求27的药物组合物,其中所述单位剂量的范围为约0.1 mg至约1 mg。

29. 权利要求27的药物组合物,其中所述单位剂量为1 mg。

30. 权利要求27的药物组合物,其中所述单位剂量的范围为约1 mg至约5 mg。

31. 权利要求27的药物组合物,其中所述单位剂量的范围为约5 mg至约10 mg。

32. 权利要求27的药物组合物,其中所述单位剂量为5 mg。

33. 权利要求27的药物组合物,其中所述单位剂量为10 mg。

34. 权利要求27的药物组合物,其中所述单位剂量为15 mg。

35. 权利要求27的药物组合物,其中所述单位剂量为20 mg。

36. 权利要求27的药物组合物,其中所述单位剂量为30 mg。

37. 权利要求27的药物组合物,其中所述单位剂量为40 mg。

38. 权利要求27的药物组合物,其中所述单位剂量为50 mg。

39. 权利要求27的药物组合物,其中所述单位剂量为75 mg。

40. 权利要求27的药物组合物,其中所述单位剂量为100 mg。

41. 权利要求27的药物组合物,其中所述单位剂量为150 mg。

42. 权利要求27的药物组合物,其中所述单位剂量为200 mg。

43. 权利要求27的药物组合物,其中所述单位剂量为250 mg。

44. 权利要求27的药物组合物,其中所述单位剂量为300 mg。

45.权利要求27-44中任一项的药物组合物,其包含立即释放制剂。

46.权利要求27-44中任一项的药物组合物,其包含控制释放制剂。

47.权利要求27-44中任一项的药物组合物,其包含持续释放制剂。

48.权利要求27-44中任一项的药物组合物,其包含口服剂型。

49.权利要求27-44中任一项的药物组合物,其中口服剂型包含片剂。

50.权利要求27-44中任一项的药物组合物,其中口服剂型包含胶囊剂。

51.权利要求27-44中任一项的药物组合物,其中口服剂型是快速溶解的。

52.权利要求27-44中任一项的药物组合物,其中所述组合物经静脉内递送。

53.权利要求27-44中任一项的药物组合物,其中所述组合物经皮下递送。

54.权利要求27-44中任一项的药物组合物,其中所述组合物经皮递送。

55.权利要求27-44中任一项的药物组合物,其中所述组合物是诱导BDNF表达以逆转、减慢或防止神经肌肉和/或神经变性和/或肌肉萎缩的有效单位剂量。

56.权利要求27-44中任一项的药物组合物,包含对亨廷顿病的治疗。

57.权利要求27-44中任一项的药物组合物,包含对多发性硬化(MS)的治疗。

58. 权利要求27-44中任一项的药物组合物,包含对创伤性脑损伤(TBI)、缺血性中风、亨廷顿病、癫痫、多发性硬化(MS)、狼疮、糖尿病、精神分裂症、重症肌无力(MG)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良、杜兴肌营养不良(DMD)、重度

烧伤、肌萎缩侧索硬化(ALS)、共济失调、巴藤病或神经元蜡样脂褐质沉积症(NCL)、阿尔茨海默病、视神经炎(ON)、莱伯遗传性视神经病(LHON)、自闭症谱系障碍(ASD)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症、帕金森病、线粒体疾病、发育障碍、代谢综合征和/或自身免疫性病症的治疗。

59.一种治疗神经肌肉、神经变性、自身免疫、发育或代谢病症的方法,包括:

在足够长以实现疾病的症状减轻的时间内,接受有效剂量的2,4-二硝基苯酚(DNP)或其药学上可接受的盐,

其中持续接受剂量范围为0.01 mg/kg体重至5 mg/kg体重的有效剂量的2,4-二硝基苯酚(DNP),以增加BDNF来减弱疾病进展或提供症状的减轻。

60.一种治疗神经肌肉、神经变性、自身免疫、发育或代谢病症的方法,包括:

提供在足够长以实现疾病的症状减轻的时间内给予有效剂量的2,4-二硝基苯酚(DNP)或其药学上可接受的盐的指示,

其中指示接受剂量范围为0.01 mg/kg体重至5 mg/kg体重的有效剂量的2,4-二硝基苯酚(DNP)。

# 用于治疗神经肌肉、神经变性、自身免疫、发育和/或代谢疾病的脑源性神经营养因子(BDNF)的诱导表达

[0001] 相关申请的交叉引用

本申请要求2015年1月22日提交的美国临时申请62/106365的优先权，其通过引用以其整体明确地结合到本文中。

[0002] 发明背景

脑源性神经营养因子(BDNF)是在神经元发育中起关键作用的数种内源蛋白之一。BDNF作为神经营养因子和/或作为肌因子(myokine)影响神经生长。因此，对诱导BDNF表达的改进方法存在需要。本发明涉及BDNF可通过给予DNP经内源诱导以增加表达，和存在可用于BDNF表达并且对患者无害的0.001 mg/kg至小于10 mg/kg之间的剂量范围的发现。此外，许多方法正进行以使BDNF跨越血脑屏障来治疗疾病宿主。例如，这些疾病包括但不限于，创伤性损伤、中风、亨廷顿病、癫痫、多发性硬化(MS)、狼疮、1型和2型糖尿病、青春晚期糖尿病(MODY)、重症肌无力(MG)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、代谢综合征、杜兴肌营养不良(DMD)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、弗里德赖希共济失调、巴藤病、阿尔茨海默病、视神经炎、莱伯遗传性视神经病(LHON)、自闭症、Rett综合征、巴藤病、Angelman综合征、利氏病、脆性-X综合征、精神分裂症、抑郁症、帕金森病和线粒体疾病。治疗通过逆转、减慢或防止神经肌肉、神经变性、自身免疫、发育和/或代谢病症的过程而起效。

## 发明领域

[0003] 本发明涉及治疗神经肌肉、神经变性、自身免疫、发育和/或代谢疾病的方法和用于治疗神经肌肉、神经变性、自身免疫、发育和/或代谢疾病的药物组合物(包括单位剂量)。特别地，本发明涉及通过给予有需要的患者线粒体解偶联剂(质子载体或离子载体) 2, 4-二硝基苯酚("DNP")或两部分二硝基苯酚亚型(2,3-、2,4-、2,5-、2,6-、3,4-或3,5-DNP)或具有可离解质子的线粒体解偶联剂或弱酸，例如CCCP、FCCP、SF 6847、氟芬那酸、PCP、TTFB等，使用约0.001 mg/kg至5 mg/kg的有效剂量，内源诱导人的全身器官以增加脑源性神经营养因子("BDNF")表达，以及DNP的相关的药物组合物和DNP的单位剂量。

[0004] 发明简述

在一个实施方案中，本发明提供通过给予剂量范围为0.01 mg/kg体重至小于10 mg/kg体重的DNP以增加BDNF来减弱疾病进展或提供症状的缓解，治疗创伤性CNS损伤、神经变性疾病和/或自身免疫疾病和/或发育障碍和/或代谢疾病的方法。在某些实施方案中，本发明提供通过用DNP治疗来诱导BDNF mRNA表达和蛋白水平以逆转、减慢或防止神经肌肉和/或神经变性和/或肌肉萎缩，治疗至少以下疾病的方法：创伤性脑损伤(TBI)、缺血性中风、亨廷顿病(成人型亨廷顿病、少年型亨廷顿病)、癫痫(群集癫痫发作、顽固性癫痫发作、非典型癫痫小发作、无张力性癫痫发作、阵挛性癫痫发作、肌阵挛性癫痫发作、强直性癫痫发作、强直-阵挛性癫痫发作、简单部分癫痫发作、复杂部分癫痫发作、继发性普遍癫痫发作、发热癫痫发作、非癫痫性癫痫发作、Gelastic和Dacrystic癫痫发作和癫痫小发作)、多发性硬化

(MS) (复发-缓解性多发性硬化(RRMS)、继发性-进行性MS (SPMS)、原发性-进行性MS (PPMS)和进行性-复发性MS (PRMS))、狼疮(全身性红斑狼疮(SLE)、盘状(皮肤)药物诱导性狼疮(dil)和新生儿狼疮)、糖尿病(1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY: MODY1、MODY2、MODY3、MODY4、MODY5、MODY6、MODY7、MODY8、MODY9、MODYIO、MODY1 1))、精神分裂症(偏执型精神分裂症、错乱型精神分裂症、紧张型精神分裂症、残留型精神分裂症、情感分裂性精神障碍)、重症肌无力(MG) (眼睛重症肌无力、先天性MG和泛发性重症肌无力)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良(杜兴肌营养不良(DMD)、Becker、肌强直、先天性、Emery-Dreifuss、面肩胛臂性、肢带性、远端和眼咽性)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、共济失调(弗里德赖希共济失调、脊髓小脑共济失调1 (SCA1)、脊髓小脑共济失调2 (SCA2)、脊髓小脑共济失调3 (SCA3)、脊髓小脑共济失调6 (SCA6)、脊髓小脑共济失调7 (SCA7)、脊髓小脑共济失调11 (SCA11)、齿状核红核苍白球丘脑下部核萎缩(DRPLA)和谷蛋白共济失调)、巴藤病或神经元蜡样脂褐质沉积症(NCL) (婴儿期NCL (INCL)、婴儿后期NCL (LINCL)、少年NCL (JNCL)或成人NCL (ANCL))、阿尔茨海默病(早期发作性阿尔茨海默病、晚期发作性阿尔茨海默病和家族性阿尔茨海默病(FAD))、视神经炎(ON)、莱伯遗传性视神经病(LHON)、自闭症谱系障碍(ASD) (Asperger综合征、全身性发育迟缓(PDD)、童年瓦解性障碍(CDD)和孤独症)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症(严重抑郁、心境恶劣、产后精神抑郁、季节性情感障碍、非典型抑郁、精神病性抑郁症、双相型障碍、月经前焦虑障碍、情境性抑郁)、帕金森病(特发性帕金森病、血管性帕金森综合征、路易体痴呆、遗传性帕金森病、药物诱导性帕金森综合征、少年帕金森病和非典型帕金森综合征)、线粒体疾病、发育障碍、代谢综合征(血压增加、高血糖水平、腰部周围体脂过量和异常胆固醇水平)和/或自身免疫性病症。

[0005] 在另一个实施方案中,本发明涉及DNP或其药学上可接受的盐、溶剂合物或水合物的组合物,其包含有效剂量的DNP,其中DNP的有效剂量范围为0.001 mg/kg体重至5 mg/kg体重。

[0006] 在又一个实施方案中,本发明涉及DNP或其药学上可接受的盐、溶剂合物或水合物的药物组合物,其包含单位剂量,其中所述单位剂量的范围为0.1 mg至300 mg。

[0007] 在又一个实施方案中,本发明涉及治疗神经肌肉或自身免疫或发育或神经变性或代谢病症的方法,包括在足够长以实现疾病的症状减轻的时间内接受有效剂量的DNP或其药学上可接受的盐,其中持续接受剂量范围为0.001 mg/kg体重至5 mg/kg体重的有效剂量的DNP,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0008] 本发明的第五个方面涉及治疗神经肌肉或自身免疫或发育或代谢或神经变性病症的方法,包括:提供在足够长以实现疾病的症状减轻的时间内给予有效剂量的DNP或其药学上可接受的盐的指示,其中指示接受剂量范围为0.001 mg/kg体重至5 mg/kg体重的有效剂量的DNP。

[0009] 附图简述

通过检查以下附图将更好地理解本发明,所述附图解释了本发明的某些性质,其中:

图1描述表明根据本发明的实施方案,给予DNP增加脑中BDNF水平的图表。

[0010] 图2a通过来自MS (实验性自身免疫脑脊髓炎)的小鼠模型的免疫印迹,描述BDNF蛋白水平的变化。

[0011] 图2b描述根据免疫印迹研究，来自MS的小鼠模型的BDNF蛋白水平的变化百分比。

[0012] 图2c描述在显示疾病进展减弱的临床评分方面，MP101对MS模型的表型进展的影响。

[0013] 图2d描述与安慰剂相比，用5 mg/kg的MP101治疗的小鼠在第16天(~发作峰值)的代表性小鼠脊髓电子显微镜图片。

[0014] 图3a描述涉及Mecp2突变体小鼠(Rett综合征的模型)在6周龄时用DNP治疗后的研究结果。

[0015] 图3b描述涉及Mecp2突变体小鼠(Rett综合征的模型)在12周龄时用DNP治疗后的研究结果。

[0016] 图4描述涉及12周龄的Mecp2突变体小鼠在口服强饲治疗1个月后的研究结果，其表明在"抱握试验"中1 mg/kg DNP的作用。

[0017] 图5a、5b和5c描述在阿尔茨海默病研究中涉及4月龄的APP/PS1小鼠在通过口服强饲递送DNP 4个月治疗后的研究结果。

[0018] 图6描述小鼠通过口服强饲用1、5和10 mg/kg的DNP治疗2周，然后提供海人酸(kanic acid)注射至脑中以确定对癫痫发作时间的影响的小鼠研究结果。

[0019] 图7a描述小鼠用DNP治疗14天以观察对保护多巴胺能神经元损失的影响的小鼠研究结果。

[0020] 图7b描述小鼠用DNP治疗14天以观察对保护多巴胺能神经元损失的影响的另一个小鼠研究结果。

[0021] 图8a描述用DNP治疗的野生型(WT)、突变体亨廷顿小鼠载体(HD)的脑容量变化的MRI图像。

[0022] 图8b描述在DNP治疗后皮层中的定量脑容量损失。

[0023] 图8c显示在DNP治疗后纹状体中定量脑容量损失。

[0024] 图8d描述显示在26周龄时使用生物标记DARPP32，用DNP治疗保护中间多刺神经元的小鼠研究结果。

[0025] 图8e描述显示在N171-82Q HD小鼠中用生物标记突触后蛋白PSD95水平，用DNP治疗保护总体神经元损失的小鼠研究结果。

[0026] 图8f描述显示在治疗17周后在锥形木和平衡木二者中用DNP治疗改进运动功能的小鼠研究结果。

[0027] 发明详述

下文中，术语"内源的"，除非另外定义，意指通过自深组织生长，例如通过自人脑生长而生长或产生的。

[0028] 或者，术语"内源的"，除非另外定义，意指由生物体或系统内部的因素引起的。或者，术语"内源的"，除非另外定义，意指在生物体或系统内产生或合成的。

[0029] 下文中，除非另外定义，术语"肌肉萎缩"意指人的肌肉(例如，呼吸隔膜)的萎缩。肌肉萎缩处于肌肉消瘦之时。肌肉萎缩的主要原因是缺少身体活动。这可在疾病或损伤使你难以或不可能移动胳膊或腿时发生。

[0030] 下文中，除非另外定义，术语"有效剂量"或"有效缓解"使用一种或多种以下定量评价客观测量，以实现剂量或缓解的有效性的经证实的评价：对于阿尔茨海默病的ADS

COG;对于亨廷顿病的HDRS;对于帕金森病的帕金森分级量表;对于多发性硬化的FSS和EDSS;对于ALS的ALSAQ;对于中风的中风评价量表,例如NIH中风量表或巴塞尔指数;对于自闭症的儿童自闭症分级量表(CARS);对于杜兴肌营养不良(DMD)的6分钟步行测试;和对于癫痫发作的癫痫发作严重性量表。

