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(54) COMPOSITIONS AND METHODS FOR NEURALGENESIS

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Related U.S. Application Data

(63) Continuation of application No. 16/077,411, filed on Aug. 10, 2018, now Pat. No. 12,156,890.

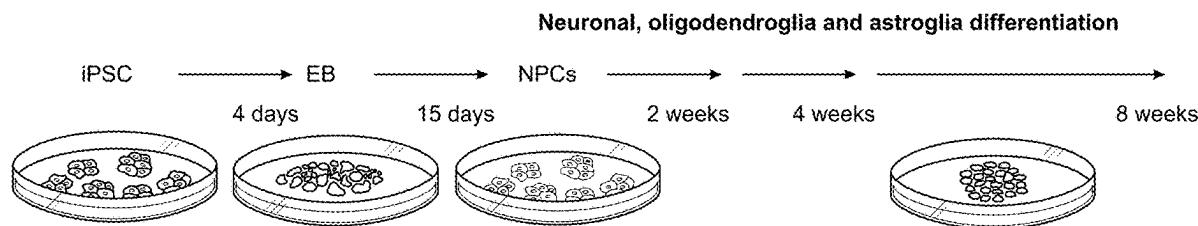
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G01N 33/50 (2006.01)*G01N 33/58* (2006.01)*G01N 33/68* (2006.01)(52) U.S. Cl.
CPC *A61K 35/30* (2013.01); *A61K 38/41* (2013.01); *C12N 5/0062* (2013.01); *C12N 5/0696* (2013.01); *G01N 33/50* (2013.01); *G01N 33/58* (2013.01); *G01N 33/6893* (2013.01); *C12N 2501/11* (2013.01); *C12N 2501/15* (2013.01); *C12N 2501/13* (2013.01); *C12N 2501/22* (2013.01)**ABSTRACT**

The present invention relates to novel compositions and methods to produce 3D organ equivalents of the brain (i.e. "mini-brains"). The invention also relates to methods of using human induced pluripotent stem cells, a combination of growth and other soluble factors and gyratory shaking. Cells from healthy or diseased donors or animals can be used to allow testing different genetic backgrounds. The model can be further enhanced by using genetically modified cells, adding micro-glia or their precursors or indicator cells (e.g. with reporter genes or tracers) as well as adding endothelial cells to form a blood-brain-barrier.

Specification includes a Sequence Listing.

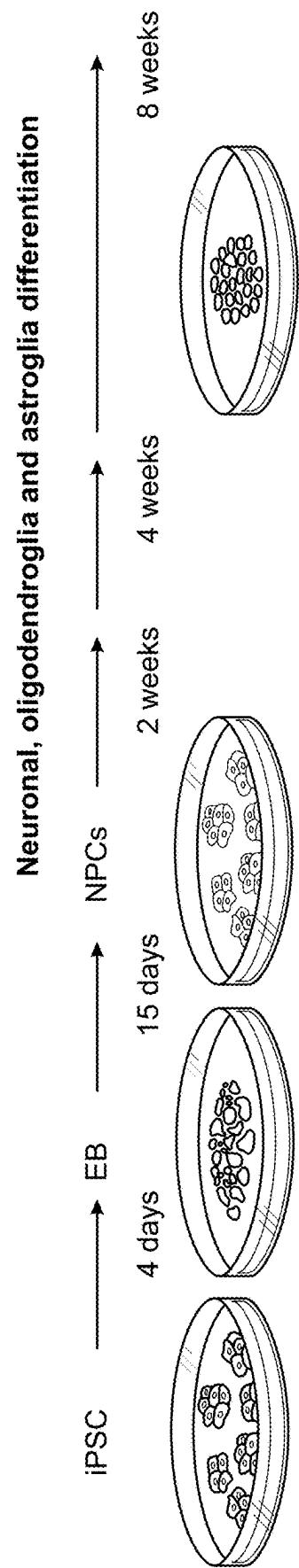


FIG. 1A

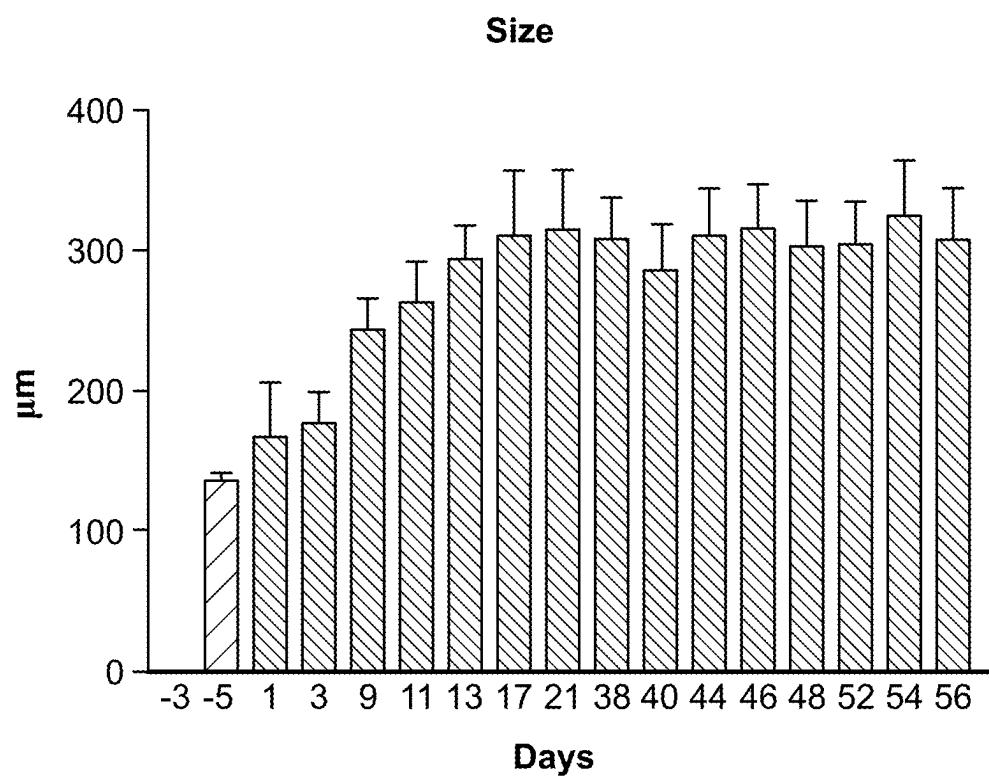


FIG. 1B

Proliferation and stem cell markers

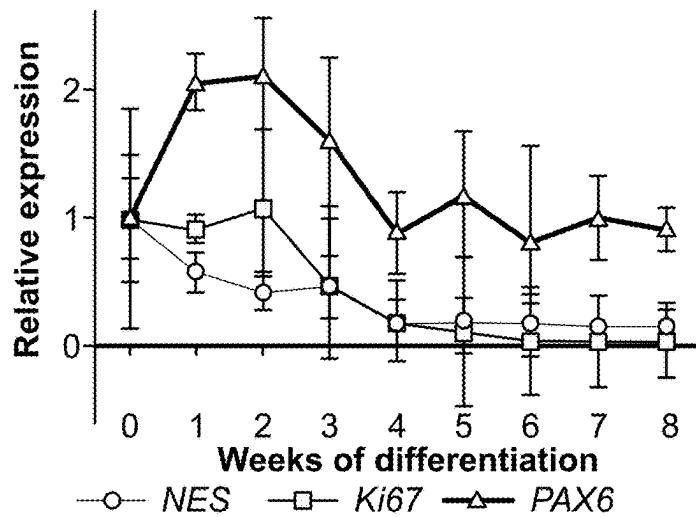


FIG. 1C1

Astroglia and oligodendroglia

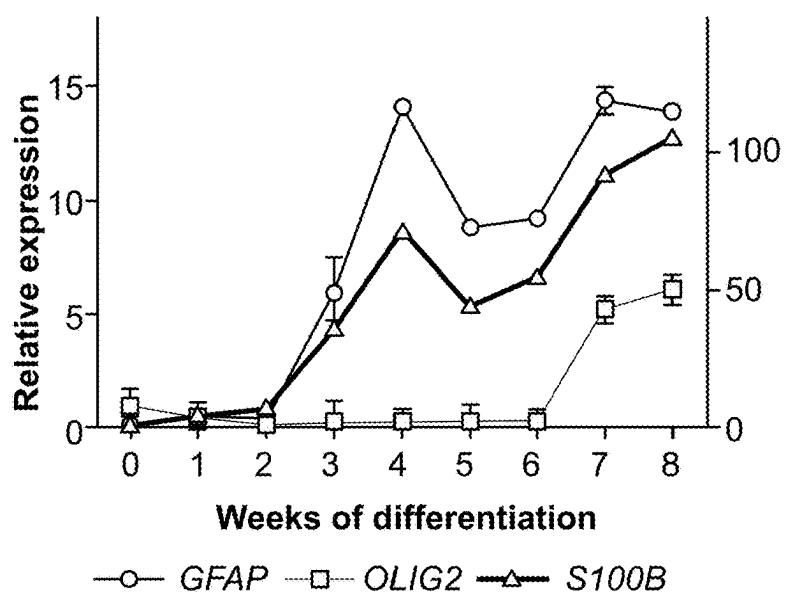
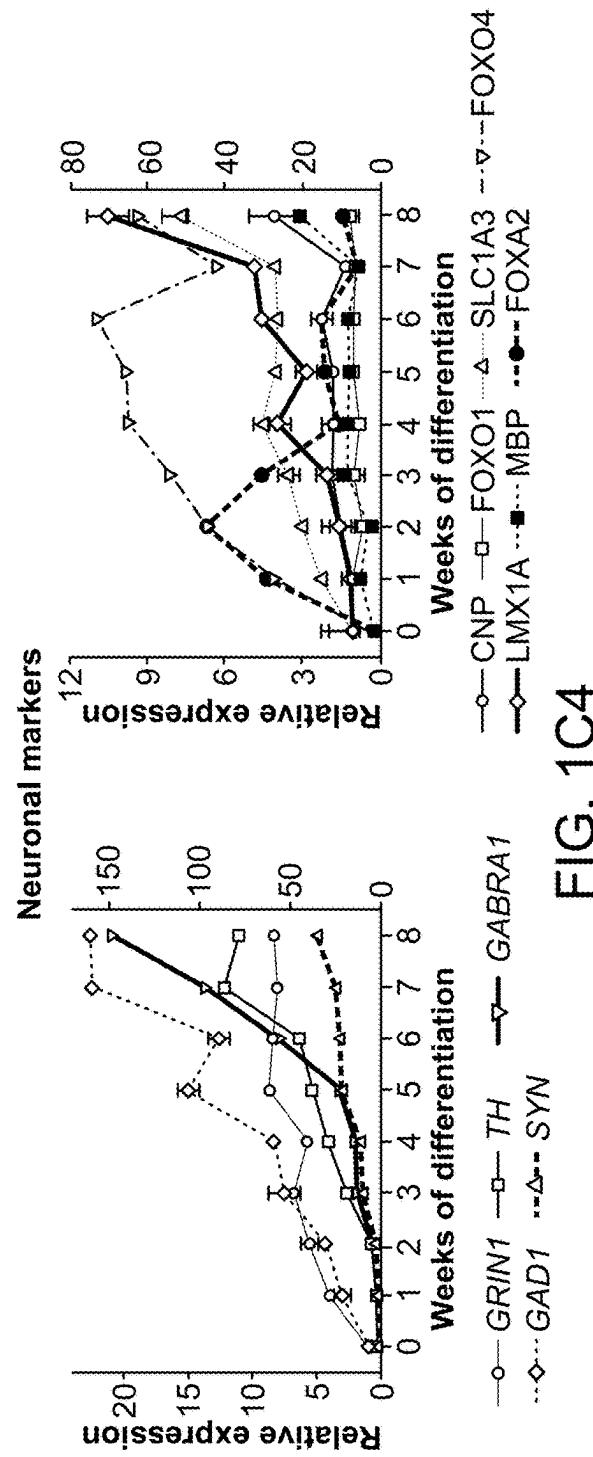
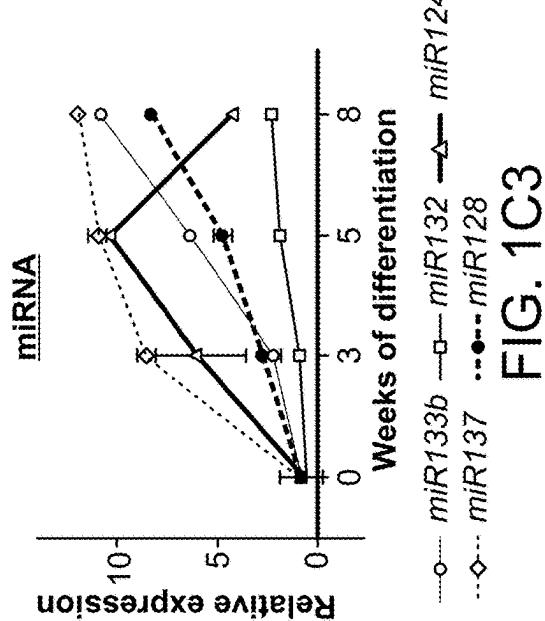


FIG. 1C2



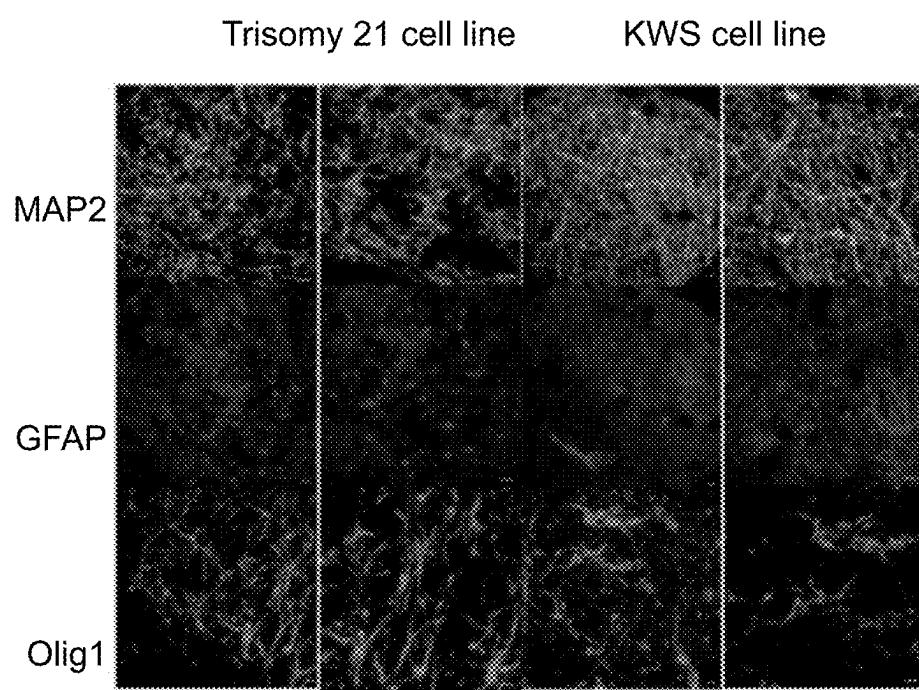
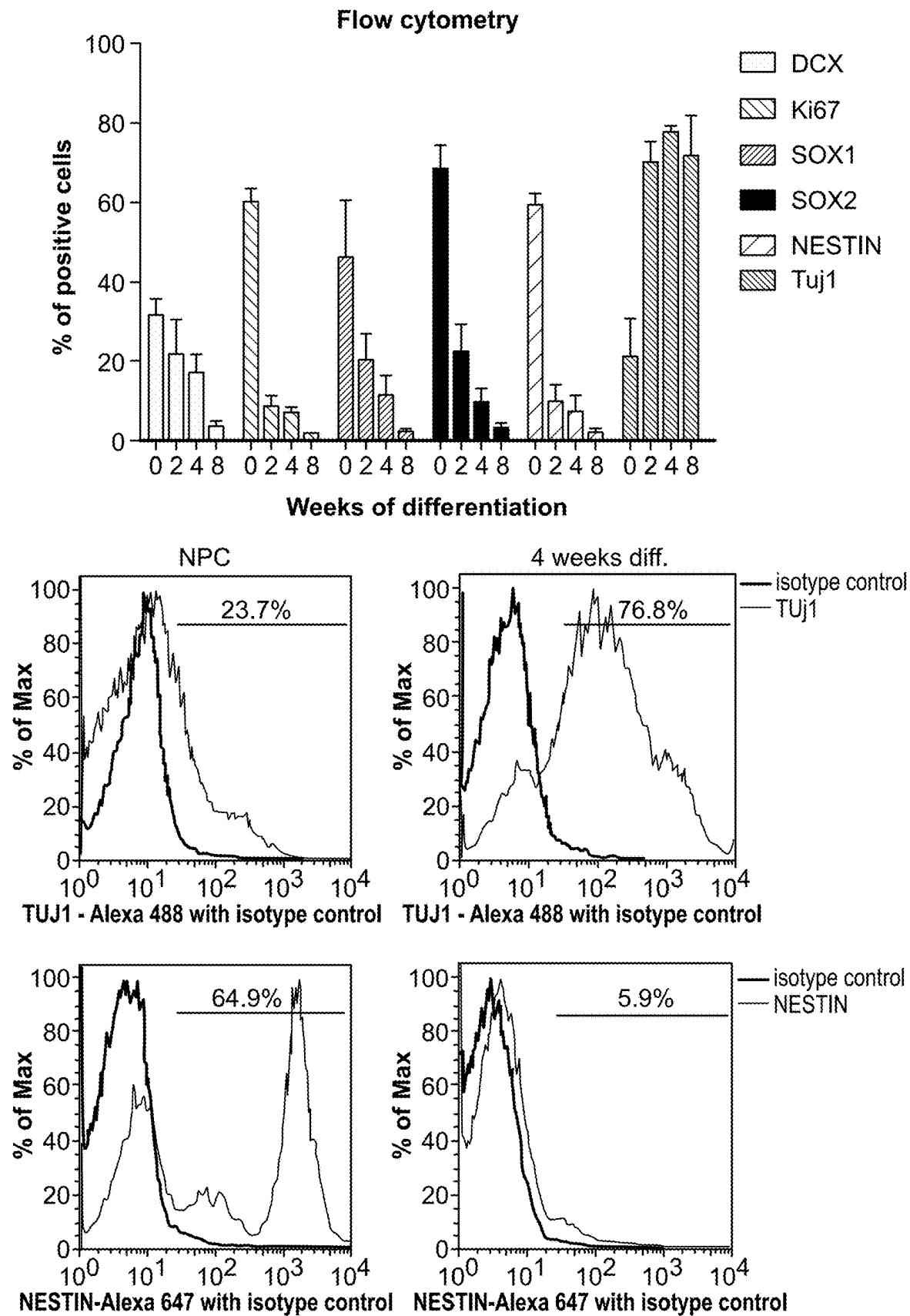


