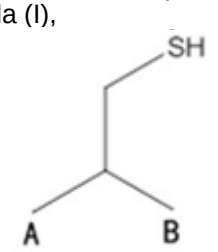
SUMMARY

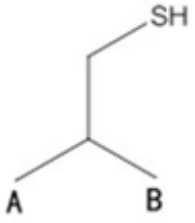
The disclosure features PrC-210 aminothiol, or its close analog, for the treatment of (i) diseases and conditions characterized by misfolding and/or aggregation of endogenous proteins, (2) diseases and conditions associated with mitochondrial dysfunction, and (3) diseases and conditions associated with chronic inflammation.

In one aspect, the disclosure provides use of a pharmaceutical composition in the manufacture of a medicament for inhibiting aggregation of a protein in a subject in need thereof, said pharmaceutical composition comprising a compound of formula (I),



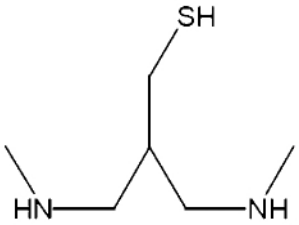
(I),

or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, wherein (i) A is $-CH_2NHR'$ and B is $-CH_2NHR$, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In a first example, the disclosure features a method of inhibiting aggregation of a protein in a subject in need thereof, the method including administering to the subject an effective amount of a compound of formula (I),



(I),

or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, and wherein (i) A is $-CH_2NHR'$ and B is $-CH_2NHR$, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In particular examples, the compound is

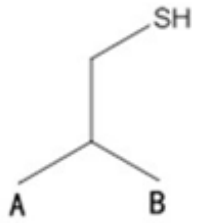


PrC-210,

or a pharmaceutically acceptable salt thereof. In some examples, the protein for which aggregation is inhibited is selected from TDP-43, alpha-synuclein, tau, amyloid beta, PolyQ htt, islet amyloid polypeptide and prions, or their unaggregated precursors. For example, the subject can have a neurodegenerative disease characterized by misfolding and/or aggregation of endogenous proteins. Neurodegenerative diseases that can be treated using the methods of the disclosure include, without limitation, Parkinson's disease, prion disease, Alzheimer's disease, multiple system atrophy, Diffuse Lewy body disease, frontotemporal dementia, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxias and other Poly-Q diseases, hereditary cerebral amyloid angiopathy, and any other neurodegenerative disease described herein. In certain examples, the neurodegenerative disease is a prion disease selected from Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, genetic human prion disease, Bovine Spongiform Encephalopathy (BSE) and Scrapie. In some examples, the neurodegenerative disease is a synucleinopathy (e.g., Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA)). In particular examples, the subject has a disease or condition characterized by amyloidosis. The amyloidosis can be selected from primary systemic amyloidosis (AL amyloidosis), reactive systemic amyloidosis (AA amyloidosis), type II diabetes, injection-localized amyloidosis, beta-2 microglobulin amyloidosis, hereditary non-neuropathic amyloidosis and Finnish hereditary systemic

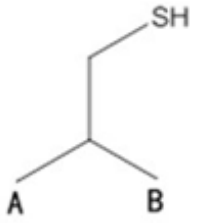
amyloidosis. In other examples, the subject has a disease or condition characterized by ocular protein aggregation. For example, the disease or condition characterized by ocular protein aggregation can be cataracts or presbyopia.

In one aspect, the disclosure provides use of a pharmaceutical composition in the manufacture of a medicament for treating a condition associated with mitochondrial dysfunction in a subject in need thereof, said pharmaceutical composition comprising a compound of a compound of formula (I),



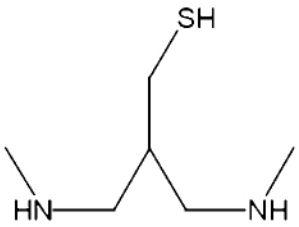
(I),

or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, wherein (i) A is -CH_2NHR' and B is -CH_2NHR, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In another example, the disclosure features a method of treating a condition associated with mitochondrial dysfunction in a subject in need thereof, the method including administering to the subject an effective amount of a compound of formula (I),



(I),

or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, and wherein (i) A is -CH_2NHR' and B is -CH_2NHR, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In particular examples, the compound is