[0031] 下文中,除非另外定义,术语"约"意指加或减所涉及的值的10%。例如,"约1 mg/kg"意指0.9 mg/kg至1.1 mg/kg。

[0032] 在创伤性CNS损伤、神经变性疾病、自身免疫疾病、发育障碍和代谢疾病的情况下,线粒体解偶联剂,例如2,4-二硝基苯酚(DNP),可有利地作为用于神经保护的治疗方法给予。线粒体解偶联可通过轻度解偶联来提高呼吸速率而对脑细胞具有保护作用,所述轻度解偶联由于以下作用机制(MOA)而产生较低的细胞应激:1) 增加氧($O_2$)消耗,其通过降低微环境中的$O_2$张力,防止形成超氧化物自由基阴离子($O_2^-$),2) 提供更多氧化水平的呼吸链中间体,例如在复合物I和III中,其称为活性氧物质(ROS)的主要来源,3) 保持NADH水平较低,这防止通过线粒体基质黄素蛋白形成ROS,和4) 较低的膜电势(ΔΨ),一种在热力学上不利于从复合物II至I的电子传递的逆转的情况。

[0033] 此外,除了用于降低ROS外,神经突长出在理论上可使用解偶联剂实现。已知DNP可用缺血后急性单剂量来降低ROS物质,和减少梗塞体积,然而通过修复改进结果和恢复的益处可用BDNF的增加表达来实现,需要长期治疗以诱导足够水平的这种神经营养因子。因此通过长期DNP治疗,梗塞体积可从受损组织的修复/生长进一步减少。

[0034] 在一个实施方案中,本发明涉及以下发现:用DNP治疗,BDNF可被内源诱导以增加表达,和存在有效的DNP的剂量范围,其不太高以致有害,也不太低而不提供效果。DNP在诱导BDNF中的有效性不随DNP的剂量增加而线性增加。在一个实施方案中,我们表明存在有益效果不再增加的DNP剂量,并且明显的是,存在DNP的有益效果实际上降低的剂量。

[0035] 尽管不受理论的束缚,DNP的作用机制可能是将非基因组事件转变为基因组事件。线粒体解偶联剂不直接作用于蛋白,而是作用于位置,即线粒体基质。由于质子(氢或$H^+$)通过细胞色素泵出,线粒体基质是pH碱性环境。由于线粒体解偶联剂是含可离解质子的弱酸,它们被吸引至线粒体基质的碱性环境,在那里,它们作为阳离子移动和放出质子($H^+$),然后作为阴离子保持非质子化回到胞质溶胶的酸性环境,然后再质子化回到阳离子和再次开始循环直到代谢和/或清除。该事件降低线粒体膜电势,导致在试图重建膜电势时能量消耗增加以及葡萄糖和脂质消耗。这种作用认为是非基因组的,因此DNP不通过蛋白直接作用或接触蛋白,而是仅进入细胞内的独特位置,该位置碰巧是具有pH碱性环境的唯一位置。其还降低线粒体内的钙。腺苷酸环化酶,一种合成3'5'-环单磷酸(环AMP或cAMP)的酶,另外被称为"第二信使",对钙和镁的变化高度敏感,和已表明DNP上调cAMP供给。上调腺苷酸环化酶和产生更多cAMP的级联作用,然后转化DNP的非基因组作用为基因组作用,这改变基因宿主的表达,包括增加BDNF的转录因子,称为cAMP-应答元件-结合蛋白(CREB)。

[0036] 仅通过实例的方式,BDNF在亨廷顿病中较低,和恢复BDNF至接近正常水平被认为对减弱疾病发作是关键的。因此,用有效跨越血脑屏障和诱导BDNF内源表达的DNP治疗对于治疗疾病是有利的,对于所述疾病,增加BDNF表达将提供神经保护作用。类似地,Rett综合征被认为是在幼年女孩中的发育障碍,并且与较低水平的BDNF有关。恢复水平回到接近正常水平可防止头生长发育障碍,其在大约18月龄时作为发作的一种标志出现。对于其它疾

病，例如多发性硬化(MS)，尚未充分研究BDNF的积极作用，但我们已在MS模型中表明BDNF水平在脑中升高和在长期DNP治疗下影响轴突保护作用免于自身免疫病症，其破坏髓鞘。其他人已表明，BDNF可在肥胖和糖尿病模型中降低葡萄糖水平。其他人已发现了，幼年、非肥胖胰岛素抵抗患者具有低的BDNF循环水平，其作为旁分泌起作用，和可能是代谢综合征的因子。因此，BDNF升高和持续增加可在神经变性、发育、自身免疫、代谢和神经肌肉病症中提供广泛作用。另外，在中枢和/或外周区室中BDNF的增加可能是有益的。

[0037] 除了脑之外，BDNF还在其它肌肉组织中表达，和认为除了保护免于神经变性之外，还作为肌因子起作用，以提供神经肌肉或肌肉保护作用。

[0038] 令人惊讶的是，已表明约0.001至5 mg/kg的剂量范围有效治疗肌肉、神经肌肉、神经变性、自身免疫、发育和/或代谢疾病，例如创伤性损伤、中风、亨廷顿病、癫痫、多发性硬化(MS)、狼疮、1型和2型糖尿病、MODY、代谢综合征、杜兴肌营养不良(DMD)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、弗里德赖希共济失调、巴藤病、阿尔茨海默病、视神经炎、自闭症、Rett综合征、巴藤病、Angelman综合征、脆性-X综合征、精神分裂症、抑郁症和帕金森病。在一个实施方案中，本发明表明使用有效剂量范围约0.01至小于10 mg/kg的DNP以诱导BDNF在哺乳动物的脑中表达，这避免诱导太多BDNF以致有害，或因诱导太少的BDNF而没有效果。

[0039] 如下文所述，线粒体解偶联剂DNP在小鼠中在口服长期治疗下以0.5 mg/kg的DNP至10 mg/kg的DNP的剂量范围测试，以滴定在脑中诱导脑内BDNF内源增加所需要的药物量。已发现DNP实际上的确在脑内诱导BDNF，但与接下来两个较低剂量相比，最高剂量10 mg/kg具有降低水平的BDNF。因此，发现存在特定和受限的DNP剂量范围，其对于实现获益于增加的BDNF水平的疾病宿主的统计学显著的存活和行为益处是必需的。在一个实施方案中，全身器官和脑、胰岛、肝和脑的疾病和病症可获益于用特定和受限的DNP剂量滴定BDNF水平，例如但不限于，创伤性脑损伤(TBI)、缺血性中风、亨廷顿病(成人型亨廷顿病、少年型亨廷顿病)、癫痫(群集癫痫发作、顽固性癫痫发作、非典型癫痫小发作、无张力性癫痫发作、阵挛性癫痫发作、肌阵挛性癫痫发作、强直性癫痫发作、强直-阵挛性癫痫发作、简单部分癫痫发作、复杂部分癫痫发作、继发性普遍癫痫发作、发热癫痫发作、非癫痫性癫痫发作、Gelastic和Dacrystic癫痫发作和癫痫小发作)、多发性硬化(MS) (复发-缓解性多发性硬化(RRMS)、继发性-进行性MS (SPMS)、原发性-进行性MS (PPMS)和进行性-复发性MS (PRMS))、狼疮(全身性红斑狼疮(SLE)、盘状(皮肤)药物诱导性狼疮(dil)和新生儿狼疮)、糖尿病(1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY: MODY1、MODY2、MODY3、MODY4、MODY5、MODY6、MODY7、MODY8、MODY9、MODY10、MODY11))、精神分裂症(偏执型精神分裂症、错乱型精神分裂症、紧张型精神分裂症、残留型精神分裂症、情感分裂性精神障碍)、重症肌无力(MG) (眼睛重症肌无力、先天性MG和泛发性重症肌无力)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良(杜兴肌营养不良(DMD)、Becker、肌强直、先天性、Emery-Dreifuss、面肩胛臂性、肢带性、远端和眼咽性)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、共济失调(弗里德赖希共济失调、脊髓小脑共济失调1 (SCA1)、脊髓小脑共济失调2 (SCA2)、脊髓小脑共济失调3 (SCA3)、脊髓小脑共济失调6 (SCA6)、脊髓小脑共济失调7 (SCA7)、脊髓小脑共济失调11 (SCA11)、齿状核红核苍白球丘脑下部核萎缩(DRPLA)和谷蛋白共济失调)、巴藤病或神经元蜡样脂褐质沉积症(NCL) (婴儿期NCL (INCL)、婴儿后期NCL(LINCL)、少年NCL (JNCL)或成人NCL (ANCL))、阿尔茨海默病(早期发作性阿尔茨海默病、

晚期发作性阿尔茨海默病和家族性阿尔茨海默病(FAD))、视神经炎(ON)、莱伯遗传性视神经病(LHON)、自闭症谱系障碍(ASD) (Asperger综合征、全身性发育迟缓(PDD)、童年瓦解性障碍(CDD)和孤独症)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症(严重抑郁、心境恶劣、产后精神抑郁、季节性情感障碍、非典型抑郁、精神病性抑郁症、双相型障碍、月经前焦虑障碍、情境性抑郁)、帕金森病(特发性帕金森病、血管性帕金森综合征、路易体痴呆、遗传性帕金森病、药物诱导性帕金森综合征、少年帕金森病和非典型帕金森综合征)、线粒体疾病、发育障碍、代谢综合征(血压增加、高血糖水平、腰部周围体脂过量和异常胆固醇水平)和/或自身免疫性病症。

[0040] 野生型C57BL/6J小鼠用2, 4-二硝基苯酚每日处理,持续两周,通过口服强饲,以0.5、1.0、5.0和10.0 mg/kg DNP或安慰剂,N=8/组。脑组织用于半定量聚合酶链反应(PCR)以测定内源的BDNF水平,其归一化至GapDH以测定mRNA的△-△CT变化。数据显示各剂量水平的DNP的△-△CT变化,显示为相对于给予安慰剂的对照组的变化百分比。

[0041] 图1显示在0.1 mg/kg DNP和10 mg/kg DNP之间,在野生型小鼠中给予DNP增加脑中的BDNF水平,和我们已鉴定了钟形曲线,使得在较高剂量10.0 mg/kg DNP下,表达较少的BDNF。在一个实施方案中,较高剂量范围的DNP可使需要较高BDNF水平的患者群获益,例如亨廷顿病、Rett综合征、癫痫和多发性硬化(MS)和其它形式的神经变性和肌肉或神经肌肉病症,因为BDNF是肌因子和可对肌肉萎缩提供积极益处。

[0042] 图2a通过来自MS、实验性自身免疫脑脊髓炎(EAE)的小鼠模型的免疫印迹,显示BDNF蛋白水平的变化。在研究的第42天,在恢复阶段期间从代表性小鼠的腰部脊髓获取组织,所述小鼠在第1天用MOG肽免疫,然后在第7天开始用MP101治疗和在第21天停止。BDNF条带的强度从安慰剂至0.5 mg/kg,至1 mg/kg增加,平台效果在5 mg/kg。未治疗的动物显示为首次实验动物。BDNF水平变化因此在用DNP (即MP101)治疗后3周。DNP不仅增加BDNF,而且增加BDNF的作用具有直到现在也并非显而易见的持久效果。

[0043] 图2b显示通过治疗后3周来自MS、实验性自身免疫脑脊髓炎(EAE)的小鼠模型的免疫印迹,BDNF蛋白水平的变化百分比。

[0044] 图2c显示在显示疾病进展减弱的临床评分上,MP101对MS模型的表型进展的影响。

[0045] 图2d显示与安慰剂相比,在第16天(~发作峰值),MP101 5 mg/kg治疗的小鼠的代表性的小鼠脊髓电子显微镜图片。与安慰剂组相比,轴突周围的保护性髓鞘和轴突完全完整。

[0046] 因此,我们通过mRNA变化测试了DNP在野生型模型的脑中诱导BDNF,和在蛋白水平上测试了DNP增加BDNF,证实了在MS模型,实验性自身免疫脑脊髓炎(EAE)中提供保护作用。

[0047] MP101在Rett综合征模型中使用Mecp2突变体小鼠测试。Rett综合征是一种在幼年女孩中的发育障碍,初步症状开始于约18月龄,包括减少的头生长。图3a、3b、3c和4显示了用0.5、1 mg/kg和5 mg/kg的MP101通过口服强饲治疗这些突变体小鼠的效果。

[0048] 在图3a和3b中,Mecp2突变体小鼠,一种Rett综合征的模型,在6周龄时用MP101(DNP)治疗和测试它们在旋转圆筒(rotarod)上行走的协调性。与用溶媒、0.5mg/kg MP101、1 mg/kg MP101和5mg/kg MP101通过口服强饲治疗的Mecp2突变体小鼠相比,野生型小鼠用作一般性行为衰退的基准。在图3a中,数据表明8周龄时,突变体溶媒治疗的小鼠失去其在rotarod上行走的能力,而野生型小鼠和药物治疗的动物掉落较少,和可操作更高速度的旋

转。在图3b中，数据显示在治疗1个月后在第12周龄时类似的发现。

[0049] 在图4中，我们表明12周龄和口服强饲治疗1个月后Mecp2突变体小鼠的结果，其表明1 mg/kg MP101的"抱握试验"的效果。

[0050] 此外，阿尔茨海默病，代表所有痴呆病例的约70%，使用APP/PS1小鼠评价，其表达APPswe突变和PS1deltaE9突变，和发生相对快速的Aβ病理和认知缺陷。在4月龄时，APP/PS1小鼠通过口服强饲递送0.5、1和5 mg/kg的MP101 (DNP)治疗4个月。图5a、5b和5c显示与溶媒处理的小鼠相比，MP101具有改进的认知。在四分仪中花费的时间量是小鼠是否记得大致位置的指示物，时间增加表明记忆增加。

[0051] 图5a、5b和5c显示当在Morris水迷宫中测试记忆隐藏平台的位置的认知时，相对于不能记忆的溶媒，在DNP的所有剂量下APP/PS1小鼠的短期记忆改进。图5a显示在具有隐藏平台的四分仪中寻找平台的移动距离，图5b显示在平台被隐藏的四分仪中花费的时间量，和图5c显示自平台的进入次数。在四分仪中花费的时间量是受试者是否记忆大致位置的指示物。

[0052] 还评价DNP用于治疗癫痫。海人酸模型是急性癫痫模型，通过在右海马中注射谷氨酸的类似物(海人酸)引起，其过度刺激神经元引起死亡。图6显示治疗野生型小鼠达14天的效果，通过口服强饲1、5和10 mg/kg的MP101 (DNP)，然后注射海人酸以确定DNP是否对通过海人酸的过度刺激和死亡的作用为保护效果。

[0053] 图6显示通过口服强饲用1、5和10 mg/kg的MP101 (DNP)治疗2周，然后海人酸注射至小鼠的脑后，存在癫痫发作时间的缩短。相对于溶媒，DNP提供神经保护作用免于由海人酸引起的过度刺激。

[0054] 用MP101 (DNP)治疗帕金森病的优点在野生型小鼠和SIRT3 KO小鼠中在MP101治疗2周后用6-OHDA注射评价。我们检查了各种MP-101剂量(0.5、1、5 mg/kg)针对黑质纹状体神经元的多巴胺能降解的神经保护作用，所述降解通过在2-3月龄雄性C57B1/6小鼠或SIRT3 KO小鼠的脑的右纹状体中单次单侧立体定位注射神经毒素6-羟基多巴胺(6-OHDA)诱导。SIRT3 KO是对谷氨酸-诱导的钙过载和兴奋性中毒的敏感性升高，和氧化和线粒体应激的模型，因此对于评价帕金森病、亨廷顿病和颞叶癫痫是理想的。图7显示MP101保护多巴胺能神经元免于6-OHDA的毒性作用。