FIG. 1C5

**FIG. 1D**

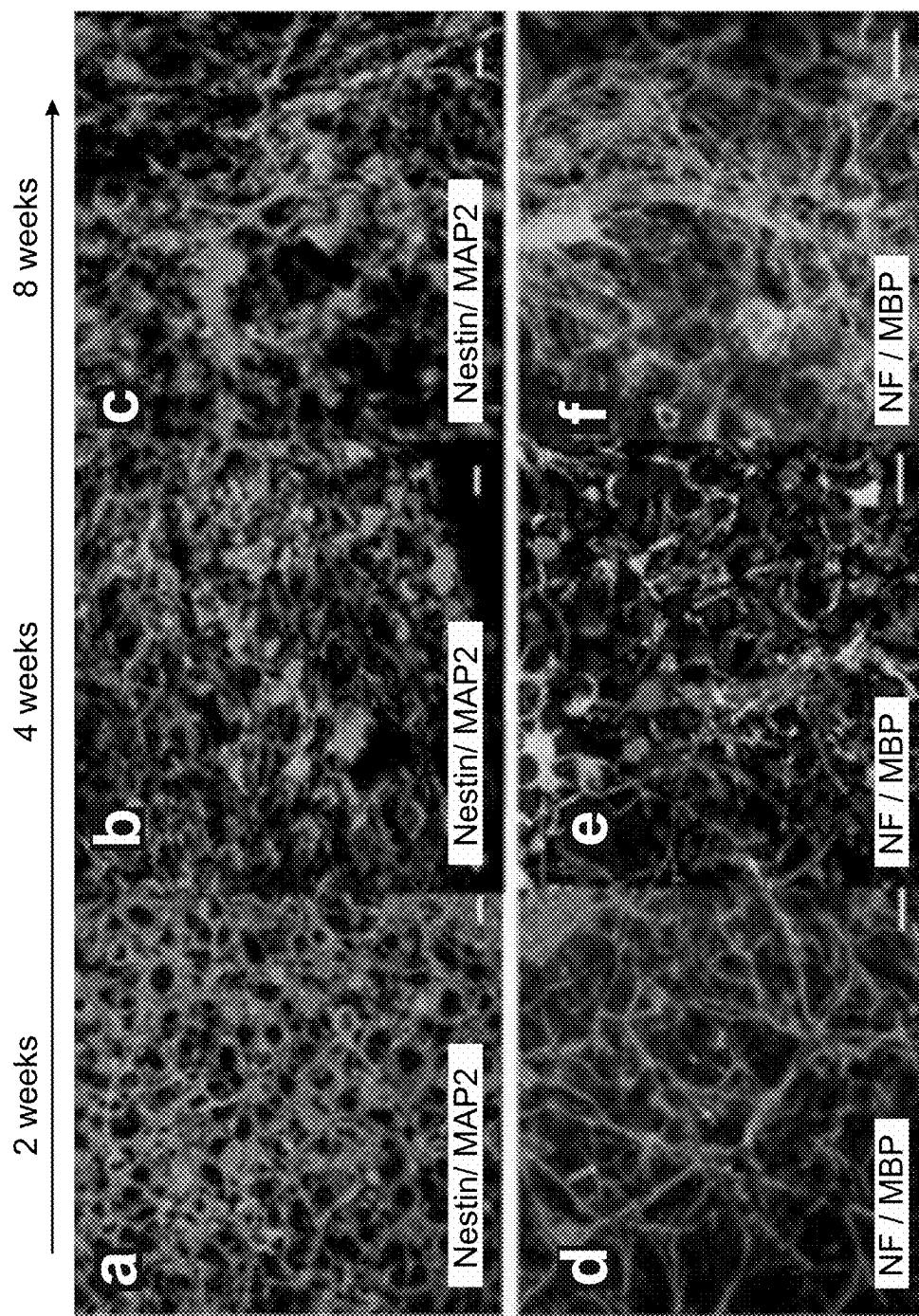


FIG. 2A

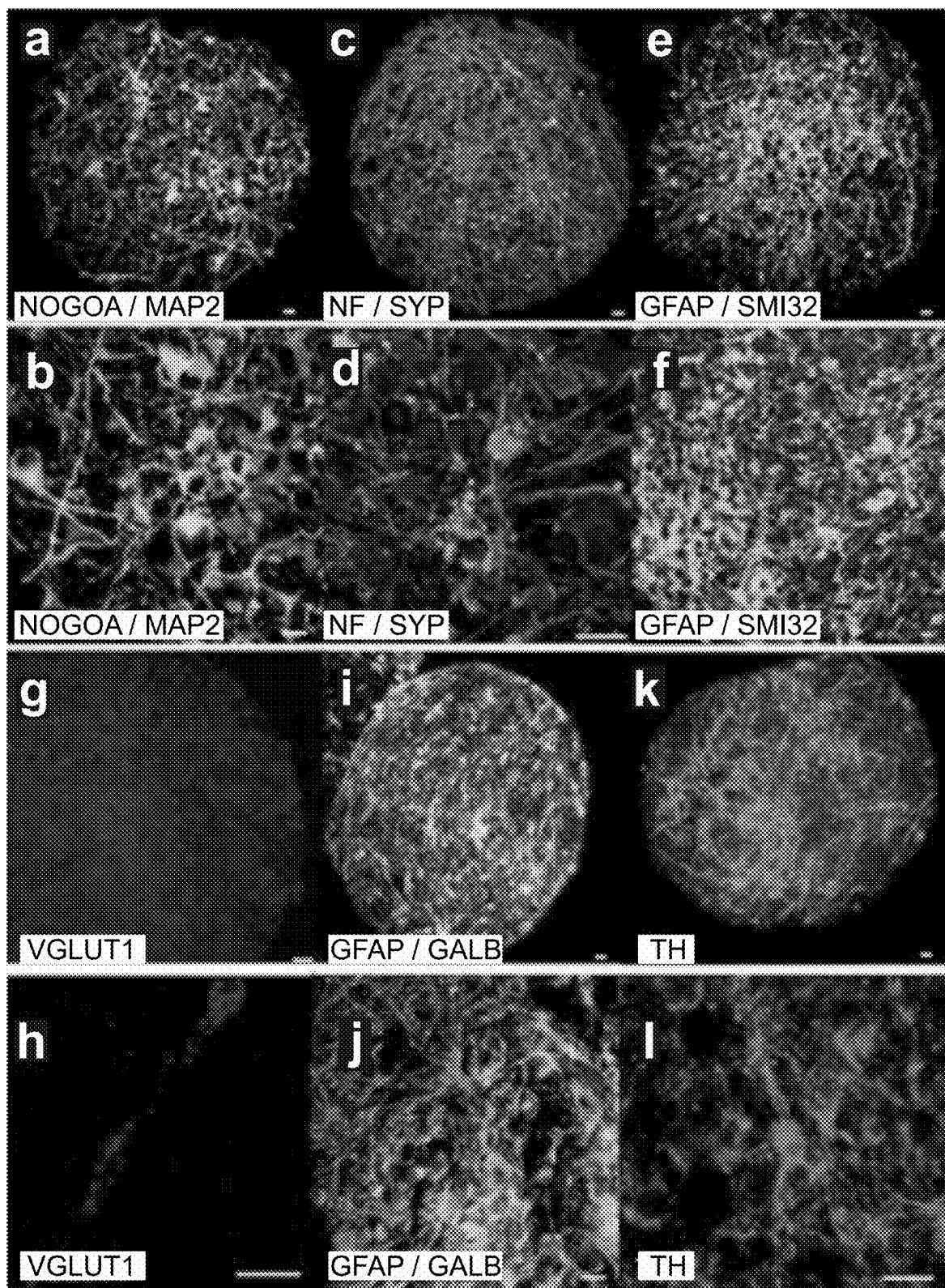


FIG. 2B

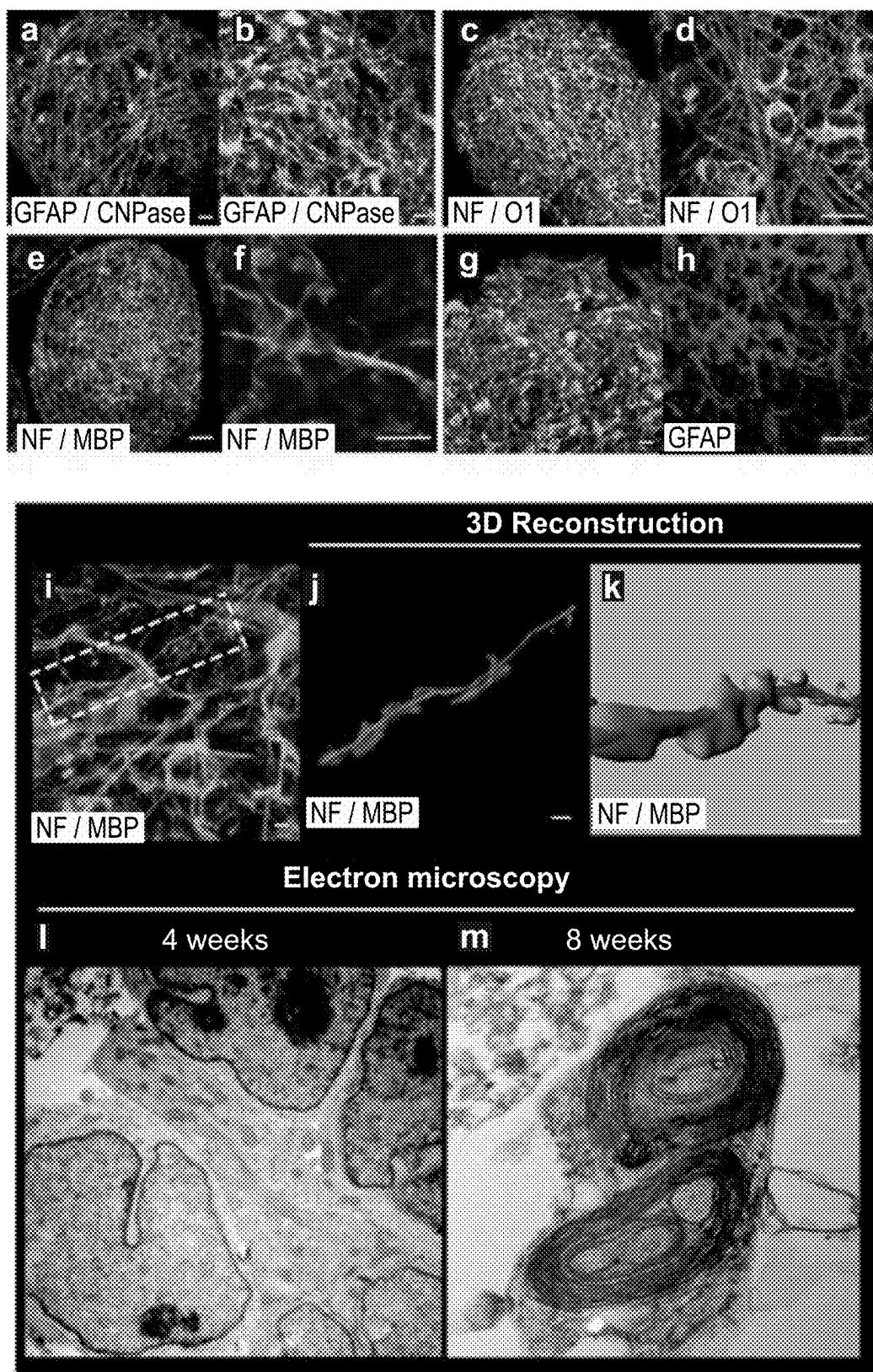


FIG. 2C

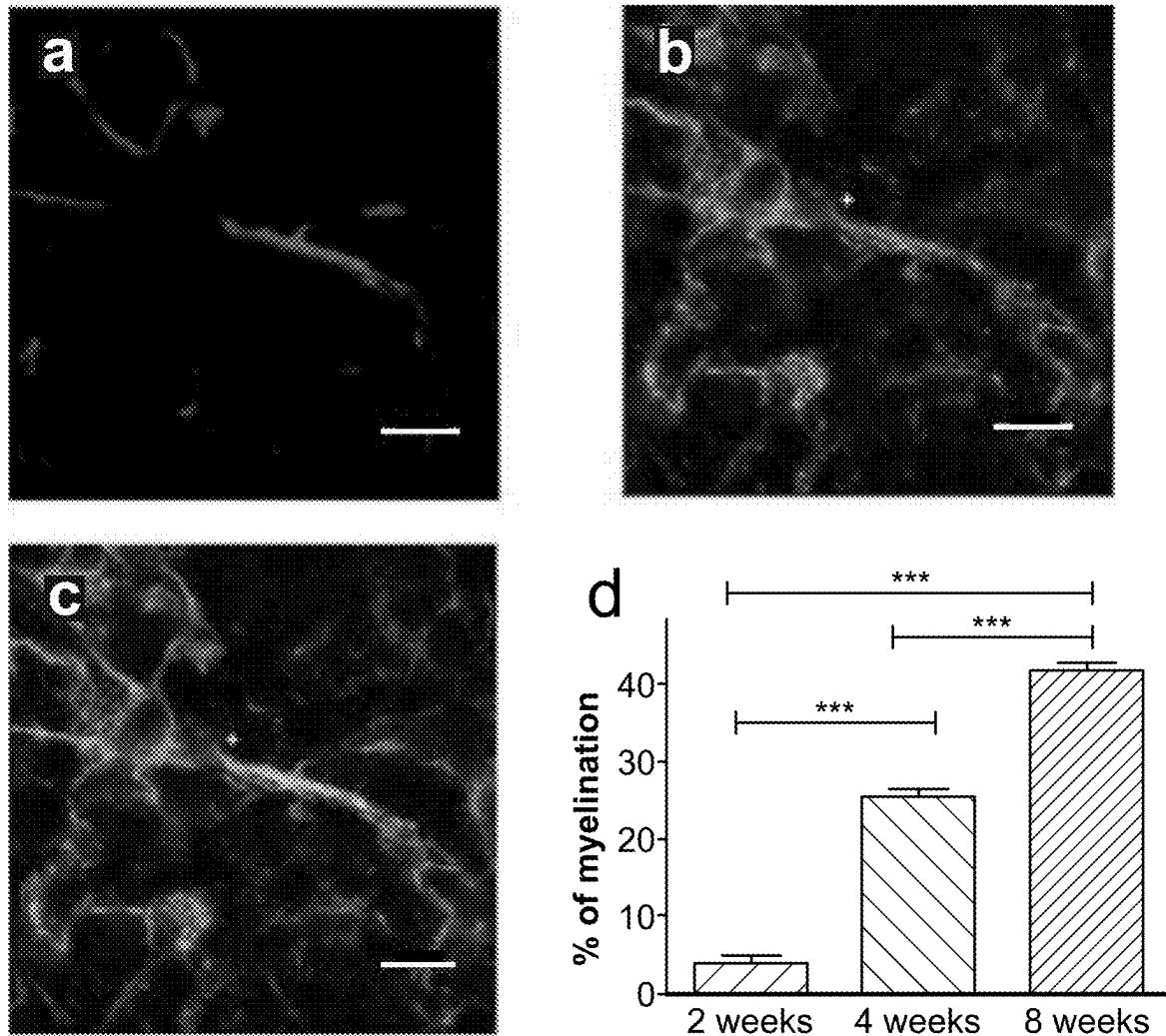


FIG. 2D

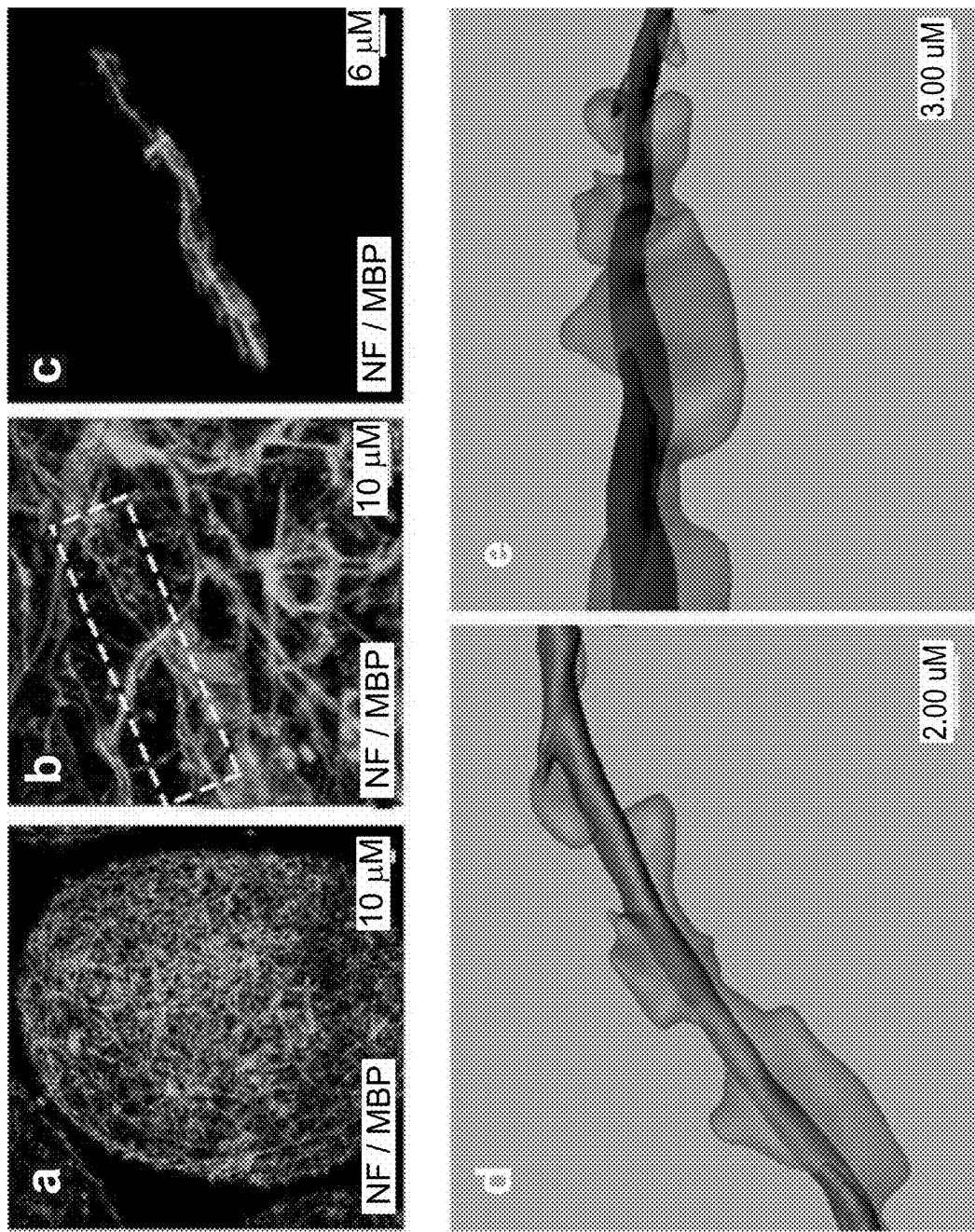


FIG. 2E

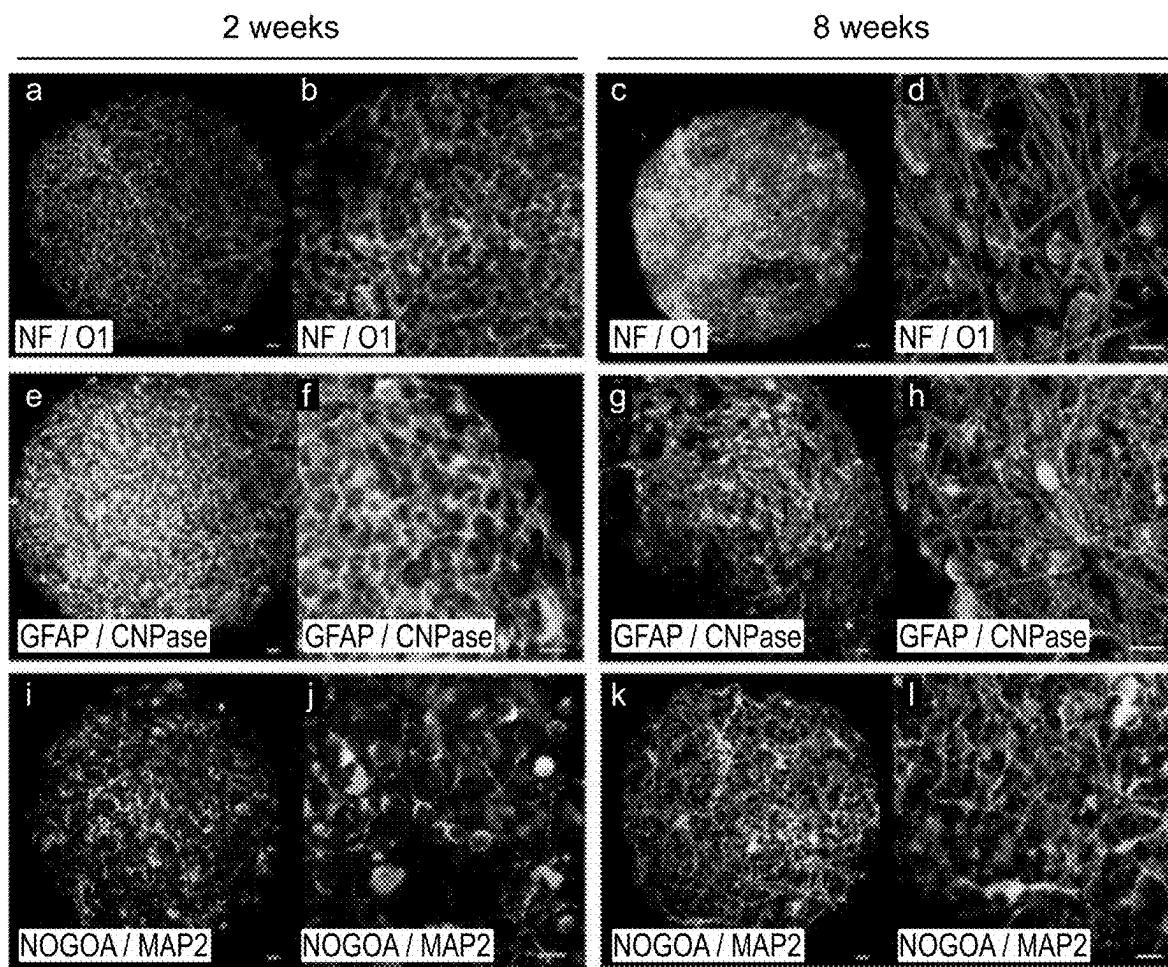


FIG. 2F

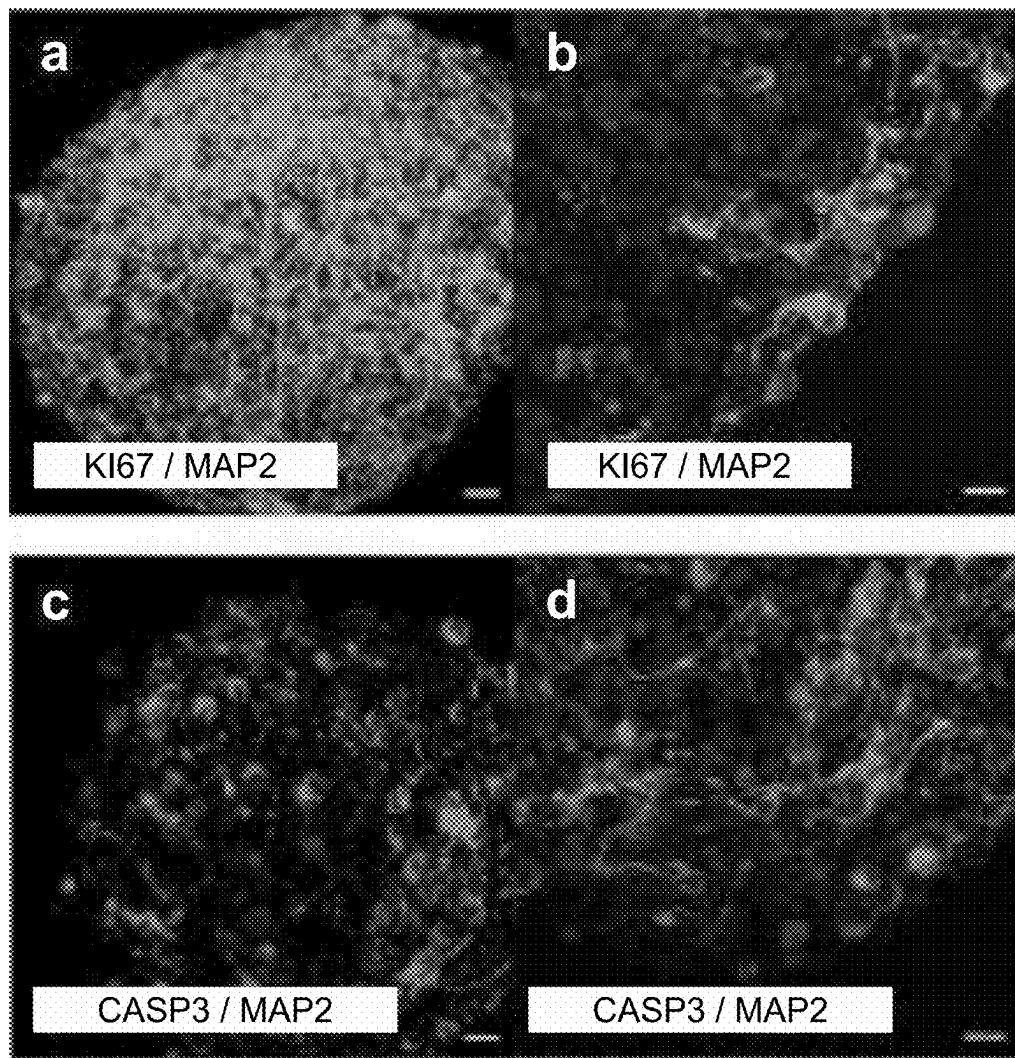


FIG. 2G

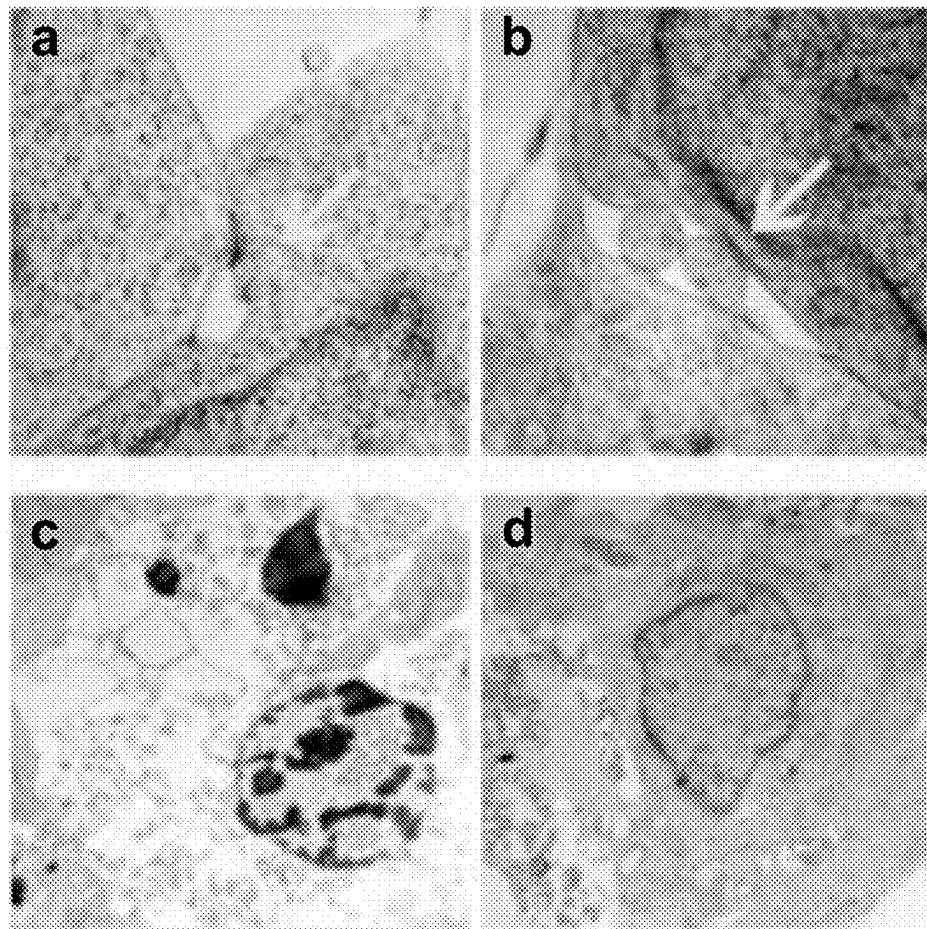


FIG. 2H

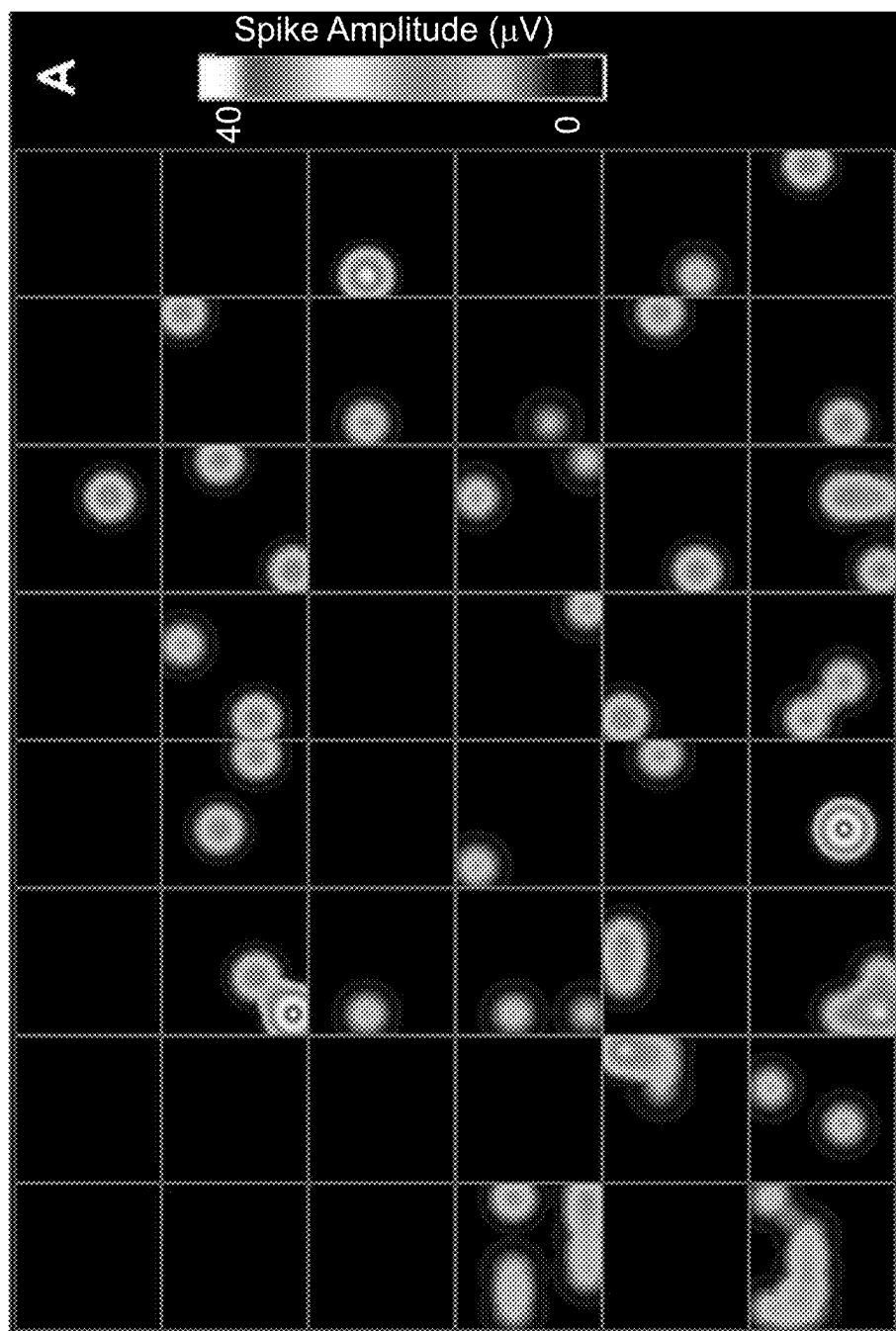


FIG. 3A

FIG. 3B

FIG. 3C

FIG. 3D

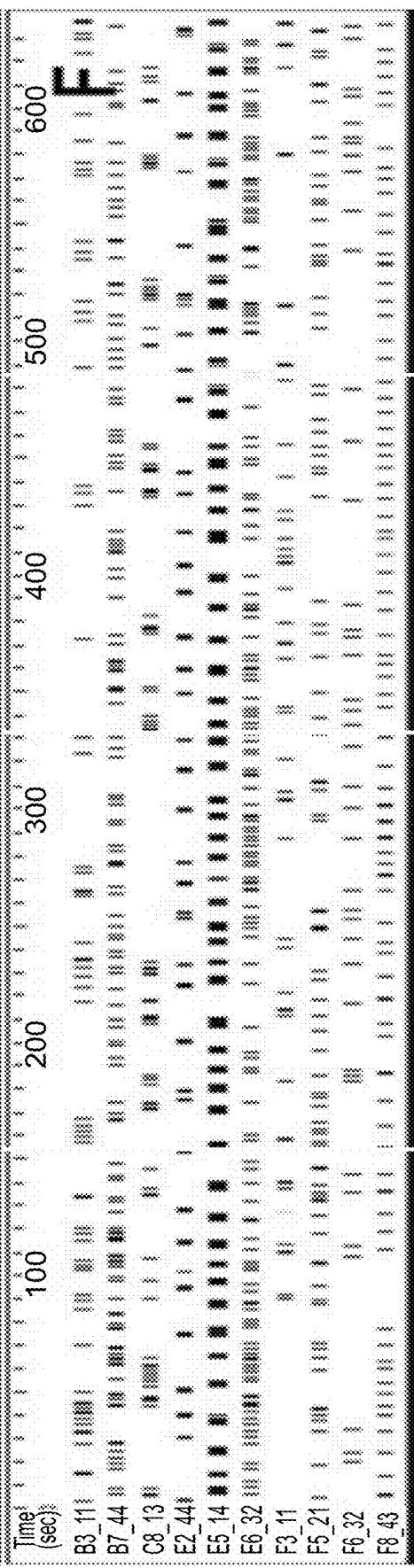
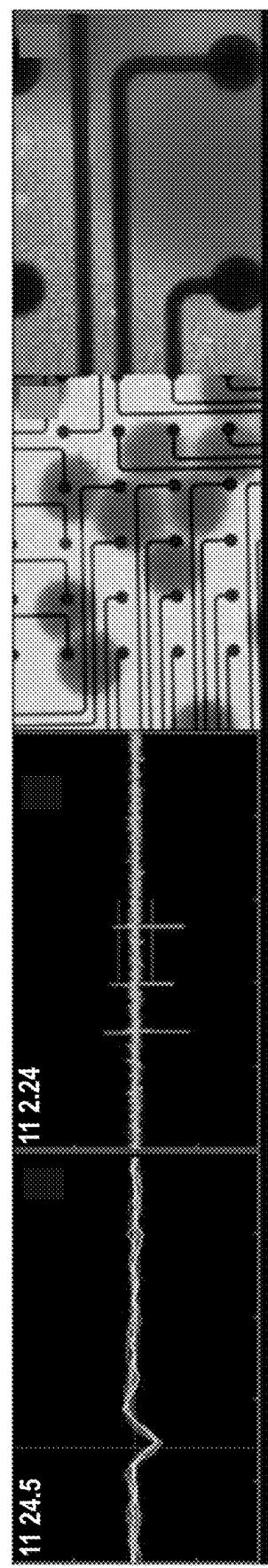


