the wild-type protein. This scenario provides an opportunity to treat diseases associated with nonsense mutations by avoiding premature termination of translation through suppression of the nonsense mutation.

[0009] There remains a need in the art for methods for treating, managing and/or preventing a disease associated with a nonsense mutation(s) in a gene(s) in a human subject by administering a compound that suppresses premature translation termination in a human(s) by mediating the misreading of a nonsense codon and producing a non-wild-type protein(s) *in vivo* in an amount sufficient to treat, manage and/or prevent the disease.

3. SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0010] The present ~~invention~~disclosure is based, in part, upon the discovery of nonsense codon suppressor agents that can be systemically administered to a subject (including a human) to suppress a nonsense codon in RNA transcribed from a gene(s) comprising a nonsense mutation(s), allowing for readthrough of the nonsense codon and the insertion of an amino acid at the location of the nonsense codon. In certain embodiments, the amino acid inserted is an amino acid other than the amino acid which occurs at the corresponding location in the wild-type protein to produce a functional readthrough protein. The functional readthrough protein produced by the suppression of the nonsense codon in RNA transcribed from a gene(s) comprising a nonsense mutation is useful for treating, preventing and/or managing a disease associated with the nonsense mutation(s) in the gene(s).

[0011] The production of a functional readthrough protein in a subject (including a human) by the suppression of a nonsense codon in RNA transcribed from a gene(s) comprising a nonsense mutation using a nonsense codon suppressor agent has several advantages over other types of therapies contemplated for the prevention, treatment and/or management of a disease associated with a nonsense mutation in a gene(s). For example, the production of a functional readthrough protein using a nonsense codon suppressor agent does not involve the introduction of foreign genetic material into a subject as it does with gene therapy. Thus, the risk of inserting foreign genetic material into the wrong location in chromosomal DNA, the risk of overexpressing the protein encoded by the foreign genetic material introduced into the subject, and the risk of transmitting a vector,

such as a virus, used to introduce the foreign genetic material into the subject to other subjects are eliminated.

[0012] The present ~~invention~~disclosure provides methods of producing in a subject (preferably, a human) in need thereof an effective amount of a functional readthrough protein(s) encoded by a nucleic acid sequence comprising a nonsense mutation, the methods comprising administering to the subject an effective amount of a nonsense codon suppressor agent(s). In particular, the present ~~invention~~disclosure provides methods for the treatment, management and/or prevention of a disease associated with a nonsense mutation in a gene(s), the methods comprising administering to a subject (preferably, a human) in need thereof an ~~effective amount of a nonsense codon suppressor agent(s)~~, wherein the effective amount of the agent(s) is the amount that is sufficient to produce an effective amount of a functional readthrough protein(s) encoded by the gene comprising the nonsense mutation. Non-limiting examples of diseases associated with a nonsense mutation in a gene(s) that can be treated, managed and/or prevented in accordance with the method of the ~~invention~~disclosure include: amyloidosis, LINCL, hemophilia, Alzheimer's disease, atherosclerosis, giantism, dwarfism, hypothyroidism, hyperthyroidism, cystic fibrosis, aging, obesity, Parkinson's disease, Niemann Pick's disease, familial hypercholesterolemia, retinitis pigmentosa, muscular dystrophy (e.g. Duchenne muscular dystrophy), spinal muscular atrophy and Marfan syndrome.

[0013] In one aspect, the present ~~invention~~disclosure provides nonsense codon suppressor agents that can be orally administered to a subject (preferably, a human) to prevent, treat and/or manage a disease associated with a nonsense mutation in a gene. The nonsense codon suppressor agents administered orally have none or few (if any) adverse side effects at the dosage(s) that produces an effective amount of functional readthrough protein. In a specific embodiment, the nonsense codon suppressor agents do not result in renal failure and/or hearing loss when orally administered to a subject (preferably, a human) at the dosage(s) that produces an effective amount of functional readthrough protein. Thus, the nonsense codon suppressor agents can be systemically (e.g., orally) administered long-term without toxicities, such as renal failure and hearing loss.

[0014] The oral administration of a nonsense codon suppressor agent enables a subject to take his/her prescribed dosage of a nonsense codon suppressor agent without the need for a medical professional to administer the agent. This reduces the medical costs associated

with preventing, treating and/or managing a disease associated with a nonsense mutation in a gene(s) because the cost of having a medical professional administer the agent has been eliminated. The oral administration of a nonsense codon suppressor agent also improves a subject's quality of life since the subject is not restricted and/or inconvenienced by appointments to see medical professionals to receive his/her dosage of nonsense codon suppressor agent. Further, the oral administration of a nonsense codon suppressor agent permits delivery of systemic therapy to all disease-affected organ sites.