[0055] 图7a和7b显示当在最后一天后右纹状体用6-OHDA注射时，通过口服强饲，DNP (MP101)治疗14天在保护多巴胺能神经元损失中的作用。图7a显示当小鼠置于圆筒中时，左和右爪在壁上接触的百分数在野生型小鼠中提高，和图7b显示在对帕金森病更易感的SIRT3 KO小鼠中，当用MP101 (DNP)治疗和置于旋转圆筒(rotarod)上时存在改进的运动协调性。

[0056] MP101 (DNP)用于亨廷顿病的小鼠模型，"Fragment模型" N171-82 HD小鼠，以确定其神经保护作用。N171-82 HD小鼠每日通过口服强饲用0.5、1和5 mg/kg的MP101治疗，大于17个周。在26周龄(治疗17个周)时，测试小鼠的行为、脑容量损失、多刺神经元和一般神经元的变化。图8a、8b、8c、8d、8e和8f显示DNP的效果(MP101药物治疗)。

[0057] 图8a-8f显示在用DNP治疗13周(22周龄)和/或17周(26周龄)后在亨廷顿病模型N171-82Q中MP101的效果。图8a显示野生型(WT)、突变体亨廷顿小鼠溶媒(HD)和MP101治疗的小鼠(HD-MP101)的脑容量变化的MRI图像。图8b显示皮层中的定量脑容量损失。图8c显示纹状体中的定量脑容量损失。HD安慰剂(HD)显示Ctx和Str二者中的损失。MP-101显示在皮

层和纹状体中较少损失。图8d显示使用生物标记DARPP32在26周龄时，用DNP治疗保护中间多刺神经元。图8e显示在N171-82Q HD小鼠中用生物标记突触后蛋白PSD95水平，用DNP治疗保护总体神经元损失。图8f显示在治疗17周后在锥形木和平衡木二者上，用DNP治疗改进运动功能。

[0058] 根据前述内容，本发明描述了涉及有效使用DNP以增加BDNF来在某些疾病中减弱疾病进展或提供症状的减轻的方法和制剂。

[0059] 使用方法

在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.001 mg/kg体重至5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0060] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.001 mg/kg体重至约5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0061] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.01 mg/kg体重至5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0062] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.01 mg/kg体重至约5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0063] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.01 mg/kg体重至1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0064] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.01 mg/kg体重至约1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0065] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在

足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.005 mg/kg体重至2 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0066] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.005 mg/kg体重至约2 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0067] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.02 mg/kg体重至0.9 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0068] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.02 mg/kg体重至约0.9 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0069] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.02 mg/kg体重至0.06 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0070] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.02 mg/kg体重至约0.06 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0071] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.05 mg/kg体重至0.09 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0072] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.05 mg/kg体重至约0.09 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0073] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代

谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在0.2 mg/kg体重至0.6 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0074] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在约0.2 mg/kg体重至约0.6 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0075] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在0.5 mg/kg体重至0.9 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0076] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在约0.5 mg/kg体重至约0.9 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0077] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在0.01 mg/kg体重至0.1 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0078] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在约0.01 mg/kg体重至约0.1 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0079] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在0.01 mg/kg体重至0.5 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0080] 在一个实施方案中,本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法,包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐,其中DNP的有效剂量在约0.01 mg/kg体重至约0.5 mg/kg体重的剂量范围中持续,以增加BDNF来减弱疾病进展或提供症状的减轻。

[0081] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.05 mg/kg体重至0.5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0082] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.05 mg/kg体重至约0.5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0083] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.05 mg/kg体重至0.9 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0084] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.05 mg/kg体重至约0.9 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0085] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.02 mg/kg体重至1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0086] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些和任何前述疾病或病况)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.02 mg/kg体重至约1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0087] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.01 mg/kg体重至0.1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0088] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.01 mg/kg体重至约0.1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾

病进展或提供症状的减轻。

[0089] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.1 mg/kg体重至1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0090] 在一个实施方案中，本发明的使用方法可包括治疗神经变性、神经肌肉、发育、代谢、自身免疫或线粒体病症(包括涉及衰老的那些)的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约0.1 mg/kg体重至约1 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0091] 在一个实施方案中，本发明的使用方法可包括治疗涉及衰老的神经肌肉或神经变性病症的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗创伤性CNS损伤或神经变性疾病的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在1 mg/kg体重至5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0092] 在一个实施方案中，本发明的使用方法可包括治疗涉及衰老的神经肌肉或神经变性病症的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗创伤性CNS损伤或神经变性疾病的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在约1 mg/kg体重至约5 mg/kg体重的剂量范围中持续，以增加BDNF来减弱疾病进展或提供症状的减轻。

[0093] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐的剂量范围为约0.001 mg/kg体重至约5 mg/kg体重、约0.001 mg/kg体重至约4 mg/kg体重、约0.001 mg/kg体重至约3 mg/kg体重、约0.001 mg/kg体重至约0.005 mg/kg体重、约0.005 mg/kg体重至约.01 mg/kg体重、约0.01 mg/kg体重至约1 mg/kg体重、约0.01 mg/kg体重至约0.1 mg/kg体重、约0.02 mg/kg体重至约0.08 mg/kg体重、约0.025 mg/kg体重至约0.06 mg/kg体重、约0.03 mg/kg体重至约0.05 mg/kg体重、约0.05 mg/kg体重至约0.1 mg/kg体重、约0.04 mg/kg体重至约0.06 mg/kg体重、约0.06 mg/kg体重至约0.09 mg/kg体重、约0.07 mg/kg体重至约0.08 mg/kg体重、约0.09 mg/kg体重至约0.11 mg/kg体重、约0.1 mg/kg体重至约0.5 mg/kg体重、约0.2 mg/kg体重至约0.4 mg/kg体重、约0.3 mg/kg体重至约0.5 mg/kg体重、约0.4 mg/kg体重至约0.6 mg/kg体重、约0.5 mg/kg体重至约1 mg/kg体重、约0.6 mg/kg体重至约0.9 mg/kg体重、约0.7 mg/kg体重至约0.8 mg/kg体重、约0.8 mg/kg体重至约1.2 mg/kg体重、约1 mg/kg体重至约5 mg/kg体重或约2 mg/kg体重至约4 mg/kg体重。

[0094] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐的剂量范围为0.001 mg/kg体重至5 mg/kg体重、0.001 mg/kg体重至4 mg/kg体重、0.001 mg/kg体重至3 mg/kg体重、0.001 mg/kg体重至0.005 mg/kg体重、0.005 mg/kg体重至0.01 mg/kg体重、0.01 mg/kg体重至1 mg/kg体重、0.01 mg/kg体重至0.1 mg/kg体重、0.02 mg/kg体重至0.08 mg/kg体重、0.025 mg/kg体重至0.06 mg/kg体

重、0.03 mg/kg体重至0.05 mg/kg体重、0.05 mg/kg体重至0.1 mg/kg体重、0.04 mg/kg体重至0.06 mg/kg体重、0.06 mg/kg体重至0.09 mg/kg体重、0.07 mg/kg体重至0.08 mg/kg体重、0.09 mg/kg体重至0.11 mg/kg体重、0.1 mg/kg体重至0.5 mg/kg体重、0.2 mg/kg体重至0.4 mg/kg体重、0.3 mg/kg体重至0.5 mg/kg体重、0.4 mg/kg体重至0.6 mg/kg体重、0.5 mg/kg体重至1 mg/kg体重、0.6 mg/kg体重至0.9 mg/kg体重、0.7 mg/kg体重至0.8 mg/kg体重、0.8 mg/kg体重至1.2 mg/kg体重、1 mg/kg体重至5 mg/kg体重或2 mg/kg体重至4 mg/kg体重。

[0095] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐为约0.001 mg/kg、约0.002 mg/kg、约0.003 mg/kg、约0.004 mg/kg、约0.005 mg/kg、约0.006 mg/kg、约0.007 mg/kg、约0.008 mg/kg、约0.009 mg/kg、约0.01 mg/kg、约0.015 mg/kg、约0.02 mg/kg、约0.025 mg/kg、约0.03 mg/kg、约0.035 mg/kg、约0.04 mg/kg、约0.045 mg/kg、约0.05 mg/kg、约0.055 mg/kg、约0.06 mg/kg、约0.065 mg/kg、约0.07 mg/kg、约0.075 mg/kg、约0.08 mg/kg、约0.085 mg/kg、约0.09 mg/kg、约0.095 mg/kg、约0.1 mg/kg、约0.15 mg/kg、约0.2 mg/kg、约0.25 mg/kg、约0.3 mg/kg、约0.35 mg/kg、约0.4 mg/kg、约0.45 mg/kg、约0.5 mg/kg、约0.55 mg/kg、约0.6 mg/kg、约0.65 mg/kg、约0.7 mg/kg、约0.75 mg/kg、约0.8 mg/kg、约0.85 mg/kg、约0.9 mg/kg、约0.95 mg/kg、约1.0 mg/kg、约1.1 mg/kg、约1.2 mg/kg、约1.3 mg/kg、约1.4 mg/kg、约1.5 mg/kg、约2 mg/kg、约2.5 mg/kg、约3 mg/kg、约3.5 mg/kg、约4 mg/kg、约4.5 mg/kg，或约5.0 mg/kg。

[0096] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐为0.001 mg/kg、0.002 mg/kg、0.003 mg/kg、0.004 mg/kg、0.005 mg/kg、0.006 mg/kg、0.007 mg/kg、0.008 mg/kg、0.009 mg/kg、0.01 mg/kg、0.015 mg/kg、0.02 mg/kg、0.025 mg/kg、0.03 mg/kg、0.035 mg/kg、0.04 mg/kg、0.045 mg/kg、0.05 mg/kg、0.055 mg/kg、0.06 mg/kg、0.065 mg/kg、0.07 mg/kg、0.075 mg/kg、0.08 mg/kg、0.085 mg/kg、0.09 mg/kg、0.095 mg/kg、约0.1 mg/kg、0.15 mg/kg、0.2 mg/kg、0.25 mg/kg、0.3 mg/kg、0.35 mg/kg、0.4 mg/kg、0.45 mg/kg、0.5 mg/kg、0.55 mg/kg、0.6 mg/kg、0.65 mg/kg、0.7 mg/kg、0.75 mg/kg、0.8 mg/kg、0.85 mg/kg、0.9 mg/kg、0.95 mg/kg、1.0 mg/kg、1.1 mg/kg、1.2 mg/kg、1.3 mg/kg、1.4 mg/kg、1.5 mg/kg、2 mg/kg、2.5 mg/kg、3 mg/kg、3.5 mg/kg、4 mg/kg、4.5 mg/kg或5.0 mg/kg。

[0097] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐为约10 mg/kg体重或更少、约5 mg/kg体重或更少、约4.5 mg/kg或更少、约4 mg/kg或更少、约3.5 mg/kg或更少、约3 mg/kg或更少、约2.5 mg/kg或更少、约2 mg/kg或更少、约1.5 mg/kg或更少、约1 mg/kg或更少、约0.95 mg/kg或更少、约0.9 mg/kg或更少、约0.85 mg/kg或更少、约0.8 mg/kg或更少、约0.75 mg/kg或更少、约0.7 mg/kg或更少、约0.65 mg/kg或更少、约0.6 mg/kg或更少、约0.55 mg/kg或更少、约0.5 mg/kg或更少、约0.45 mg/kg或更少、约0.4 mg/kg或更少、约0.35 mg/kg或更少、约0.3 mg/kg或更少、约0.25 mg/kg或更少、约0.2 mg/kg或更少、约0.15 mg/kg或更少、约0.1 mg/kg或更少、约0.09 mg/kg或更少、约0.08 mg/kg或更少、约0.07 mg/kg或更少、约0.06 mg/kg或更少、约0.05 mg/kg或更少、约0.04 mg/kg或更少、约0.03 mg/kg或更少、约0.02 mg/kg或更少、

约0.01 mg/kg或更少或约0.005 mg/kg或更少。在所有情况下，本文所述的剂量大于0 mg/kg。

[0098] 在一个实施方案中，以本文所述的任何形式或组合，为本文所述的任何目的给予DNP或其药学上可接受的盐为约4 mg/kg或更多、约3.5 mg/kg或更多、约3 mg/kg或更多、约2.5 mg/kg或更多、约2 mg/kg或更多、约1.5 mg/kg或更多、约1 mg/kg或更多、约0.95 mg/kg或更多、约0.9 mg/kg或更多、约0.85 mg/kg或更多、约0.8 mg/kg或更多、约0.75 mg/kg或更多、约0.7 mg/kg或更多、约0.65 mg/kg或更多、约0.6 mg/kg或更多、约0.55 mg/kg或更多、约0.5 mg/kg或更多、约0.45 mg/kg或更多、约0.4 mg/kg或更多、约0.35 mg/kg或更多、约0.3 mg/kg或更多、约0.25 mg/kg或更多、约0.2 mg/kg或更多、约0.15 mg/kg或更多、约0.1 mg/kg或更多、约0.09 mg/kg或更多、约0.08 mg/kg或更多、约0.07 mg/kg或更多、约0.06 mg/kg或更多、约0.05 mg/kg或更多、约0.04 mg/kg或更多、约0.03 mg/kg或更多、约0.02 mg/kg或更多、约0.01 mg/kg或更多、约0.009 mg/kg或更多、约0.007 mg/kg或更多、约0.005 mg/kg或更多、约0.003 mg/kg或更多或约0.001 mg/kg或更多。在所有情况下，本文所述的剂量小于10 mg/kg。

[0099] 在一些实例中，有效剂量经口服递送。在一些实例中，有效剂量静脉内递送。在一些实例中，有效剂量通过与盐水一起静脉内滴注的方式静脉内递送。在一些实例中，有效剂量通过与其它药物、维生素、流体或营养物一起静脉内滴注的方式静脉内递送。在一些实例中，有效剂量皮下递送。在一些实例中，有效剂量局部递送。在一些实例中，有效剂量经皮递送。在一些实例中，有效剂量与其它需要的药物、维生素、流体或营养物组合。