FIG. 3F

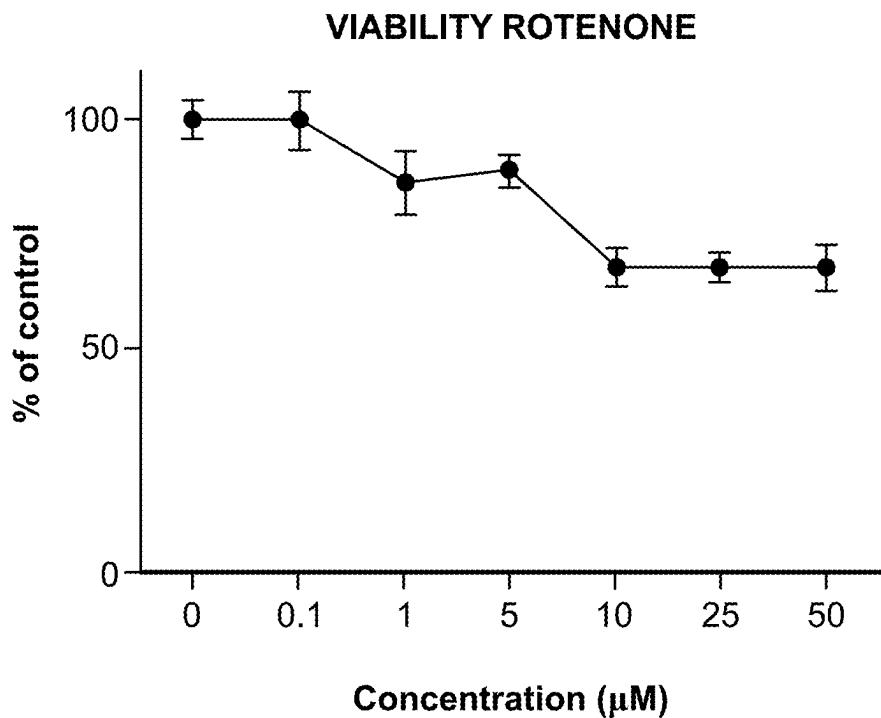


FIG. 4A

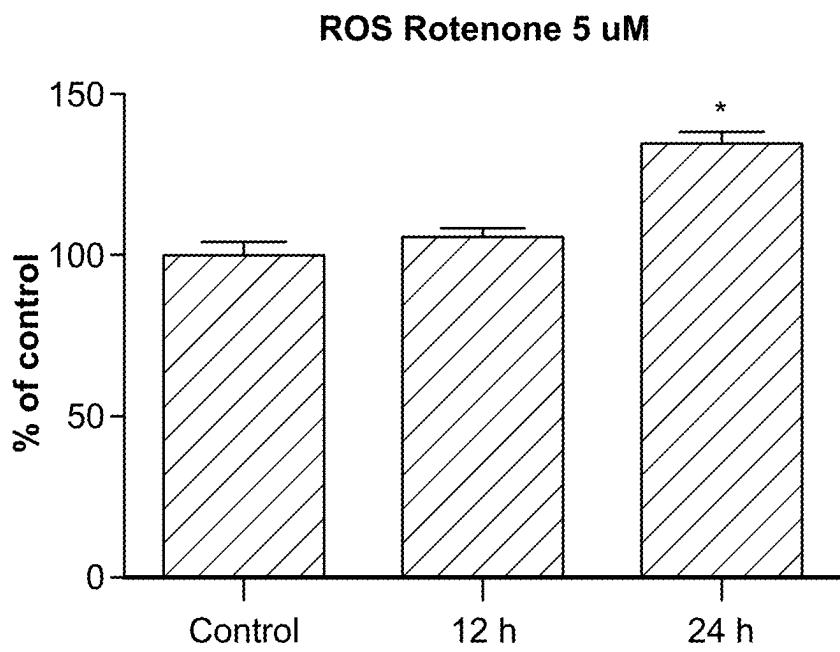


FIG. 4B

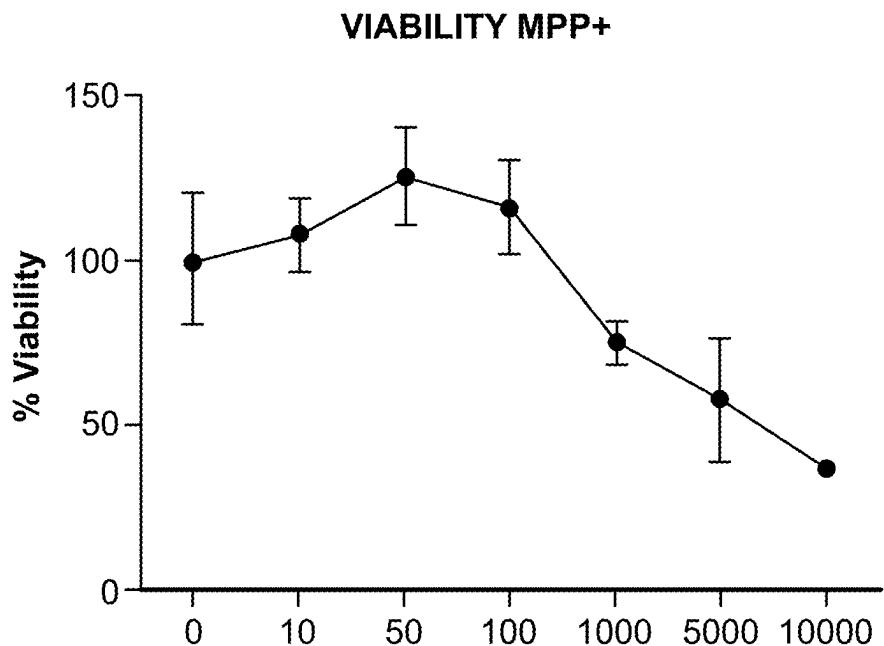


FIG. 4C

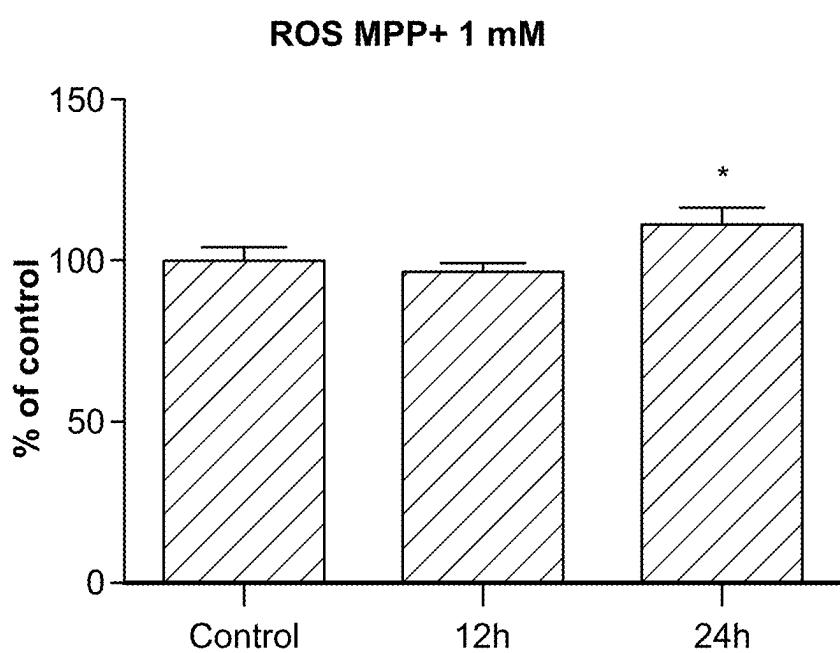


FIG. 4D

FIG. 4E

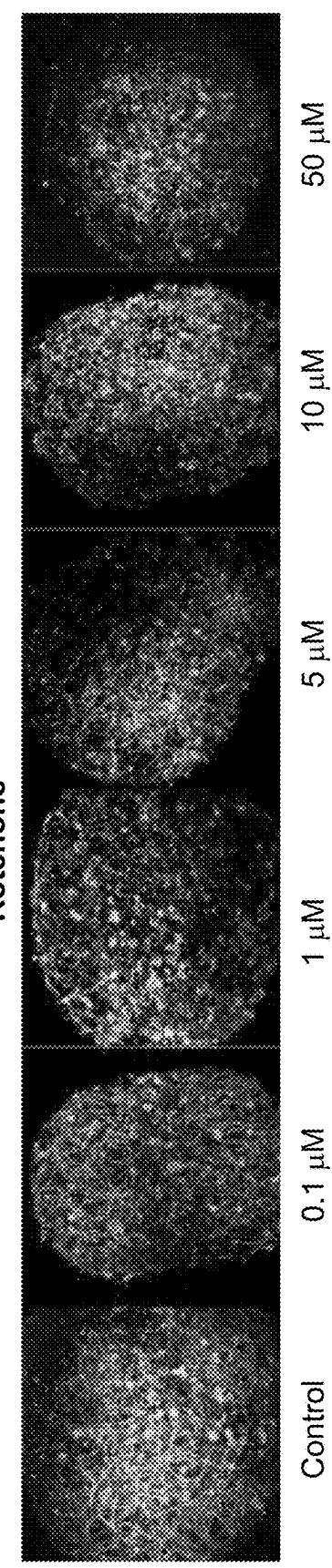
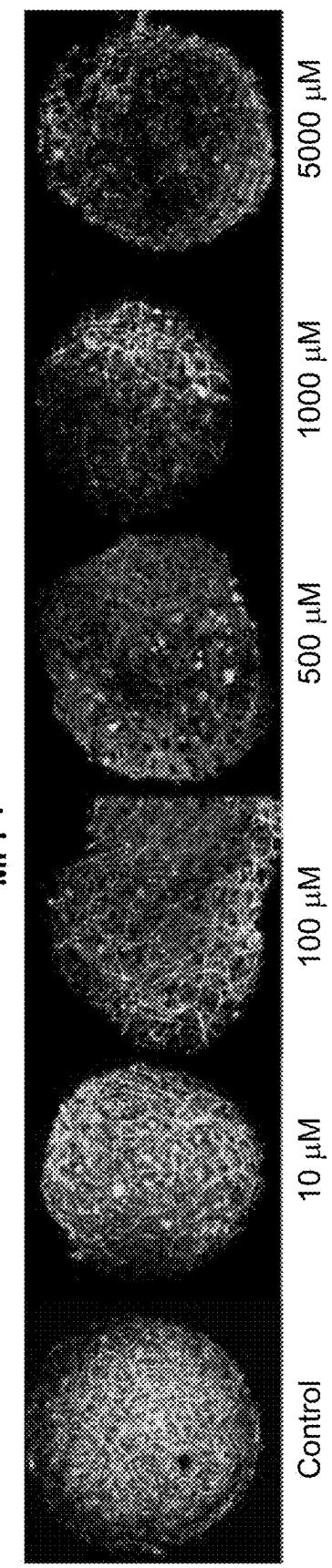


FIG. 4F



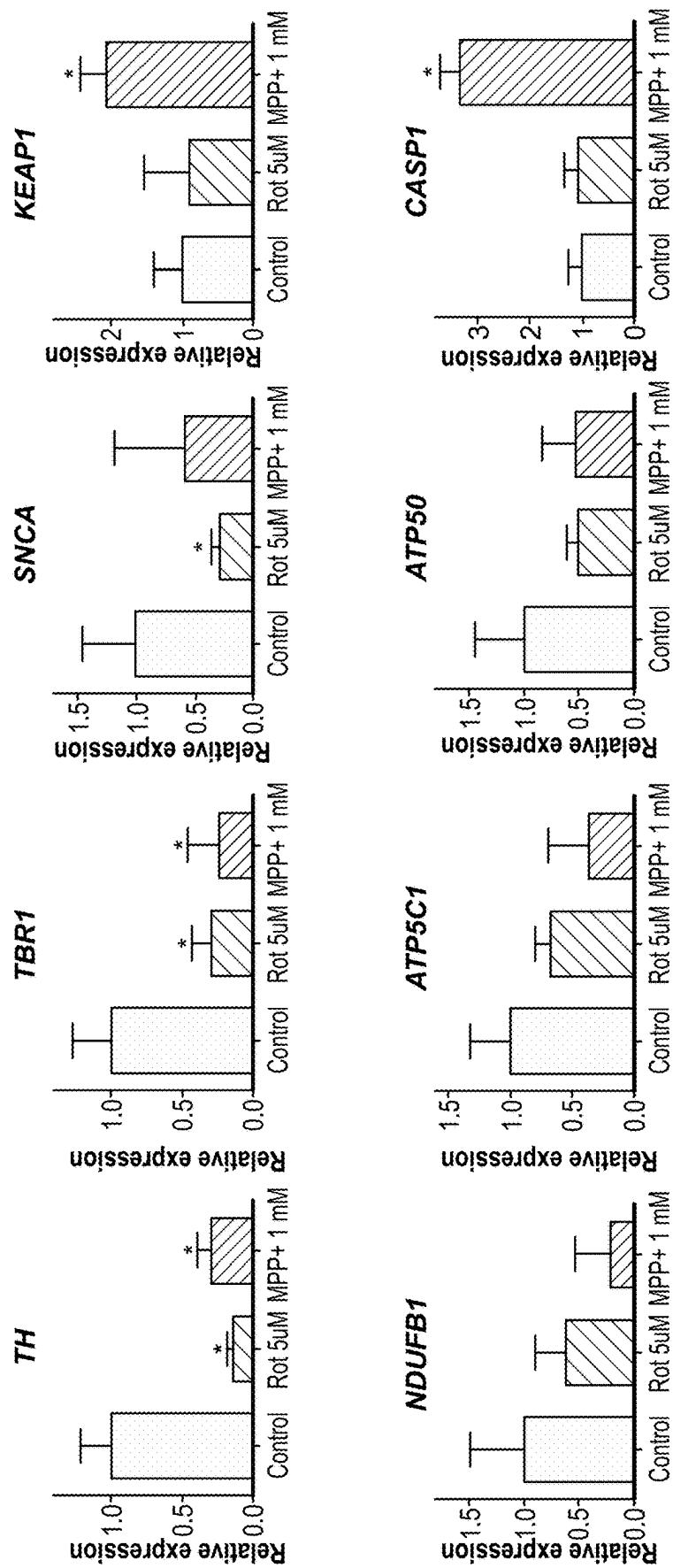


FIG. 4G

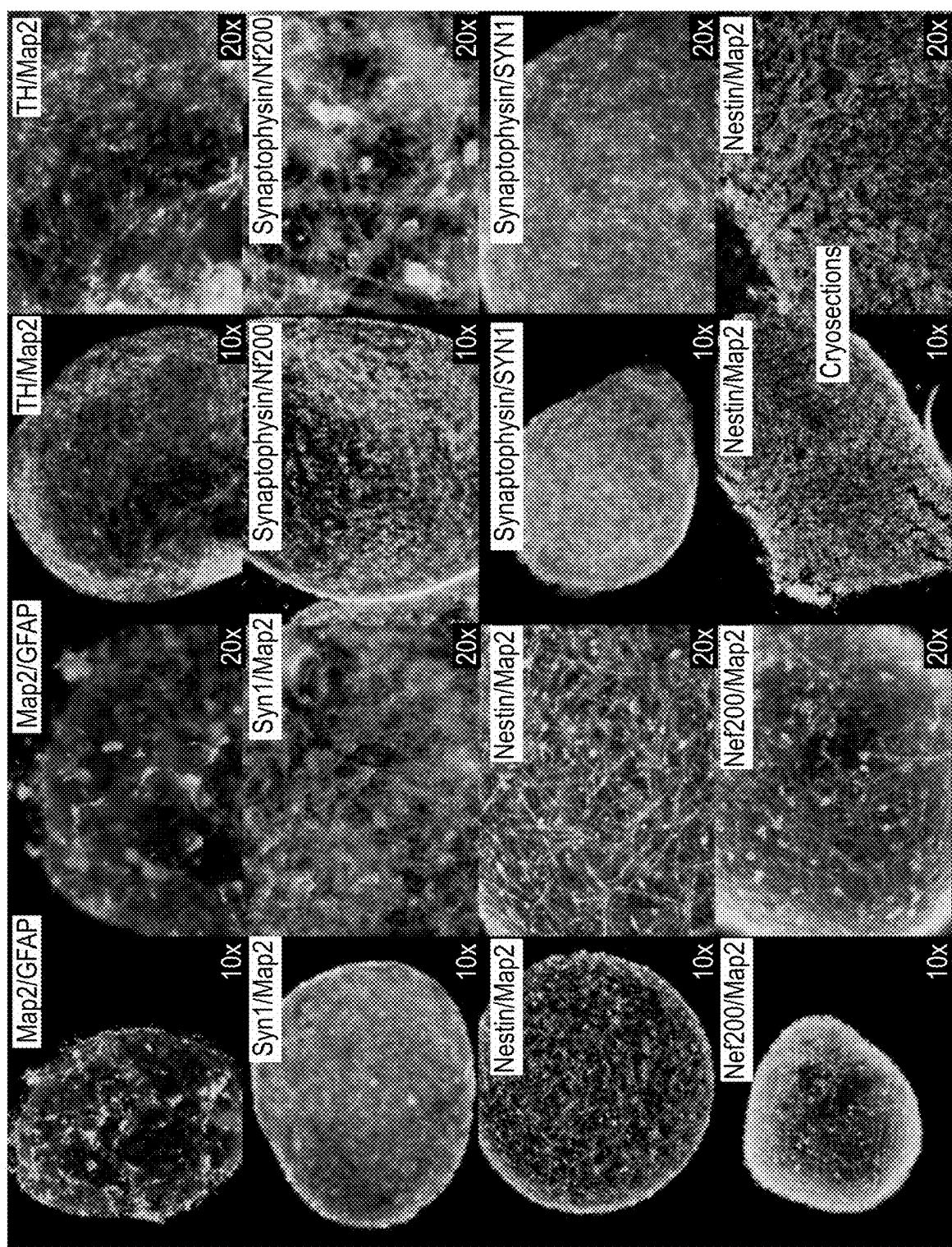


FIG. 5A

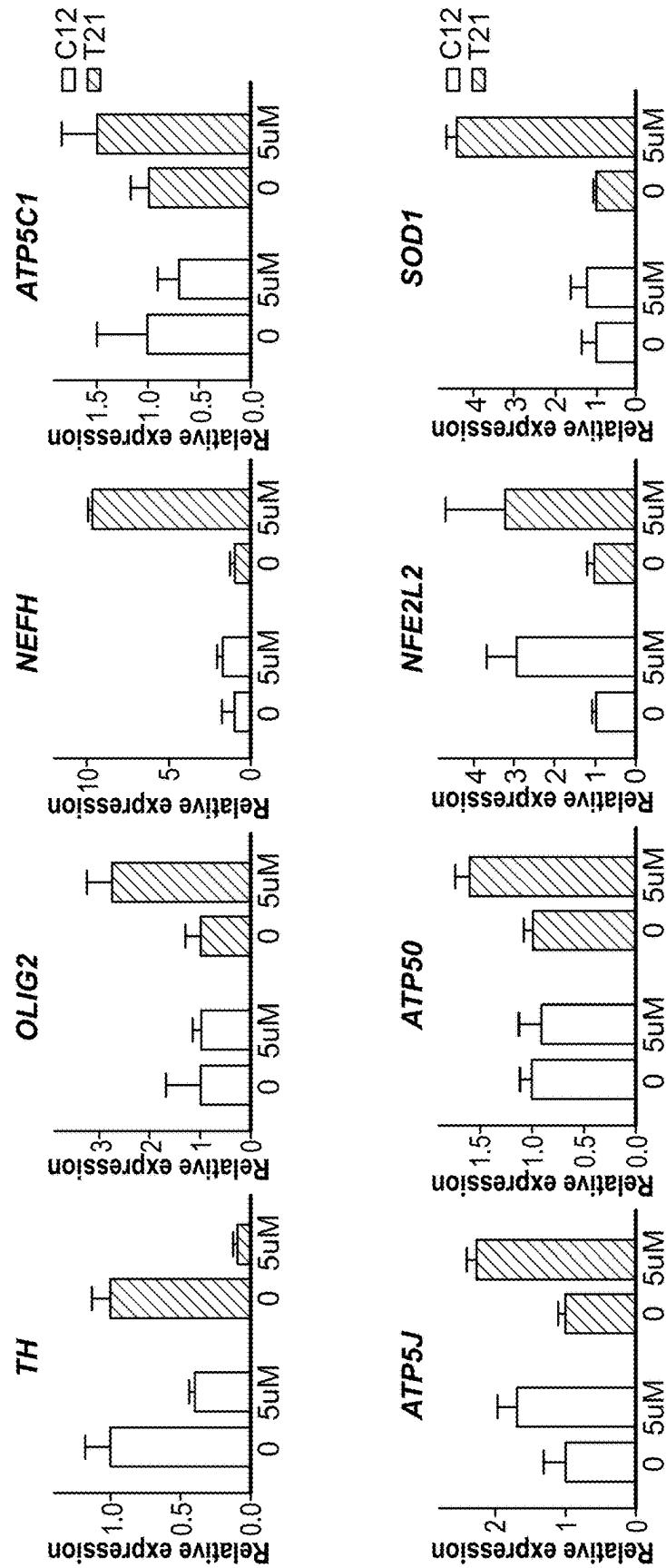


FIG. 5B

Amp/Deletion Table							Overlap Normal CNVs? β
Chr	Amp/Del	Start-Stop (bp)	Size (kb)	Chr Band	# Probes	Log2 Ratio	Genes α
2	GAIN	44,479,791-49,652,038	5,172	p21-p16.3	219	0.3280633	SLC3A1, SIX3, SIX2, PRKCE, EPAS1, PI GF, SOCS5, MCFD2, TTC7A, CALM2, MSH2, KCNK12, MSH6, FBXO11, LHC GR, FSHR, PREPL, CAMKMT, UNQ697 5, SRBD1, LOC388946, ATP6V1E2, R HOQ, CRIP, LOC388948, LOC10013 4259, C2orf61, EPCAM, MIR559, FO XN2, KLRQ1, STON1- GTF2A1L, STON1, GTF2A1L
10	GAIN	124,347,870-124,351,275	3	q26.13	6	0.782955	DMBT1
11	GAIN	54,872,150-55,032,155	160	q11	5	0.619389	TRIM48
14	GAIN	19,265,142-20,421,677	1,157	q11.2	22	0.490838	OR11H12, POTE9, POTEM, OR11H2, OR4Q3, OR4M1, OR4N2, OR4K2, O R4K5, OR4K1
14	GAIN	67,306,385-67,514,841	208	q23.3	28	0.5553366	GRHN
18	LOSS	132,387-14,158,122	14,026	p11.32-p11.21	541	-0.89217	Too Numerous
18	DEL	7,694,140-7,821,430	127	p11.23	6	-4.90876	PTPRM
18	LOSS	14,556,513-15,047,825	491	p11.21	14	-0.5347	ANKRD30B, MIR3156-2
X	GAIN	58,141,950-58,428,287	286	p11.1	9	0.478356	Yes

FIG. 5C

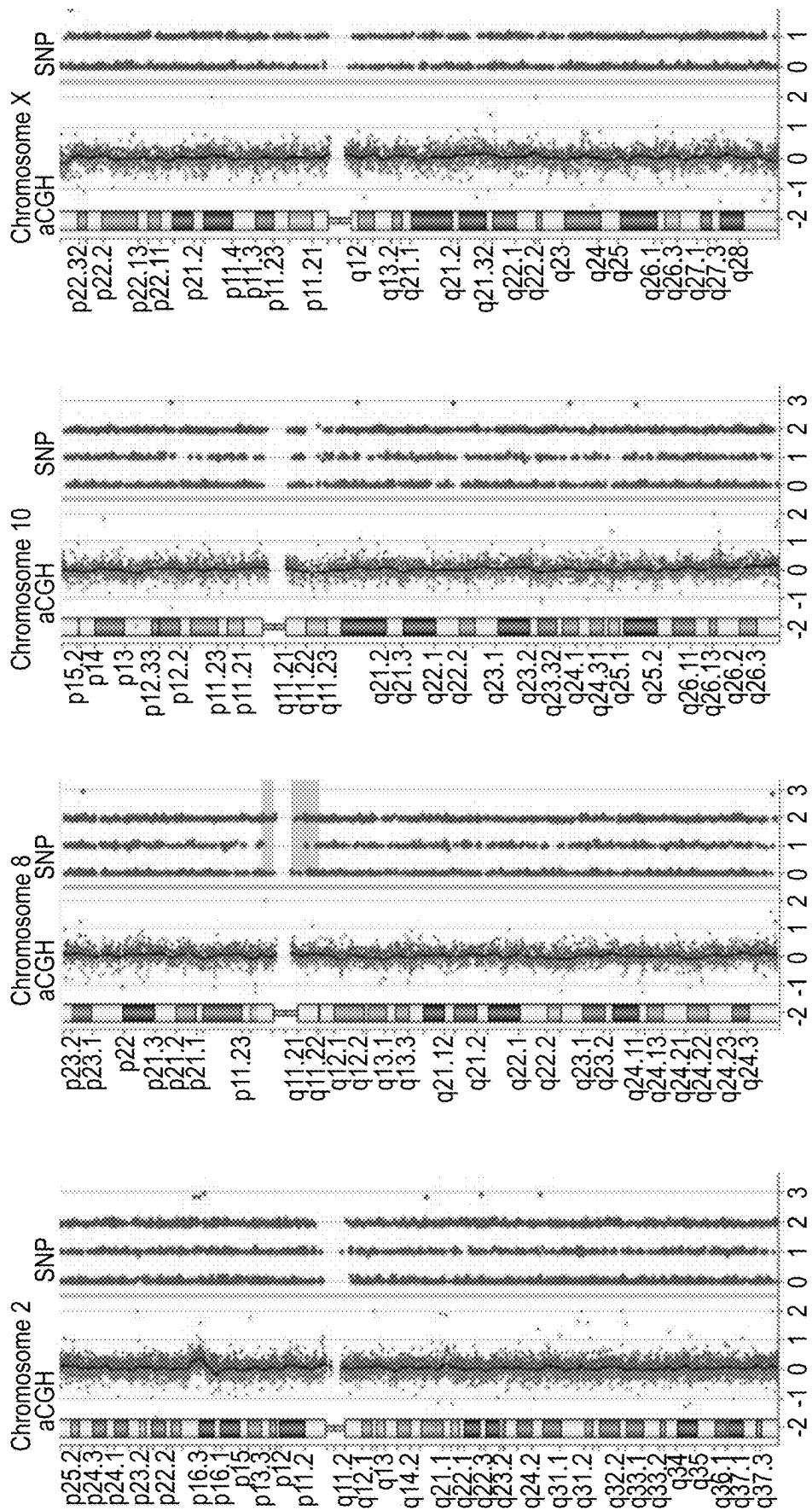
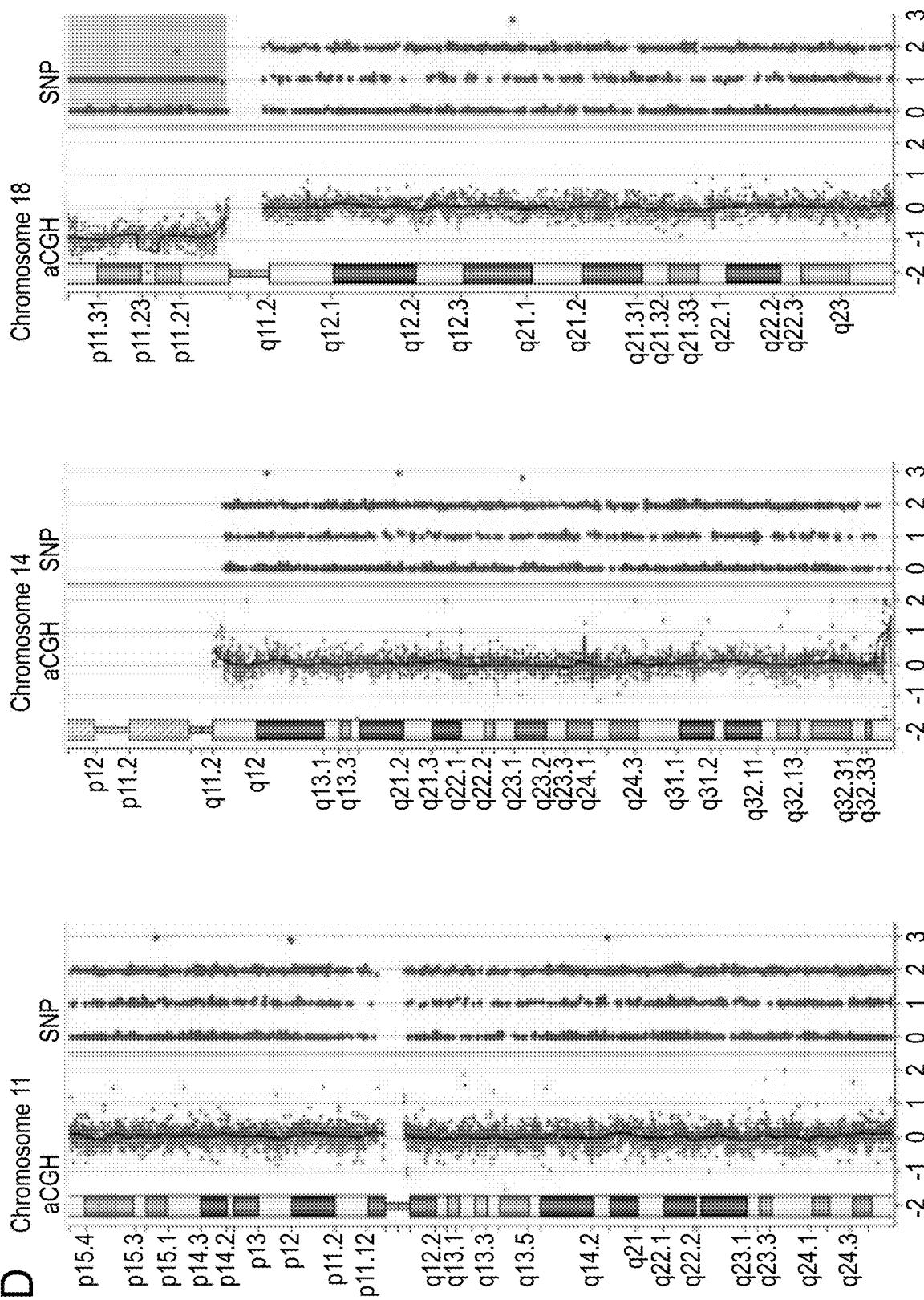