[0015] In another aspect, the present ~~invention~~disclosure provides nonsense codon suppressor agents that do not exhibit significant antibacterial activity against a gram-negative microorganism and/or a gram-positive microorganism. In contrast to nonsense codon suppressor agents with antibacterial activity, the use of nonsense codon suppressor agents that do not exhibit significant antibacterial activity against a gram-negative microorganism and/or a gram-positive microorganism do not contribute to the development of bacterial resistance to drugs with antibiotic activity. Further, the use of nonsense codon suppressor agents that do not exhibit significant antibacterial activity against a gram-negative microorganism and/or a gram-positive organism will be unlikely to induce complications related to pathological overgrowth of normal microbial flora as can happen with many chronically administered antibiotics.

[0016] Thus, the present ~~invention~~disclosure provides functional readthough proteins encoded by nucleic acid sequences comprising a nonsense mutation that are produced by methods that include administering a nonsense codon suppressor agent(s) that is well-tolerated in subjects and does not have significant antibacterial activity against a gram-negative microorganism and/or a gram-positive microorganism.

[0016a] In one aspect, there is provided the use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of:

a. duchenne muscular dystrophy in a patient with a nonsense mutation at position 1417 or 492 of dystrophin;

b. cystic fibrosis in a patient with a nonsense mutation at position 414, 493, 542, 1162, 122, 1455, 822, 60, 764, 1291, 849, 434, 88, 1158 or 6542 of CFTR;

c. hemophilia A in a patient with a nonsense mutation at position 1535, 2116, 1395, 139, 583, 1941, 2116, or 1778 of factor VIII;

d. hemophilia B in a patient with a nonsense mutation at position 333, 252, 31118, 116, or 338 of factor IX;

e. mucopolysaccharidosis III A in a patient with a nonsense mutation at position 40 or 233 of SGSH;

f. Charcot-Marie Tooth disease type 4A in a patient with a nonsense mutation at position 194 of ganglioside-induced differentiation-associated protein 1 (GDAP1);

g. Charcot-Marie Tooth disease in a patient with a nonsense mutation at amino acid position 132 of connexin 32;

h. neurofibromatosis in a patient with a nonsense mutation at position 1947, 1306 or 2496 of NF1;

i. polycystic kidney disease in a patient with a nonsense mutation at position 4086, 3818 or 3817 of PKD1; or

j. tuberous sclerosis complex in a patient with a nonsense mutation at position 897 of TSC1;

k. duchenne muscular dystrophy in a patient with a nonsense mutation at position 1417, 3625, or 492 of dystrophin, wherein for a patient with a nonsense mutation at position 1417 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 1417 of dystrophin except leucine, wherein for a patient with a nonsense mutation at position 3625 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 3625 of dystrophin except glutamine, and wherein for a patient with a nonsense mutation at position 492 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 492 of dystrophin except glutamine;

l. cystic fibrosis in a patient with a nonsense mutation at position 414, 493, 1316, 553, 542, 1162, 122, 1455, 822, 60, 764, 1291, 849, 434, 88, 1158 or 6542 of CFTR, wherein for a patient with a nonsense mutation at position 414 of CFTR, functional readthrough protein is produced having any amino acid residue at position 414 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 493 of CFTR, functional readthrough protein is produced having any amino acid residue at position 493 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 1316 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1316 of CFTR except tryptophan, wherein for a patient with a nonsense mutation at position 553 of CFTR, functional readthrough protein is produced having any amino acid residue at position 553 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 542 of CFTR, functional readthrough protein is produced having any amino acid residue at position 542 of CFTR except glycine, wherein for a patient with a nonsense mutation at position 1162 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1162 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 122 of CFTR, functional readthrough protein is produced having any amino acid residue at position 122 of CFTR except tyrosine, wherein for a patient with a nonsense mutation at position 1455 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1455 of CFTR except

serine, wherein for a patient with a nonsense mutation at position 822 of CFTR, functional readthrough protein is produced having any amino acid residue at position 822 of CFTR except glutamic acid, wherein for a patient with a nonsense mutation at position 60 of CFTR, functional readthrough protein is produced having any amino acid residue at position 60 of CFTR except glutamic acid, wherein for a patient with a nonsense mutation at position 764 of CFTR, functional readthrough protein is produced having any amino acid residue at position 764 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 1291 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1291 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 849 of CFTR, functional readthrough protein is produced having any amino acid residue at position 849 of CFTR except tyrosine, wherein for a patient with a nonsense mutation at position 434 of CFTR, functional readthrough protein is produced having any amino acid residue at position 434 of CFTR except serine, wherein for a patient with a nonsense mutation at position 88 of CFTR, functional readthrough protein is produced having any amino acid residue at position 88 of CFTR except leucine, wherein for a patient with a nonsense mutation at position 1158 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1158 of CFTR except arginine, and wherein for a patient with a nonsense mutation at position 6542 of CFTR, functional readthrough protein is produced having any amino acid residue at position 6542 of CFTR except glycine;