[0100] 在一些实例中，有效剂量用于通过用DNP治疗诱导BDNF以治疗、预防或缓解任何以下疾病或病况：创伤性脑损伤(TBI)、缺血性中风、亨廷顿病(成人型亨廷顿病、少年型亨廷顿病)、癫痫(群集癫痫发作、顽固性癫痫发作、非典型癫痫小发作、无张力性癫痫发作、阵挛性癫痫发作、肌阵挛性癫痫发作、强直性癫痫发作、强直-阵挛性癫痫发作、简单部分癫痫发作、复杂部分癫痫发作、继发性普遍癫痫发作、发热癫痫发作、非癫痫性癫痫发作、Gelastic和Dacrystic癫痫发作和癫痫小发作)、多发性硬化(MS) (复发-缓解性多发性硬化(RRMS)、继发性-进行性MS (SPMS)、原发性-进行性MS (PPMS)和进行性-复发性MS (PRMS))、狼疮(全身性红斑狼疮(SLE)、盘状(皮肤)药物诱导性狼疮(dil)和新生儿狼疮)、糖尿病(1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODY10, MODY11))、精神分裂症(偏执型精神分裂症、错乱型精神分裂症、紧张型精神分裂症、残留型精神分裂症、情感分裂性精神障碍)、重症肌无力(MG)(眼睛重症肌无力、先天性MG和泛发性重症肌无力)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良(杜兴肌营养不良(DMD)、Becker、肌强直、先天性、Emery-Dreifuss、面肩胛臂性、肢带性、远端和眼咽性)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、共济失调(弗里德赖希共济失调、脊髓小脑共济失调1 (SCA1)、脊髓小脑共济失调2 (SCA2)、脊髓小脑共济失调3 (SCA3)、脊髓小脑共济失调6 (SCA6)、脊髓小脑共济失调7 (SCA7)、脊髓小脑共济失调11 (SCA11)、齿状核红核苍白球丘脑下部核萎缩(DRPLA)和谷蛋白共济失调)、巴藤病或神经元蜡样脂褐质沉积症(NCL) (婴儿期NCL (INCL)、婴儿后期NCL(LINCL)、少年NCL (JNCL)或成人NCL (ANCL))、阿尔茨海默病(早期发作性阿尔茨海默病、晚期发作性阿尔茨海默病和家族性阿尔茨海默病(FAD))、视神经炎(ON)、莱伯遗传性视神

经病(LHON)、自闭症谱系障碍(ASD) (Asperger综合征、全身性发育迟缓(PDD)、童年瓦解性障碍(CDD)和孤独症)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症(严重抑郁、心境恶劣、产后精神抑郁、季节性情感障碍、非典型抑郁、精神病性抑郁症、双相型障碍、月经前焦虑障碍、情境性抑郁)、帕金森病(特发性帕金森病、血管性帕金森综合征、路易体痴呆、遗传性帕金森病、药物诱导性帕金森综合征、少年帕金森病和非典型帕金森综合征)、线粒体疾病、发育障碍、代谢综合征(血压增加、高血糖水平、腰部周围体脂过量和异常胆固醇水平)和/或自身免疫性病症。

[0101] 在一些实例中,用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.005 mg/kg至1.0 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.01 mg/kg至0.5 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.01 mg/kg至0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.02 mg/kg至0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.02 mg/kg至0.4 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.025 mg/kg至0.4 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.025 mg/kg至0.08 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.03 mg/kg至0.075 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.035 mg/kg至0.4 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.035 mg/kg至0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.035 mg/kg至0.09 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.035 mg/kg至0.08 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.035 mg/kg至0.075 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.045 mg/kg至0.055 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.055 mg/kg至0.085 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.055 mg/kg至0.065 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.065 mg/kg至0.075 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.075 mg/kg至0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.07 mg/kg至0.09 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.085 mg/kg至0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.09 mg/kg至0.2 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.1 mg/kg至0.3 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是0.2 mg/kg至0.4 mg/kg。

[0102] 在一些实例中,用于治疗、预防或缓解亨廷顿病的症状的有效剂量是约0.005 mg/kg至约1.0 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.01 mg/kg至约0.5 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.01 mg/kg至约0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.02 mg/kg至约0.1 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.02 mg/kg至约0.4 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.025 mg/kg至约0.4 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.025 mg/kg至约0.08 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有效剂量是约0.03 mg/kg至约0.075 mg/kg。在一些实例中,用于治疗、预防或缓解亨廷顿病的有

效剂量是约0.035 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.035 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.035 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.035 mg/kg至约0.08 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.035 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.045 mg/kg至约0.055 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.055 mg/kg至约0.085 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.055 mg/kg至约0.065 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.065 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.075 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.07 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.085 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.09 mg/kg至约0.2 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.1 mg/kg至约0.3 mg/kg。在一些实例中，用于治疗、预防或缓解亨廷顿病的有效剂量是约0.2 mg/kg至约0.4 mg/kg。

[0103] 在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.001 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.002 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.003 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.004 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.005 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.01 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.025 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.035 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.05 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.075 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.1 mg/kg或更多。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.5 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.35 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.25 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.075 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.05 mg/kg或更少。在一些实例中，用于治疗、预防或缓解亨廷顿病的症状的有效剂量是0.01 mg/kg或更少。在所有情况下，本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0104] 在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是0.01 mg/kg至5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是0.01 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是0.05 mg/kg至5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)

的症状的有效剂量是0.05 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.06 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.07 mg/kg至0.9 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.075 mg/kg至0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.07 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.08 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.1 mg/kg至0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.3 mg/kg至0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.4 mg/kg至0.7 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.7 mg/kg至0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.8 mg/kg至1 mg/kg。

[0105] 在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是约0.05 mg/kg至约5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是约0.01 mg/kg至约1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是约0.05 mg/kg至约5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的症状的有效剂量是约0.05 mg/kg至约1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.06 mg/kg至约1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.07 mg/kg至约0.9 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.075 mg/kg至约0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.07 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.08 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.1 mg/kg至约0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.3 mg/kg至约0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.4 mg/kg至约0.7 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.7 mg/kg至约0.8 mg/kg。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是约0.8 mg/kg至约1 mg/kg。

[0106] 在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是1.0 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.9 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.8 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.7 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.6 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.5 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.4 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.3 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.2 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.09 mg/kg或更少。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.08 mg/kg或更少。在一些实例中，用于治

疗、预防或缓解多发性硬化(MS)的有效剂量是0.07 mg/kg或更少。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.05 mg/kg或更少。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.01 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.05 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.06 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.07 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.08 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.09 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.1 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.15 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.2 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.25 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.3 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.35 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.4 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.45 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.5 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.55 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.6 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.65 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.70 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.75 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.8 mg/kg或更多。在一些实例中,用于治疗、预防或缓解多发性硬化(MS)的有效剂量是1.0 mg/kg或更多。在所有情况下,本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0107] 在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.05 mg/kg至1 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.5 mg/kg至1 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.6 mg/kg至0.9 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.7 mg/kg至0.8 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是约0.5 mg/kg至约1 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是约0.6 mg/kg至约0.9 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是约0.7 mg/kg至约0.8 mg/kg。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.1 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.4 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.5 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.6 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.7 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.8 mg/kg或更多。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是1 mg/kg或更少。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.9 mg/kg或更少。在一些实例中,用于治疗、预防或缓解癫痫的有效剂量是0.8 mg/kg或更少。

在一些实例中，用于治疗、预防或缓解癫痫的有效剂量是0.7 mg/kg或更少。在一些实例中，用于治疗、预防或缓解癫痫的有效剂量是0.5 mg/kg或更少。在所有情况下，本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0108] 在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.005 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.02 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.01 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.02 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.025 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.025 mg/kg至0.08 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.03 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.035 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.035 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.035 mg/kg至0.09 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.035 mg/kg至0.08 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.035 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.045 mg/kg至0.055 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.055 mg/kg至0.085 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.055 mg/kg至0.065 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.065 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.075 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.07 mg/kg至0.09 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.085 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是0.09 mg/kg至0.2 mg/kg。

[0109] 在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是约0.005 mg/kg至约1.0 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.02 mg/kg至约1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.01 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.02 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.025 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.025 mg/kg至约0.08 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.03 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.035 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.035 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.035 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.035 mg/kg至约0.08 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.035 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.045 mg/kg至约0.055 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.055 mg/kg至约

0.085 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.055 mg/kg至约0.065 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.065 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.075 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.07 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.085 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解Rett综合征的有效剂量是约0.09 mg/kg至约0.2 mg/kg。

[0110] 在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.01 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.02 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.03 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.04 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.05 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.06 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.07 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.08 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.09 mg/kg或更多。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.5 mg/kg或更少。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.3 mg/kg或更少。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.075 mg/kg或更少。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.05 mg/kg或更少。在一些实例中，用于治疗、预防或缓解Rett综合征的症状的有效剂量是0.01 mg/kg或更少。在所有情况下，本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0111] 在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是0.01 mg/kg至1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是0.01 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是0.05 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.05 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.06 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.07 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.08 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.09 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.075 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.09 mg/kg至0.2 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.1 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.2 mg/kg至0.5 mg/kg。

[0112] 在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是约0.01 mg/kg至约1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是约0.01 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的症状的有效剂量是约0.05 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有

效剂量是约0.05 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.06 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.07 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.08 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.09 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.075 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.09 mg/kg至约0.2 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.1 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是约0.2 mg/kg至约0.5 mg/kg。

[0113] 在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是1.0 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.5 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.4 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.3 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.2 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.09 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.08 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.07 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.05 mg/kg或更少。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.01 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.05 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.06 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.07 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.08 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.09 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.1 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.15 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.2 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.25 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.3 mg/kg或更多。在一些实例中，用于治疗、预防或缓解多发性硬化(MS)的有效剂量是0.35 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.4 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.45 mg/kg或更多。在一些实例中，用于治疗、预防或缓解帕金森病的有效剂量是0.5 mg/kg或更多。在所有情况下，本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0114] 在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是.005 mg/kg至1.0 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.01 mg/kg至0.5 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.02 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.025 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.025 mg/kg至0.08 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效

剂量是0.03 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.035 mg/kg至0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.035 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.035 mg/kg至0.09 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.035 mg/kg至0.08 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.035 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.045 mg/kg至0.055 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.055 mg/kg至0.085 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.055 mg/kg至0.065 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.065 mg/kg至0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.075 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.07 mg/kg至0.09 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.085 mg/kg至0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.09 mg/kg至0.2 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.1 mg/kg至0.3 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是0.2 mg/kg至0.4 mg/kg。

[0115] 在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是约0.005 mg/kg至约1.0 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.01 mg/kg至约0.5 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.02 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.025 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.025 mg/kg至约0.08 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.03 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.035 mg/kg至约0.4 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.035 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.035 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.035 mg/kg至约0.08 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.035 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.045 mg/kg至约0.055 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.055 mg/kg至约0.085 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.055 mg/kg至约0.065 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.065 mg/kg至约0.075 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.075 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.07 mg/kg至约0.09 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.085 mg/kg至约0.1 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.09 mg/kg至约0.2 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.1 mg/kg至约0.3 mg/kg。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的有效剂量是约0.2 mg/kg至约0.4 mg/kg。

[0116] 在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.001 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.002 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.003 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.004 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.005 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.01 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.025 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.035 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.05 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.075 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.1 mg/kg或更多。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.5 mg/kg或更少。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.35 mg/kg或更少。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.25 mg/kg或更少。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.1 mg/kg或更少。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.075 mg/kg或更少。在一些实例中，用于治疗、预防或缓解阿尔茨海默病的症状的有效剂量是0.05 mg/kg或更少。在所有情况下，本文所述的剂量大于0 mg/kg和小于5 mg/kg。

[0117] 在一些实例中，本发明是治疗任何这些疾病或治疗神经肌肉、神经变性、自身免疫、发育、代谢或涉及衰老的任何病症的方法，包括在足够长以实现疾病的症状减轻的时间内给予需要治疗创伤性CNS损伤或神经变性疾病的患者有效剂量的DNP或其药学上可接受的盐，其中DNP的有效剂量在0.001 mg/kg体重至5 mg/kg体重的剂量范围中持续，以诱导脑中的BDNF表达。事实上，本发明包括给予DNP，其中DNP的剂量可作为避免诱导太多BDNF，或因诱导太少的BDNF而没有效果的方式，用于预防人的损害。如自本文的公开内容还显而易见的，本发明还包括提高BDNF的表达，这提供保护免于肌肉萎缩或肌肉功能障碍，因为BDNF不仅在脑中，而且在肌肉中表达，和可作为肌因子起作用。

[0118] 在一些实例中，本发明是治疗神经肌肉或神经变性或自身免疫或发育或代谢病症的方法，包括在足够长以实现疾病的症状减轻的时间内接受有效剂量的DNP或其药学上可接受的盐，其中持续接受剂量范围为0.001 mg/kg体重至5 mg/kg体重的DNP的有效剂量，以增加BDNF来减弱疾病进展或提供症状的减轻。在一些实例中，本发明是治疗神经肌肉或神经变性或自身免疫或发育或代谢病症的方法，包括在足够长以实现疾病的症状减轻的时间内提供给予有效剂量的DNP或其药学上可接受的盐的指示，其中指示接受的DNP的有效剂量的剂量范围为0.001 mg/kg体重至5 mg/kg体重。

[0119] 在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效果，在接受DNP的最后一次剂量后达至多三周。在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效果，在接受DNP的最后一次剂量后达至多两周。在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效

果，在接受DNP的最后一次剂量后达至多一周。在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效果，在接受DNP的最后一次剂量后达至多三天。在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效果，在接受DNP的最后一次剂量后达至多两天。在一些实例中，本发明是治疗任何本文鉴定的疾病的方法，由此有效剂量的DNP对BDNF水平的持续升高具有持续的效果，在接受DNP的最后一次剂量后达至多一天。

[0120] 在一个实施方案中，本文涵盖的剂量可基于受试者的重量作为组合物给予。在一个实施方案中，可按受试者的单位重量给予剂量(例如，mg本文所述的组合物/kg受试者的重量)。在一个实施方案中，本文涵盖的剂量可仅基于剂量的重量，而不管受试者的重量，作为组合物给予(例如，mg本文所述的组合物/给予受试者的剂量)。在一个实施方案中，基于载体中的活性成分的重量给予剂量。在另一个实施方案中，基于载体中的组合物的活性成分的总重量给予剂量。在我们的剂量范围中，我们假定平均成年患者重量为大约60 kg。

[0121] 组合物

在一些实施方案中，药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物，包含有效剂量的DNP，其中DNP的有效剂量的范围为0.001 mg/kg体重至5 mg/kg体重；0.01 mg/kg至1 mg/kg；0.01 mg/kg至0.1 mg/kg；0.1 mg/kg至0.5 mg/kg；或1 mg/kg至5 mg/kg。在一些实施方案中，药物组合物是诱导BDNF表达以逆转、减慢或预防神经肌肉和/或神经变性和/或肌肉萎缩的有效剂量。

[0122] 在一些实施方案中，药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物，包含有效剂量的DNP，其中DNP的有效剂量的范围为约0.001 mg/kg体重至约5 mg/kg体重；约0.01 mg/kg至约1 mg/kg；约0.01 mg/kg至约0.1 mg/kg；约0.1 mg/kg；约0.1 mg/kg至约0.5 mg/kg；约0.5 mg/kg；约1 mg/kg；约1 mg/kg至约5 mg/kg；约5 mg/kg。在一些实施方案中，药物组合物是诱导BDNF表达以逆转、减慢或预防神经肌肉和/或神经变性和/或肌肉萎缩的有效剂量。

[0123] 在一些实施方案中，药物组合物是立即释放制剂。在一些实施方案中，药物组合物是快速溶解的。在一些实施方案中，药物组合物是持续释放制剂。在一些实施方案中，药物组合物是控制释放制剂。

[0124] 在其它实施方案中，如本文他处更详细说明的，活性成分的剂量和给药方案可基于待治疗的受试者的健康和病况，以及需要的治疗结果进行优化。

[0125] 单位剂量

在一些实施方案中，药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物，包含单位剂量，其中所述单位剂量的范围为约0.1 mg至约300 mg；其中所述单位剂量的范围为约0.1 mg至约1 mg；其中所述单位剂量的范围为约1 mg至约5 mg；其中所述单位剂量为约1 mg；其中所述单位剂量为约2 mg；其中所述单位剂量为约3 mg；其中所述单位剂量为约4 mg；其中所述单位剂量为约5 mg；其中所述单位剂量的范围为约5 mg至约10 mg；其中所述单位剂量为约6 mg；其中所述单位剂量为约7 mg；其中所述单位剂量为约8 mg；其中所述单位剂量为约9 mg；其中所述单位剂量为约10 mg；其中所述单位剂量的范围为约10 mg至约15 mg；其中所述单位剂量为约11 mg；其中所述单位剂量为约12 mg；其中所述单位剂量为约13 mg；其中所述单位剂量为约14 mg；其中所述单位剂量为约15 mg；其中所述单位