FIG. 5C (CONTINUED)

FIG. 5D



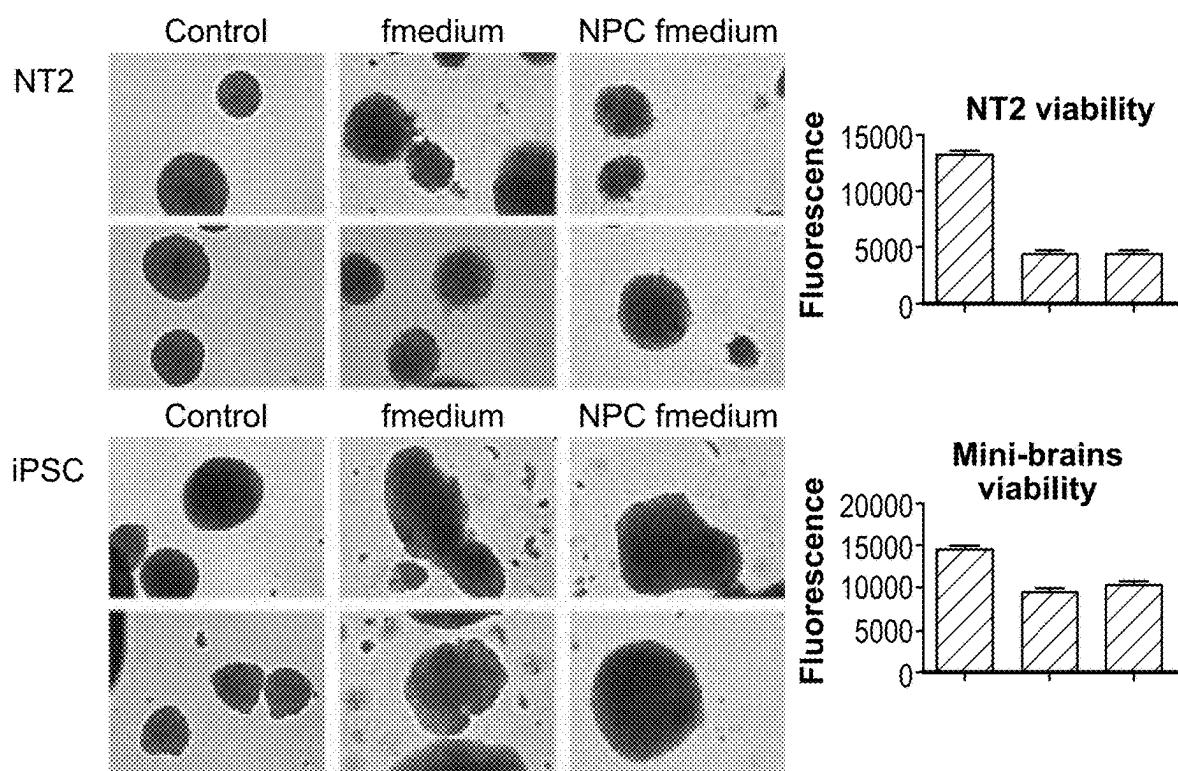


FIG. 6

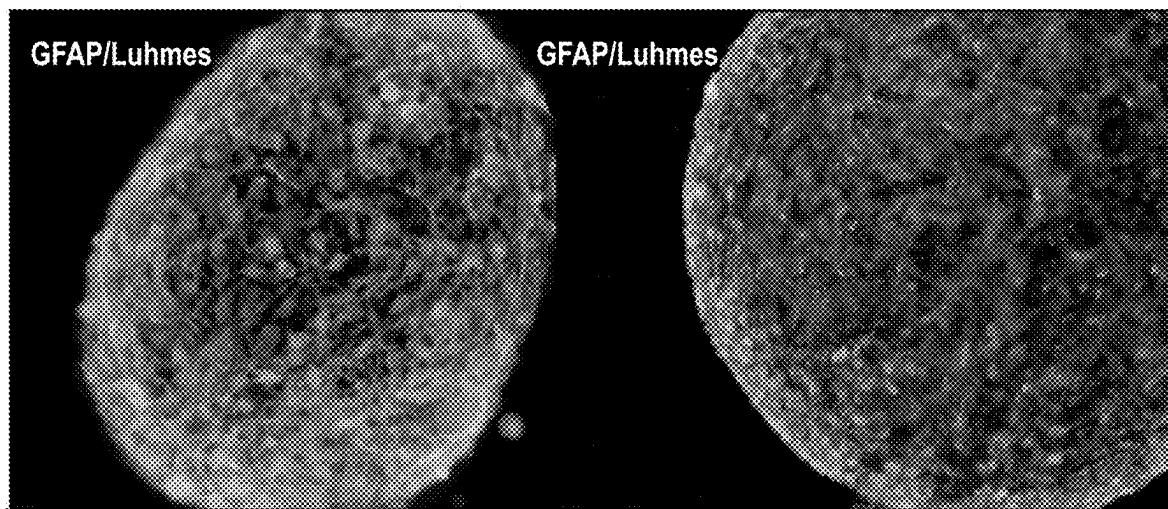


FIG. 7

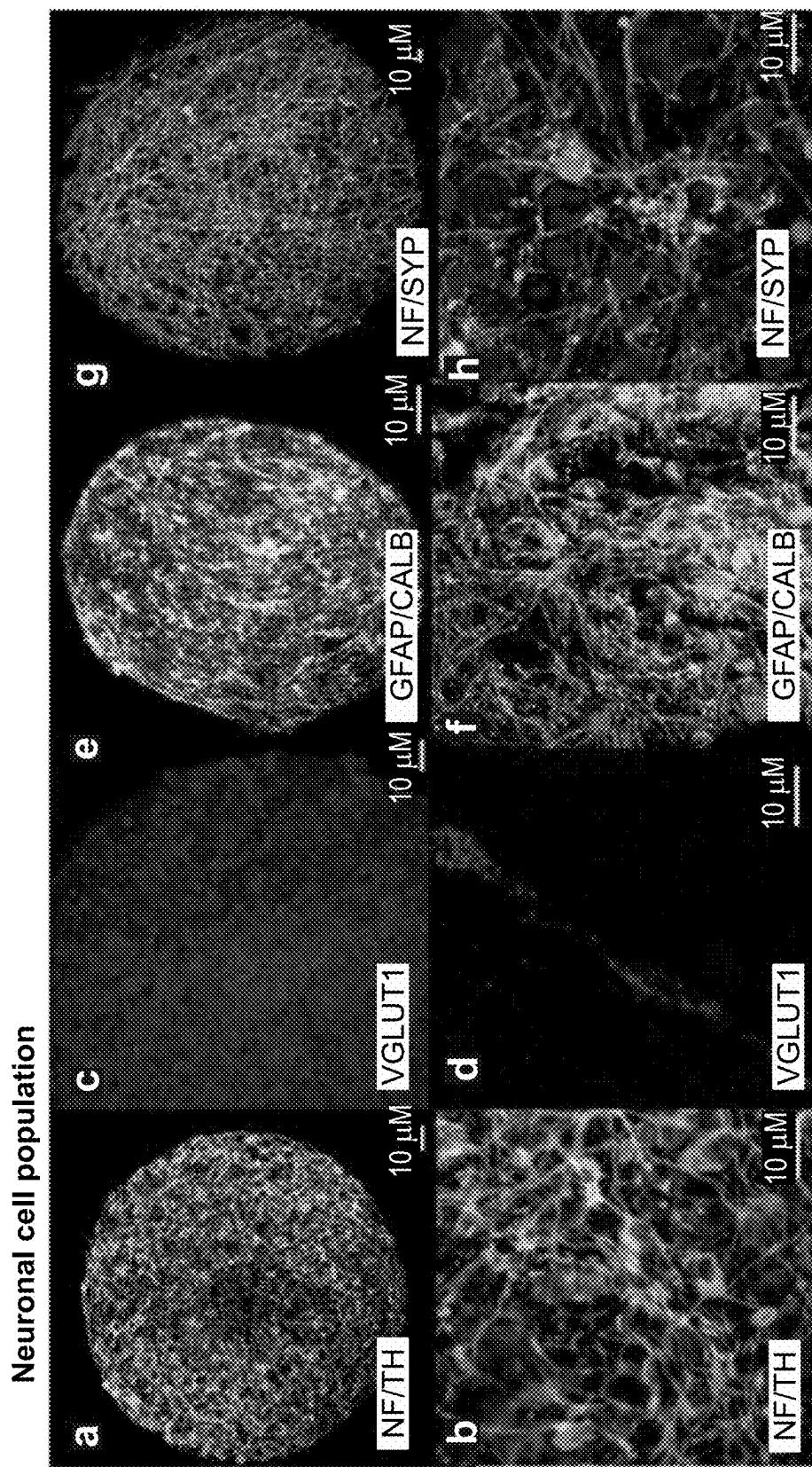


FIG. 8A

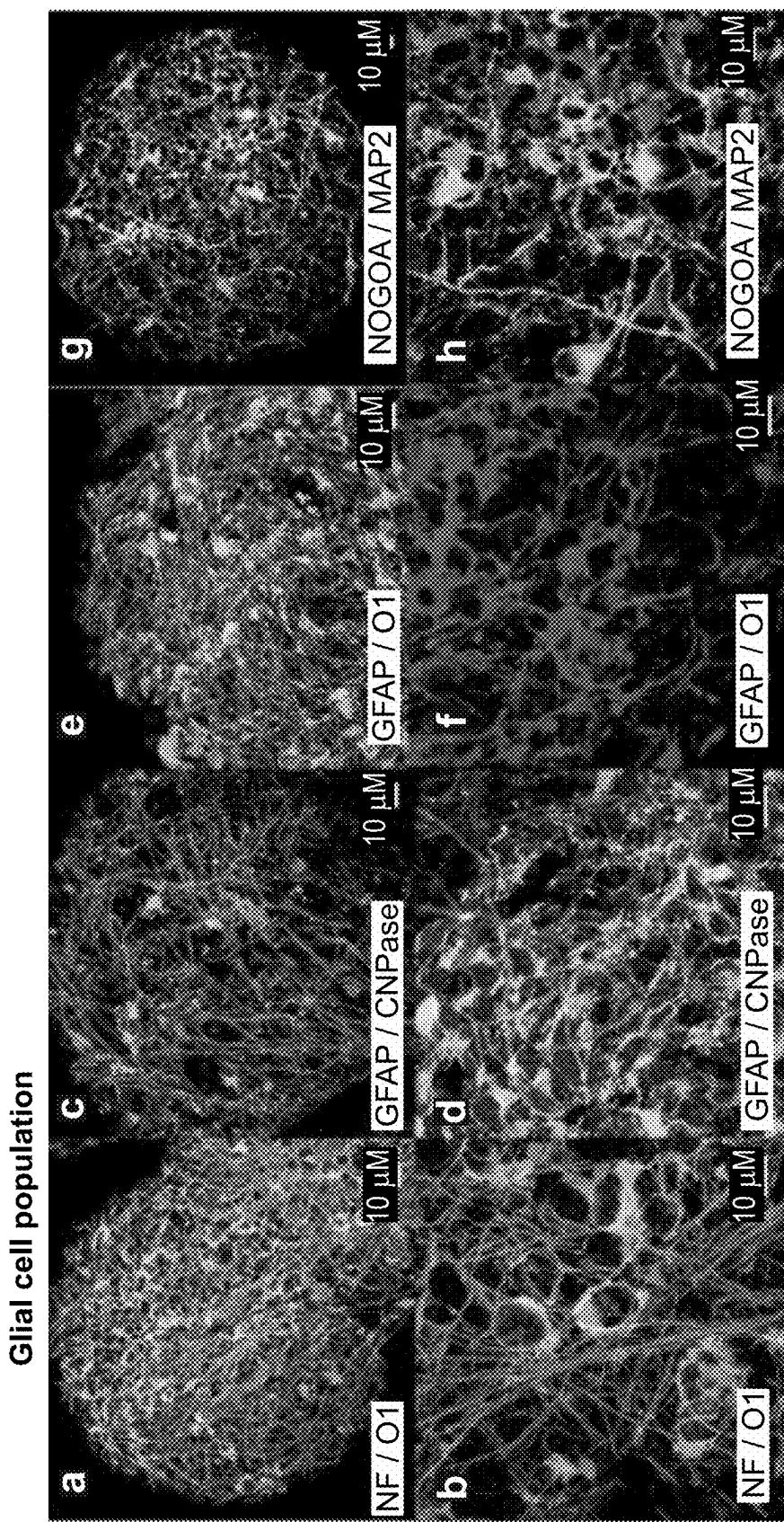


FIG. 8B

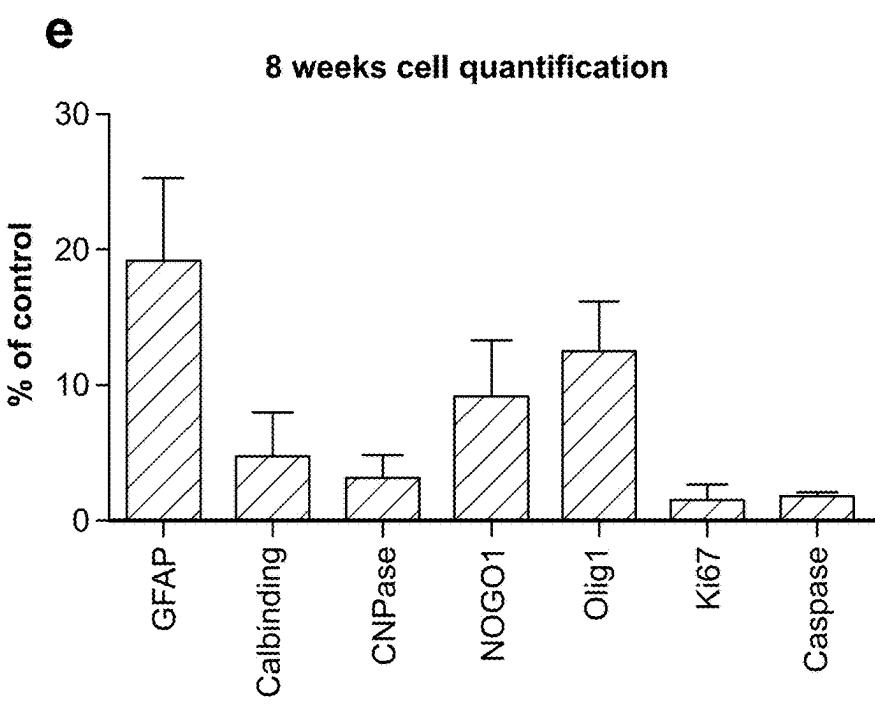
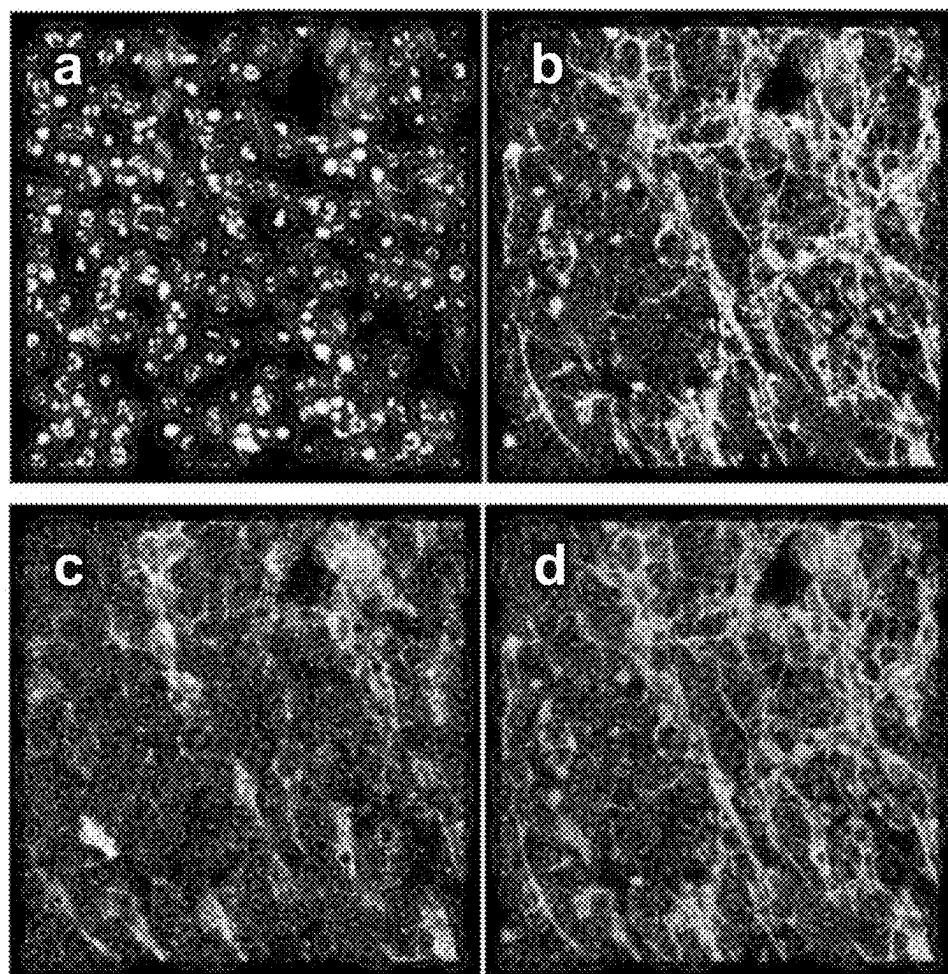


FIG. 8C

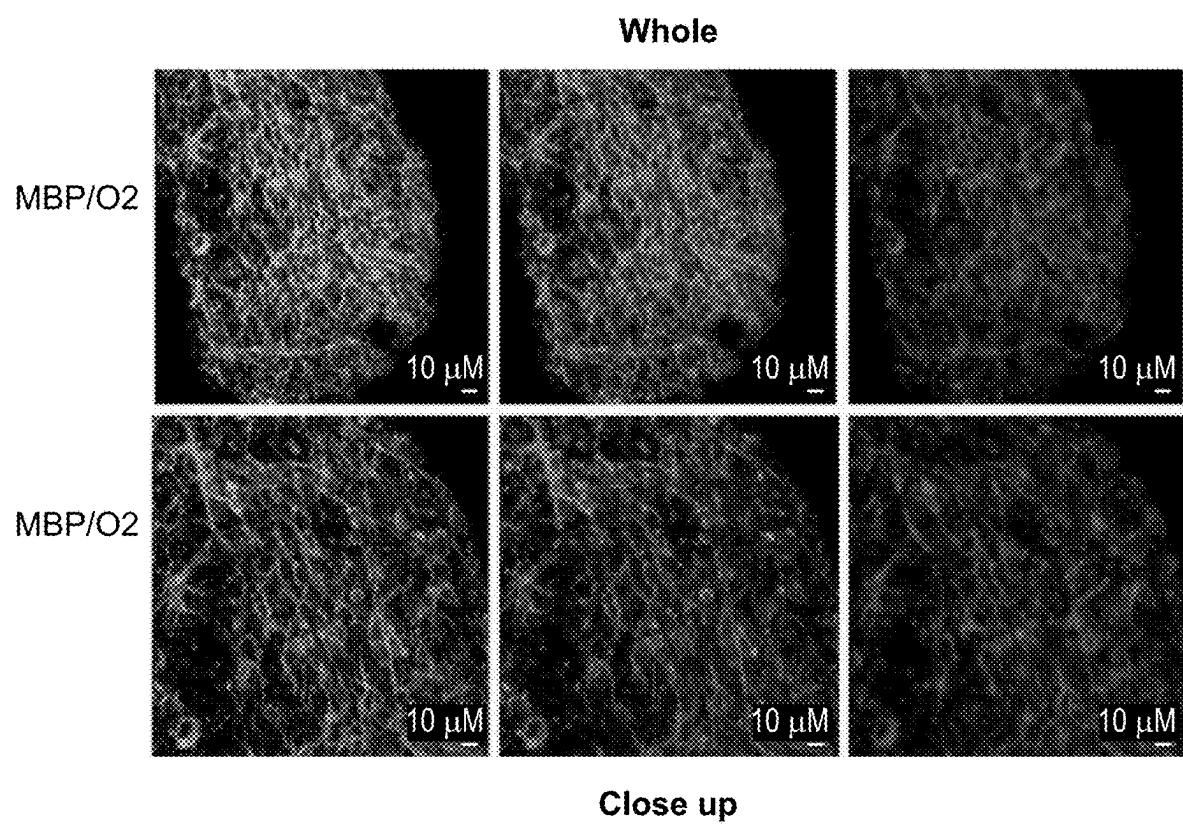


FIG. 8D

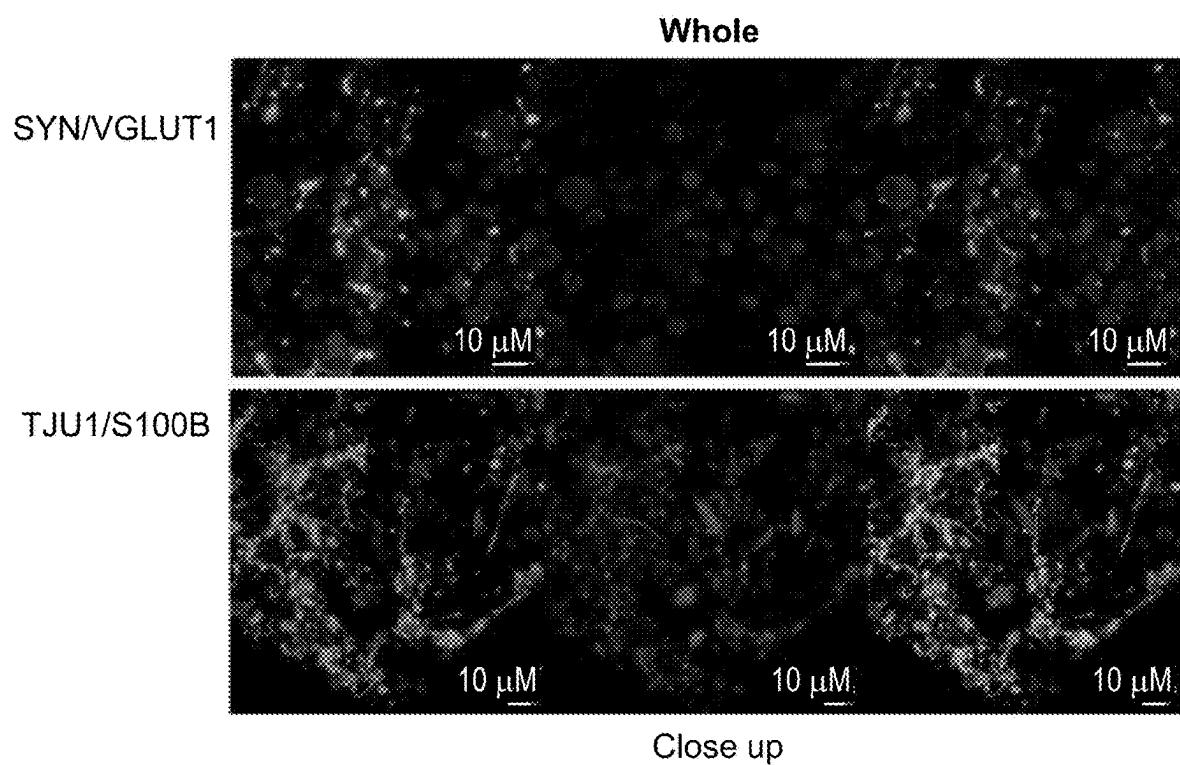


FIG. 8E

COMPOSITIONS AND METHODS FOR NEURALGENESIS

RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/294,112, filed Feb. 11, 2016, which is incorporated herein by reference in its entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] The invention was made with government support under the following grant awarded by the National Institute of Health (NIH): U18TR000547. The government has certain rights in the invention.

SEQUENCE LISTING

[0003] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Mar. 21, 2017, is named 48317-518001WO_SL.txt and is 329,024 bytes in size.

BACKGROUND OF THE INVENTION

[0004] Simple neural in vitro systems do not reflect the physiology, cellular interactions, or genetics of mammalian brain tissue. Accordingly, there is an unmet need to develop human models of brain disorders and/or diseases.

SUMMARY OF THE INVENTION

[0005] The present invention provides brain microphysiological systems (BMPS) that can be produced from induced pluripotent stem cells (iPSCs). Furthermore, the invention provides for reproducible BMPS that differentiate into mature neurons and glial cells (astrocytes and oligodendrocytes) in the central nervous system. This model is electrophysiologically active in a spontaneous manner and may be reproduced with patient cells. The derivation of 3D BMPS from iPSCs has applications in the study and treatment of neurological diseases.

[0006] In an aspect, the disclosure provides an in vitro brain microphysiological system (BMPS), comprising two or more neural cell types aggregated into a spheroid mass, wherein the spheroid mass has a diameter that is less than about 500 μm and the in vitro BMPS is electrophysiologically active in a spontaneous manner.

[0007] In an embodiment, the two or more neural cell types comprise at least a mature neuron and glial cell.

[0008] In an embodiment, the two or more neural cell types further comprise cells selected from the group consisting of astrocytes, polydendrocytes, oligodendrocytes, and combinations thereof.

[0009] In an embodiment, the in vitro BMPS has neural characteristics selected from the group consisting of synaptogenesis, neuron-neuron interactions, neuronal-glial interactions, axon myelination, and combinations thereof.

[0010] In an embodiment, two or more neural cell types of the in vitro BMPS express one or more biomarker selected from the group consisting of GRIN1, GAD1, GABA, TH, LMX1A, FOXO1, FOXA2, FOXO4, CNP, MBP, TH, TUBIII, NEUN, SLC1A6, and any combination thereof.

[0011] In an aspect, the disclosure provides a synthetic neurological organ comprising two or more neural cell types aggregated into a spheroid mass, wherein the spheroid mass has a diameter that is less than 500 μm and the in vitro BMPS is electrophysiologically active in a spontaneous manner.

[0012] In an embodiment, the two or more neural cell types comprise at least a mature neuron and glial cells.

[0013] In an embodiment, the mature neuron and glial cells further comprise cells selected from the group consisting of astrocytes, polydendrocytes, oligodendrocytes, and combinations thereof.

[0014] In an embodiment, the synthetic neurological organ further comprises neural characteristics selected from the group consisting of synaptogenesis, neuron-neuron interactions, neuronal-glial interactions, axon myelination, and combinations thereof.

[0015] In an embodiment, the synthetic neurological organ mimics the microenvironment of the central nervous system (CNS).

[0016] In an aspect, the disclosure provides a method of reproducibly producing an in vitro brain microphysiological system (BMPS), comprising: inducing one or more pluripotent stem cell (PSC) types; differentiating the one or more PSC types to form one or more neural progenitor cell (NPC) types; exposing the one or more NPC types to gyratory shaking or stirring; and differentiating the one or more NPC types into one or more neural cell types aggregated into a spheroid mass, wherein the spheroid mass has a diameter that is less than 500 μm.

[0017] In an embodiment, the one or more pluripotent stem cells are selected from the group consisting of human or animal embryonic stem cells, iPSC, adult stem cells, fibroblasts, embryonic fibroblasts, peripheral blood mono-nuclear cells, neuronal precursor cells, mesenchymal stem cells, and combinations thereof.

[0018] In an embodiment, inducing further comprises: adding micro-glia or micro-glia precursor cells.

[0019] In an embodiment, the micro-glia or micro-glia precursor cells are selected from the group consisting of monocytes, human monocytes, pro-monocyte cell lines, iPSC-derived monocytes, hematopoietic stem cells, isolated microglia, immortalized microglia, and combinations thereof.

[0020] In an embodiment, gyratory shaking comprises constant or regular gyratory shaking or stirring for 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, or 8 or more weeks.

[0021] In an embodiment, the one or more growth factors are selected from the group consisting of GDNF, BDNF, GM-CSF, B27, basic FGF, basic EGF, NGF, CNTF, and any combination thereof.