m. hemophilia A in a patient with a nonsense mutation at position 1029, 1792, 1535, 2116, 427, 1395, 139, 583, 1941, 1966, 2116, or 1778 of factor VIII, wherein for a patient with a nonsense mutation at position 1029 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1029 of factor VIII except tryptophan, wherein for a patient with a nonsense mutation at position 1792 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1792 of factor VIII except tyrosine, wherein for a patient with a nonsense mutation at position 1535 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1535 of factor VIII except tryptophan, wherein for a patient with a nonsense mutation at position 2116 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 2116 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 427 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 427 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 1395 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1395 of factor VIII except serine, wherein for a patient with a nonsense mutation at position 139 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 139 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 583 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 583 of factor VIII except arginine, wherein for a patient with a

nonsense mutation at position 1941 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1941 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 1966 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1966 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 2116 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 2116 of factor VIII except arginine, and wherein for a patient with a nonsense mutation at position 1778 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1778 of factor VIII except glutamine;

n. hemophilia B in a patient with a nonsense mutation at position 333, 252, 31118, 116, or 338 of factor IX, wherein for a patient with a nonsense mutation at position 333 of factor IX, functional readthrough protein is produced having any amino acid residue at position 333 of factor IX except arginine, wherein for a patient with a nonsense mutation at position 252 of factor IX, functional readthrough protein is produced having any amino acid residue at position 252 of factor IX except arginine, wherein for a patient with a nonsense mutation at position 31118 of factor IX, functional readthrough protein is produced having any amino acid residue at position 31118 of factor IX except cysteine, wherein for a patient with a nonsense mutation at position 116 of factor IX, functional readthrough protein is produced having any amino acid residue at position 116 of factor IX except arginine, and wherein for a patient with a nonsense mutation at position 338 of factor IX, functional readthrough protein is produced having any amino acid residue at position 338 of factor IX except arginine;

o. mucopolysaccharidosis III A in a patient with a nonsense mutation at position 40 or 233 of SGSH, wherein for a patient with a nonsense mutation at position 40 of SGSH, functional readthrough protein is produced having any amino acid residue at position 40 of SGSH except tyrosine and wherein for a patient with a nonsense mutation at position 233 of SGSH, functional readthrough protein is produced having any amino acid residue at position 233 of SGSH except arginine;

p. Charcot-Marie Tooth disease type 4A in a patient with a nonsense mutation at position 194 of ganglioside-induced differentiation-associated protein 1 (GDAP1), wherein for a patient with a nonsense mutation at position 194 of GDAP1, functional readthrough protein is produced having any amino acid residue at position 194 of GDAP1 except serine;

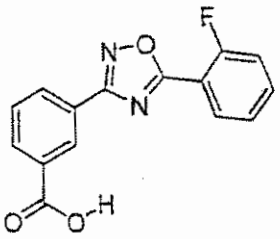
q. Charcot-Marie Tooth disease in a patient with a nonsense mutation at amino acid position 132 of connexin 32, wherein for a patient with a nonsense mutation at position 132 of connexin 32, functional readthrough protein is produced having any amino acid residue at position 132 of connexin 32 except tryptophan;

r. neurofibromatosis in a patient with a nonsense mutation at position 1947, 1306 or 2496 of NF1, wherein for a patient with a nonsense mutation at position 1947 of NF1, functional readthrough protein is produced having any amino acid residue at position 1947 of NF1 except arginine, wherein for a patient with a nonsense mutation at position 1306 of NF1, functional readthrough protein is produced having any amino acid residue at position 1306 of NF1 except arginine, and wherein for a patient with a nonsense mutation at position 2496 of NF1, functional readthrough protein is produced having any amino acid residue at position 2496 of NF1 except arginine;

s. polycystic kidney disease in a patient with a nonsense mutation at position 4086, 3818 or 3817 of PKD1, wherein for a patient with a nonsense mutation at position 4086 of PKD1, functional readthrough protein is produced having any amino acid residue at position 4086 of PKD1 except cysteine, wherein for a patient with a nonsense mutation at position 3818 of PKD1, functional readthrough protein is produced having any amino acid residue at position 3818 of PKD1 except tyrosine, and wherein for a patient with a nonsense mutation at position 3817 of PKD1, functional readthrough protein is produced having any amino acid residue at position 3817 of PKD1 except cysteine; or

t. tuberous sclerosis complex in a patient with a nonsense mutation at position 897 of TSC1, wherein for a patient with a nonsense mutation at position 897 of TSC1, functional readthrough protein is produced having any amino acid residue at position 897 of TSC1 except glutamine;

wherein the nonsense codon suppressor agent has the formula:



or a pharmaceutically acceptable salt thereof.