剂量的范围为约15 mg至约20 mg;其中所述单位剂量为约16 mg;其中所述单位剂量为约17 mg;其中所述单位剂量为约18 mg;其中所述单位剂量为约19 mg;其中所述单位剂量为约20 mg;其中所述单位剂量的范围为约20 mg至约30 mg;其中所述单位剂量为约25 mg;其中所述单位剂量为约30 mg;其中所述单位剂量的范围为约30 mg至约40 mg;其中所述单位剂量为约35 mg;其中所述单位剂量为约40 mg;其中所述单位剂量的范围为约40 mg至约50 mg;其中所述单位剂量为约45 mg;其中所述单位剂量为约50 mg;其中所述单位剂量的范围为约50 mg至约100 mg;其中所述单位剂量为约75 mg;其中所述单位剂量为约100 mg;其中所述单位剂量的范围为约100 mg至约200 mg;其中所述单位剂量为约150 mg;其中所述单位剂量为约200 mg;其中所述单位剂量的范围为约200 mg至约300 mg;其中所述单位剂量为约200 mg;其中所述单位剂量为约250 mg;或其中所述单位剂量为约300 mg。

[0126] 在一些实施方案中,药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物,包含单位剂量,其中所述单位剂量的范围为0.1 mg至300 mg;其中所述单位剂量的范围为0.1 mg至1 mg;其中所述单位剂量的范围为1 mg至5 mg;其中所述单位剂量为1 mg;其中所述单位剂量为2 mg;其中所述单位剂量为3 mg;其中所述单位剂量为4 mg;其中所述单位剂量为5 mg;其中所述单位剂量的范围为5 mg至10 mg;其中所述单位剂量为6 mg;其中所述单位剂量为7 mg;其中所述单位剂量为8 mg;其中所述单位剂量为9 mg;其中所述单位剂量为10 mg;其中所述单位剂量的范围为10 mg至15 mg;其中所述单位剂量为11 mg;其中所述单位剂量为12 mg;其中所述单位剂量为13 mg;其中所述单位剂量为14 mg;其中所述单位剂量为15 mg;其中所述单位剂量的范围为15 mg至20 mg;其中所述单位剂量为16 mg;其中所述单位剂量为17 mg;其中所述单位剂量为18 mg;其中所述单位剂量为19 mg;其中所述单位剂量为20 mg;其中所述单位剂量的范围为20 mg至30 mg;其中所述单位剂量为25 mg;其中所述单位剂量为30 mg;其中所述单位剂量的范围为30 mg至40 mg;其中所述单位剂量为35 mg;其中所述单位剂量为40 mg;其中所述单位剂量的范围为40 mg至50 mg;其中所述单位剂量为45 mg;其中所述单位剂量为50 mg;其中所述单位剂量的范围为50 mg至100 mg;其中所述单位剂量为75 mg;其中所述单位剂量为100 mg;其中所述单位剂量的范围为100 mg至200 mg;其中所述单位剂量为150 mg;其中所述单位剂量为200 mg;其中所述单位剂量的范围为200 mg至300 mg;其中所述单位剂量为200 mg;其中所述单位剂量为250 mg;或其中所述单位剂量为300 mg。

[0127] 在一些实施方案中,药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物,包含单位剂量,其中所述单位剂量的范围为0.1 mg或更多;其中所述单位剂量的范围为0.5 mg或更多;其中所述单位剂量的范围为1 mg或更多;其中所述单位剂量为5 mg或更多;其中所述单位剂量为10 mg或更多;其中所述单位剂量为15 mg或更多;其中所述单位剂量为20 mg或更多;其中所述单位剂量为30 mg或更多;其中所述单位剂量为40 mg或更多;其中所述单位剂量为50 mg或更多;其中所述单位剂量为100 mg或更多;其中所述单位剂量为150 mg或更多;其中所述单位剂量为200 mg或更多;或其中所述单位剂量为250 mg或更多,但在所有情况下不大于300 mg。

[0128] 在一些实施方案中,药物组合物包括DNP或其药学上可接受的盐、溶剂合物或水合物,包含单位剂量,其中所述单位剂量为0.25 mg或更少,但在所有情况下大于0;其中所述单位剂量为0.5 mg或更少;其中所述单位剂量为1 mg或更少;其中所述单位剂量为5 mg或

更少;其中所述单位剂量为10 mg或更少;其中所述单位剂量为15 mg或更少;其中所述单位剂量为20 mg或更少;其中所述单位剂量为30 mg或更少;其中所述单位剂量为40 mg或更少;其中所述单位剂量为50 mg或更少;其中所述单位剂量为100 mg或更少;其中所述单位剂量为150 mg或更少;其中所述单位剂量为200 mg或更少;其中所述单位剂量为250 mg或更少;或其中所述单位剂量为300 mg或更少。

[0129] 在一些实施方案中,所述单位剂量为立即释放制剂。在一些实施方案中,所述单位剂量为延长释放制剂。在一些实施方案中,所述单位剂量为持续释放制剂。在一些实施方案中,所述单位剂量为控制释放制剂。在一些实施方案中,所述单位剂量为口服剂型。在一些实施方案中,口服剂型为片剂。在一些实施方案中,口服剂型为胶囊剂。在一些实施方案中,所述单位剂量为不含填充剂的胶囊剂。在一些实施方案中,口服剂型为快速溶解的。

[0130] 在一些实施方案中,所述单位剂量经静脉内递送。在一些实施方案中,所述单位剂量通过与盐水一起静脉内滴注的方式递送。在一些实施方案中,所述单位剂量通过与盐水、其它药物、维生素和/或营养品一起静脉内滴注的方式递送。在一些实施方案中,所述单位剂量皮下递送。在一些实施方案中,所述单位剂量局部递送。在一些实施方案中,所述单位剂量经皮递送。在一些实施方案中,所述单位剂量为贴剂的形式。

[0131] 在一些实施方案中,所述单位剂量为诱导BDNF表达以逆转、减慢或预防神经肌肉和/或神经变性和/或肌肉萎缩的有效量。在一些实施方案中,所述单位剂量为治疗亨廷顿病。在一些实施方案中,所述单位剂量为治疗多发性硬化(MS)。在一些实施方案中,所述单位剂量为治疗癫痫。在一些实施方案中,所述单位剂量为治疗帕金森病。在一些实施方案中,所述单位剂量为治疗阿尔茨海默病。在一些实施方案中,所述单位剂量为治疗Rhett综合征。在一些实施方案中,所述单位剂量为治疗但不限于创伤性脑损伤(TBI)、缺血性中风、亨廷顿病(成人型亨廷顿病、少年型亨廷顿病)、癫痫(群集癫痫发作、顽固性癫痫发作、非典型癫痫小发作、无张力性癫痫发作、阵挛性癫痫发作、肌阵挛性癫痫发作、强直性癫痫发作、强直-阵挛性癫痫发作、简单部分癫痫发作、复杂部分癫痫发作、继发性普遍癫痫发作、发热癫痫发作、非癫痫性癫痫发作、Gelastic和Dacrystic癫痫发作和癫痫小发作)、多发性硬化(MS) (复发-缓解性多发性硬化(RRMS)、继发性-进行性MS (SPMS)、原发性-进行性MS(PPMS)和进行性-复发性MS (PRMS))、狼疮(全身性红斑狼疮(SLE)、盘状(皮肤)药物诱导性狼疮(dil)和新生儿狼疮)、糖尿病(1型糖尿病、2型糖尿病、青春晚期糖尿病(MODY: MODY1, MODY2, MODY3, MODY4, MODY5, MODY6, MODY7, MODY8, MODY9, MODYIO, MODYl l))、精神分裂症(偏执型精神分裂症、错乱型精神分裂症、紧张型精神分裂症、残留型精神分裂症、情感分裂性精神障碍)、重症肌无力(MG) (眼睛重症肌无力、先天性MG和泛发性重症肌无力)、类风湿性关节炎(RA)、格雷夫斯病、格-巴二氏综合征(GBS)、肌营养不良(杜兴肌营养不良(DMD))、Becker、肌强直、先天性、Emery-Dreifuss、面肩胛臂性、肢带性、远端和眼咽性)、重度烧伤、衰老、肌萎缩侧索硬化(ALS)、共济失调(弗里德赖希共济失调、脊髓小脑共济失调1 (SCA1)、脊髓小脑共济失调2 (SCA2)、脊髓小脑共济失调3 (SCA3)、脊髓小脑共济失调6 (SCA6)、脊髓小脑共济失调7 (SCA7)、脊髓小脑共济失调11 (SCA11)、齿状核红核苍白球丘脑下部核萎缩(DRPLA)和谷蛋白共济失调)、巴藤病或神经元蜡样脂褐质沉积症(NCL) (婴儿期NCL (INCL)、婴儿后期NCL (LINCL)、少年NCL (JNCL)或成人NCL (ANCL))、阿尔茨海默病(早期发作性阿尔茨海默病、晚期发作性阿尔茨海默病和家族性阿尔茨海默

病(FAD))、视神经炎(ON)、莱伯遗传性视神经病(LHON)、自闭症谱系障碍(ASD) (Asperger综合征、全身性发育迟缓(PDD)、童年瓦解性障碍(CDD)和孤独症)、Rett综合征、Angelman综合征、利氏病、Prader Willi综合征、脆性-X综合征、抑郁症(严重抑郁、心境恶劣、产后精神抑郁、季节性情感障碍、非典型抑郁、精神病性抑郁症、双相型障碍、月经前焦虑障碍、情境性抑郁)、帕金森病(特发性帕金森病、血管性帕金森综合征、路易体痴呆、遗传性帕金森病、药物诱导性帕金森综合征、少年帕金森病和非典型帕金森综合征)、线粒体疾病、发育障碍、代谢综合征(血压增加、高血糖水平、腰部周围体脂过量和异常胆固醇水平)和/或自身免疫性病症。

[0132] 剂量可作为每日单次剂量、每日两次剂量、每日三次或更高频率给予。剂量可每周三次、每周两次、每周一次或更低频率给予。在一个实施方案中,给予频率可以是一天1-5次。在另一个实施方案中,给予频率可以是一天2-4次。在另一个实施方案中,给予频率可以是一天至少3次。在另一个实施方案中,给予频率可以是一天两次。在另一个实施方案中,给予频率可以是一天一次。在另一个实施方案中,给予频率可以低于一天一次。在其它实施方案中,给予频率可以是每2天一次,或每3天一次或每4天一次或每5天一次或每6天一次。在另一个实施方案中,给予频率可以一周一次。在另一个实施方案中,给予频率可以随时间改变,以某一比率开始,例如一天一次或两次,然后在第一天治疗后,降低至较低频率,例如每2天一次,或每3天一次,或一周一次。在另一个实施方案中,给予频率可随时间改变,以某一比率开始,例如一天一次或两次,然后在前两天或三天治疗后,降低至较低频率,例如每2天一次或每3天一次,或一周一次。在另一个实施方案中,给予频率可随时间改变,以某一比率开始,例如一天一次或两次,然后在第一周治疗后,降低至较低频率,例如每2天一次或每3天一次或一周一次。在另一个实施方案中,当要求或需要治疗性治疗时,给予频率可以是按需要的。

[0133] 因为MS的EAE模型中的研究表明在2周的DNP治疗后,在治疗后3周存在统计学升高水平的BDNF蛋白(图2b),剂量频率可以是长期的,以升高BDNF蛋白水平,接着是少见剂量或"停药期"。少见剂量用作维持剂量以保持升高水平的BDNF。因此,在较高频率剂量的初始期后,剂量的频率可然后下降至每周一次、每两周一次、每三周一次或每月一次。

[0134] 根据本文包括的公开内容将理解,如何确定受试者是否需要另外和/或继续的剂量。还将理解,选择的给药频率可需要活性成分的剂量的调整。根据本文包括的公开内容还将理解,活性成分的选择剂量可需要给药频率的调整。本文包括的公开内容,结合本领域的技术,将能够使技术人员优化活性成分的剂量和给予活性成分的频率二者,以治疗有需要的受试者。

[0135] 单位剂量也可根据患者的大小进行调整。本文提供的数值基于60 kg患者。相同的疗法可提供给更小或更大的患者,但减少或增加剂量。仅通过实例的方式,20 kg的儿童可需要更小得多的剂量。

[0136] 组合物的共给予

在一个实施方案中,本文所述的组合物与一种或更多种其它药物或消费品结合给予。这样的其它药物或消费品可以本领域已知的形式和剂量,或备选地,如上文对于使用本文所述的组合物给予活性成分所述的,给予或共给予。仅通过实例的方式,对于中风患者,DNP可与组织纤溶酶原激活物(tPA)一起给予。

[0137] 对于糖尿病,DNP可与胰岛素(Humulin N, Novolin N)或其它生物制品一起给予,作为注射剂或作为口服片剂,与二甲双胍(Glucophage, Glumetza等)、磺脲类(格列本脲(DiaBeta, Glynase), 格列吡嗪(Glucotrol)和格列美脲(Amaryl)等)、氯茴苯酸类(epaglinide (Prandin)和那格列奈(Starlix))、噻唑烷二酮类(罗格列酮(Avandia)和吡格列酮(Actos))、DPP-4抑制剂(sitagliptin (Januvia), saxagliptin (Onglyza)和linagliptin (Tradjenta))、GLP-1受体激动剂((Byetta)和liraglutide (Victoza))、SGLT2抑制剂(canagliflozin (Invokana)和/或dapagliflozin (Farxiga))一起。

[0138] 对于亨廷顿病,DNP可与丁苯那嗪(Xenazine)、抗精神病药例如氟哌啶醇(Haldol)或其它,像金刚烷胺、左乙拉西坦(Keppra)和/或氯硝西泮(Klonopin)一起给予。

[0139] 对于帕金森病,DNP可与卡比多巴-左旋多巴(Rytary, Sinemet)、多巴胺激动剂例如普拉克索(Mirapex)、罗匹尼罗(Requip)和罗替戈汀(作为贴剂给予, Neupro)、短效注射多巴胺激动剂、阿扑吗啡(Apokyn)、MAO-B抑制剂(Eldepryl, Zelapar)或儿茶酚-O-甲基转移酶(COMT)抑制剂(恩他卡朋(Comtan)、托卡朋(Tasmar)等)、抗胆碱能类(苯甲托品(Cogentin)、苯海索)和/或金刚烷胺一起给予。

[0140] 对于阿尔茨海默病,DNP可与胆碱酯酶抑制剂(多奈哌齐(Aricept)、加兰他敏(Razadyne)和利凡斯的明(Exelon))和/或美金刚(Namenda)一起给予。