[0022] In an aspect, the disclosure provides a method of cryopreserving an in vitro brain microphysiological system (BMPS), comprising: differentiating BMPS aggregates into

one or more mature neurons; incubating the aggregates in a cryopreserving medium; and exposing the aggregates to freezing temperatures of -60° C. or colder.

[0023] In an embodiment, differentiating further comprises: inducing differentiation of one or more pluripotent stem cell types by incubation with one or more growth factors.

[0024] In an embodiment, the one or more pluripotent stem cells are selected from a group consisting of human or animal embryonic stem cells, iPSC, adult stem cells, fibroblasts, embryonic fibroblasts, peripheral blood mononuclear cells, neuronal precursor cells, mesenchymal stem cells, and combinations thereof.

[0025] In an embodiment, inducing further comprises: adding micro-glia precursor cells.

[0026] In an embodiment, micro-glia precursor cells are selected from the group consisting of monocytes, human monocytes, iPSC-derived monocytes, hematopoietic stem cells, pro-monocyte cell lines, isolated microglia, immortalized microglia, and combinations thereof.

[0027] In an embodiment, the one or more growth factors are selected from the group consisting of GDNF, BDNF, GM-CSF, B27, basic FGF, basic EGF, NGF, CNTF, and any combination thereof.

[0028] In an embodiment, the cryopreserving medium is a medium selected from the group consisting of regular cryopreservation medium (95% FBS and 5% DMSO), STEMdiff Neural Progenitor Freezing Medium (Stem Cells Technologies), solutions with cryoprotectants, and combinations thereof.

[0029] In an embodiment, exposing the aggregates to freezing temperatures further comprises freezing aggregates over a temperature gradient of about 1° C. per hour to below -60° C. over up to 48 hours.

[0030] In an embodiment, cryopreserving further comprises additives selected from the group consisting of DMSO, HES, glycerol, serum, and any combination or derivative thereof.

[0031] In an aspect, the disclosure provides a method of transporting a brain microphysiological system (BMPS) or mini-brain, comprising: producing the BMPS or mini-brain of claim 1, incubating the BMPS or mini-brain at 37° C., and maintaining the temperature at 37° C. with constant application of heat while moving the BMPS or mini-brain.

[0032] In an embodiment, maintaining the temperature comprises use of heating pads, heaters, insulation, insulated boxes, heat packs, electric blankets, chemical pads, and combinations thereof.

[0033] In an aspect, the disclosure provides a method of studying a neurological disease or disorder comprising: producing an in vitro brain microphysiological system (BMPS); exposing the in vitro BMPS to conditions that replicate or induce the neurological disease or disorder; adding an agent to treat the neurological disease or disorder; and assessing the effect of the agent on the neurological disease or disorder.

[0034] In an embodiment, the neurological disease or disorder is selected from the group consisting of neurodegenerative disorder, muscular dystrophy, Parkinson's Disease, Huntington's Disease, Autism Spectrum Disorder and other neurodevelopmental disorders, Down's Syndrome, Multiple Sclerosis, Amyotrophic lateral sclerosis, brain cancer, encephalitis, infection, trauma, stroke, and paralysis.

[0035] In an aspect, the disclosure provides a method of treating a patient having a neurological disease or disorder, comprising: extracting a stem cell from the patient with a genetic background pre-disposed for the neurological disease or disorder; producing a brain microphysiological system (BMPS) or mini-brain with the genetic background; treating the BMPS or mini-brain with an agent targeting the neurological disease or disorder; and assessing the effect of the agent on the BMPS or mini-brain.

[0036] In an embodiment, the neurological disease or disorder is selected from the group consisting of neurodegenerative disorder, muscular dystrophy, Parkinson's Disease, Huntington's Disease, Autism Spectrum Disorder and other neurodevelopmental disorders, Down's Syndrome, Multiple Sclerosis, Amyotrophic lateral sclerosis, brain cancer, encephalitis, infection, trauma, stroke, and paralysis.

[0037] In an embodiment, the BMPS includes two or more neuronal cell types that include one or more genetically modified cells. The BMPS wherein the one or more genetically modified cells include one or more reporter genes. The BMPS further comprises one or more endothelial cells capable of forming a blood-brain-barrier.

[0038] In an embodiment, the synthetic neurological organ may include two or more neural cell types that include one or more genetically modified cells. The synthetic neurological organ including one or more genetically modified cells that include one or more reporter genes. The synthetic neurological organ further comprising one or more endothelial cells capable of forming a blood-brain-barrier.

[0039] In an aspect, the disclosure provides a method of reproducibly producing an in vitro brain microphysiological system (BMPS), comprising: exposing one or more NPC types to gyratory shaking or stirring; and differentiating the one or more NPC types into one or more neural cell types aggregated into a spheroid mass, wherein the spheroid mass has a diameter that is less than 500 μm.

[0040] In an embodiment, the spheroid mass has a diameter that is less than about 450 μm, 400 μm, 350 μm, or 300 μm, or a diameter that is between about 350 μm and about 300 μm, or a diameter that is between about 330 μm and about 300 μm, or a diameter that is about 310 μm.

[0041] In an embodiment, the two or more neural cell types of the in vitro BMPS express one or more biomarker selected from the group consisting of GRIN1, GAD1, GABA, TH, LMX1A, FOXO1, FOXA2, FOXO4, CNP, MBP, TH, TUBIII, NEUN, SLC1A6, and any combination thereof.

[0042] In an embodiment, the two or more neural cell types of the in vitro BMPS express one or more biomarker selected from the group consisting of GRIN1, GAD1,

GABA, TH, LMX1A, FOXO1, FOXA2, FOXO4, CNP, MBP, TH, TUBIII, NEUN, SLC1A6, and any combination thereof.

[0043] In an embodiment, the two or more neural cell types of the in vitro BMPS express one or more biomarker selected from the group consisting of GRIN1, GAD1, GABA, TH, LMX1A, FOXO1, FOXA2, FOXO4, CNP, MBP, TH, TUBIII, NEUN, SLC1A6, and any combination thereof.

[0044] In an embodiment, inducing comprises a single PSC.

[0045] In an embodiment, the an in vitro brain microphysiological system (BMPS) may be produced according to the above described method.

[0046] It is also contemplated within the scope of the invention that the addition of other cells inside (see e.g., FIG. 6) and outside (see e.g., FIG. 7) the BMPS may be used to modify the structure/composition of the BMPS, such as, e.g., by forming a blood-brain-barrier. It is also contemplated that the BMPS described herein may include genetically modified pluripotent stem cells, or be combined with other organoids (see e.g., Example 11).

Definitions

[0047] By "agent" is meant any small compound, antibody, nucleic acid molecule, or polypeptide, or fragments thereof.

[0048] By "alteration" is meant a change (increase or decrease) in the expression levels or activity of a gene or polypeptide as detected by standard art known methods such as those described herein. As used herein, an alteration includes a 10% change in expression levels, preferably a 25% change, more preferably a 40% change, and most preferably a 50% or greater change in expression levels.

[0049] By "ameliorate" is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

[0050] In this disclosure, "comprises," "comprising," "containing," and "having" and the like may have the meaning ascribed to them in U.S. Patent law and may mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0051] "Detect" refers to identifying the presence, absence or amount of the analyte to be detected.

[0052] By "effective amount" is meant the amount of an agent needed to ameliorate the symptoms of a neurological disease relative to an untreated patient. The effective amount of active agent(s) used to practice the present invention for therapeutic treatment of a neurological disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

[0053] By "fragment" is meant a portion of a polypeptide or nucleic acid molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nucleotides or amino acids, or more.

[0054] By "gene" is meant a locus (or region) of DNA that encodes a functional RNA or protein product, and is the molecular unit of heredity.

[0055] By "marker" is meant any protein or polynucleotide having an alteration in expression level or activity that is associated with a disease or disorder.

[0056] By "modulate" is meant alter (increase or decrease). Such alterations are detected by standard art known methods such as those described herein.

[0057] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9.

[0058] With respect to sub-ranges, "nested sub-ranges" that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

[0059] By "reduces" is meant a negative alteration of at least 10%, 25%, 50%, 75%, or 100%.

[0060] By "reference" is meant a standard or control condition.

[0061] By "pluripotency" is meant stem cells with the potential to differentiate into any of the three germ layers: endoderm (e.g., interior stomach lining, gastrointestinal tract, the lungs), mesoderm (e.g., muscle, bone, blood, urogenital), or ectoderm (e.g., epidermal tissues and nervous system). However, one of skill in the art will understand that cell pluripotency is a continuum, ranging from the completely pluripotent cell that can form every cell of the embryo proper, e.g., embryonic stem cells and iPSCs (see below), to the incompletely or partially pluripotent cell that can form cells of all three germ layers but that may not exhibit all the characteristics of completely pluripotent cells. Induced pluripotent stem cells, commonly abbreviated as iPSCs are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of certain genes and transcription factors. These transcription factors play a key role in determining the state of these cells and also highlight the fact that these somatic cells do preserve the same genetic information as early embryonic cells. The ability to induce cells into a pluripotent state was initially pioneered using mouse fibroblasts and four transcription factors, Oct4, Sox2, Klf4 and c-Myc; —a process called reprogramming. The successful induction of human

iPSCs derived from human dermal fibroblasts has been performed using methods similar to those used for the induction of mouse cells. These induced cells exhibit similar traits to those of embryonic stem cells (ESCs) but do not require the use of embryos. Some of the similarities between ESCs and iPSCs include pluripotency, morphology, self-renewal ability, a trait that implies that they can divide and replicate indefinitely, and gene expression.

[0062] By "stem cells" is meant undifferentiated biological cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells. They are found in multicellular organisms. In mammals, there are two broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. In a developing embryo, stem cells can differentiate into all the specialized cells—ectoderm, endoderm and mesoderm (see induced pluripotent stem cells)—but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. There are three known accessible sources of autologous adult stem cells in humans: 1. Bone marrow, which requires extraction by harvesting, that is, drilling into bone (typically the femur or iliac crest). 2. Adipose tissue (lipid cells), which requires extraction by liposuction. 3. Blood, which requires extraction through apheresis, wherein blood is drawn from the donor (similar to a blood donation), and passed through a machine that extracts the stem cells and returns other portions of the blood to the donor. Stem cells can also be taken from umbilical cord blood just after birth. Of all stem cell types, autologous harvesting involves the least risk. By definition, autologous cells are obtained from one's own body.

[0063] By "subject" is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, or feline.

[0064] As used herein, the terms "treat," "treating," "treatment," and the like refer to reducing or ameliorating a neurological disorder and/or symptoms associated therewith. It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

[0065] As used herein, the terms "prevent," "preventing," "prevention," "prophylactic treatment" and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

[0066] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a," "an," and "the" are understood to be singular or plural.

[0067] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

[0068] A "therapeutically effective amount" is an amount sufficient to effect beneficial or desired results, including clinical results. An effective amount can be administered in one or more administrations.

[0069] By "GRIN1 polypeptide" (or glutamate ionotropic receptor NMDA type subunit 1) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q05586.

(SEQ ID NO: 1)
 1 mstmrltlta l1fscsvara acdpkivnig avlstrkheq mfrevangnq krhgswkigl
 61 natsvthkpn a1qmalsvce dlissqvyai lvshppptnd hftptpvsyt agfyripvlg
 121 lttrmsiysd ksihlsflrt vppyshqssw wfemmrlysw nhiillvsdd hegraaqkrl
 181 etlleeresk aekvlqfdpg tknvtallme akelearvii lsaseddaat vyraaamlnm
 241 tgsgyvvwlvg ereisgnalr yapdqgilqlq lingknesah isdavgvvaq avhelleken
 301 itdpprgcvg ntiniwktgpl fkrvlmssky adgvtgrvef nedgdrkfan ysimmlqnrk
 361 lvqvgiyngt hvipndrkii wpggetekpr gyqmstrlki vtihqepfv ykp tlsdgdc
 421 keeftvngdp vkkvictgpn dtspgsprht vpqccygfc1 dliklartm nftyevhlva
 481 dgkfgtqerv nnsnkkekng mmgellsgqa dmivapltin neraqyiefs kpfkyqglti
 541 lvkkeiprst ldsfmqpfqs tlwllvgles hvavmlyll drfspfgrfk vnseeeeeda
 601 ltssamwfs wgvllnsgig egaprsfsar ilgmvwagfa miivasylan laafvlldr
 661 eeritgindp rlrnpdsdkfi yatvkqssvd iyfrqrvels tmyrhmekhn yesaaeaiqa
 721 vrdnk1hafi wdsavlefea sqkcdlvttg elffrsgfqi gmrkdspwkq nvslsilksh
 781 engfmedldk twvryqecd s snapatltf enmagvfmlv aggivagifl ifieiaaykrh
 841 kdarrkqmql afaavnvwk nlqdrksgra epdpkkatf raitstlass fkrrrsskdt
 901 stgggrgalq nqkdtvlpr aiereegqlq lcsrhres

[0070] By "GRIN1 nucleic acid molecule" (or glutamate ionotropic receptor NMDA type subunit 1) is meant a polynucleotide encoding an GRIN1 polypeptide. An exemplary GRIN1 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_007327.

(SEQ ID NO: 2)

1 gtcggccgag cgtccggacc ggaaccagcg ccgtccgggg agccgcggcc gccgcggccg
61 ggcccttcc aagccgggcg ctccggagctg tgccggggcc cgcttcagca ccggggacag
121 cgccggccgc gtggggctga gccccgagcc cccgcgcacg cttcagcgcc ctccctcg
181 gcccacgtcc cgggacccgcg getccgggggg agacgtggcg tccgcagccc gccccggccg
241 gcgacgcacg gacggcccgaa aagecccgccg gggatgcgcg cgaggccccc gcgttcgcgc
301 cgccgcacgc caggccgcg gccccggcc atgagcacca tgccctgtct gacgctcgcc
361 ctgctgttct cctgctccgt cggccgtgcgacc ccaagatcgt caacatttgc
421 ggggtgtga gcaacgggaa gcaacgagc atgttccgcg aggccgtgaa ccaggccaac
481 aagccggacgc gctccctggaa gattcagctc aatgccaccc cccgtcagca caagcccaac
541 gccatccaga tggctctgtc ggtgtgcgag gacccatctt ccagccaggctt ctacgcccatt
601 ctatgttgcgat atccacactac ccccaacgcac cacttcactc ccacccctgt ctccctacaca
661 gccggcttctt accgcataacc cgtgtgggg ctgaccaccc goatgtccat ctactcgac
721 aagagcatcc accttagctt cctggccacc gtcggccctt actccacca gtcggccgt
781 tggtttggaa tggatgtgtt ctacagctgg aaccacatca ttctgttgtt cagcgacgc
841 cacgaggggcc gggccggctca gaaacgcctg gagacgtgc tggaggagcg tgagtccaaag
901 gcacagaagg tgctgcgtt tgaccaggacc accaagaacgc tgacggccctt gctgtggag
961 gcaaaaggac tggaggcccg ggtcatcattt ctttctgcctt gcaaggacgc tgctgcact
1021 gtataccgcg cagccgcgtt gctgaacatgc acgggcctcg ggtacgtgtt gctggctggc
1081 gagcgcgaga tctcgggaa cggccgtgcgta taacggccatcc cgggatgcg
1141 ctcatcaacgc gcaagaacgc gtcggccacatc atcagcgacgc ccgtggccgtt ggtggccag
1201 gccgtgcacgc agctccctcgaa gaaggagaac atcaccgcacc cggccggggg ctggcggt
1261 aacaccaaca tctggaaagac cggccgcctt ttcaagagatg tgctgtatgtt ttccaagtat
1321 gggatgggg tggatggcg cgtggatgtt aatgaggatg gggaccggaa gtcggccaaac
1381 tacagcatca tgaacctgca gaacgcctt cttggatgc tggcatctt caatggccacc
1441 cacgtcatcc ctaatgcacgc gaaatgcattt tggccaggccg gagagacaga gaagectcg
1501 gggtaaccaga tgtccaccatc actgaagatt gtgacgttcc accaggagcc ctctgtgtac
1561 gtcaaggccca cgctgtgtt gggacatgc aaggaggatg tcacagtcaa cggccaccc
1621 gtcaagaagg tgatctgcac cggcccaac gacacgtgcg cggccaggccc cggccacacg
1681 gtgccttgcgtt gttgttgcattt gacccatgc tcaagctggc acggaccatg
1741 aacttcaccc acggatgtca cctggatggca gatggcaatgt tcggcacaca ggagcgggt
1801 aacaacacca acaagaaggaa gtggaaatggg atgtatggcg agctgttcag cggccaggca
1861 gacatgtatgc tggcgccgc aaccataaac aacgagcgccg cgcagatcatc cgatgtttcc
1921 aagcccttca agtaccagggtt cctgtactattt ctggatgc aaggatgttcc cggccacacg
1981 ctggacttgcgtt tcatgcagcc gttccaggcc acactgtggc tggatgttggg gtcgtcggt
2041 cacgtgggtgg ccgtgtatgtt gttacccgttgc gaccgttca gcccttcgg cccgttcaag

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2101 gtgaacagcg aggaggagga ggaggacgca ctgaccctgt cctccggccat gtggttctcc
2161 tggggcgtcc tgctcaactc cgccatcggg gaaggcgccc ccagaagctt ctcagcgcgc
2221 atccctgggca tggtgtggc cggtttgcc atgatcatcg tggccctcta caccgccaac
2281 ctggcggccct tccctgggtct ggaccggccg gaggagcgca tcacggccat caacgaccct
2341 cggtcgagga accccctcgga caagtttatc tacgccacgg tgaagcagag ctccgtggat
2401 atctacttcc ggcgcaggt ggagctgago accatgtacc ggcataatgga gaagcacaac
2461 tacgagagtg cggcggaggc catccaggcc gtgagagaca acaagctgca tgccttcata
2521 tgggactcgg cgggtgtggta gtteggagggc tccgtcagaatgtt gogacctgggt gacgactgg
2581 gagctgtttt tccgtctggg ctteggcata ggcatgcgca aagacagccc ctggaaagcag
2641 aacgtctccc tgcctatcct caagtccac gagaatggct tcatggaaga cctggacaag
2701 acgtgggttc ggtatcagga atgtactcg cgcagcaacg cccctgcgac ccttactttt
2761 gagaacatgg ccggggctt catgtggta gctggggca tgcgtggccgg gatttccctg
2821 attttcatcg agattgccta caagggcac aaggatgctc gccggaaagca gatgcagctg
2881 gcctttgccc ccgttaacgt gtggcggaaag aacctgcagg atagaaagag tggtagagca
2941 gacccctgacc ctaaaaagaa agccacattt agggctatca cctccaccct ggcttccagc
3001 ttcaagagggc gtaggtcctc caaagacacg agcacccggg gtggacgcgg cgctttgcaa
3061 aacccaaaag acacagtgtc gcccgcacgc gctattgaga gggaggaggg ccagctgcag
3121 ctgtgttccc gtcataaggaa gagctgagac tccccggccg ccctctctg cccctcccc
3181 cgcagacaga cagacacacg gacgggacag cggccggcc cacgcagagc cccggagcac
3241 cacggggtcg ggggaggagc accccacggc tccccggc tgcgtgtccgc cgccggccgg
3301 ttggccggctt ggccggcata ccccgcccg gccccggc tgcggccgcgtt gttggctaa
3361 cggccgcctt gtctgtgtat ttctatttt cagcagtacc atcccactga tatcacgggc
3421 ccgtcaacc tctcagatcc ctccggcagc accgtgggtt gaggccccgg gaggeggccca
3481 cctgcccagt tagccggcc aaggacactg atgggtctcg ctgctcggga aggctgagg
3541 gaagccacc cggcccccggc actgcccacc ctggccctcc cgtccgtccg cccggccacc
3601 ccgtcgccgt gggggcagcc cctgtggac caaggtgcgg accggagcgg ctgaggacgg
3661 ggcagagctg agtcggctgg gcagggccgc agggcgctcc ggcagaggca gggccctggg
3721 gtctctgagc agtggggagc gggggctaac tggcccccagg cggaggggtt tggagcagag
3781 acggcagccccc catccttccc gcagcaccag cctgagccac agtggggcccc atggccccag
3841 ctggctgggtt cggcccttcc cggccgcctt cgtccctctg cagcctgagc tccaccctcc
3901 cctcttcttgc cggcaccggcc caccacacc ccgtctggcc cttgacccca cacggccgggg
3961 ctggccctgc cctcccccac ggccgtccct gacttccctg ctggcagcgc cttccggccgc
4021 ctggccggcc ctcctccaga ctggagaggg ctggcccttcc cttctctcg tccggccctgc
4081 agcccaacac gggcctcccc gggggctccc ggacgctggc tggggactgtt cttaaccct
4141 gccctgcacc ttgggcacgg gagagcgcca cccggccggcc cccggccctcg ctccgggtgc
4201 gtgaccggcc cggccacccatc tacagaacca gcactccag ggccggagcgc cgtgccttcc
4261 ccgtcgccgc cgtgcgcagc cgcgtctgc ccctccgtcc ccagggtgc ggcgcgcacc
4321 gcccaaccccc caccctccgg tggatgcagt ggtgatgcct aaaggaatgt cacgcagttt
4381 taaaaaaaaaaaaaaa

[0071] By "GAD1 polypeptide" (or glutamate decarboxylase 1) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q99259.

(SEQ ID NO: 3)
 1 masstpsssa tssnagadpn ttlnlrpttyd twcgvahgct rklglkicgf lqrtnsleek
 61 srlvsafker qssknllsce nsdrdarfrr tetdfsnlfa rdllpkngc eqtvqfllev
 121 vdillnyvrk tfdrstkvld fhhphqlleg megfnlelsd hpesleqilv dcrdtlkvgv
 181 rtghprffnq lstgldiigl agewtstan tnmfteyiaap vfvlmeqitl kkmreivgws
 241 skdgdgifsp ggaisnmysi maarykyfpe vktkgmaavp klvlftseqs hysikkagaa
 301 lgfgtdnvil ikcnergkii padfeakile akqkgyvpfy vnatagttvy gafdpiqueia
 361 dicekynlw1 hvdaawgggl lmsrkhrlkl ngieransvt wnphkmmgvl lqcsailvke
 421 kgilqgcnqm cagylfqpdk qydvsydtgd kaiqcgrov ifkfwmwka kgtvgfenqi
 481 nkclelaeyl yaknreef emvfngpeh tnvcfwyipq slrgvpdspq rrekhkvap
 541 kikalmmesg ttmvgyqpqq dkanffrmvi snpaatqsd1 dfliieierl ggdl

[0072] By "GAD1 nucleic acid molecule" (or glutamate decarboxylase 1) is meant a polynucleotide encoding an GAD1 polypeptide. An exemplary GAD1 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC036552.

(SEQ ID NO: 4)
 1 agcgtgtggc agaggagaaa cgctgaaacc ggaccgaaac ctgcctctag gcttagcgat
 61 ggctaaaaac cggctgggac aagagggagg caagcaacat tccgactcgc tgctttctgg
 121 ctgtctggag tgcaaggta ctgtggttct tctctggcca agtccgaggg agaacgtaaa
 181 gatatgggcc tttttccccc tctcaccttg tctcaccaaa gtccctagtc cccggagcag
 241 tttagccttct tttttccagg gaattagcca gacacaacaa cgggaaccag acaccgaacc
 301 agacatgccc gccccgtgcg ccctcccccc gctggccac acgcccggctg ctgagtgc
 361 aatggggctt gtagcggctc ggctggaaaa tcgcactactg agcgctcccc tgcgtctcta
 421 gcccagttccc ccacacccctt gcgtttgtt ctggccttgg acccccaccc cgaccccgac
 481 cccgcctcgat ctcggcgctt cactccaggat cgccgcgtat caccgcaga ctcgagagcg
 541 gcccaggctt acgctccctg cgccccagta ccggagctag cgccgcacgtc tcctccgctg
 601 ccccccaccc tgcgcacccc taccaggccg gctcgctgc ttccctccctt ctgtctctc
 661 cagagccgga tcttcaaggg gagcctccgt gccccggct gtcagtccc tccggtgtgc
 721 aggaccccccgg aagtccccc cgcacagctc tcgtttctt ttgcagectg tttctgcgcc
 781 ggaccaggctg aggactctgg acagtagagg cccggggacg accgagctga tggcgtttc
 841 gaccccatct tcgtccgcaa cctccctcgaa cgccggagcg gaccccaata ccactaacct
 901 ggcgcacca acgtacgata cctggcggcg cgtggcccat ggatgcacca gaaaactggg
 961 gctcaagatc tgcggcttct tgcacaggac caacagcctg gaagagaaga gtcgcctgt
 1021 gagtgcccttc aaggagaggc aatccctccaa gaaacctgtt tcctgtgaaa acagcgcaccc
 1081 ggatgcccgc ttccggcgca cagagactga cttctcta at ctgtttgtca gagatctgt
 1141 tccggctaaag aacggtgagg agcaaaccgt gcaattcctc ctggaaagtgg tggacatact
 1201 cctcaactat gtccgcaga catttgatcg ctccaccaag gtgctggact ttcatcaccc
 1261 acaccagttg ctggaggca tggagggctt caacttggag ctctctgacc accccgagtc

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1321 cctggagcag atccctggttg actgcagaga caccttgaag tatggggttc gcacaggta
1381 tcctcgattt ttcaccgc tctccactgg attggatatt attggccttag ctggagaatg
1441 gctgacatca acggccaata ccaacatgtt tacatatgaa attgcaccag tgtttgctt
1501 catggAACAA ataacactta agaagatgag agagatagt ggatggtaa gtaaagatgg
1561 tggatggata ttttctcctg ggggcGCCat atccaacatg tacagcatca tggctgctcg
1621 ctacaAGTAC ttcccggaaag ttaagacaaa gggcatggcg gctgtgccta aactggctt
1681 cttcacCTCA gaacagagtc actattccat aaagaaaagct ggggctgcac ttggctttgg
1741 aactgacaat gtgatttga taaagtgc当地 taaaaggggg aaaataattc cagctgattt
1801 tgaggcaaaa attcttgaag ccaaACAGAA gggatATGTT ccctttatg tcaatgcAAC
1861 tgctggcAcg actgtttatg gagctttga tccgatacaa gagattgcag atatatgtga
1921 gaaatataac ctttggttgc atgtcgatgg atttaacttc tcacaattgg ccaataggat
1981 catctgcctt gctactgaac taatgactaa caaaggctgt gtcacgtggc atcccaacta
2041 ttcagtaaac atgcatcatg gctgcctggg gaggtggcgt gctcatgtcc aggaagcacc
2101 accataaact caacgcata gaaaggGCCa actcagtca cttggAACCCt cacaagatga
2161 tgggcgtgct gttcgagtgc tctgcatttcc tcgtcaagga aaagggtata ctccaaggat
2221 gcaaccagat gtgtgcagga taccttttcc agccagacaa gcagtatgtat gtccttacg
2281 acaccgggaa caaggaattt cagtggtggc gcccacgtgg tatcttcaag ttctggctga
2341 tgtggaaagc aaaggcaca gtgggatttggaaaaccagat caacaaatgc ctggaaactgg
2401 ctgaataacct ctatgcAAG attaaaaaca gagaagaattt tgagatggtt ttcAatggcg
2461 agcctgagca cacaacgc ttttttggatattccaca aagcctcagg ggtgtgccag
2521 acagccctca acgacgggaa aagctacaca aggtggctcc aaaaatcaaa gcccgtatga
2581 tggagttagg tacgaccatg gttggctacc agccccaaagg ggacaaggcc aacttttcc
2641 ggtggctat ctccaaacca gcccgtaccc agtctgacat tgacttcctc attggaggaga
2701 tagaaagact gggccaggat ctgtaatcat ctttcgcaga acatgagttt atggaaatgc
2761 cttttccctc tggcaactcca gaacaaacct ctatgttg ctggaaacaca caggccattt
2821 cattgaggga aaacataata tcttgaagaa tattgttaaa accttactta aagcttgg
2881 gttcttagtta gcagggaaaat gttttttttt taaaagggtt cacattagga acagagtata
2941 tatgtacagt tatacataacc tctctctata tatacatgtt tagtgagtgt ggcttagtaa
3001 tagatcacgg cttttccc gtcaccaagg aatttactttt accttcagca gttaccgagg
3061 agctaaacat gtcaccaacc agcttgcata acaactccag gaaaactgtt tttcaaaacg
3121 ccatgtccta ggggcacagg gaaatgtgt tggtgagaat cgacccact gtcacgttt
3181 ctccacctga agtgcgtatg gatgagaaaa aacaccacca aatgacaagt cacaccctcc
3241 ccatttagtat cctgttaggg gaaaatagta gcagagtcat tggtacaggt gtactatggc
3301 tgtatTTTA gagattaattt tgtgttagatt gtgtaaattt ctgttgtctg accttgg
3361 tgggggggggg agactatgtg tcatgatTC aatgattgtt taattgttagg tcaatgaaat
3421 atttgcttat ttatattcag agatgtacca tgtaaagag ggtcttgta ttttttccc
3481 atttgtaatg tatttttattt atatatgaaatg taagttctga aactgttta tggtatTTT
3541 gtgcattgtt gagccaaaga gaaaagatta aaatgtgatgatgtt gatTTTtattt
3601 tgcccttaaa ataatgattt aagcattttt ctgtctgtaa gagaattcta agattgtaca

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3661 taaagtata tataatggaaa tcctgttact taaatacgat ctgctttct cttacgctct
3721 ctgtctggc gtacgtctgg tgtttcaat gctttcttag caactgttgg ataataacta
3781 gatctccgt aattttgtag tagttgatga ccaatctctg ttactcgctt agctgaaacc
3841 taaggcaaca tttccgaaga ccttcgaag atctcagata aagtgaccag gctcacaact
3901 gttttgaag aaggaaatt cacactgtgc gttttagagt atgcaagaag aatataaa
3961 aataaaaata ttctccatgg agaatttcaa caaaaaaaaaaaaaaa

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[0073] By “GABA polypeptide” (or gamma-Aminobutyric acid) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P30531.