[0016b] In another aspect, there is provided the use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the production of a functional readthough protein in a subject, wherein

a. the functional readthrough protein has any amino acid residue at position 1417 of dystrophin except leucine, any amino acid residue at position 3625 of dystrophin except glutamine, or any amino acid residue at position 492 of dystrophin except glutamine;

b. the functional readthrough protein has any amino acid residue at position 414 of CFTR except glutamine, any amino acid residue at position 493 of CFTR except glutamine, any amino acid residue at position 1316 of CFTR except tryptophan, any amino acid residue at position 553 of CFTR except arginine; any amino acid residue at position 542 of CFTR except glycine, any amino acid residue at position 1162 of CFTR except arginine, any amino acid residue at position 122 of CFTR except tyrosine, any amino acid residue at position 1455 of CFTR except serine, any amino acid residue at position 822 of CFTR except glutamic acid, any amino acid residue at position 60 of CFTR except glutamic acid, any amino acid residue at position 764 of CFTR except arginine, any amino acid residue at position 1291 of CFTR except glutamine, any amino acid residue at position 849 of CFTR except tyrosine, any amino acid residue at position 434 of CFTR except serine, any amino acid residue at position 88 of CFTR except leucine, any amino acid residue at position 1158 of CFTR except arginine, or any amino acid residue at position 6542 of CFTR except glycine;

c. the functional readthrough protein has any amino acid residue at position 1029 of Factor VIII except tryptophan, any amino acid residue at position 1792 of Factor VIII except tyrosine, any amino acid residue at position 1535 of Factor VIII except tryptophan, any amino acid residue at position 2116 except arginine, any amino acid residue at position 427 of Factor VIII except arginine, any amino acid residue at position 1395 of Factor VIII except serine, any amino acid residue at position 139 of Factor VIII except glutamine, any amino acid residue at position 583 of Factor VIII except arginine, any amino acid residue at position 1941 of Factor VIII except arginine, any amino acid residue at position 1966 of Factor VIII except arginine, any amino acid residue at position 2116 of Factor VIII except arginine, or any amino acid residue at position 1778 of Factor VIII except glutamine;

d. the functional readthrough protein has any amino acid residue at position 333 of Factor IX except arginine, any amino acid residue at position 252 of Factor IX except arginine, any amino acid residue at position 31118 of Factor IX except cysteine, any amino acid residue at position 116 of Factor IX except arginine, or any amino acid residue at position 338 of Factor IX except arginine;

e. the functional readthrough protein has any amino acid residue at position 40 of SGSH except tyrosine or any amino acid residue at position 233 of SGSH except arginine;

f. the functional readthrough protein has any amino acid residue at position 194 of ganglioside-induced differentiation-associated protein 1 except a serine;

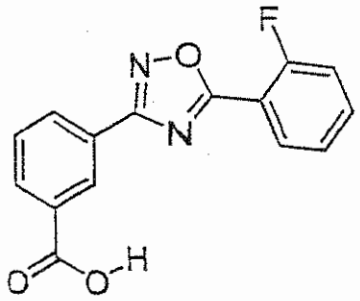
g. the functional readthrough protein has any amino acid residue at position 132 of connexin 32 except tryptophan;

h. the functional readthrough protein has any amino acid residue at position 1947 of NF1 except arginine, any amino acid residue at position 1306 of NF1 except arginine, or any amino acid residue at position 2496 of NF1 except arginine;

i. the functional readthrough protein has any amino acid residue at position 4086 of PKD1 except cysteine, any amino acid residue at position 3818 of PKD1 except tyrosine, or any amino acid residue at position 3817 of PKD1 except cysteine; or

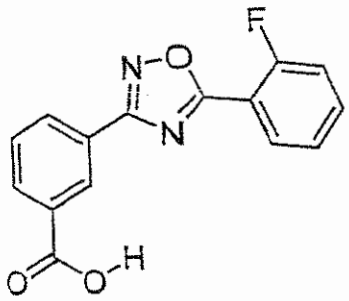
j. the functional readthrough protein has any amino acid residue at position 897 of TSC1 except glutamine;

and wherein the nonsense codon suppressor agent has the formula:



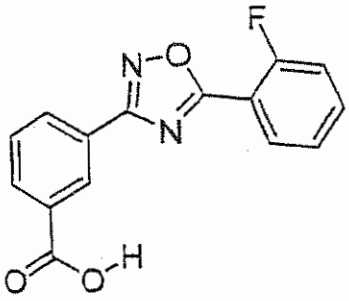
or a pharmaceutically acceptable salt thereof.

[0016c] In another aspect, there is provided the use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of achromatopsia associated with a nonsense mutation, wherein the agent has the formula:



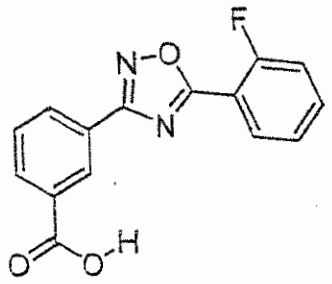
or a pharmaceutically acceptable salt thereof.