[0141] 对于抑郁症,DNP可与选择性5-羟色胺再吸收抑制剂(SSRI) (luoxetine(Prozac)、帕罗西汀(Paxil, Pexeva)、舍曲林(Zoloft)、西酞普兰(Celexa)和依他普仑(Lexapro))、去甲肾上腺素-多巴胺再吸收抑制剂(NDRIs)、丁氨苯丙酮(Wellbutrin, Aplenzin, Forfivo XL)、非典型抗抑郁药(曲唑酮、米氮平(Remeron)、vortioxetine(Brintellix)、维拉佐酮(Viibryd)等)和/或三环抗抑郁药(丙米嗪(Tofranil)、去甲替林(Pamelor)、单胺氧化酶抑制剂(MAOIs)、反苯环丙胺(Parnate)、苯乙肼(Nardil)、异卡波肼(Marplan)等)一起给予。

[0142] 对于精神分裂症,DNP也可与非典型抗精神病药(阿立哌唑(Abilify)、Asenapine(Saphris)、氯氮平(Clozaril)、伊潘立酮(Fanapt)等)、常规或典型的,和/或抗精神病药(氯丙嗪、氟奋乃静、氟哌啶醇(Haldol)、奋乃静等)一起给予。

[0143] 对于MS,DNP可与皮质甾类(泼尼松、静脉内甲泼尼龙)、β干扰素、醋酸格拉默(Copaxone)、二甲基富马酸酯(Tecfidera)、Fingolimod (Gilenya)、特立氟胺(Aubagio)、那他珠单抗(Tysabri)、阿仑单抗(Lemtrada)和/或米托蒽醌等一起给予。

[0144] 对于癫痫,DNP可与卡马西平、氯巴占、氯硝西泮、eslicarbazepine、乙琥胺、加巴喷丁、lacosamide、拉莫三嗪、左乙拉西坦、奥卡西平、perampanel、苯巴比妥、苯妥英、普加巴林、扑米酮、瑞替加滨、卢非酰胺、丙戊酸钠、噻加宾、托吡酯、氨己烯酸和/或唑尼沙胺等一起给予。

[0145] 对于创伤性脑损伤(TBI),DNP可与利尿药、抗癫痫药和/或Coma-诱导药一起给予。

[0146] 对于狼疮,DNP可与非甾体抗炎药(NSAID) (甲氧萘丙酸钠(Aleve)和布洛芬(Advil, Motrin IB等))、抗疟药例如羟氯喹(Plaquenil)、皮质甾类(泼尼松等)和/或免疫抑制剂(硫唑嘌呤(Imuran, Azasan)、麦考酚酯(CellCept)、来氟米特(Arava)、甲氨蝶呤(Trexall)等)一起给予。

[0147] 对于Prader Willi综合征,DNP可与人生长激素(HGH)和/或性激素治疗(对于雄性

的睾酮或对于雌性的雌激素和黄体酮)等一起给予。

[0148] 对于格雷夫斯病,DNP可与抗-甲状腺药物(丙硫氧嘧啶和甲巯咪唑(Tapazole))和/或β阻滞剂(普萘洛尔(Inderal)、阿替洛尔(Tenormin)、美托洛尔(Lopressor, Toprol-XL)、纳多洛尔(Corgard))一起给予。

[0149] 对于肌营养不良,DNP可与皮质甾类例如泼尼松和/或心脏药物例如加压素-转化酶(ACE)抑制剂或β阻滞剂一起给予。

[0150] DNP还可与疼痛缓解药物、维生素、营养物、水合流体或其它药物一起给予。

[0151] 术语"共给予"或"组合疗法"用于描述一种疗法,其中至少两种组分,其可包括本文所述的一种或多种产品组分,同时用于治理、解决或影响本文所述的皮肤病况或其它病症。在一个实施方案中,有效量的至少两种组分同时用于治疗、解决或影响本文所述的皮肤病况或其它病症。在另一个实施方案中,至少两种活性成分,其组合包含有效量,同时用于治疗、解决或影响本文所述的皮肤病况或其它病症。在一个实施方案中,至少两种组分的治疗结果可以是单独使用各组分获得的治疗结果的加和,其为直接加和,或加和至低于分别用两种组分获得的结果的程度。在一个实施方案中,用至少两种组分的治疗结果可以是协同的,至各种程度。在一个实施方案中,用至少两种组分的治疗结果可大于分别使用各组分获得的治疗结果。在一个方面,至少两种活性成分的治疗结果小于分别使用各活性成分获得的结果,而组合物中的其它活性成分与单独获得的治疗结果大约相同。在一个方面,组合物中所有活性成分的治疗结果小于分别用各活性成分获得的结果。

[0152] 尽管术语共给予包括同时给予患者两种组分,但不需要同时给予患者各组分,尽管通过组合物递送的有效量的各个活性成分将同时存在于患者中。

[0153] 本文所述的产物组合物可有利地与至少一种其它治疗剂组合给予,以提供对皮肤病况或其它病症的改进治疗。本发明的组合、用途和治疗方法还可在治疗对其它已知治疗不能足够响应的患者或消费者中提供益处。在一个实施方案中,本文所述的产品组合物可给予已经历用至少一种其它皮肤护理组合物治疗的患者,以对本文所述的病况的任何组合提供改进的治疗。在一个实施方案中,本文所述的产品组合物与一种或多种洗剂、泡沫剂或霜剂共给予。

[0154] 技术人员将进一步理解,除了剂量和给药方案的上述实施方案之外,剂量和给药方案二者将根据治疗的受试者的病况,按需要考虑和各自调整。

[0155] 本领域技术人员将理解,可对上文所示和描述的实例性的实施方案进行变化,而不偏离其广泛的发明构思。因此应理解,本发明不限于所示和描述的实例性的实施方案,但其意图涵盖在由权利要求定义的本发明的精神和范围内的修饰。例如,实例性实施方案的具体特征可以是或可以不是所要求保护的发明的一部分,和所公开的实施方案的各种特征可组合。

[0156] 除非本文特别说明,术语"一个"、"一种"和"所述"不限于一个要素,而是应理解为意指"至少一个"。

[0157] 应理解,为清楚理解本发明,本发明的至少一些附图和描述已被简化集中于相关的要素,而为清楚的目的,消除本领域普通技术人员将理解的其它要素也可包含本发明的一部分。然而,因为这样的要素是本领域众所周知的,和因为它们不必然促进更好理解本发明,这样的要素的描述不在本文中提供。

[0158] 此外，在本发明的方法不依赖于本文所述的特定步骤次序的方面，特定步骤次序不应解释为对权利要求的限制。涉及本发明的方法的任何权利要求不应限制于以书写的次序执行它们的步骤，和本领域技术人员可容易地理解，步骤可改变和仍保持在本发明的精神和范围内。

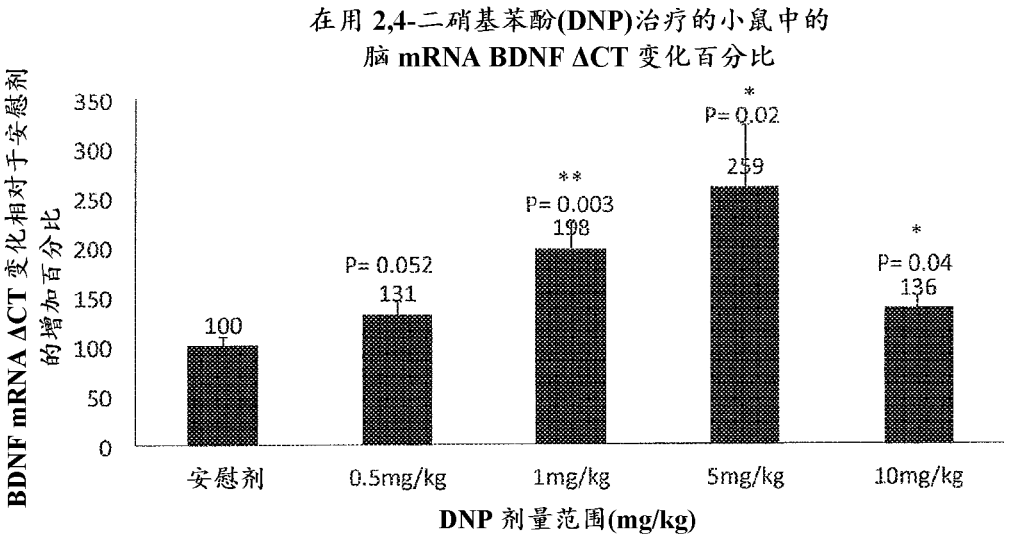

在用 2,4-二硝基苯酚(DNP)治疗的小鼠中的
脑 mRNA BDNF ΔCT 变化百分比
BDNF mRNA ΔCT 变化相对于安慰剂的增加百分比
350
300
250
200
150
100
50
0
100
P= 0.052
131
**
P= 0.003
198
*
P= 0.02
259
*
P= 0.04
136
安慰剂
0.5mg/kg
1mg/kg
5mg/kg
10mg/kg
DNP 剂量范围(mg/kg)

图 1

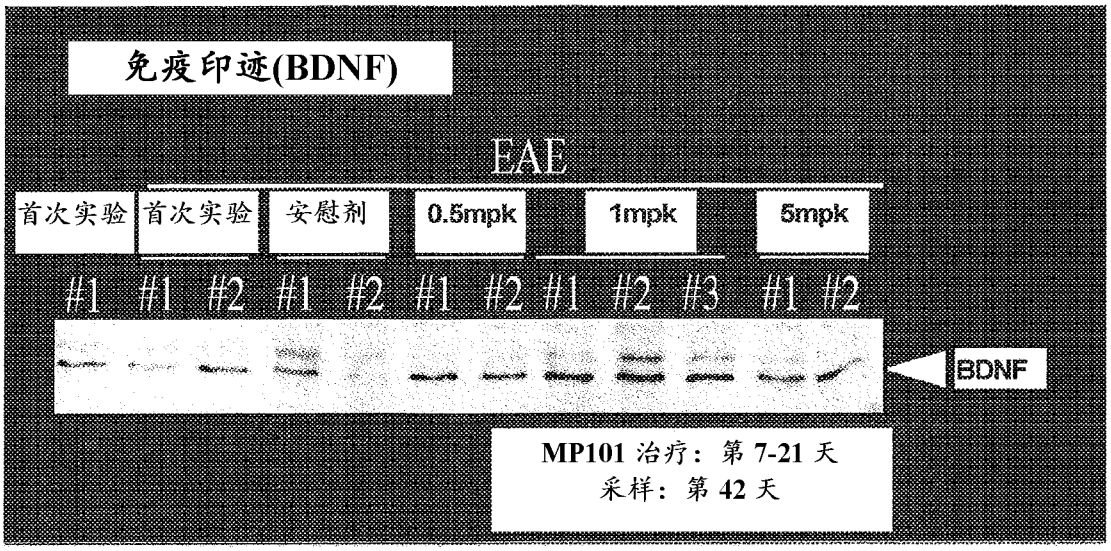

免疫印迹(BDNF)
EAE
首次实验
首次实验
安慰剂
0.5mpk
1mpk
5mpk
#1 #1 #2 #1 #2 #1 #2 #1 #2 #3 #1 #2
BDNF
MP101 治疗：第 7-21 天
采样：第 42 天

图 2a

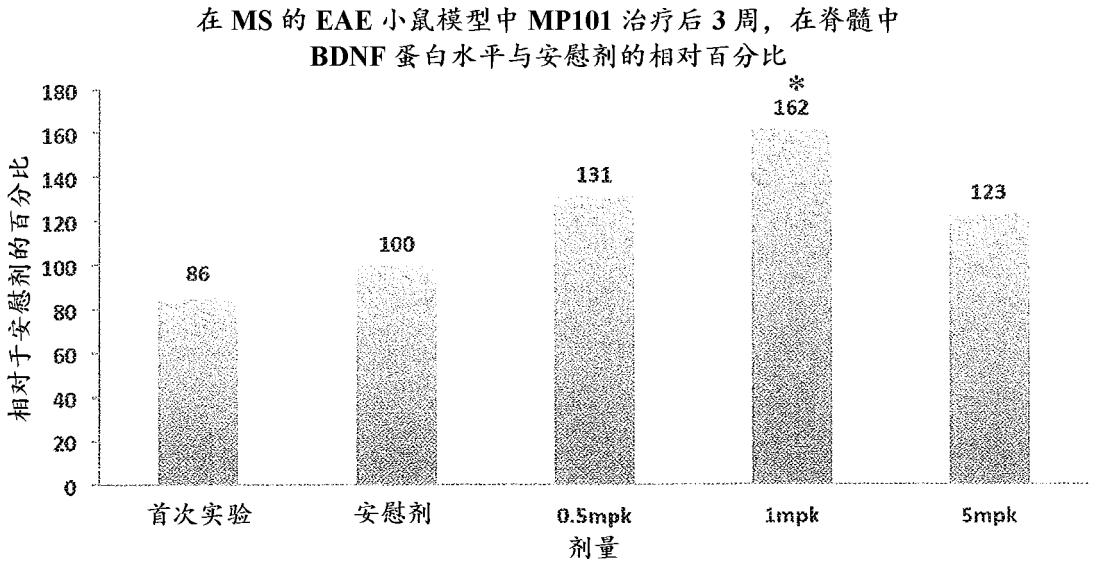

在 MS 的 EAE 小鼠模型中 MP101 治疗后 3 周，在脊髓中
BDNF 蛋白水平与安慰剂的相对百分比
相对于安慰剂的百分比
180
160
140
120
100
80
60
40
20
0
86
100
131
*
162
123
首次实验
安慰剂
0.5mpk
1mpk
5mpk
剂量

图 2b

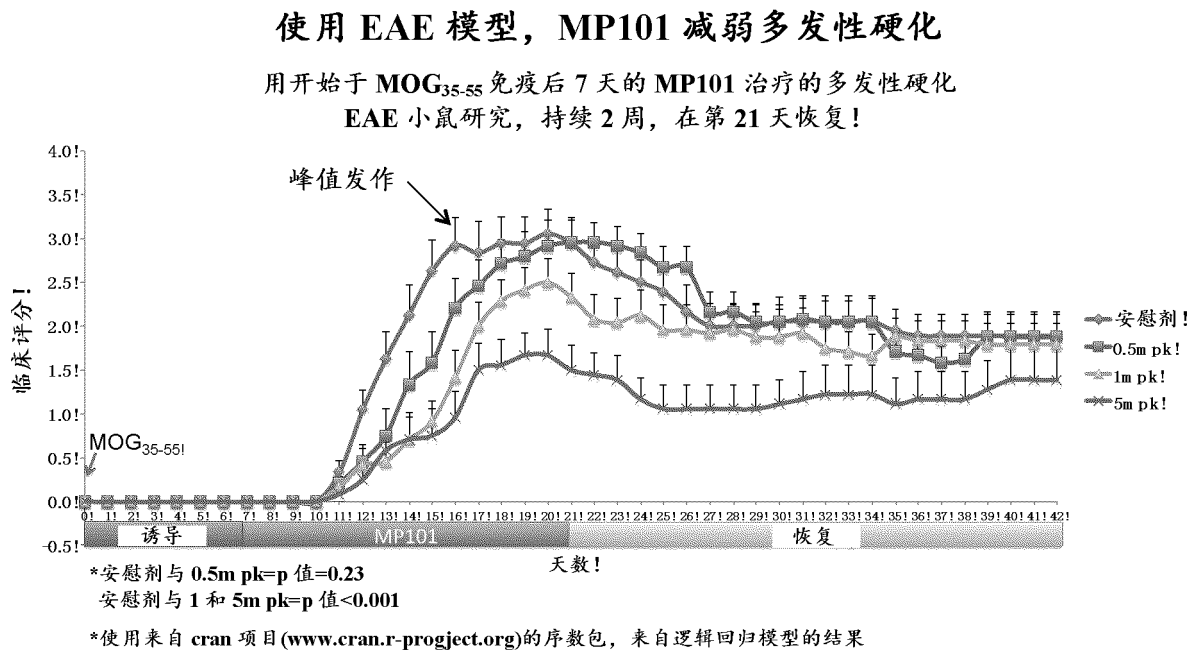

使用 EAE 模型，MP101 减弱多发性硬化
用开始于 MOG35-55 免疫后 7 天的 MP101 治疗的多发性硬化
EAE 小鼠研究，持续 2 周，在第 21 天恢复！
峰值发作
临床评分！
4.0！
3.5！
3.0！
2.5！
2.0！
1.5！
1.0！
0.5！
0.0！
-0.5！
MOG35-55！
诱导
MP101
恢复
天数！
安慰剂！
0.5m pk！
1m pk！
5m pk！
*安慰剂与 0.5m pk=p 值=0.23
安慰剂与 1 和 5m pk=p 值<0.001
*使用来自 cran 项目(www.cran.r-progject.org)的序数包，来自逻辑回归模型的结果