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(SEQ ID NO: 5)
1 matngskvad ggistevsea pvandkpktl vvkvqkkaad lpdrtwkgr fdflmscvgy
61 aiglgnvwrf pylcgknggg aflipyfltl ifagvpvlfl ecslgqytsi gglgvwklap
121 mfkvgvlaaa vlsfwlniyy iviiswaiyy lynsfittlp wkqcdnpwnt drcfnsy whole
181 ntnmtsavv efwernmhqm tdgldkpgqi rwplaitlai awilvyfciw kgvgwtgkvv
241 yfsatypyim liilffrgvt lpgakegilf yitpnfrkls dsevwlda at qiffsyglgl
301 gslialgsyn sfhnnyrds iivccinsct smfagfvifs ivgfmahvtk rsiadvaasg
361 pglaflaype avtqlpispl wailffsmll mlgidsgfct vegfitalvd eyprllrnrr
421 elfiaavcii syliglsnit qggiyvfklf dyysasgmsl lflvffecvs iswfgyvnrf
481 ydnijemvgs rpciwwklcw sfftspiivag vfifsvaqmt pltmgnyvfp kwgqgvgwl
541 alssmvlipg ymaymfltk gslkqriqvma vqpsedivrp engpeqpqag sstskeayi

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[0074] By “GABA nucleic acid molecule” (or gamma-Aminobutyric acid) is meant a polynucleotide encoding an GABA polypeptide. An exemplary GABA nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. U76343.

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(SEQ ID NO: 6)
1 gtagttcac taaggtggaa tggatagcag ggtctcaggc acaaccagta atggagagac
61 aaaaccantg tatcacaaga tggagttgt gctgtcagtg gctggggaga tcattggctt
121 aggcaacgtc tggaggtttc cctatctctg ctacaaaat gggggaggtg ccttcttc
181 cccctacctc gtcttcctct ttacctgtgg cattcctgtc ttccctctgg agacagcact
241 aggccagtagc actagccagg gaggcgtcac agccctggagg aagatctgcc ccattttga
301 gggcattggc tatgcctccc agatgatcgt catcctcctc aacgtctact acatcattgt
361 gttggcctgg gcctgttct acctcttcag cagttcacc atcgacctgc cctggggcgg
421 ctgttacat gagtggaaaca cagaacactg tatggatgtc cagaagacca acggctccct
481 gaatggtacc tctgagaatg ccacctctcc tgtcatcgag ttctgggagc ggcgggtctt
541 gaagatctct gatggatcc agcacctggg ggcctgcgc tggagatgg ctctgtgcct
601 cctgctggcc tgggtcatct gctacttctg catctggaa ggggtgaagt ccacaggca
661 ggtggtgtac ttcacggcca catttcctta cctcatgtc gtggctctgt taattcgagg
721 ggtgacgttg cctggggcag cccaaaggaat tcagtttac ctgttacccaa acctcacgcg
781 tctgtggat ccccaggtgt ggtatggatgc aggcacccag atattctct ctttcgcct

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841 ctgtcttggg tgcctgacag ccctggccag ctacaacaaga taccacaaca actgctacag
901 cggcacacgc tttgtggccg gctttgccat cttctccatc ctgggcttca tgtctcagga
961 gcaggggggc cccattctg aggtggccga gtcaaggccc ggccctggctt tcatacgctta
1021 cccgcgggct gtgggtatgc tgcccttc tccctctgg gctgtgttt tcttcttcat
1081 ggtcgttctc ctgggactgg atagcagtt tgggtgtgtaa gaaaggctgg tgacagcgct
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1201 agtatctgtc gtctcttcc ctgtggggct gatcatgtc acagaggcg gaatgtacgt
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1381 catgattggg tacaggccat ggcctttat caaatactgt tggctttcc tcacaccagg
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1561 gtctgcattc ctgcctggag cctctacaga ctggaaaccc tcaaggggccc cttagagag
1621 agaatccgctc agctcatgtg cccagccgag gacctggcccc agcggaaaccc agcaggaccc
1681 tgggtttcccg ccaccccccag gacctcaactg ctcaactca cagagctaga gtctcaactgc
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1801 acgtggcaga agcagccccca tgggtttccct gccccccgacc tggagtggat aagacaagag
1861 gggtatttttggat ggtccacccct gctgagctgg aggccctccca ctgcaacttt tcagctcagg
1921 ggttggtaa cagatgtgaa aaggccagtg ccaagagtgt ccctcggaga cccttgaagg
1981 c

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[0075] By "TH polypeptide" (or Tyrosine Hydroxylase) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_002692.

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(SEQ ID NO: 7)
1 mptpdattpq akgfravse ldkqaeaim vrgqgapgps ltgspwpgta apasyyptp
61 rsprfigrrq sliedarker eaavaaaaaa vpsepgdple avafeekegk avlnllfespr
121 atkpsalsra vkvfetfeak ihhletrpaq rpraggphle yfvrlervrrg dlaallsgvr
181 qvsedvrsqa gpkvpwfprk vseldkchhl vtkfdpdl dhpqfsdqvy rqrrkliae
241 afqyrgdipi prveytaeei atwkevyttl kglyathacg ehleafalle rfsgyredni
301 pqledvrsrfl kertgfqlrp vagllsardf laslafrvfq ctqyirhass pmhspepdcc
361 hellghvpml adrtfaqfsq diglaslgas deeiellstl ywftvefglc kqngevkayg
421 agllssygel lhclseepei rafdppeaaav qpyqdqtyqs vyfvesesfsd akdklrsyas
481 riqrpfsvkf dptlaiddvl dspqavrrsl egvqdeldtl ahalsraig

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[0076] By "TH nucleic acid molecule" (or Tyrosine Hydroxylase) is meant a polynucleotide encoding an TH polypeptide. An exemplary TH nucleic acid molecule is provided at NCBI Accession No. NG_008128.

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(SEQ ID NO: 8)
1 gggggggggc agtgtgtgtccagcatgtg tgggtgtgtg tgcatacgtaca cgtgtgcacc
61 tggatcgctt gttgtgtgtc atgtgtatgt tacacgtgtc atgcatacgac gcacatgtgt
121 agtgtgtgtc cgtgtgtgtt gttgtgtgtt gtcatacgtatg agcacaacttg tatatgtgt

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181 gtgtactgtg tcataatatga gtgtgtttgc ctgtgttagtg catgcacatc cgtgtgtca
241 tctgggtgtt ccgtgggtca ttacgagtgc atcgatgtg ttcgtgtac atgagtacac
301 ttgtatgtgt ggtgtgtaca ggtgccatgt aagtgtgctt gtacatatat gcatgtatgt
361 gtcataatgc tctgtgtgtg catgtgtgtg gtgcacacat gtgttatgtc tgagtgtgcc
421 tgtatgtgtg ctatgtacac gtcataatgtg agtgtgtctt catgtgcagt gtgtggatgc
481 tgcttggatcc tgggtgtgtt acctgtgtca tgggtgtca cacgtgcatg gagtgtgtg
541 tgtgtgtctt tgggtgtgtt gtgtgtcatgt gtgtgtgtt cacacagatg cctgcatttg
601 cctaggcaact tgcaagagga caccatgctg gctctcaaag atcacaggc cacctgagcc
661 ctgtgcacac cacagccagg ccattggctag accctgcaga gcccacaggc gatgcctgtc
721 agccaggcggg cccagaacac ctccctggct cctcccccagg acatggctgg gtcctccag
781 caggccttggg tttgggaagg gcccgtgtt ggcaggctg gtgtgtggg gcaaggctgg
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901 ctgaccctgc cccacgcggg gagtgggcac cagtcctggc gcacagacgt gtcgggtat
961 taatctgggt gattaaggct cgggctgaga ggctgtttag agagaacacg ctccattgtg
1021 gagctggctc agcatttcctt acggccatgg tggcggggc tggtaaccaca gggacggcgg
1081 aagtgggtgg ggggggggg gtatggaggg aagccagag ggctccgtc aggaagggtgg
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2401 ctgcctgtt ggggggggg gctggaggca gggcagggtgc aggcacatgtca gggcaggact
2461 cacctccaca ggggtccagg ggcctccca gctcagcac ctggcctggg ctccctgttc

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2521 cagagagct ggcccaagg aagagtctag taagtttagt tcccatggg ctccatgaa
2581 agcacaactg gccccggcagg aaaccgaatt aaaaagcaat atttgtatca gtggaagaca
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2701 catcaggcat gtctcttcctc ctggctggg cacctgagca ctggggccgc cctggcaga
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2821 cctggggag gcaaatacgaa ctcttctgg ggacatttag gggagctcg gggagccatg
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7201 gtggggctgt gtgggctgag ttcttgatccc ctctatagca gaggtgcagc tgcccgaggcc
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9361 attgcacactt ggtgagacctt ccgtgcagctt aggggtggg gaggagcccg ggggatgcct
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9481 ggccggaaag aagaggact tgcaggctc agaatgttgg gttggggagga agaggctacc

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10621 ggaagggttc tgcggccagg gaagtgtccc agagacccctt ggaggggtctgg ctgacaccccc
10681 cgggtcccccc acctcgagca tgacccaggc ctgcctctcc ccattcctca tccctccctgc
10741 tccacaggac attggcctgg cgtccctggg ggcctcgat gaggaaattt agaagctgtc
10801 cacgggtgggt tgacccatcc ctgcaggggc tgggggtgtgg gtttgggggt ctgaatccag
10861 gcctcaccctt ctgcgcgtcc aggtgtgggc ctctccctcc acccacgaat tggacacccctc
10921 accctggccct gctgcaccc tggcctggcc tccctggggg tggatccctg gtcacgggtg
10981 accaggggctt gcccgggtggg cggcagctgt ctctgggtctt atgctggccg gttttcccgcc
11041 agctgtactg gttcacggtg gagttcgggc tggtaagca gaaacggggag gtgaaggcc
11101 atgggtccgg gtcgtgtcc tccatcgggg agcttctgtt gagatgtctt cttgtgtca
11161 gccccccagca gagggggcagg gtcgggggac ggtgcaggga ggggacaggc tccctgggg
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11461 tgagatcg gcttcgacc ctgaggctgc ggccgtgcag ccctaccaag accagacgta
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11581 taggctgtca gggcaagccc cccatgggtcc ccccaaaactg ggcacggcc gcttccttc
11641 tggcccttgag cagggtggc cctgtgagcc caggtcacag atgagaaaac cgaccctgg
11701 ttgcagcagc ccccacacag caggacacc atccgtgaga aggacccctt cgtctgggg
11761 gggggcagacc tacaggactg ggggtgtctg ggtggccggg tcaaggccag tcttggaggt
11821 gctgacagag cctgagctttt gtgaggacgt cctgtggaaac ctgtccggc cccctgcctt

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11881 gggatgggaa gaagtcaggg ggataagacag agtcaagggtg ggggacaggg cgggagtggg
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12001 cctctagcct catcctcata aaaggctca tcattttccc tccagcctct tatgcactgg
12061 gggaaactgag gccaggggct atgtgtccag cgacagggg tgctgaattc cacccacagg
12121 ctttagggata tggtcaagga aagttccctg gaggaggccc agtggaggtt cagggaggga
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12361 ggctgcagac tctggccccc agttgacgag ggctctgccc ctctcctccc caggagctat
12421 gcctcacgca tccacgcaccc ctttccctgt aagttcgacc cgtacacgct ggcacatcgac
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12661 ggtgccccccc atgcctcccc tgcgtccagg ctccactgc ccctgcaccc ttcttcagc
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12841 ccaatcaccc tcacaataaa agaaactgtg gtctctacac ctgcctggcc ccacatctgt
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13081 agcagctcca gaggctcggg caccctggcc gagtcgcccc atctccgtgg ggtgcctcc
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13261 gctgacaggg ctcccaagccc ttgagagaaa cagggatggaa ggaacagctg ccctgatgcc
13321 ctcacccacc cggagcggc cctgcgaacc aaggggaacc tcagtgtggc cccagcatg
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13501 aggggcctgg acattgcctt ccagagagag caccaaacac cctccaggct tgaccggcca
13561 ggggttcccc ttccctacctt ggagagagca gccccaggcc atctgcagg ggggtgtggg
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13681 atcctggatc tcagtccttcc ggcgcacaac actggcaaac tcctactcat ccacgaaggc
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13861 cctggggaaag tgcctgcctt gcctcccccc ggcctgcca ggcctggct ctggccctt
13921 acctgggttc ccccatcca gcctccctcc ctacacactc ctctcaagga ggcacccatg
13981 tcctctccag ctgcggggcc tcagagca gtcggcgtctt ggggcagccca cccatgtcc
14041 tgctgtggca tggctcaggg tggaaaggcc ggaaggagg ggtcctgcag atagctggtg
14101 cccactacca aaccgcgtcg gggcaggaga gccaaaggct ggggtgtgtc agagcggccccc
14161 cgagaggttc cgaggctgag gccagggtgg gacataggga tgcgaggggc cggggcacag

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14221 gatactccaa cctgcctgcc cccatggctc catctccctg ctctctggac ctctgtatcc
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14341 cctcaccatg ggtcaggctg gacccctcagg tgccctgttct ggggagctgg gagggccggaa
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14641 ttgtccccag gtccccaggt catgcctcc ttctgccacc ctggggagct gaggggctca
14701 gctggggctg ctgtcctaag gcagggtggg aactaggcgcc agggcaggga ggggacccct
14761 ccctcactcc cactctccca ccccccaccac ctggcccat ccatggcggc atcttggcc
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[0077] By "LMX1A polypeptide" (or LIM homeobox transcription factor 1-alpha) is meant a polypeptide or

fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q8TE12.

(SEQ ID NO: 9)

```

1 mldglkmeen fqsaidtsas fssllgravs pksvcegcqr vildrlflr1 ndsfwheqcv
61 qcascckeple ttcfyrdkk1 yckydyeklf avkcgfcfea iapnefvmlra qksvyhlsclf
121 cccvcerqlq kgdefvlkeg qllckgdyek erellslvp aasdsgksdd eeslcksahg
181 agkgtaeegk dhkrpkprrt ilttqqrraf kasfevsskp crkvretlaa etglsvrvvq
241 vwfqnqrakm kklarrqqqq qqdqqntqrl ssaqtnngggg agmegimnpy talptpqql1
301 aieqsvyssd pfrqgltpqmpgdhmhpqg aeplfhldsd ddttslnlgd cflatseagp
361 lqsrvgnpid hlysmqnsyf ts

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[0078] By "LMX1A nucleic acid molecule" (or LIM homeobox transcription factor 1-alpha) is meant a polynucleotide encoding an LMX1A polypeptide. An exemplary LMX1A nucleic acid molecule is provided at NCBI Accession No. AH011517.

(SEQ ID NO: 10)

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1 gtatagggttggccggagtc ggattcgggaa tggaaaacct gggcaaggat atgttaggtgg
61 gggtaggggg ggcaggagaa ggagaaacgc agttgggggg cggaggccata agtacataac
121 gtgttgactt caagtgaaat cagatcagcc agacgacttc gctgtgactg atctctcctc
181 ccaccctaca ttctcttggc tggaccctat cctcctggct gattctggc gcccggaca
241 ctcctcagt tctttccag gagtgccgtg gctgctggcg ccgagtcacgg gccccacgg
301 acgtcagacg catcggttct tctctctac aggtcctccc gggccggccc gaacatgtcg
361 gacggcctaa agatggagga gaacttccaa agcgcgatcg acacctcgcc ctcttctcc
421 tcgctgtgg gtgagtgttc aggccgtcgcc tcctggggcc actcttttc cgcttggcg
481 tggactctgg agcccccgtc tctgggaccc ggtccgcgat agggaaagcta ggcggccctct
541 tcatacacta aattgagccc catcaactatc tgtccgtcag tgcttgggg tcgtccctac
601 ccaaataaat ccaacaagcc gccccaggcc tcacgcactg ggcaccgaat tccccaaagc
661 cgcgaggggc gggcgagctt gttcgtaggc gtctgagtgg caagtgatataaaaatccca

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721 gggctggatt tttaatctcg gagctgatcg acgtctata aatgcggccc ttttctcg
781 gcctagaggc aatagcatcc gagaccgag gcctggagcg cccaagttcg aggaggctc
841 tctccccac caactccagc cccaatttcg cccatggca agggcgagag agactttct
901 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn
961 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gggccccgc caggtttgc
1021 atggtctacc tgccggcgt gtcacccgc caacgtctgt tggctaca ggcagagcgg
1081 tgagcccaa gtctgtctgc gagggtctgc agcgggtcat ctggacagg tttctgtc
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1501 caggctgtt gctgttaat gtggggctg ctgcaggcc atcgctccca atgagttgt
1561 tatgcgggcc cagaagagt tataccacct gagctgttc tgctgtgtc tctgegagcg
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1681 ctatgagaag gagcggggc tgctcagcc ggtgagccca gcagcctcag actcaggtga
1741 gtgccaggtg gtggcaggg ctgcgggtgg gtgggttagag tggagttggg tggctgtctg
1801 cattgttct tccctagatg nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn
1861 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn
1921 catacagctc caggaactgg ctgcaggga ctcacaacat tgcgtttgc ttcttcagg
1981 taaaagtat gatgaagaaa gtctctgca gtcagccat gggcaggaa aaggaactgc
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2401 ttccatagag cacaatggg acagtaataa tgataggtt ccattgtggt ttagacccag
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2641 tagttttggc ctgtttcaaa taggactgtc atggacattc atgtaaaaaa aaatacagt
2701 gtttaatgag acaggagttt attctttctgt gtcacagtcc agaggtgagc aaggcaaggc
2761 tggtgggtgg ctctgttatac catctctgt gtccaaaggcgt ctgcgtccagt tgcaccatg
2821 ttccagtc ccaggttagag aaagaggaaa tggagggca ggcctgtt ttttaaggat
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2941 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn atgcatatgc atggcttata
3001 gctaaaggcac aacaatagac taaagtctaa accacttgc ggcctaattt ccagagcaag

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3061 agaaatccag aaacacctt tgggaatgca catgtaaattt aataattttt attttgttc
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4021 cagatacgtt cagtttctca tcttgcttag ttctccttcc aggctaattt atttaataga
4081 agacacctcg gtgacttggc tctttccaaa ataacataaa gtagtaaaaa taatgatagt
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4261 tcacagatga gcaaacaag gctctgcaag attgaatgtg gcccttagatc ggttaaggca
4321 gggggctggg actagaactc taactgtgtt ccacaggcca tgggccttct catcttacc
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4441 nnn
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4621 ggccatcgag cagagtgtct acagtcaga tcccttcga cagggtctca cccacccca
4681 gatgccttgg aaccacatgc acccttatgg taagaggac ttaageccct cgggcctct
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4801 nnn
4861 nnn
4921 accctcatgc cagtgtttca tctccatttc aggtgccag cccctttcc atgacactgg
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5041 gcctctgcag tccagagtgg gaaacccat tgaccatctg tactccatgc agaattctta
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5161 attcttttag gggtcactgg cttaggaca gggaggccag ggaagagggtg gggtggggag
5221 ggagtttgc tggggatgct gttgtataat gatatgggtg agctcagcat ttccaaagac
5281 tgaatacatt atggattgca tagtttaatg

[0079] By "FOXO1 polypeptide" (or Forkhead box protein O1) is meant a polypeptide or fragment thereof having

at least about 85% amino acid identity to NCBI Accession No. Q12778.

(SEQ ID NO: 11)
 1 maeapqvvei dpdfepplprp rsctwplprp efsqsnsats spapsgsaaa npdaaaglps
 61 asaaaavsaadf msnlsllees edfpqapgsv aaavaaaaaa aatggcgdf qgpeagclhp
 121 appqpppppgp lsqhppvppa aagplaggpr kssssrrnaw gnlsyadlit kaiessaekr
 181 ltlsqiywem vksvpfyfkdk gdsnssagwk nsirhnlslh skfirvqneg tgksswwmln
 241 peggksgksp rrraasmdnn skfaksrsra akkkaslqsg qegagdsgps qfskwpspg
 301 shsnddfdnw stfrprtssn astisgrlsp imteqddlge gdvhsmvypw saakmastlp
 361 slseisnpen menlldnlnl lssptsltvs tqsspgtmmq qtpcysfapp ntslnspspn
 421 yqkytyggss msplpqmpiq tlqdnkssyg gmsqyncapq llkelltsds pphndimtpv
 481 dpgvaqpnsr vlgqnvmmgp nsvmstygsq ashnkmmnps shthpghaqq tsavngrplp
 541 htvstmphts gmnrltqvkt pvqvlphpm qmsalggys vsscngygrm gllhqeklps
 601 dldgmfierl dcldmesiern dlmdgdtldf nfdnvlpnq s fphsvkttth swvsg

[0080] By "FOXO1 nucleic acid molecule" (or Forkhead box protein 01) is meant a polynucleotide (e.g., mRNA) encoding an FOXO1 polypeptide. An exemplary FOXO1 nucleic acid molecule is provided at NCBI Accession No. NM_002015.

(SEQ ID NO: 12)
 1 gcagccgcca cattcaacag gcagcagcgc agcgggcgcg ccgctgggga gagcaagcgg
 61 cccgcggcgt ccgtccgtcc ttccgtccgc ggccctgtca gctggagcgc ggcgcaggg
 121 ctgccccggc cccggcgctc tggccggccg tccagtcgtc gcggcgacc cccaggaggcc
 181 tcgatgtgga tggcccccggc aagttaaatgtt ctgggctcgc gtttccactc cgccgcgcct
 241 tcctcccaagt ttccgtccgc tcgcccacc ggcttcgttc ccccaaatact cggaccgtcc
 301 cttcgcgcgc cttcccggtc cggcccgatg gtcgcgttct cccctcttg gtcctctgc
 361 ggctggggga gggggggggg tcaccatggc cgaggcgcc caggtggtgg agatcgaccc
 421 ggacttcgag ccgctgcccc ggccgcgtc gtgcacccgtt ccgcgtccca ggccggagtt
 481 tagccagtc aactcggcca cttccagccc ggccgcgtcg ggccagcgcc ctgccaacccc
 541 cgacgcgcgc gggggctgc ctcggccctc ggctgcgtc gtcaagcgcg acttcatgag
 601 caacctgagc ttgctggagg agagcgagga cttcccgcaag ggcggccgtt ccgtggccgc
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 721 cccggaggcg ggctgcgtc acccagcgcc acccgccgcg cccggccgtc ggccgcgtgc
 781 gcagcacccg ccgggtcccc ccgcgcgcgc tggccgcgtc gggggccagc cgcccaagag
 841 cagctcgcc cccgcacacg cgtggggca cctgtccatc gcccacccca tcaccaaggc
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1261 ttccaaatgg cctgcaagcc ctggctctca cagcaatgtac gactttgata actggagttac
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1501 aaatctttg gataatctca accttctctc atcacaaca tcattaactg ttgcaccca
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1621 cagtttgaat tcacccagcc caaactacca aaaatataca tatggcaat ccagcatgag
1681 ccctttgccc cagatgccta tacaacact tcaggacaat aagtcgagtt atggaggtat
1741 gagtcagttat aactgtgcgc ctggactctt gaaggagttt ctgactctg actctccctc
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1981 tgcagttaac gggcgcccc tggccacac ggtaagcacc atgccccaca cctcggttat
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2461 gttaaaaaaaaaaa aaaaacccct cttttttcc ttcgtcaga ctggcagca
2521 aagacattttt tccatgtacag gatgtttgcc caatgtgtgc aggttatgtt ctgtgttaga
2581 taaggactgt gccattggaa atttcattac aatgaagtgc caaactcact acaccatata
2641 attgcagaaa agatttcag atcctgggtt gcttcaagt tttgtatata agcagtagat
2701 acagattgtt tttgtgtgtt tttttggttt ttctaaatat ccaattggc caaggaaagt
2761 ttatactttt ttgtataac tgcgtggc ctcatgttctt gataagttaa actttttgtt
2821 gtactaccc ttttctggc aactgacggc tcacaaagaa ctgaatctcc attctgcattc
2881 tccatttgcac agccttggac ctgttacgt tgcacacagaa ttccatgttag aaccaagtag
2941 cctgttatca atctgttcaa ttaatggact tgtaatggaa ttggaaaaaaa aaagattaaaa
3001 tgccagctttt gtacaggctt tttctatttt tttttgttta tttttgttatt tgcaatattt
3061 tacaacacatt taaaatggttc taatttccatg ataaatgttattttt ttgtatgttta ttgttggac
3121 ttaagaacat ttttggata gatattgttac tgtaataatg ttttctttaa actagagtct
3181 acttttttttca atagtcagttt tgtaatggact tgtaatggaa ttggaaaaaaa aaagattaaaa
3241 ataattttca ttttgttattc taactggatt agtactaattt ttatacatgc ttaactggtt
3301 tgcgttacactt gggatgttac ttgtatgtt ttctgtactaa tcttaatca ttgtatgtt
3361 tacttgcata ttcaacgtttt caggccctgg ttggggcaggaa aagtgtatgtt tagttatggaa
3421 cactttgcgt ttcttattta ggataactta atatgtttt atgtatgtt tttaaagaaaa
3481 ttccatgtc ttctactgaa ctatgcgtac tgcataatgc caagtcttctt cttagagaccc

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3541 ctgttagtcct gggaggcctc ataatgttg tagatcagaa aaggagatc tgcatctaaa
3601 gcaatggtcc tttgtcaaac gagggatttt gatccacttc accatttga gttgagcttt
3661 agcaaaaagtt tccccctata attcttgct cttgtttcag tccaggtgga ggttggttt
3721 gtagttcgc cttgaggaat tatgtcaaca ctcatacttc atctcattct cccttctgcc
3781 ctgcagatta gattacttag cacactgtgg aagtttaagt ggaaggaggg aatttaaaaa
3841 tgggacttga gtggtttga gaatttgtt tcataagttc agatggtag caaatggaat
3901 agaacttact taaaaattgg ggagatttt ttgaaaacca gctgttaagtt gtgcatttag
3961 attatgttaa aagccttggc ttaagaattt gaaaatttct ttagcctgta gcaacctaaa
4021 ctgtatattcc tatcattatg ttttattact ttccaattac ctgtactga cagaccaaatt
4081 taattggctt tgtgtccat tttagtccatc agtattttca agtcatgtgg aaagccaaaa
4141 gtcatacaca tgaagagaac aggtgcacag cactgttctt cttgtgttct tgagaaggat
4201 ctaattttc ttttatatacg ccacatcaca cttgctttgt cttgtatgtt aattgcattt
4261 tcattggctt ggtatttcctt aatgtttaa caagaacaca agtgttccctg ataagatttc
4321 ctacagtaag ccagctctat tgtaagcttc ccactgtgat gatcattttt ttgaagattt
4381 attgaacagc caccactcta tcatactcat tttggggcag tccaaagacat agctggttt
4441 agaaacccaa gttcctctaa gcacagcctc ccgggtatgt aactgaactt ggtgccaag
4501 tacttgttga ctaatttcta ttactacgta ctgtcaattt cttccctgc cattactgca
4561 tcataataca aggaacctca gagccccat ttgttcattt aagaggcaac tacagccaaa
4621 atcaactgtta aaatcttact acttcatggt gtactctta gaaaaatata tcttcctcct
4681 gagtctgggt aattataacct ctcccaagcc cccattgtgtt gttgaaatcc tgtcatgaat
4741 cttggtagc tctctgagaa cagtgaaatc caggaaagg catctggtct gtctggaaag
4801 caaacattat gtggccctcg gtatTTTT tcctgttga atactgactt tctggagtaa
4861 tgagttatata tcagttattt tacatgattt ctttgtaaa tgtgcaaattt atatcaccta
4921 tgcagcccttg ttgattttt tttctctgggt ttgtactgtt attaaaagca tattgttattt
4981 tagagctattt cagatattttt aaatataaaat atgtattgtt tccgtatattt agacgtatgg
5041 aatatattttt ggtatagat gtattacttg gaaagttctg ctttgacaaa ctgacaaat
5101 ctaaatgagc acatgtatcc cagtgagcag taaatcaatg gaacatccca agaagaggat
5161 aaggatgctt aaaatggaaa tcattctcca acgtatataca aattggactt gttcaactgc
5221 tggatattatg ctaccaataa ccccaagcccc aactttttt tcttacattt aagcttccat
5281 gagttcttaa ttatataacta attttttttt agaagttctt tttctgggtt tagttggaa
5341 ataatcatcc attaaaaaaa atgtattgtt gtttatgcga acagaccaac ctggcattac
5401 agttggcctc tccttgaggt gggcacagcc tggcagtgtg gcccgggtg gccatgtt
5461 tcccatcagg acgttagtcat gcctcctgc tttcgctacc cgagtttagt aacagtgcag
5521 attccacgtt ttgttccga tactctgaga agtgcctgat gttgatgtac ttacagacac
5581 aagaacaatc ttgtctataa ttgtataaaat ccataatgtt acataaattt tttttttt
5641 gcttgggttgc ttcttttctt aattatgcag aataagctt ttataggaa ttttttgtt
5701 agcttattttt tacttgatgtt aagtcttgcg aagccacaa

[0081] By "FOXA2 polypeptide" (or Forkhead box protein A2) is meant a polypeptide or fragment thereof having

at least about 85% amino acid identity to NCBI Accession No. Q9Y261.

(SEQ ID NO: 13)
 1 mlgavkmegh epsdwssyya epegyssvsn mnaglgmngm ntymsmssaaa mgsgsgnmsa
 61 gsmnmssyvg agmuspsealm spgagamamg ggsagaaggva gmphlspsl splggqaaga
 121 mgglapyanm nsmspmygqa glsrardpkt yrrsythapk ppsyislitm aiqqspnkm
 181 tlseiyqwim dlfpfyrrqnq qrwqnsirhs lsfndcfklv prspdkgpgkg sfwtlhpdsg
 241 nmfengcylr rqkrfkcekq lalkeaaagaa gsgkkaaaga qasqaqlgea agpasetpag
 301 tespahssasp cgehkrggll elkgtppaal sppepapspg qqqqaaahll gpphhpglpp
 361 eahlkpehhy afnhpfsinn lmsseqqhhh shhhhqphkm dlkayeqvnmh ypgygspmpg
 421 slamgpvtnk tgldasplaa dtssyyqgvys rpimnss

[0082] By "FOXA2 nucleic acid molecule" (or Forkhead box protein A2) is meant a polynucleotide (e.g., mRNA) encoding an FOXA2 polypeptide. An exemplary FOXA2 nucleic acid molecule is provided at NCBI Accession No. NM_021784.

(SEQ ID NO: 14)
 1 cccgcccact tccaactacc gcctccggcc tgccccaggga gagagaggga gtggagccca
 61 gggagagggga gcgcgagaga gggagggagg agggggacggg gtttggctg acttttttt
 121 aaaagagggt ggggggtgggg ggtgattgt ggtcgtttg tgtggctgtt aaattttaaa
 181 ctgccatgca ctcggcttcc agtatgctgg gagcggtgaa gatggaaggg cacgagccgt
 241 ccgactggag cagctactat gcagagcccg aggctactc ctccgtgagc aacatgaacg
 301 cccgcctggg gatgaacggc atgaacacgt acatgagcat gtcggggcc gccatggca
 361 gcccgtctggg caacatgagc gccccgtcca tgaacatgtc gtcgtacgtg ggcgtctggca
 421 tgagccccgtc cctggggggg atgtcccccgc ggcggggccg catggggggc atggggggc
 481 cggccggggc ggccggcggt gccccatgg ggcggcactt gagtcccagc ctgagccgc
 541 tcggggggca ggcggccggg gcatggggc gcctggggcc ctacgccaac atgaactcca
 601 tgagccccat gtacgggcag gccccctga gccgcggcc cgaccccaag acctacaggc
 661 gcagctacac gcacgcaaag cccctact cgtacatctc gtcataacc atggccatcc
 721 agcagagccc caacaagatg ctgacgctga gcgagatcta ccagtggatc atggacctct
 781 tccccctcta cccgcagaac cagcagcggt ggcagaactc catccgcac tcgctctct
 841 tcaacgactg ttcctgaag gtggccgtg cggccgacaa gcccggcaag ggctccctct
 901 ggaccctgca ccctgactcg ggcaacatgt tcgagaacgg ctgctacctg cccggccaga
 961 agcgcttcaa gtgcgagaag cagctggcgc tgaaggaggc cgcaggccgc gccggcagcg
 1021 gcaagaaggc gcccggcggg gcccaggct cacaggctca actcggggag gcccggggc
 1081 cggccctcga gactccggcg ggcaccgagt cgcctcactc gaggcgcctcc cctgtggccagg
 1141 agcacaagcg agggggcctg ggagagctga agggggacgccc ggctggggcg ctgagcccc
 1201 cagagccggc gcccctctcc gggcagcgc agcaggccgc gcccacactg ctggggccgc
 1261 cccaccaccc gggccctggcg cctggggccc acctgaagcc ggaacaccac tacgttca
 1321 accaccacca accccacaaa atggacactca aggcctacga acaggtgtatg cactaccccg
 1381 accaccacca accccacaaa atggacactca aggcctacga acaggtgtatg cactaccccg

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1441 gctacgggtc ccccatgcct ggcagcttgg ccatgggccc ggtcacgaac aaaacgggcc
1501 tggacgcctc gccccctggcc gcagatacct cctactacca ggggggtgtac tcccgcccc
1561 ttatgaactc ctcttaagaa gacgacggct tcaggccccg ctaactctgg caccccgat
1621 cgaggacaag tgagagagca agtgggggtc gagactttgg ggagacgggtg ttgcagagac
1681 gcaagggaga agaaatccat aacacccca ccccaacacc cccaaagacag cagtcttctt
1741 caccgcgtgc agccgttccg tcccaaacag agggccacac agatacccca cgttctatat
1801 aaggagaaaa acgggaaaaga atataaagtt aaaaaaaaaaagc ctccggtttc cactactgtg
1861 tagactctcg cttcttcaag cacctgcaga ttctgatttt ttgttgttg ttgttctct
1921 ccattgtgt tgttgcaggg aagtcttact taaaaaaaaaa aaaaaatttt gtgagtgact
1981 cggtgtaaaa ccatgttagtt ttaacagaac cagagggttg tactattgtt aaaaacagg
2041 aaaaaaaaaata atgttaagggt ctgttgtaaa tgaccaagaa aaagaaaaaa aaagcattcc
2101 caatcttgac acggtaaat ccaggtctcg ggtccgatta atttatgtt tctgcgtgt
2161 ttatttatgg cttataatg tgtattctgg ctgcaagggc cagagtccca caaatctata
2221 ttaaagtgtt ataccgggtt ttatcccttg aatctttctt tccagatttt tctttcttt
2281 acttggctta caaaatatac aggcttggaa attatttcaa gaaggaggga gggataccct
2341 gtctgggtgc aggttgttatt ttatcttggc ccagggagtg ttgtgtttt cccacattt
2401 tattaataaa atttcagac ataaaaaa

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[0083] By “FOXO4 polypeptide” (or Forkhead box protein 04) is meant a polypeptide or fragment thereof having

at least about 85% amino acid identity to NCBI Accession No. P98177.

(SEQ ID NO: 15)

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1 mdpgnensat eaaaiidldp dfepqsrprs ctwplprpei anqpseppev epdlgekvht
61 egrsepillp srlepapggp qpgilgavtg prkgsrrna wgnqsyaeli sqairesapek
121 rltlaqiyew mvrtvpyfkd kgdsnssagw knsirhnls1 hskfikvhne atgksswml
181 npeggksgka prrraasmgs sskllrgrsk apkkkpsvlp appegatpts pvghfakwsg
241 spcsrnreea dmwtfrprs ssnassvstr lsplrpesev laeeipasvs syaggvpvtl
301 neglelldgl nltsshslls rsglsgfsdq hpgvtgplht yssslfsepae gplsagegcf
361 sssqaleall tsdtppppad vlmtqvdpil sqaptllllg glpsssklat gvglcpkple
421 apgpsslvpt lsmiappvm asapipkalg tpvlpptea asqdrrmpqdl dldmymenle
481 cdmdniisdl mdegeglfdn fepdp

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[0084] By “FOXO4 nucleic acid molecule” (or Forkhead box protein 04) is meant a polynucleotide (e.g., mRNA) encoding an FOXO4 polypeptide. An exemplary FOXO4 nucleic acid molecule is provided at NCBI Accession No. NM_005938.

(SEQ ID NO: 16)