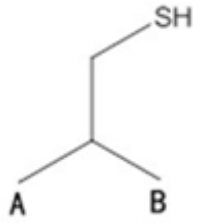


PrC-210,

or a pharmaceutically acceptable salt thereof. In some examples, the condition associated with mitochondrial dysfunction is a neurodegenerative disorder, a neuropsychiatric disorder, diabetes, metabolic disease, an ocular disorder associated with mitochondrial dysfunction, an ischemia related

condition, aging, mitochondrial toxicity associated with therapeutic agents, or migraine. For example, the condition associated with mitochondrial dysfunction can be a neurodegenerative disorder selected from Friedrich's ataxia, amyotrophic lateral sclerosis, mitochondrial myopathy, encephalopathy, lactacidosis, stroke (MELAS), myoclonic epilepsy with ragged red fibers (MERFF), epilepsy, Parkinson's disease, Alzheimer's disease, and Huntington's disease. In some examples, the condition associated with mitochondrial dysfunction is a neuropsychiatric disorder selected from bipolar disorder, schizophrenia, depression, addiction disorders, anxiety disorders, attention deficit disorders, personality disorders, autism (i.e., Autism Spectrum Disorder), and Asperger's Syndrome. In some examples, the method ameliorates mitochondrial toxicity of therapeutic agents administered to the subject. In certain examples, the condition associated with mitochondrial dysfunction is an ocular disorder associated with mitochondrial dysfunction selected from glaucoma, diabetic retinopathy and age-related macular degeneration. In particular examples, the condition associated with mitochondrial dysfunction is an ischemia related condition resulting from vascular occlusion, arteriosclerosis, heart valve diseases, tachycardia, or hypo- or hypertension.

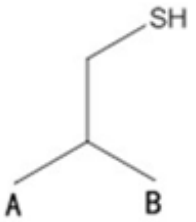
In one aspect, the disclosure provides use of a pharmaceutical composition in the manufacture of a medicament for treating a chronic inflammatory condition in a subject in need thereof, said pharmaceutical composition comprising a compound of a compound of formula (I),



(I),

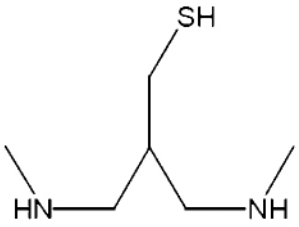
or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, wherein (i) A is -CH_2NHR' and B is -CH_2NHR, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In another example, the disclosure features a method of treating a chronic inflammatory condition in

a subject in need thereof, the method including administering to the subject an effective amount of a compound of formula (I),



(I),

or a pharmaceutically acceptable acid addition salt thereof, in an amount sufficient to inhibit the aggregation of the protein or peptide, and wherein (i) A is $-CH_2NHR'$ and B is $-CH_2NHR$, or A = -NRR' and B = H; and (ii) each of R and R′ are, independently, selected from H, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, with the proviso that R and R' are not both H if B = H. In particular examples, the compound is



PrC-210,

or a pharmaceutically acceptable salt thereof. In some examples, the chronic inflammatory condition is selected from rhinosinusitis, arthritis, dermatitis, vasculitis, acute malaria, sickle cell disease, a gastrointestinal inflammatory condition, or an inflammatory pulmonary condition. In particular examples, the chronic inflammatory condition is an inflammatory pulmonary condition selected from asthma, chronic obstructive pulmonary disease (COPD), physical trauma-induced pulmonary conditions, emphysema, bronchitis, sarcoidosis, histiocytosis, lymphangiomyomatosis, acute lung injury, chronic lung disease, bronchopulmonary dysplasia, pneumonia, airway exacerbations, and acute respiratory distress syndrome (ARDS). In some examples, the chronic inflammatory condition is a gastrointestinal inflammatory condition selected from inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD), and colitis. In some examples, the chronic inflammatory condition is an autoimmune disease. For example, the methods of the disclosure can be used to treat an autoimmune disease selected from multiple sclerosis, diabetes Type I, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, pancreatitis, psoriasis, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, paraneoplastic autoimmune diseases, autoimmune hepatitis, bullous pemphigoid, myasthenia gravis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, celiac disease, thyroiditis, Sjogren's syndrome, Guillain-Barre disease, Raynaud's phenomenon, Addison's disease, primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis, and diabetes. In some examples, the chronic inflammation is in connection with lipid depositions, such as in the case of arteriosclerosis, heart valves sclerosis or leakage or endothelic damage of arteries, vascular damage during dialysis and metabolic syndrome. In particular examples the chronic inflammatory condition is a neuroinflammatory disease. Neuroinflammatory diseases that can be treated using the methods of the disclosure include multiple sclerosis, neuromyelitis