图 2c

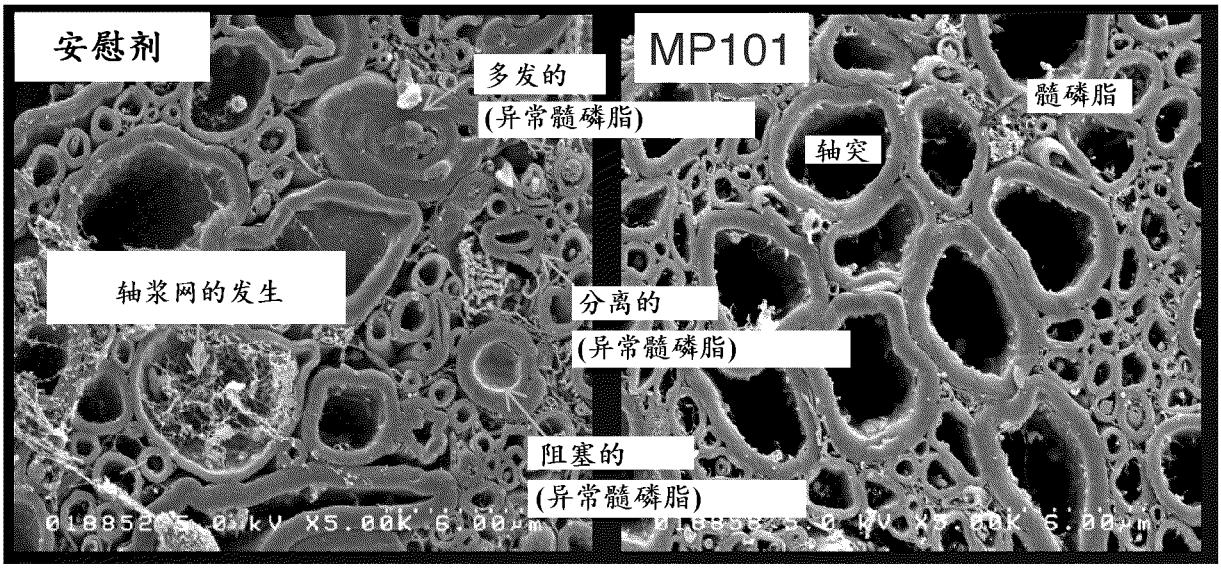

安慰剂
多发的
(异常髓磷脂)
轴浆网的发生
分离的
(异常髓磷脂)
阻塞的
(异常髓磷脂)
MP101
髓磷脂
轴突

图 2d

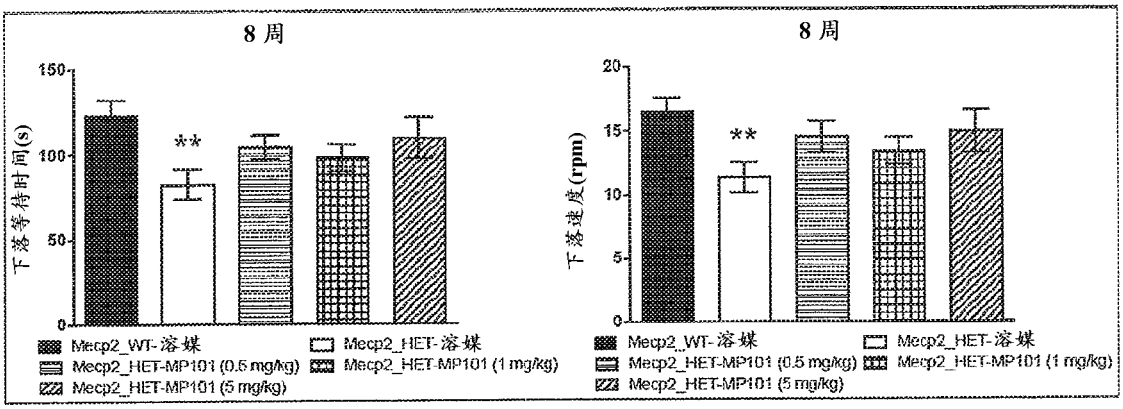

8 周
下落等待时间(s)
150
100
50
0
**
Mecp2_WT-溶媒
Mecp2_HET-溶媒
Mecp2_HET-MP101 (0.5 mg/kg)
Mecp2_HET-MP101 (1 mg/kg)
Mecp2_HET-MP101 (5 mg/kg)
8 周
下落速度(rpm)
20
15
10
5
0
**
Mecp2_WT-溶媒
Mecp2_HET-溶媒
Mecp2_HET-MP101 (0.5 mg/kg)
Mecp2_HET-MP101 (1 mg/kg)
Mecp2_HET-MP101 (5 mg/kg)

图 3a

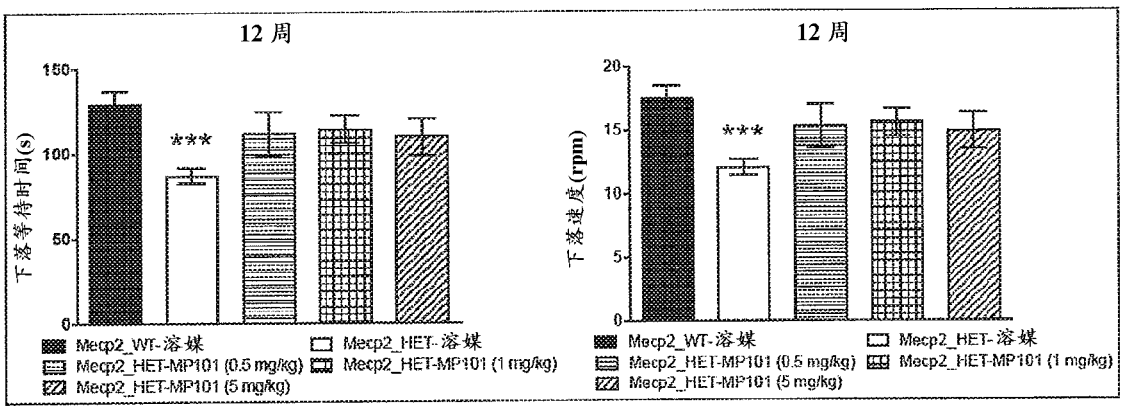

12 周
下落等待时间(s)
150
100
50
0
***
Mecp2_WT-溶媒
Mecp2_HET-溶媒
Mecp2_HET-MP101 (0.5 mg/kg)
Mecp2_HET-MP101 (1 mg/kg)
Mecp2_HET-MP101 (5 mg/kg)
12 周
下落速度(rpm)
20
15
10
5
0
***
Mecp2_WT-溶媒
Mecp2_HET-溶媒
Mecp2_HET-MP101 (0.5 mg/kg)
Mecp2_HET-MP101 (1 mg/kg)
Mecp2_HET-MP101 (5 mg/kg)

图 3b

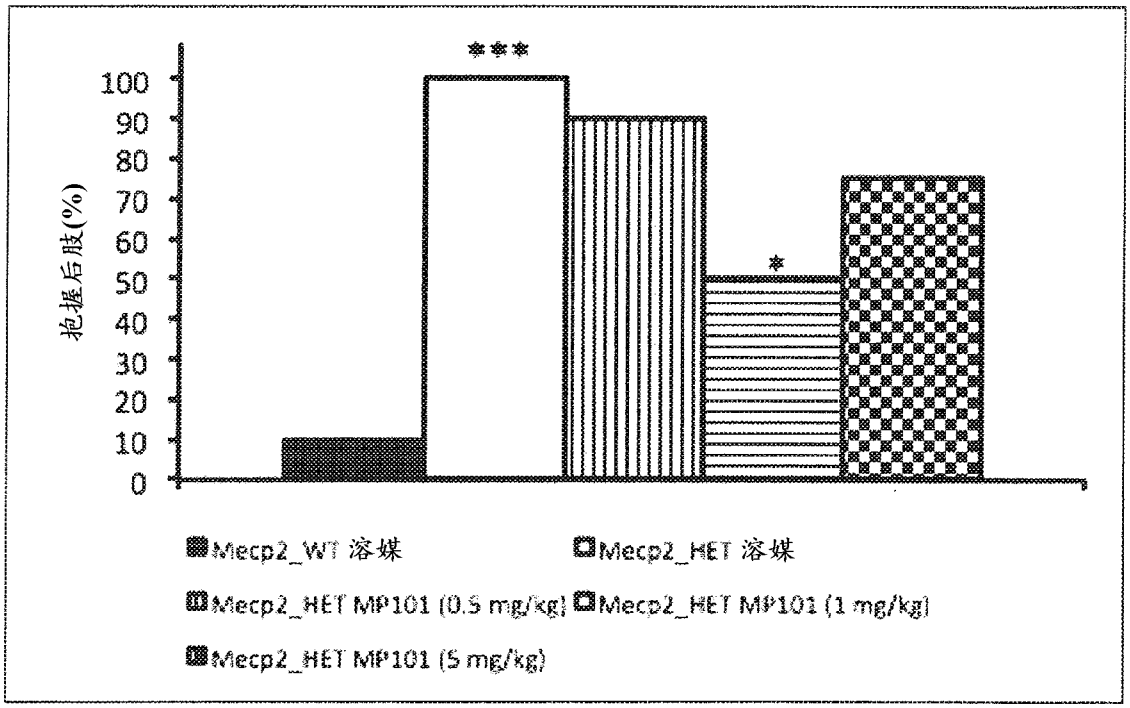

抱握后肢(%)
100
90
80
70
60
50
40
30
20
10
0
***
*
Mecp2_WT 溶媒
Mecp2_HET 溶媒
Mecp2_HET MP101 (0.5 mg/kg)
Mecp2_HET MP101 (1 mg/kg)
Mecp2_HET MP101 (5 mg/kg)

图 4

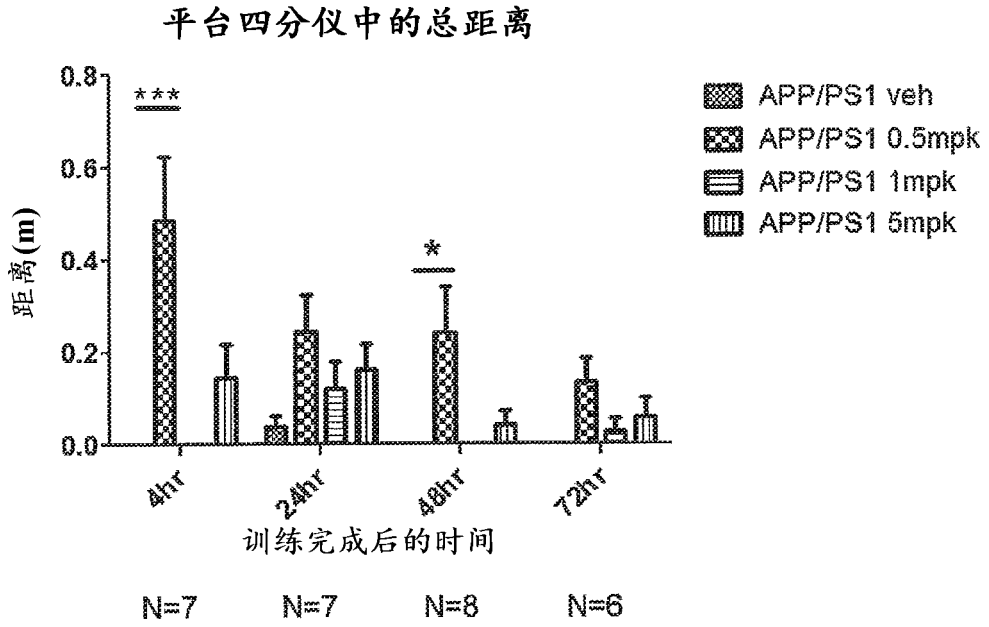

平台四分仪中的总距离
距离(m)
0.8
0.6
0.4
0.2
0.0
***
*
APP/PS1 veh
APP/PS1 0.5mpk
APP/PS1 1mpk
APP/PS1 5mpk
4hr
24hr
48hr
72hr
训练完成后的时间
N=7
N=7
N=8
N=6

图 5a

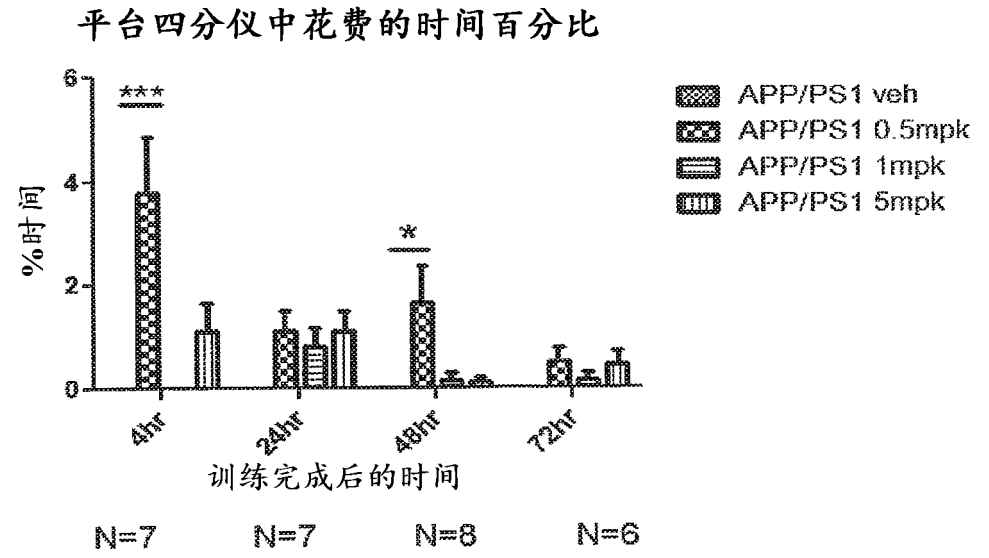

平台四分仪中花费的时间百分比
APP/PS1 veh
APP/PS1 0.5mpk
APP/PS1 1mpk
APP/PS1 5mpk
%时间
***
*
4hr
24hr
48hr
72hr
训练完成后的时间
N=7
N=7
N=8
N=6