```

1 aaaagggggga gggactgcg gctaaggaga cgttcgggtga tgggagcgcataatatgagg
61 ggatacagtgc cctcagggtt aaaagagcag gaagctgagt gagaggttgc agaaaaaagtg
121 tcttcgtcg gcagagggtta caggtggcat ctcagaaaga gctttgaggc tacaggctgt

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181 agtcgggaag gggatcgag aactgtgtga agggacagct tagggactag cgtcctggga
241 ctaggggaa gttcgcgact ttctgaagac tggcaggaat gtgcctcctg gccctcgatg
301 cttccccctt gaggggaggc atcgtgaggg actgtggcg gcttcactga acgctgagcc
361 ggggaggctt aactccacgt atggatccgg ggaatgagaa ttcagccaca gaggtgcgg
421 cgatcataga cctagatccc gacttgcgac cccagagcc tcggcgatcc tgcacctggc
481 ccottccccc accagagatc gctaaccagc cgtccgagcc gcccggaggta gagccagatc
541 tggggaaaaa ggtacacacg gggggcgct cagagccat cctgttgccc tctcggtcc
601 cagagccggc cggggggcccc cagccccggaa tcctgggggc tgtaacaggt cctcggaagg
661 gaggctcccg cccggatgcc tggggaaatc agtcatatgc agaactcatc agccaggcca
721 ttgaaagcgc cccggagaag cgactgacac ttgcccagat ctacgagtgg atggtccgta
781 ctgtacccta cttcaaggac aagggtgaca gcaacagctc agcaggatgg aagaactcga
841 tccggccacaa cctgtccctg cacagcaagt tcatcaaggt tcacaacggag gcccggca
901 aaagcttgcgtg aaccctgagg gaggcaagag cggcaagcc cccggccgccc
961 gggccgcctc catggatagc agcagcaagc tgctccgggg ccgcagtaaa gcccccaaga
1021 agaaaccatc tggctgcca gctccacccg aagggtgccac tccaaacggc cctgtggcc
1081 actttgcca gttggcaggc agcccttgcgt ctggaaaccg tgaagaagcc gatatgtgga
1141 ccaccttccg tccacgaaatc agttcaatgc ccagcagtgt cagcacccgg ctgtccccct
1201 tgaggccaga gtctgaggtg ctggcggagg aaataccagc ttcaagtgcg agttatgcg
1261 ggggtgtccc tccacccctc aatgaaggc tagagctgtt agatgggctc aatctcacct
1321 cttccattc cctgctatct cggagtggc tctctggcct ctcttgcag catctgggg
1381 ttaccggccc cttacacacc tacagcagct ccctttcag cccagcagag gggccctgt
1441 cagcaggaga agggtgcttc tccagctccc aggctctgga ggcctgctc acctctgata
1501 cggccaccacc ccctgtgac gtcctcatga cccaggtaga tccattctg tccaggcgtc
1561 cgactttct gttgtgggg gggcttcctt ctcctggaa gttggccacg ggcgtcgcc
1621 tgggtccaa gccccatagag gtcaggccg ccagcgtct ggtcccacc ctgttatga
1681 tagcaccacc tccagtcgt gcaagtgc ccatccccaa ggctctgggg actctgtgc
1741 tcacacccca tactgaagct gcaagccaa agagaatgcc tcaggatcta gatcttgata
1801 tggatgttggaa gacccctgggatgtgacatgg ataacatcat cagtgacccctc atggatgagg
1861 ggcggggact ggacttcaac tttggcggc atccctgagat catgcctgga agctttgtcc
1921 cctgcttcag atgtggagcc aggctgttcc atatctactc ttacccttg agccctcccc
1981 aggaatttgg gaccctgtt tagagctagg gtggggctgt gtcacacaca ggtgttgaag
2041 aaattataaa gataaaagctg ccccatctgg ggacgatatg gggaggggaga tgggggggg
2101 aaggggagag gtttttctc actgtgcca tttagggggta agggcccttc tcaggagcc
2161 tcatcggtt tcccttattcc tacccactta ggctttgtt caagatgagc aatgtgttg
2221 gaaatgtgaa gtcaccaggc gccttacccc tgccttggg agcaggattt ttttgttagag
2281 agtcttatct gagctgagcc aggctagctg gagctgttcc ttcttatgca gtggccctt
2341 aggccagtgaa tggcggtgg gtgggtttagggatct ggaaggccaa aggtctgagc
2401 actggagtggtt ctcggccagcc caaatcaccc tttagaaggct gcaagataaca gaaaggctt
2461 ttataaaactt taaaagaaat ataaacacaa atatagagat tttaacca tggcagggtg

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2521 ctagtggtgg gcagaatgct ttttttctt tctgaaggct ttgtgatagt gacatgatac
2581 aaacactaca gacaataaat attaggagac acagggaaagt ggggagaggt ggggagtaat
2641 agtaaacaca gggaaagagct cccctacgga ccaggtatag agaaaaggct atgcagaaat
2701 aggttagagt ttccctaaca aaaaagctaa cccaggtccc ctcatccctt caacttgtc
2761 ctgggagtggt gtgggttag ggtgcagcca cactcttcta tgacccagca tggttagtg
2821 ctatggtggg agagtagcatt gaaggcctgg aattagcttg gggccaggaa agggactggg
2881 aggggagaga agagaaggag ggaaggattt aggtggtaa agtaggtac agagacctcc
2941 ctgttcaagg cccctgacag ctgtccctgc ctttcttccc cttccctgac tgcaaaaaaa
3001 atgtgaaagt gtgtgtggca gcaggcageg gggagggggag gaacaggaa gggggagctg
3061 gggagcttgg ctgagggctt gggaaatgag cagggatggg gggggatgtg gatcaggtt
3121 actagcacct gccaggaggg ccatctgggg ctcccttc acccccagccc ccaaaggcagc
3181 cttccccca gtgcctttt categcccc tcccccaccc ctgctgtggg ttcccatcat
3241 ttccctgtgtc agcgcttggc ctaccatgt tgtatcatgt gctagattgg agtggggaaag
3301 tgtgtcaaat caataaatga ataaattcaa taaatgccta taaccagcaa aaaaaaaaaaa
3361 aaaaa

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[0085] By "CNP polypeptide" (or 2',3'-cyclic-nucleotide 3'-phosphodiesterase) is meant a polypeptide or fragment

thereof having at least about 85% amino acid identity to NCBI Accession No. P09543.

(SEQ ID NO: 17)

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1 mnrgfsrksh tflpkiffkrk msssgakdkp elqfpflqde dtvatlleck tlfilrglpg
61 sgkstlarvi vdkyrdgtkm vsadaykitp gargaeseey krldedlaay crrrdirilv
121 lddtnherer leqlfemadq yqyqvvlvep ktawrldcaq lkekknqwqls addlkklkpg
181 lekdflplyf gwfltkksse tlrkagqvfl eelgnhkafk kelrqfvpgd eprekmdlvt
241 yfgkrppgvl hcttkfcdyg kapgaeeyaq qdvlkkksysk aftltisalf vtpkttgarv
301 elseqqqlqlw psdvdkspt dnlprgsrah itlgcaadv avqtgldlile ilrqekggsr
361 geevvgelsrg klyslngrw mltlaknmev raijtgyygg gkpvtqgsr kggalqscsi
421 i

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[0086] By "CNP nucleic acid molecule" (or 2',3'-cyclic-nucleotide 3'-phosphodiesterase) is meant a polynucleotide (e.g., mRNA) encoding an CNP polypeptide. An exemplary CNP nucleic acid molecule is provided at NCBI Accession No. BC011046.

(SEQ ID NO: 18)

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1 ctccgcgcag ggggggggcc cgggagcgct ggtgcggca gaggcgccga cggtggcgcc
61 cttccctatc atgaggcttc tccggaaaaa gccacacatt cctgcccag atcttctcc
121 gcaagatgtc atcctcaggc gccaaggaca agcctgagct gcagttccc ttccctcagg
181 atgaggacac agtggccacg ctgctagat gcaagacgct cttcatcttgc cgccgcctgc
241 caggaagcgg caagtccacg ctggcacggg tcatcgtggc caagtaccgt gatggcacca
301 agatgggtgc ggctgacgct tacaagatca cccccggcgc tcgaggagcc ttctccgagg
361 agtacaagcg gctcgatgag gacctggctg cctactgccc ccggccggac atcagaattc
421 ttgtgcttga tgacaccaac cacgaacggg aacggctggg gcaagctcttt gaaatggccg

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481 accagtagcca gtaccagggtg gtgctgggtgg agcccaagac ggcgtggcgg ctggactgtg
541 cccagctcaa ggagaagaac cagtggcagc tgtcggtga tgacctgaag aagctgaagc
601 ctgggctgga gaaggacttc ctggcgtct acttcggtct gttcctgacc aagaagagct
661 ctgagaccct ccgcaaaagcc ggccagggtct tccttggaa gctggggAAC cacaaggcct
721 tcaagaagga gctgcgacaa ttgcgtccctg gggatgagcc caggagaag atggacttgg
781 tcacctactt tggaaagaga cccccaggcg tgctgcattt cacaaccaag ttttgtact
841 acgggaaggc tcccggggca gaggagtacg ctcaacaaga tgggttaaag aaatcttact
901 ccaaggcctt caccgtgacc atctctgccc tctttgtgac acccaagacg actggggccc
961 gggtggagtt aagcgagcag caactgcagt tggcccgag tgatgtggac aagctgtcac
1021 ccactgacaa cctgcccggg gggagcccg cccacatcac cctcggtgt gcagctgacg
1081 tagaggccgt gcagacgggc cttgacctct tagagattct gggcaggag aagggggggca
1141 gcccggcga ggaggtgggc gagctaagcc gggcaagct ctattccttggcaatgggc
1201 gctggatgtgacccctggcc aagaacatgg aggtcaggcc catcttcacg gggtaactacg
1261 ggaaaggcaa acctgtgccc acgcaaggta gcccggagg gggcgccttg cagtcctgca
1321 ccatcatatg agtgttctca ccaccactta tgcccctaga agggaaaggaaac
1381 gtgcctctg tttgatcctt gttttgtgac attttttttt ttttttttt tactcaaagt
1441 taacctacatgt gtaactttttt aaaaacttgt aaaataactg accctccctt cctgtccggcc
1501 ctcttcctt ctaatgtca cgctccaaac acaagggtggg caggaggca ccattcaggaa
1561 acctggacca aagctgacga ggctgggcca agccaggat gggccacag ccagaaccccc
1621 gagccctact tccaggttct ggttagctca gccccagccc agcccagctg ctctgcccag
1681 agctgggtga gtggggagac acctcagac cccgaaaaac ccactgaccg gaggcaaaag
1741 gcaactggggc tgggggttagt ttccatggt cacagagaac tagtgggtggc tctgagaagg
1801 ggaggacactc tgggcttga ttccatctcc ttgtctttt tctttttttt tagagacagg
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1921 ctcctgggtcaagcaatcc tcctgagtga tcccattttt taatcagtgt agccccaaaga
1981 aggctggggc tatttaccag ggtaaaaaa ggagcttacc tccacccctt ggtcttaagt
2041 ccctgcccccc tccccttcac accataacta ggtaacagtt tgataacttag ggaagaaagc
2101 agaacagtttta agcagccgc acatccccgc tggctggggg cctcactcca ggaaggggct
2161 ggactggctg tccttccag tggcctggct ccgctgtgtg gatggggaga tcggggccag
2221 aggcagaacc ctggtgagga agctccagtc ctgcctctca cccagcccat ctgcctcca
2281 tggtgccctt ggaggccctt ggcctccctt taacaggggc tggtgccac caagagccaa
2341 tggagtagac ccctggctgg taaggccaa gtcacccggg ttgcttctgg gaaggggttt
2401 ctaacactag tctgtgtgt gtgggtccctg ggggtccctc cactgcctc tggcttgc
2461 cagggccctt ctaatcggt tgcactcaa caaaagtgtt ttggattttt gttactatcc
2521 tggctttggcc caacctcagc aacctgtaag actgataatggaaataatca tggtaatcc
2581 agcaaaaaaaaaaaaaaaa

[0087] By "MBP polypeptide" (or myelin basic protein) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P02686.

(SEQ ID NO: 19)
 1 mgnhagkrel naekastnse tnrgesekkr nlgelsrtts ednevfgead anqnnngtssq
 61 dtavtdskrt adpknawqda hpadpgsrph lirlfsrdap gredntfkdr psesdelqti
 121 qedsaatses ldvmasqkrp sqrhgskyla tastmdharh gflprhrdtg ildsigrffg
 181 gdrgapkrhs gkdshhpart ahygslpqks hgrtqdenpv vhffknivtp rtpppsqqkg
 241 rglslsrfsw gaegqrpgfg yggrasdyks ahkgfkgvda qgtlkskifkl ggrdsrsgsp
 301 marr

[0088] By "MBP nucleic acid molecule" (or myelin basic protein) is meant a polynucleotide (e.g., mRNA) encoding an MBP polypeptide. An exemplary MBP nucleic acid molecule is provided at NCBI Accession No. M13577.

(SEQ ID NO: 20)
 1 gaaaacagtgcagccaccccgagagcctggatgtgatgg cgtcacagaa gagaccctcc
 61 cagaggcactgatccaagta cctggccaca gcaagttacca tggaccatgc caggcatggc
 121 ttccctcccaa ggcacagaga cacgggcata cttgactcca tcggggcgctt cttdggcggt
 181 gacaggggtgcgccaaagcg gggctctggc aaggactcac accaccggc aagaactgct
 241 cactatggctccctgcgaagtcacac ggcggaccc aagatgaaaa cccctgtac
 301 cacttcttca agaacattgt gacgcctcgc acaccacccc cgtcgcaggg aaaggggaga
 361 ggactgtccccctgacttgcatt tagctggggg gccgaaggcc agagaccagg atttggctac
 421 ggaggcagag cgtccgactataatcggtcacaaggat tcaagggagt cgatgcccac
 481 ggacacgttttccaaattttaaactgggat ggaagagata gtcgcctgg atcacccatg
 541 gctagacgtgaaaacccacctggttccggaaatcctgtcc tcaagttttttaataactg
 601 ccttaaaactttaatccccatggccctgt tacctaatta gaggatgaa cccctcccc
 661 aatgcctgcg gagttgtgca cgttagtaggg tcaggccacg gcaaccttcc
 721 ggccaaacagttaaatggaa catggaaaaca gaaaacggtaaaaactgtcc cttdttgtgt
 781 gaagatcacgttcctccccctgcaatgtgc ccccaacgc acgtgggtct tcaggggcc
 841 aggtgcacacgtccctccacgttcacccctccacccgtggcttttttcgcggctgg
 901 ctggccacccttgcgtttttgtggactactgcatggaggcacacagctgcagagacaga
 961 gaggacgtggccggcagaga ggactgttgacatggcaacgttccttttttctctg
 1021 tccttccttcaccccttaaaatgtactca ttttcctaa caggattaga cagtcacagg
 1081 gtggctactacatgtgggatgttggatgtgacatgcggctggc agctgttaga
 1141 gtccaaacgtggccagcaca gagagggggc caccctccccggccgtggctccacac
 1201 cccaaatttcgttgatggcgtggcagag ggaggaaacggggcaacggggctggc
 1261 aatggccctca cataggaaac agggcttccatggagatggatgtggaga tgcacac
 1321 gtggccctgtgacgttcacccgtccctgcataatggggccccagagcagcctatgaa
 1381 cctcggttccaaaccacagccacagccggagatccaggaaagacttgcgcactcagac
 1441 agaagggttag gaggctctacatggccacgttcacccgtccgcagccatagacactggc
 1501 tgtgaccggggctgtgtggca gccggcgtggc acatggccca gactaaccctccctgagaa
 1561 gataaccggc tcatttcactt cctccctggaa gacgcgtggtagcagcgttaggacacaggcgtg

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1621 cacctgtcc cgaattactc accgagacac acgggctgag cagacggccc ctgtatgga
1681 gacaaagaga tcttctgacc atatccttct taacacccgc tggcatctcc ttgcgcct
1741 ccctccctaa cctactgacc cacctttga ttttagcgca cctgtgattt ataggcctc
1801 caaagagtcc cacgctggca tcaccctccc cgaggacgga gatgaggagt agtcagcgtg
1861 atgccaaaac gcgttctttaatccaattc taattctgaa tgttcgtgt gggcttaata
1921 ccatgttat taatatata tag cctcgatgtat gagagagttt caaagaacaa aactccagac
1981 acaaacctcc aaattttca gcagaagcac tctgcgtcgc tgagctgagg tcggctctgc
2041 gatccatacg tggccgcacc cacacagcac gtgtgtgac gatggctgaa cgaaaagtgt
2101 acactgttcc tgaatattga aataaaacaa taaactttt

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[0089] By "TUBIII polypeptide" (or TUBB3, tubulin beta chain 3) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_001184110.

```

(SEQ ID NO: 21)
1 mdsvrsgafg hlfrpdnfif gqsgagnnw kghyteael vdsvldvvrk ecencdclqq
61 fqlthslggg tgsgmgtlli skvreeypdr imntfsvvps pkvsdtvvep ynatlsihql
121 ventdetyci dnealydicf rtlklatpty gdlnhlvsat msgvtttslrf pgqlnadlrk
181 lavnmvpfpr lhffmpgfap ltargsqgyr altvpeltqq mfdaknmmaa cdprhgrylt
241 vatvfrgrms mkevdeqmla iqsknssyfv ewipnnvkva vcdippgrlk msstfignst
301 aigelfkris eqftamfrkk aflhwytgeg mdemeftae snmndlvsy qyyqdataee
361 egemyeddee eseaqgpk

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[0090] By "TUBIII nucleic acid molecule" (or TUBB3, tubulin beta chain 3) is meant a polynucleotide (e.g., mRNA) encoding an TUBIII polypeptide. An exemplary TUBIII nucleic acid molecule is provided at NCBI Accession No. BC000748.

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(SEQ ID NO: 22)
1 gccccggcccg cccgcgcccc tccgcagccg cccgccagac ggcgcaggat tgagggagat
61 cgtgcacatc caggccggcc agtgccgaa ccagatcggtt gccaagtctt gggaaagtcat
121 cagtgtatc catggcatcg accccagccg caactacgtg ggccactcgg acttgcagct
181 ggagcggatc agcgtctact acaacgaggc ctcttctcac aagtacgtgc ctcgagccat
241 tctgggtggac ctggAACCCG gaaccatggc cagtgccgc tcaggggcct ttggacatct
301 cttcaggccct gacaatttca tctttggtca gagtgggggc ggcaacaact gggccaaggg
361 tcactacacg gagggggccgg agctgggtgg ttcgggtcctg gatgtgggtgc ggaaggagtg
421 taaaaactgc gactgcctgc agggcttcca gctgaccac tcgctggggg gccgcacccgg
481 ctccggcatg ggcacgttgc tcatcagcaa ggtgcgtgag gagtatcccg accgcacatcat
541 gaacacccatc agcgtcgatc cctcacccaa ggtgtcagac acgggtgggg agccctacaa
601 cgccacgctg tccatccacc agctgggtgg aacacccggat gagacctact gcatcgacaa
661 cgaggcgctc tacgacatct gctccgcac cctcaagctg gccacgccc cctacgggg
721 cctcaaccac ctggtatcgg ccaccatgg cggagtcacc acctccctgc gcttccgggg
781 ccagctcaac gctgacactgc gcaagctggc cgtcaacatg gtgccttcc cgccgtcgca

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841 cttcttcatg cccgggttcg cccccctcac agcccggggc agccagcagt accggggcct
901 gaccgtgccc gagctcaccc agcagatgtt cgatgccaag aacatgtatgg ccgcctgcga
961 cccgcgcac ggccgttacc tgacgtgtgc caccgtgttc cggggccgca tgcgttgcga
1021 ggaggtggac gagcagatgc tggecatecca gagaagaac acgagctact tcgtggagtg
1081 gatccccaaac aacgtgaagg tgccgtgtg tgacatcccc ccccgccggcc tcaagatgtc
1141 ctccacccctc atcgggaaca gcacggccat ccaggagctg ttcaagcgca tctccgagca
1201 gttcacggcc atgttccggc gcaaggcctt cctgcactgg tacacggggcg agggcatgg
1261 cgagatggag ttcacccggg ccgagagcaa catgaacgcac ctggtgtccg agtaccagca
1321 gtaccaggac gccacggcccg aggaagaggg cgagatgtac gaagacgcac agggaggagtc
1381 ggaggcccaag ggccccaagt gaagctgctc gcagctggag tgagaggcag gtggggcccg
1441 gggccgaagg cagcagtgtc taaacccccc gagccatctt gtcggccaca ccctgttcc
1501 ccctcgccct agggctccct tgccgcccctc ctgcagtatt tatggcctcg tcctccccac
1561 ctaggccacg tgtgagctgc tcctgtctct gtcttattgc agctccaggc ctgacgtttt
1621 acggttttgt ttttactgg tttgtgtta tatttcggg gatacttaat aaatctattt
1681 ctgtcagata ccctaaaaaa aaaaaaaaaa aaaaaaaaaa

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[0091] By “NEUN polypeptide” (or Feminizing Locus on X-3, Fox-3, RNA-binding protein fox-1 homolog 3, or Hexaribonucleotide Binding Protein-3) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_001076044.