[0016d] In another aspect, there is provided the use of a nonsense codon suppressor agent having the formula:



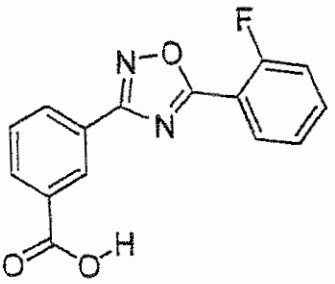
in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated for oral administration to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount of between 0.1 mg/kg and 500 mg/kg per day, divided into three doses with the first and second doses each being 25% of the total amount administered and the third dose being 50% of the total amount administered.

[0016e] In another aspect, there is provided the use of a nonsense codon suppressor agent having the formula:



in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated to be administered to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount sufficient to produce a plasma concentration of 0.1 µg/ml to 500 µg/ml of the agent for at least 2 hours.

[0016f] In another aspect, there is provided the use of a nonsense codon suppressor agent having the formula:



in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated to be administered to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount which does not exhibit significant antibacterial activity against a gram-negative microorganism and/or a gram-positive microorganism.

4. DESCRIPTION OF THE FIGURES

[0017] FIG 1. Schematic of mRNA derived from luciferase reporter constructs.

[0018] FIGS. 2A-2E. mRNA derived from Luciferase-CD40 reporter in mRNA constructs.

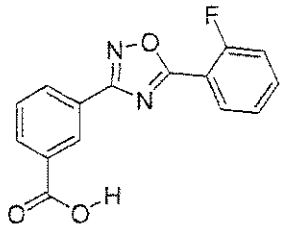
[0019] FIG 3. Schematic of mouse β-tubulin mRNA.

5. DETAILED DESCRIPTION OF THE INVENTION

[0020] The present invention is based, in part, upon the discovery of nonsense codon suppressor agents that can be systemically administered to a subject (including humans) to

CLAIMS

1. Use of a compound having the formula :

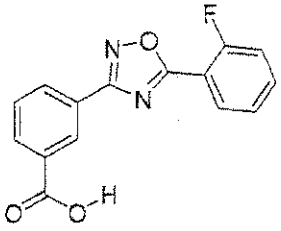


or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of:

a. duchenne muscular dystrophy in a patient with a nonsense mutation at position 1417, 3625, or 492 of dystrophin; or

b. cystic fibrosis in a patient with a nonsense mutation at position 414, 493, 1316, 553, 542, 1162, 122, 1455, 822, 60, 764, 1291, 849, 434, 88, 1158 or 6542 of CFTR.

2. Use of a compound having the formula:



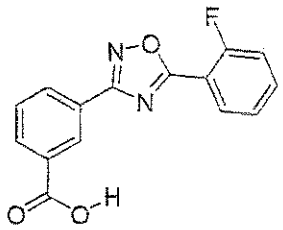
or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the production of a functional readthrough protein in a subject having muscular dystrophy or cystic fibrosis, wherein

a. the functional readthrough protein has any amino acid residue at position 1417 of dystrophin except leucine, any amino acid residue at position 3625 of dystrophin except glutamine, or any amino acid residue at position 492 of dystrophin except glutamine;

b. the functional readthrough protein has any amino acid residue at position 414 of CFTR except glutamine, any amino acid residue at position 493 of CFTR except

glutamine, any amino acid residue at position 1316 of CFTR except tryptophan, any amino acid residue at position 553 of CFTR except arginine; any amino acid residue at position 542 of CFTR except glycine, any amino acid residue at position 1162 of CFTR except arginine, any amino acid residue at position 122 of CFTR except tyrosine, any amino acid residue at position 1455 of CFTR except serine, any amino acid residue at position 822 of CFTR except glutamic acid, any amino acid residue at position 60 of CFTR except glutamic acid, any amino acid residue at position 764 of CFTR except arginine, any amino acid residue at position 1291 of CFTR except glutamine, any amino acid residue at position 849 of CFTR except tyrosine, any amino acid residue at position 434 of CFTR except serine, any amino acid residue at position 88 of CFTR except leucine, any amino acid residue at position 1158 of CFTR except arginine, or any amino acid residue at position 6542 of CFTR except glycine.

3. The use of either of claims 1 or 2, wherein the effective amount of the compound having formula:



or a pharmaceutically acceptable salt thereof, is between 0.1 mg/kg and 500 mg/kg per day, divided into three doses with the first and second doses each being 25% of the total amount administered and the third dose being 50% of the total amount administered.