图 5b

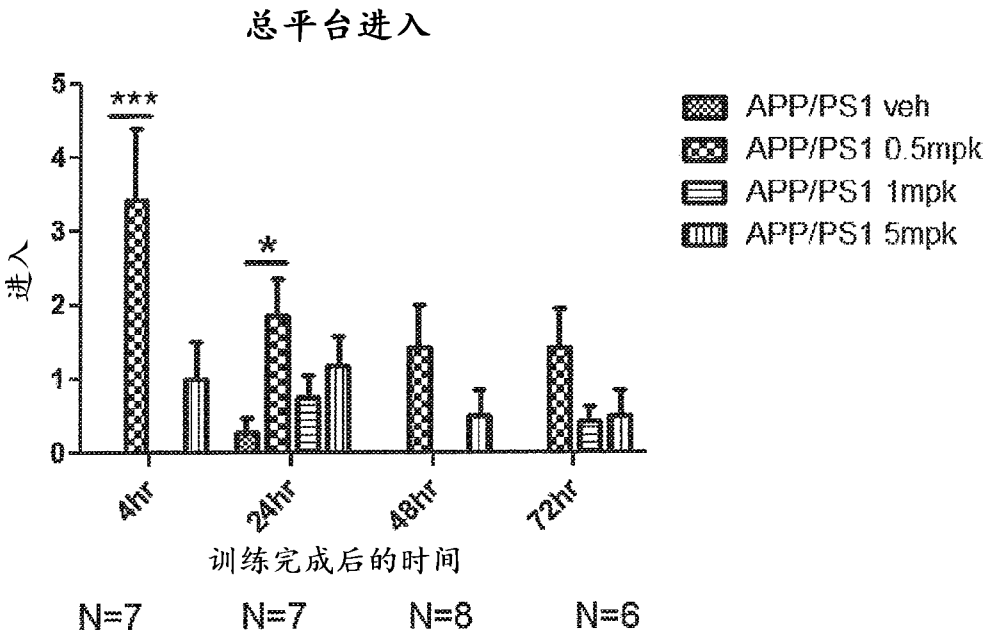

总平台进入
APP/PS1 veh
APP/PS1 0.5mpk
APP/PS1 1mpk
APP/PS1 5mpk
进入
***
*
4hr
24hr
48hr
72hr
训练完成后的时间
N=7
N=7
N=8
N=6

图 5c

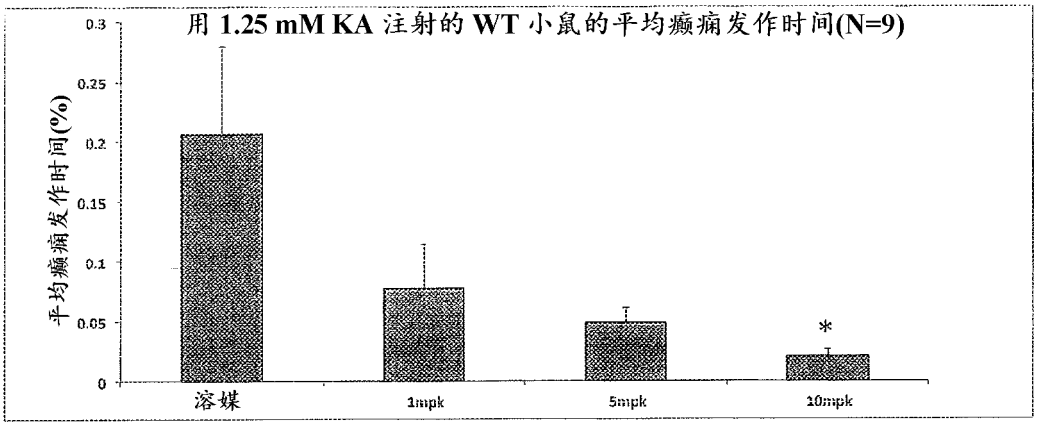

用 1.25 mM KA 注射的 WT 小鼠的平均癫痫发作时间(N=9)
平均癫痫发作时间(%)
0.3
0.25
0.2
0.15
0.1
0.05
0
*
溶媒
1mpk
5mpk
10mpk

图 6

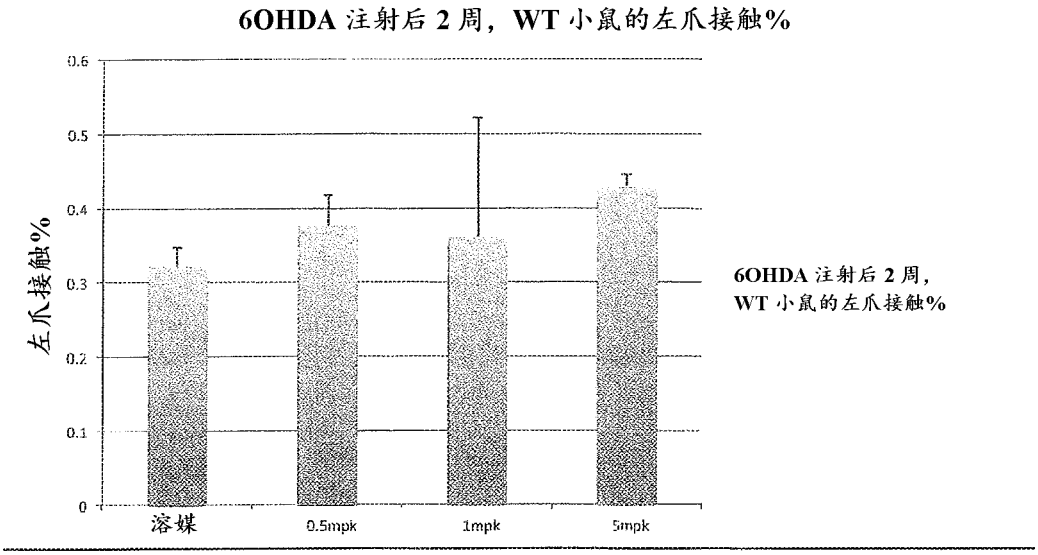

6OHDA 注射后 2 周，WT 小鼠的左爪接触%
左爪接触%
0.6
0.5
0.4
0.3
0.2
0.1
0
溶媒
0.5mpk
1mpk
5mpk
6OHDA 注射后 2 周，
WT 小鼠的左爪接触%

图 7a

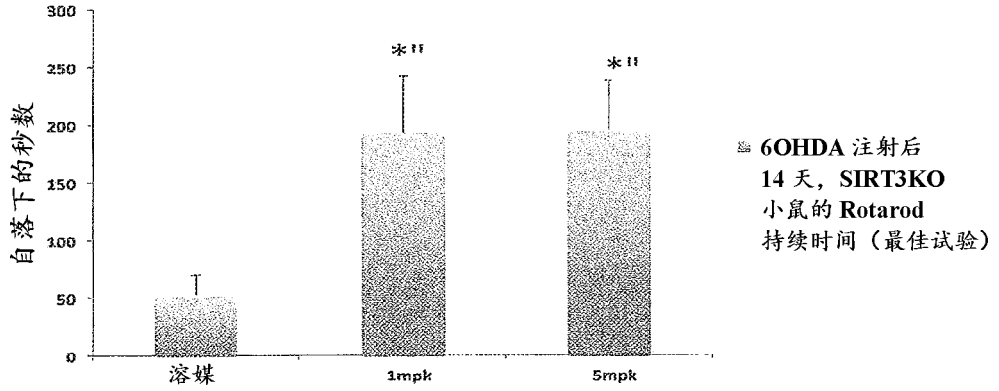

自落下的秒数
300
250
200
150
100
50
0
*!!
*!!
溶媒
1mpk
5mpk
6OHDA 注射后
14 天，SIRT3KO
小鼠的 Rotarod
持续时间（最佳试验）

图 7b

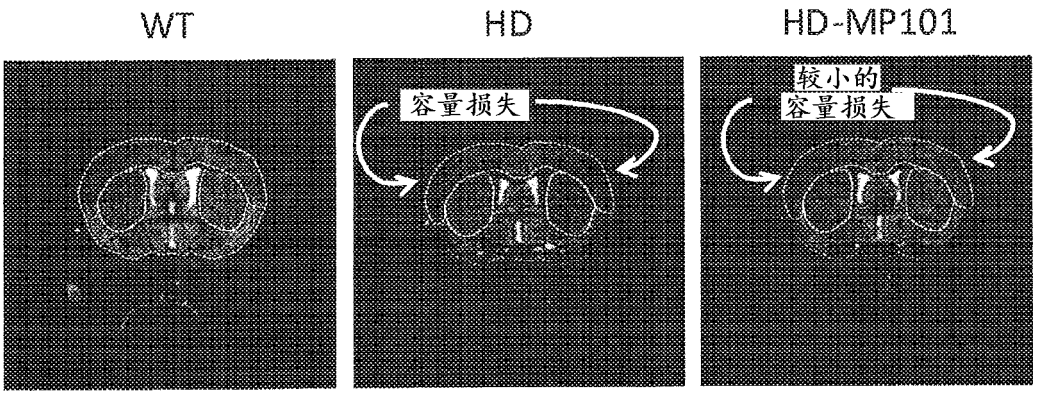

WT
HD
HD-MP101
容量损失
较小的
容量损失

图 8a

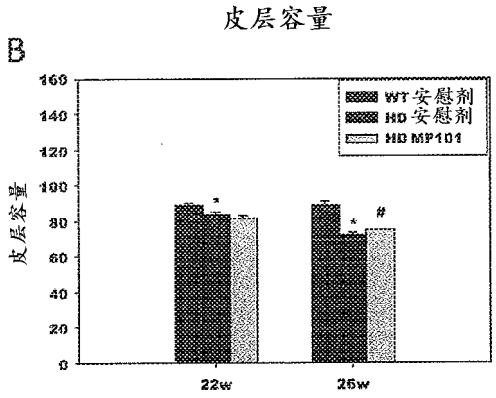

皮层容量
B
皮层容量
160
140
120
100
80
60
40
20
0
WT安慰剂
HD安慰剂
HD MP101
*
*
#
22w
26w

图 8b

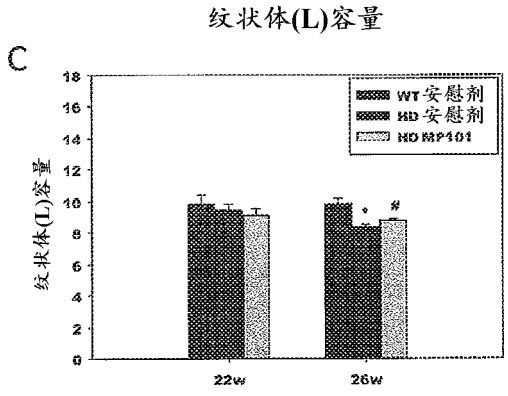

纹状体(L)容量
C
纹状体(L)容量
18
16
14
12
10
8
6
4
2
0
WT安慰剂
HD安慰剂
HD MP101
*
#
22w
26w

图 8c

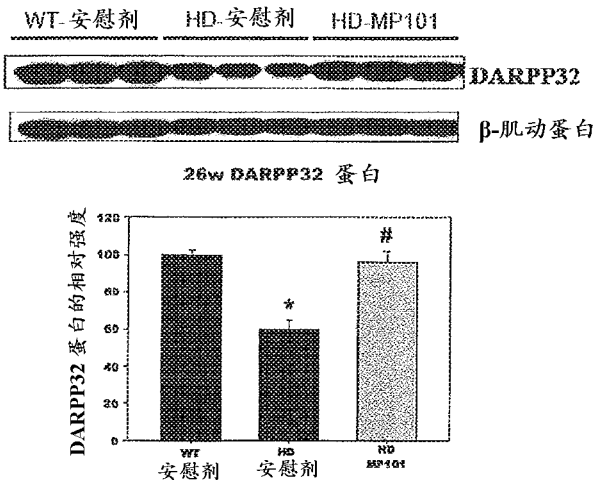

WT-安慰剂
HD-安慰剂
HD-MP101
DARPP32
β-肌动蛋白
26w DARPP32 蛋白
DARPP32 蛋白的相对强度
120
100
80
60
40
20
0
*
#
WT
安慰剂
HD
安慰剂
HD
MP101

图 8d

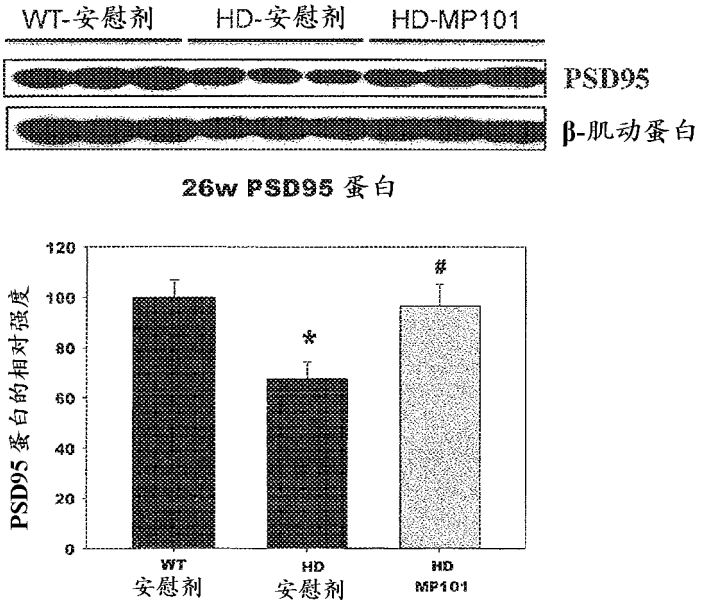
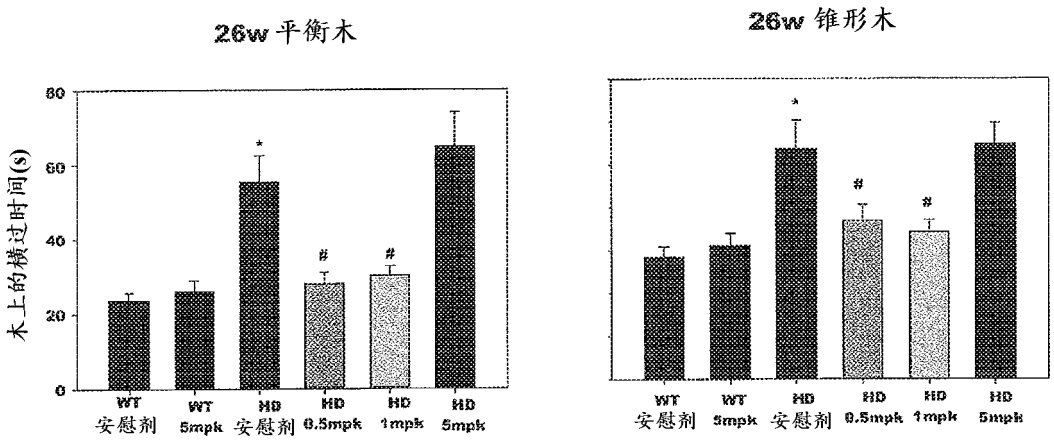

WT-安慰剂
HD-安慰剂
HD-MP101
PSD95
β-肌动蛋白
26w PSD95 蛋白
PSD95 蛋白的相对强度
120
100
80
60
40
20
0
*
#
WT
安慰剂
HD
安慰剂
HD
MP101

图 8e




数值为平均值和 SEM。使用单向 ANOVA 检验。N=14-16。
*相对于 WT 安慰剂组，p<0.005；#相对于 HD 安慰剂组，p<0.005。

图 8f