Claims

1. Use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of:

a. duchenne muscular dystrophy in a patient with a nonsense mutation at position 1417 or 492 of dystrophin;

b. cystic fibrosis in a patient with a nonsense mutation at position 414, 493, 542, 1162, 122, 1455, 822, 60, 764, 1291, 849, 434, 88, 1158 or 6542 of CFTR;

c. hemophilia A in a patient with a nonsense mutation at position 1535, 2116, 1395, 139, 583, 1941, 2116, or 1778 of factor VIII;

d. hemophilia B in a patient with a nonsense mutation at position 333, 252, 31118, 116, or 338 of factor IX;

e. mucopolysaccharidosis III A in a patient with a nonsense mutation at position 40 or 233 of SGSH;

f. Charcot-Marie Tooth disease type 4A in a patient with a nonsense mutation at position 194 of ganglioside-induced differentiation-associated protein 1 (GDAP1);

g. Charcot-Marie Tooth disease in a patient with a nonsense mutation at amino acid position 132 of connexin 32;

h. neurofibromatosis in a patient with a nonsense mutation at position 1947, 1306 or 2496 of NF1;

i. polycystic kidney disease in a patient with a nonsense mutation at position 4086, 3818 or 3817 of PKD1; or

j. tuberous sclerosis complex in a patient with a nonsense mutation at position 897 of TSC1;

k. duchenne muscular dystrophy in a patient with a nonsense mutation at position 1417, 3625, or 492 of dystrophin, wherein for a patient with a nonsense mutation at position 1417 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 1417 of dystrophin except leucine, wherein for a patient with a nonsense mutation at position 3625 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 3625 of dystrophin except glutamine, and wherein for a patient with a nonsense mutation at position 492 of dystrophin, functional readthrough protein is produced having any amino acid residue at position 492 of dystrophin except glutamine;

l. cystic fibrosis in a patient with a nonsense mutation at position 414, 493, 1316, 553, 542, 1162, 122, 1455, 822, 60, 764, 1291, 849, 434, 88, 1158 or 6542 of CFTR, wherein for a patient with a nonsense mutation at position 414 of CFTR, functional readthrough protein is produced having any amino acid residue at position 414 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 493 of CFTR, functional readthrough protein is produced having any amino acid residue at position 493 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 1316 of CFTR, functional readthrough protein is produced having any amino acid

residue at position 1316 of CFTR except tryptophan, wherein for a patient with a nonsense mutation at position 553 of CFTR, functional readthrough protein is produced having any amino acid residue at position 553 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 542 of CFTR, functional readthrough protein is produced having any amino acid residue at position 542 of CFTR except glycine, wherein for a patient with a nonsense mutation at position 1162 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1162 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 122 of CFTR, functional readthrough protein is produced having any amino acid residue at position 122 of CFTR except tyrosine, wherein for a patient with a nonsense mutation at position 1455 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1455 of CFTR except serine, wherein for a patient with a nonsense mutation at position 822 of CFTR, functional readthrough protein is produced having any amino acid residue at position 822 of CFTR except glutamic acid, wherein for a patient with a nonsense mutation at position 60 of CFTR, functional readthrough protein is produced having any amino acid residue at position 60 of CFTR except glutamic acid, wherein for a patient with a nonsense mutation at position 764 of CFTR, functional readthrough protein is produced having any amino acid residue at position 764 of CFTR except arginine, wherein for a patient with a nonsense mutation at position 1291 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1291 of CFTR except glutamine, wherein for a patient with a nonsense mutation at position 849 of CFTR, functional readthrough protein is produced having any amino acid residue at position 849 of CFTR except tyrosine, wherein for a patient with a nonsense mutation at position 434 of CFTR, functional readthrough protein is produced having any amino acid residue at position 434 of CFTR except serine, wherein for a patient with a nonsense mutation at position 88 of CFTR, functional readthrough protein is produced having any amino acid residue at position 88 of CFTR except leucine, wherein for a patient with a nonsense mutation at position 1158 of CFTR, functional readthrough protein is produced having any amino acid residue at position 1158 of CFTR except arginine, and wherein for a patient with a nonsense mutation at position 6542 of CFTR, functional readthrough protein is produced having any amino acid residue at position 6542 of CFTR except glycine;

m. hemophilia A in a patient with a nonsense mutation at position 1029, 1792, 1535, 2116, 427, 1395, 139, 583, 1941, 1966, 2116, or 1778 of factor VIII, wherein for a patient with a nonsense mutation at position 1029 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1029 of factor VIII except tryptophan, wherein for a patient with a nonsense mutation at position 1792 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1792 of factor VIII except tyrosine, wherein for a patient with a nonsense mutation at position 1535 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1535 of factor VIII except tryptophan, wherein for a patient with a nonsense mutation at position 2116 of factor VIII, functional readthrough protein is produced having

any amino acid residue at position 2116 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 427 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 427 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 1395 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1395 of factor VIII except serine, wherein for a patient with a nonsense mutation at position 139 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 139 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 583 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 583 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 1941 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1941 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 1966 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1966 of factor VIII except arginine, wherein for a patient with a nonsense mutation at position 2116 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 2116 of factor VIII except arginine, and wherein for a patient with a nonsense mutation at position 1778 of factor VIII, functional readthrough protein is produced having any amino acid residue at position 1778 of factor VIII except glutamine;

n. hemophilia B in a patient with a nonsense mutation at position 333, 252, 31118, 116, or 338 of factor IX, wherein for a patient with a nonsense mutation at position 333 of factor IX, functional readthrough protein is produced having any amino acid residue at position 333 of factor IX except arginine, wherein for a patient with a nonsense mutation at position 252 of factor IX, functional readthrough protein is produced having any amino acid residue at position 252 of factor IX except arginine, wherein for a patient with a nonsense mutation at position 31118 of factor IX, functional readthrough protein is produced having any amino acid residue at position 31118 of factor IX except cysteine, wherein for a patient with a nonsense mutation at position 116 of factor IX, functional readthrough protein is produced having any amino acid residue at position 116 of factor IX except arginine, and wherein for a patient with a nonsense mutation at position 338 of factor IX, functional readthrough protein is produced having any amino acid residue at position 338 of factor IX except arginine;

o. mucopolysaccharidosis III A in a patient with a nonsense mutation at position 40 or 233 of SGSH, wherein for a patient with a nonsense mutation at position 40 of SGSH, functional readthrough protein is produced having any amino acid residue at position 40 of SGSH except tyrosine and wherein for a patient with a nonsense mutation at position 233 of SGSH, functional readthrough protein is produced having any amino acid residue at position 233 of SGSH except arginine;

p. Charcot-Marie Tooth disease type 4A in a patient with a nonsense mutation at position 194 of ganglioside-induced differentiation-associated protein 1 (GDAP1), wherein for a patient with a nonsense mutation at position 194 of GDAP1, functional readthrough protein is produced having any amino acid residue at position 194 of GDAP1 except serine;

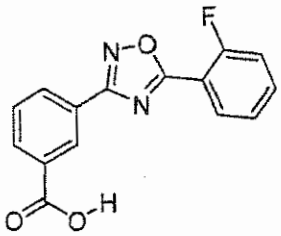
q. Charcot-Marie Tooth disease in a patient with a nonsense mutation at amino acid position 132 of connexin 32, wherein for a patient with a nonsense mutation at position 132 of connexin 32, functional readthrough protein is produced having any amino acid residue at position 132 of connexin 32 except tryptophan;

r. neurofibromatosis in a patient with a nonsense mutation at position 1947, 1306 or 2496 of NF1, wherein for a patient with a nonsense mutation at position 1947 of NF1, functional readthrough protein is produced having any amino acid residue at position 1947 of NF1 except arginine, wherein for a patient with a nonsense mutation at position 1306 of NF1, functional readthrough protein is produced having any amino acid residue at position 1306 of NF1 except arginine, and wherein for a patient with a nonsense mutation at position 2496 of NF1, functional readthrough protein is produced having any amino acid residue at position 2496 of NF1 except arginine;

s. polycystic kidney disease in a patient with a nonsense mutation at position 4086, 3818 or 3817 of PKD1, wherein for a patient with a nonsense mutation at position 4086 of PKD1, functional readthrough protein is produced having any amino acid residue at position 4086 of PKD1 except cysteine, wherein for a patient with a nonsense mutation at position 3818 of PKD1, functional readthrough protein is produced having any amino acid residue at position 3818 of PKD1 except tyrosine, and wherein for a patient with a nonsense mutation at position 3817 of PKD1, functional readthrough protein is produced having any amino acid residue at position 3817 of PKD1 except cysteine; or

t. tuberous sclerosis complex in a patient with a nonsense mutation at position 897 of TSC1, wherein for a patient with a nonsense mutation at position 897 of TSC1, functional readthrough protein is produced having any amino acid residue at position 897 of TSC1 except glutamine;

wherein the nonsense codon suppressor agent has the formula:



or a pharmaceutically acceptable salt thereof.

2. Use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the production of a functional readthrough protein in a subject, wherein

a. the functional readthrough protein has any amino acid residue at position 1417 of dystrophin except leucine, any amino acid residue at position 3625 of dystrophin except glutamine, or any amino acid residue at position 492 of dystrophin except glutamine;

b. the functional readthrough protein has any amino acid residue at position 414 of CFTR except glutamine, any amino acid residue at position 493 of CFTR except glutamine, any amino acid residue at position 1316 of CFTR except tryptophan, any amino acid residue at position 553 of CFTR except arginine; any amino acid residue at position 542 of CFTR except glycine, any amino acid residue at position 1162 of CFTR except arginine, any amino acid residue at position 122 of CFTR except tyrosine, any amino acid residue at position 1455 of CFTR except serine, any amino acid residue at position 822 of CFTR except glutamic acid, any amino acid residue at position 60 of CFTR except glutamic acid, any amino acid residue at position 764 of CFTR except arginine, any amino acid residue at position 1291 of CFTR except glutamine, any amino acid residue at position 849 of CFTR except tyrosine, any amino acid residue at position 434 of CFTR except serine, any amino acid residue at position 88 of CFTR except leucine, any amino acid residue at position 1158 of CFTR except arginine, or any amino acid residue at position 6542 of CFTR except glycine;

c. the functional readthrough protein has any amino acid residue at position 1029 of Factor VIII except tryptophan, any amino acid residue at position 1792 of Factor VIII except tyrosine, any amino acid residue at position 1535 of Factor VIII except tryptophan, any amino acid residue at position 2116 except arginine, any amino acid residue at position 427 of Factor VIII except arginine, any amino acid residue at position 1395 of Factor VIII except serine, any amino acid residue at position 139 of Factor VIII except glutamine, any amino acid residue at position 583 of Factor VIII except arginine, any amino acid residue at position 1941 of Factor VIII except arginine, any amino acid residue at position 1966 of Factor VIII except arginine, any amino acid residue at position 2116 of Factor VIII except arginine, or any amino acid residue at position 1778 of Factor VIII except glutamine;

d. the functional readthrough protein has any amino acid residue at position 333 of Factor IX except arginine, any amino acid residue at position 252 of Factor IX except arginine, any amino acid residue at position 31118 of Factor IX except cysteine, any amino acid residue at position 116 of Factor IX except arginine, or any amino acid residue at position 338 of Factor IX except arginine;

e. the functional readthrough protein has any amino acid residue at position 40 of SGSH except tyrosine or any amino acid residue at position 233 of SGSH except arginine;

f. the functional readthrough protein has any amino acid residue at position 194 of ganglioside-induced differentiation-associated protein 1 except a serine;

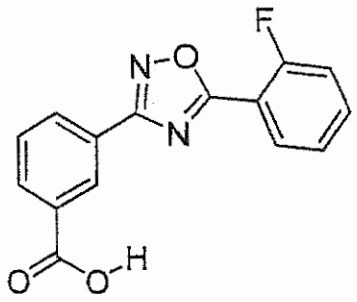
g. the functional readthrough protein has any amino acid residue at position 132 of connexin 32 except tryptophan;

h. the functional readthrough protein has any amino acid residue at position 1947 of NF1 except arginine, any amino acid residue at position 1306 of NF1 except arginine, or any amino acid residue at position 2496 of NF1 except arginine;

i. the functional readthrough protein has any amino acid residue at position 4086 of PKD1 except cysteine, any amino acid residue at position 3818 of PKD1 except tyrosine, or any amino acid residue at position 3817 of PKD1 except cysteine; or

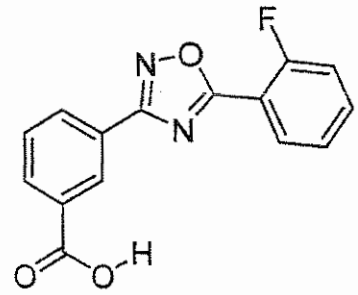
j. the functional readthrough protein has any amino acid residue at position 897 of TSC1 except glutamine;

and wherein the nonsense codon suppressor agent has the formula:



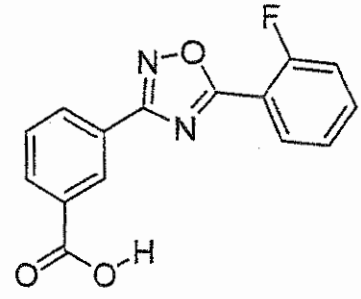
or a pharmaceutically acceptable salt thereof.

3. Use of a nonsense codon suppressor agent or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of achromatopsia associated with a nonsense mutation, wherein the agent has the formula:



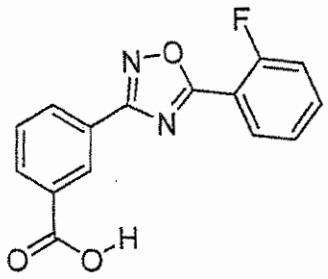
or a pharmaceutically acceptable salt thereof.

4. Use of a nonsense codon suppressor agent having the formula:



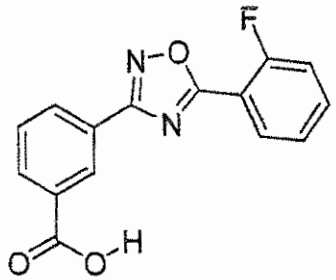
in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated for oral administration to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount of between 0.1 mg/kg and 500 mg/kg per day, divided into three doses with the first and second doses each being 25% of the total amount administered and the third dose being 50% of the total amount administered.

5. Use of a nonsense codon suppressor agent having the formula:



in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated to be administered to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount sufficient to produce a plasma concentration of 0.1 μg/ml to 500 μg/ml of the agent for at least 2 hours.

6. Use of a nonsense codon suppressor agent having the formula:



in the preparation of a medicament for the production of an effective amount of a functional readthrough protein encoded by a nucleic acid sequence comprising a nonsense mutation, wherein the medicament is formulated to be administered to a human subject, and wherein the medicament is formulated for administration of the nonsense codon suppressor agent in an amount which does not exhibit significant antibacterial activity against a gram-negative microorganism and/or a gram-positive microorganism.