```

(SEQ ID NO: 23)
1 maqpyppaqy ppppqngipa eyappphpt qdysqgtpvp tehgmtlytp aqthpeqpgs
61 eastqpiagt qtvpqtdeaa qtdsqplhps dptekqqpkr lhvsnipfrf rdpdlrqmfg
121 qfgkildvei ifnergskgf gfvtffetssd adrareklnq tivegrkiev nnatarvmtn
181 kktgnpytng wklnpvvgav ygpefyavtg fpypttgcayrghalrgr gravyntfra
241 apppppiptg gavvyqdgyf gaeiyggya yryaqaaaa aaysdsygrv yaaadpyhht
301 igpaatysisig tm

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[0092] By “NEUN nucleic acid molecule” (or Feminizing Locus on X-3, Fox-3, RNA-binding protein fox-1 homolog 3, or Hexaribonucleotide Binding Protein-3) is meant a

polynucleotide (e.g., mRNA) encoding an NEUN polypeptide. An exemplary NEUN nucleic acid molecule is provided at NCBI Accession No. NM_001082575.

```

(SEQ ID NO: 24)
1 gatacagcag cagctgggtgc tcctggccag gctgtgcgtg ctctctctgc ctctctctct
61 cggactctct ctgtactctc tcctctctct ctgtggcct ggtgaaatgt
121 tcttggctgt aggacacacag agccttggac tcaaggctgt tggagtgcag gacacctgt
181 ctccggctct ggagggtgaa attctgcctc tgagaagcta acagtcttcc tgggttcgccc
241 actccctccc agcagcccc tccttgcac ggacggtcca gaaggagccc cactggggcc
301 tccccgtca gcaaaggcaga cctcacccctc cactaccac ttgaagtcaac agcagccaga
361 gggaaattctg ccaccatctt cccaggtctg cagccctcc agctggaaac ctgctccctgg
421 agccatccct ctgcaaacag agagccaga gtgcctcggg gaaaattggc tgaataaaaag
481 agcgatcagg acgccacggc tccgcctgaa gcgatggccc agccctaccc ccccgcccaag

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541 tacccccctc cgccacagaa cggcatccat gccgagtagc ccccgcccc accgcacccc
601 acgcaggact actccggcca gacccggtc cccacagagc atggcatgac cctgtacaca
661 ccagcacaga cccacccga gcagccaggc tccgaggcca gcacacagcc catgccggg
721 acccagacag tgccgcagac agacgagggc gcacagacgg acagccagcc gctccacccc
781 tccgacccta cagagaagca gcagccaaag cggctacacg totccaacat ccccttccgg
841 ttcaaggacc ccgacttgcg gcaaatttc gggcaatttc gaaaaatttt agacgtggag
901 atcatttta acgagccccgg ctccaagggt tttgggtttg taactttga aactagctca
961 gatgctgacc gagccccggga gaagctgaat gggacgatcg tagagggacg gaaaatttgag
1021 gtcaataatg ccacggcccg agtgtatgacc aacaagaaga cggggaaaccc ctacaccaac
1081 ggctgaaagc taaatccagt ggteggcgca gtctacgggc ctgaattcta tgcaatgtacg
1141 gggttccctt accccaccac cggcacagcc gttgcctacc gggcgccaca tcttcggggc
1201 cggggccggg ccgtgtataa tacatttcgg gctgcgcac cccacccccc catcccgact
1261 tacggagccg tcgtgtatca ggtggattt tatgggtctg agatttatgg aggctacgca
1321 gcttacagat acgctcagcc cgctgcagcg gggcagcc acagcgacag ttacggcaga
1381 gtctacgcag ctgcccaccc gtaccatcac accatcgggc cccggccgac ctacagcatt
1441 ggaaccatgt gaaacattcc accgtttcc ttcggacca tgaaggccaa aaacaaaaaaaa
1501 aaaaaaaaaa tcacaaaaca aaaaaaaca aaaaagatgt taagatccaa gcaaaaaaaaa
1561 aaaaaccaac caaaccacaa ggcattcaac caagtccaa tcccgcttcc tgccacacg
1621 cccgcaccga gggagcacgc cggcaggggc gccgaggacg ggcggccagga caggacggcc
1681 ccaccgcgtc ctggctggca gcacagtggg aacacgcccc tccgtctcag gcagtggggg
1741 agttggggg gaagggggcct cccttgggg acccgtgggg ggctctgttt tccatccagt
1801 cttccttcc cagccccaa ctcccaagac agacagtgtg gagccccagcg gggggggagc
1861 aggccccggc ctgagcaggc aggegctgtc agcaagactt gatctttgtg gcaatgtgt
1921 ccagggggcc ggcggggctg aggggtgcgg gcagcttca tcccaaggggc tccactgggc
1981 cccgtcaccc tcctgtcgcg tccccgtcg tccacccccc tcctgccccg cagcccccc
2041 cgtccccca gctggcgag gaagccgtcc aacagtagcc cccggggccag ctcccaacag
2101 aaagggtga cgtggctcca ggactcaggc gcgcgtccatg ggaggacgaa ggaagcccc
2161 ccagccagga gccactcctc acaectccaa gtgtggccaa gtggggccctg aggccaaggaa
2221 cttacttgct cttcctggcc atctctccct ttctggagga ggcggggggc ctgtgtacac
2281 caaggctgac ctcgtgtcgc ctgtggac ccagccctcc ctgcgcgtcc cctgtgagcc
2341 cagtccaccg tggggcccca gggccaggga cggggccagcg cccggctgca tcgcgagggt
2401 gggagtcaca gtggctgtgg gcctggacgg gcacagccag agcaggggcc catgggaagg
2461 gcaaggatg gggaaagctg gggggggccc ttcctgtctc ccaaggcagg tgcgtgt
2521 gcgggagcag caccaaggac agccaggctt acccgggtggg aggagcaggaa gcagagcagg
2581 tggcagggag gaacccctgg cgaggcaggc agcactgaag tagggaaagca gcaaaaaata
2641 caggctccca acgtggctcc actgtctcat gaagtgtcaa aaatttaaaa atacacctca
2701 ctttctattc agcatcagct attgaaatgg aattctccct ttctattccc gtgtacata
2761 gccccacgccc ctgcctccgg ctttgcctc tgtacagagc cccctgtccc ctctgtgtt

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2821 ccggaccctt ttcttgacgc agctcaaccc cccgactcac tcagatcccc aggactgcag
2881 ccgagcccg ggcttccttt cttaaccattc tgtatgcttc caaggtgtga ccattcaaac
2941 taacagtatt attaaagatta ttaataaaga tttcttctt caaacaggaa aaaaaaaaaa
3001 aaaaaaaaa

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[0093] By “SLC1A6 polypeptide” (or Excitatory amino acid transporter 4; Sodium-dependent glutamate/aspartate transporter; Solute carrier family 1 member 6) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P48664.

```

(SEQ ID NO: 25)
1 msshgnslfl resgqrlgrv gwlqlrqlqesl qqrarlrtrlr lqtmtlehv1 rflrrnafil
61 ltvsvavvivg slafalrpyq ltyrqikyfs fpgeellmrml qmlvlplivs slvtgmasld
121 nkatgrmgmr aavyymvtti iavfigilmv tiihpgkgsk eglhregrie tiptadafmd
181 lirnmfpnnl veacfkqfqft qystrvvrt mvrtengsep gasmpppfsv engtsflevn
241 tralgtlqem lsfeetvpvp gsanginalg lvvfvsvafgl viggmkhkgr vlrdffdsln
301 eaimrlvgii iwyapvgilf liagkileme dmavlgqqlg myltlvivgl flhagivlp
361 iyflvthrn pfpfiggmlqa litamgtsss satlpitfrc leeglgvdrr itrflvlpvga
421 tvnmdgtaly ealaafiaq vnnyelnlgq ittisitata asvgaagipq aglvtmvivil
481 tsvglptedi tliaivdwfl drlrtmtnvl gdsigaavie hlsqrelelq eaeltlpslg
541 kpykslmaqe kgasrgrggn esam

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[0094] By “SLC1A6 nucleic acid molecule” (or Excitatory amino acid transporter 4; Sodium-dependent glutamate/aspartate transporter; Solute carrier family 1 member

6) is meant a polynucleotide (e.g., mRNA) encoding an SLC1A6 polypeptide. An exemplary SLC1A6 nucleic acid molecule is provided at NCBI Accession No. BC040604.

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(SEQ ID NO: 26)
1 ggcatacgcc gtcccggtc cgcgcgggtg cctccacggt ccggccccg cgccgggtct
61 gcacagtccc tggcggtcc ccgcggccccc ggccggggcgc ttgcggggc tccggctcct
121 gcatccgggc gcagcgcgcga ggcegagggc cgggcaggcc gccccggccg ctccggacgc
181 cggatgtaa gaggctccga aaagcagccc acgcacatcta tcagatctaa gtgtcttagag
241 gtcgggagaa ccaagtggga aagaccacc ctcacccctc acctttaga aactgggaaac
301 actagaaggg acatttctg agcaggaaac ccaagagaca gggttttacg ctgtcaccca
361 agttggagtg cagtggtacg atcatagctc attgcagccct caaactccctg ggttcaagcg
421 atcctcctgc tttagcctct tgtagtagcta ggactacagg cacaggccac cgtgcctggc
481 taatttttaa tttttaaaaa agagacaggg tctggctatg ttgcccaggc tggccatgaa
541 ctccctggct caagcggttc tccagccctc acctcccaa gtgttggat tgcaggcatg
601 agccactgctc tctggccac agatgctaag tgctgtctgc tcttctccag gggtcagcaa
661 attttttcg caaatggccc aagagtaat attttgagct ttgtggcccg tacaatctct
721 gtccccaaacaa ctcaactcag gcattgttagc ttgaaagcag ctgttagacaa taggtatcc
781 atgagtgtagg ctgtgtgcca ataaaacttt atttacaaaa acaagcagta ggctgaattt
841 gactagcaga ccatagttt tcaataccgt attatgtctt gtaaggaga gaaaggaacc

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901 agacaaaact ctagcctcgagtttccct gactgttcag atcttagctg aatgtatctc
961 cttggtatct acaggaact tcctgctgtg gcttagggac tgaaaaacata atatcccaga
1021 gggattccct gtgttagtctg tggttcactc tttgggattt tttttttttt ttccacagca
1081 aggagaagca gcattgtgg ttcaggagat gggccatatt ggagcaggat cctaagtggg
1141 gcttggcatt gggaaatttg attagctcta gaggacgcag gatctggaaa atcagggcag
1201 atttcccatc ccttggatatt ggtggggagt tgaggagggc aaggaaagatc ccagaaaagc
1261 cagtggcagc aaaacacaaa ggccaggac ctacgtactg gtaaaactga gacccaag
1321 aaacctgcagc ctcgacactgg ttgaaattcag atagaccatg agcageccatg gcaacagcct
1381 gttccttcgg gagagcggcc agcggctggg ccgggtggc tggctgcagc ggctgcagga
1441 aagcctgcagc cagagagcac tgccgcacgcg cctgcgcctg cagaccatga ccctcgagca
1501 cgtgctgcgc ttcctgcgcc gaaacgcctt cattctgctg acggtcagcg ccgtggtcat
1561 tggggtcagc ctggcctttt ccctgcgccccc atatcagctc acctaccgc agatcaagta
1621 cttctctttt cctggagagc ttctgtatgag gatgctgcag atgctggtgt tacctctcat
1681 tgtctcagc ctggcacag gatggcattc cctggacaac aaggccacgg ggccggatggg
1741 gatgcgggca gctgtgtact acatggtgac caccatcattc gcggtttca tcggcatcct
1801 catggtacc atcatccatc ccggaaaggg ctccaaaggag gggctgcacc gggaggggcc
1861 gatcgagacc atccccacag ctgatgcctt catggacctg atcagaataa tggccacc
1921 aaaccttgcg gaggcctgct tcaaaccatg caagacgcag tacagcacga ggggtgttac
1981 caggaccatg gtgaggacag agaacgggc tgagccgggt gactccatgc ctccctcatt
2041 ctcagtgagg aacggaaacca gttccctggaa aaatgtcaact cgggccttgg gtaccctgca
2101 ggagatgctg agctttgagg agactgtacc cgtgcctggc tccgcatttgc gcatcaacgc
2161 cctggccctc gtggctttct ctgtggcattt tgggtggcatttgc tggatggca tggaaacacaa
2221 gggcagagtc ctcaggact tcttcacag cctcaatgag gctattatga ggctgggtgg
2281 catcattatc tggtgatcc tggatgtgc ccacggaaag gtggagccag agctggaaag
2341 tcaggctgtg gggaaactgc cgaaggctt gctggggacc ttgggttattt catttacgt
2401 ttgggtgatt cacttaccca ctcaccaact catttacca tggatgttgc ggttggattt
2461 atcaactgtt cacttcatttgc ttcatgttgc catttacca ttcttctatg cattgggttag
2521 ttcatggaat atctcaactt ttcatttgcatttgc tggatgttgcatttgc gcatcaactgc
2581 ttgttgcatttgc tggatgttgc ctttgcatttgc tatgttgcatttgc tggatgttgc
2641 ttgttgcatttgc tggatgttgc ctttgcatttgc tatgttgcatttgc tggatgttgc
2701 catttacca tggatgttgc ctttgcatttgc tatgttgcatttgc tggatgttgc
2761 ctttgcatttgc tatgttgc ctttgcatttgc tatgttgcatttgc tggatgttgc
2821 cttcaataca ttgaccaaagc catttacca tggatgttgc ctttgcatttgc tatgttgc
2881 catttgcatttgc tatgttgc ctttgcatttgc tatgttgc ctttgcatttgc tatgttgc
2941 attgacaaat aaaaactgttca tatattttca tggcaaaaa aaaaaaaaaaaaa

[0095] By “NOGOA polypeptide” (or neurite outgrowth inhibitor A; neurite outgrowth inhibitor isoform A; human reticulon-4; human reticulon-4 isoform A) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_065393.

```
(SEQ ID NO: 27)
1 medldqsplv sssdspprpq pafkyqfvre pedeeeeeee eeedededle elevlerkpa
61 aglsaapvpt apaagaplmd fgndfvppap rgplpaappv aperqpswdp spvsstvpap
121 splsaaavsp sklpdeddepp arpppppas vspqaepvwt ppapapaapp stpaapkrrg
181 ssgsvdetlf alpaasepvi rssaanmdlk eqpgntisag qedfpsvlle taaslpslsp
241 lsaasfkehe ylgnlstvlp tegtlqenvs easkevseka ktllidrdlt efseleysem
301 gssfsvspka esavivanpr eeiivknkde eeklvsnnil hnqquelpta tklykedevv
361 ssekakdsfn ekrvaveapm reeyadfkpf ervwevkdsk edsdmlaagg kiesnleskv
421 dkkcfaadsle qtnhekdses snddtsfpst pegikdrsga yitcapfnpa atesiatiif
481 pllgdptsen ktdekkieek kaqivteknt stkt.snpflv aaqdsetdyv ttdnltkvte
541 evvanmpegl tpdlvqeace selnevtgtk iayetkmdlv qtsevmqesl ypaaqlcpsf
601 eeseatpspv lpdivmearp nsavpsagas viqppssple assvnyesik hepenpppye
661 eamsvslkkv sgikeeikep eninaalget eapyisiacd liketklsae papdfsdyse
721 makveqppvd hselvedssp dsepvdflsd dsipdvpkq detvmlvkes ltetsfesmi
781 eyenkeklsa lppeggkpyl esfklslndt kdtllpdevs tlkkkeipl qmeelstavy
841 snndlifiske aqiretetfs dsspieiide fptliissktd fsksklareyt dlevshksei
901 anapdgagsl pctelphdls lknipkvee kifsddfsk ngsatskvvll lppdvsalat
961 qaeiesivkp kvlvkeakk lpsdtekdr spsaifsael sktsvvdlly wrdikkgtvv
1021 fgaslfllls ltvfsivsvt ayialallsv tisfriykgv iqaiqksdeg hpfraylese
1081 vaiseelvqk ysnsalghvn ctikelrrlf lvddlvdslk favlmwvfty vgalfngltl
1141 lilalislfs vpviyerhqa qidhylqlan knvkdamaki qakipglkrk ae
```

[0096] By “NOGOA nucleic acid molecule” (or neurite outgrowth inhibitor A; neurite outgrowth inhibitor isoform A; human reticulon-4; human reticulon-4 isoform A) is

meant a polynucleotide encoding an NOGOA polypeptide. An exemplary NOGOA nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_020532.

```
(SEQ ID NO: 28)
1 agtccctgcc ctccccctggg gagggtgagt cacgc当地ac tggcgccgaga gtccgctggc
61 ctcactccta gtcatactgg gcggcgccgg caagtgggga cagggcggtt ggcgcatacac
121 cggcgccggag gcaggaggag cagtcattt gttccggggag ccgtcaccac agtaggtccc
181 tcggctcaagt cggcccaagcc cctctcagtc ctcccccaacc cccacaaccg cccggggctc
241 tgagacgccc ccccgccggc ggcggcagca gctgcagcat catctccacc ctccagccat
301 ggaagacctg gaccagtctc ctctggcttc gtctcggac agcccacccc ggccgcagcc
361 cgcgttcaag taccagttcg tgaggagggc cgaggacgag gaggaagaag aggaggagga
421 agaggaggac gaggacgaaag acctggagga gctggagggtg ctggagagga agccgcgcgc
481 cgggctgtcc cggggcccaag tgcccaccgc ccctggccgc ggcgcgcggcc ttatggactt
541 cggaaatgac ttctgtccgc cggcgcggccgg gggacccctgg cccggccgcgc ccccccgtcgc
601 cccggagccgg cagccgtctt gggaccccgag cccgggtgtcg tccaccgtgc cccgcgcacatc
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661 cccgctgtct gctgccgcag ttcgcctc caagctccct gaggacgacg agcctccggc
721 cgggcctccc ctcctcccc cggecagcgt gagcccccag gcagagcccg tgtggacccc
781 gccagcccg gtcggcccg cgccccctc caccggccg ggcggcaagc gcaggggctc
841 ctccgggtca gtggatgaga cccttttgc ttttcgtgtc gcatctgagc ctgtgatacg
901 ctccctgtca gaaaatatgg acttgaagga gcagccaggt aacactattt cggctggta
961 agaggatttccatctgtcc tgcttggaaac tgctgtttctc tgtctcttc
1021 ctcagccgtcttcaaag aacatgaata ccttggtaat ttgtcaacag tattacccac
1081 tgaaggaaca cttcaagaaa atgtcagtga agcttctaaa gaggtctcag agaaggcaaa
1141 aactctactc atagatagag atttacaga gtttcagaa tttagaatact cagaaatggg
1201 atcatcggttc agtgtctctc caaaagcaga atctgcccgtatagtagcaa atccctaggaa
1261 agaaataatc gtgaaaaata aagatgaaga agagaagttt gtttagtaata acatccttca
1321 taatcaacaa gagttaccta cagctttac taaattgggtt aaagaggatg aagtgtgtc
1381 ttcagaaaaaa gcaaaagaca gttttaatga aaagagagttt gcagtggaaag ctccatgag
1441 ggaggaatat gcagacttca aaccatttga gcgagttatgg gaagtggaaag atagtaagga
1501 agatagtatgat atgtggctg ctggggtaa aatcgagacg aacttggaaa gtaaagtggaa
1561 taaaaaatgt tttgcagata gccttgagca aactaatcac gaaaaagata gtgagtag
1621 taatgatgat acttcttcc ccagtcgcgca agaaggatata aaggatcggtt caggagcata
1681 tatcacatgt gtcctttta acccagcago aactgagacg attgcaacaa acatcttcc
1741 tttgttaga gatcctactt cagaaaaataa gaccgtgaa aaaaaatag aagaaaagaa
1801 ggcccaata gtaacagaga agaataactag caccaaaaca tcaaaccctt ttctttagc
1861 agcacaggat tctgagacag attatgtcac aacagataat ttaacaaagg tgactgagga
1921 agtcgtggca aacatgcctg aaggcctgac tccagattt gtagggaaatg catgtgaaag
1981 tgaattgtat gaaatgtactg gtacaaatgtatgatgaa aaaaaatgg acttgggtca
2041 aacatcagaa gttatgcaag agtcaactcta tcctgcgcga cagcttgcac catcttgc
2101 agagtcagaa gtcactcctt caccagttt gcctgacattt gttatggaa caccattgaa
2161 ttctgcagtt cctagtgctg gtgttccgt gatacagcccg agctcatcac cattagaagc
2221 ttcttcagtt aattatgaaa gcataaaaca tgagcctgaa aaccccccac catatgaa
2281 ggccatgatgtatcactaa aaaaagtatc aggaataaag gaagaaattha aagagcctgaa
2341 aaatattaaat gcagcttcc aagaaacaga agctccttat atatctatttgcatgtgatt
2401 aattaaagaa acaaagcttt ctgctgaacc agctccggat ttctctgatt attcagaaat
2461 ggccaaatgtt gaacagccag tgcctgatca ttctgagctt gttgaagatt cctcacctgaa
2521 ttctgaaacca gttgactttaat ttagtgcgtt ttcaataactt gacgttccac aaaaacaaga
2581 tgaaactgtg atgcttgcgtt aagaaatgtt cactgagact tcattttgatgtt caatgtatgaa
2641 atatgaaat aaggaaaaac tcagtgctttt gccacctgag ggagggaaagc catatggaa
2701 atcttttaag ctcagtttag ataacacaaa agataccctg ttacctgatg aagtttcaac
2761 attgagcaaa aaggagaaaaa ttcccttgcgtt gatggaggag ctcagttactg cagtttattc
2821 aaatgatgac ttatattttt ctaaggaagc acagataaga gaaactgaaa cgtttccaga
2881 ttccatctcca attgaaattha tagatgatgtt ccctacatttgc atcagttctaa aactgattc
2941 attttctaaa ttagccaggaa aatataactgaa cctagaagta tcccacaaaaa gtgaaattgc

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3001 taatccccg gatggagctg ggtcattgcc ttgcacagaa ttgccccatg accttcttt
3061 gaagaacata caacccaaag ttgaagagaa aatcagttc tcagatgact tttctaaaaa
3121 tgggtctgct acatcaaagg tgctcttatt gcctccagat gtttctgctt tggccactca
3181 agcagagata gagagcatag ttaaacccaa agttcttgta aaagaagctg agaaaaaaact
3241 tccttcggat acagaaaaag aggacagatc accatctgct atatttcag cagagctgag
3301 taaaactca gttgttacc tcctgtactg gagagacatt aagaagactg gagtgggttt
3361 tgggccagc ctattctgc tgcttcatt gacagtattc agcattgtga gcgtaacagc
3421 ctacattgcc ttggccctgc tctctgtgac catcagctt aggatataca agggtgtgat
3481 ccaagctatc cagaaatcag atgaaggcca cccattcagg gcatatctgg aatctgaagt
3541 tgctatatct gaggagttgg ttcagaagta cagtaattct gotcttggtc atgtgaactg
3601 cacgataaaag gaactcaggc gcctttctt agttgatgat ttagttgatt ctctgaagtt
3661 tgcagtggtt atgtgggtat ttacctatgt tgggccttg tttatggtc tgacactact
3721 gatttggct ctcatttcac tcttcagtgt tcctgttatt tatgaacggc atcaggcaca
3781 gatagatcat tatctaggac ttgeaaataa gaatgttaaa gatgctatgg ctaaaatcca
3841 agcaaaaatc cctggattga agcgc当地 tgaatgaaaa cgcccaaaat aatttagtagg
3901 agttcatctt taaagggat attcattga ttatacgggg gagggtcagg gaagaacgaa
3961 ccttgaatgtt gcagtgactt ttcacagatc gttgttagat ctttattttt agccatgcac
4021 tggatgttggg aaaaattacc tgttctgtact gcatgtgtt catcatcttta agtattgtaa
4081 gctgctatgtt atggatttaa accgtaatca tatcttttc ctatctatct gaggcactgg
4141 tggatataaa aacctgtata ttttactttt ttcagatag tcttgcggca tcttggcaag
4201 ttgcagatgtt ggtggagctt gaaaaaaaaaaa aaaaaagcc ctttcagtt tggactgt
4261 gtatggccg tggatgttgc tgcagatttt ctgaaatgaa atggttggg agacgagatc
4321 ataccggtaa agcaggaaatc acaaagctt ctttctgtt atggttcttgg tggatgttgc
4381 cttttactgtt tatattaattt gccaatataa gtaaatatag attatataatg tataatgttt
4441 cacaagctt agacctttac cttccagcca ccccacatc ctgtatgtt cagatgttgc
4501 cattggatgtt acatgtgttagt ttccaaagca cataagctt aagaagaaat atttcttaga
4561 gcaatccat ctgtttcaa catgaaatgc cacacacata gactccaac atcaatttca
4621 ttgcacagac tgactgttagt taatttgtc acagaatcta tggactgaat ctaatgcttc
4681 caaaaatgtt gtttgggttgc aaatatcaaa cattgtttagt caagaaattha ttaattacaa
4741 aatgaaatgtt tataccattt tggatgttgc tggatgttgc taaatctgtt gatgttgcattt
4801 tggatgttgc aagcaagta tcaataaagc ttatagactt aaaaaaaaaa aaaaaaaaaa
4861 aaaaaaaaaa a

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[0097] By “oligodendrocyte O1 polypeptide” (or oligodendrocyte marker O1; oligodendrocyte transcription factor 1; olig1) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q8TAK6.

(SEQ ID NO: 29)

```

1 myyavsqarv navpgtmlrp qrpgdlqlga slyelvgyrq ppsssssts stsstssst
61 tapllpkaar ekpeapaepg gpgpgsgahp ggsarpdake eqqqqlrrki nsrerkrmqd

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121 lnlamdalre vilpysaahc qgapgrklsk iatlllarny illlgsslqe lrralgegag
 181 paaprlllaqg lpllaaapgs vllapgavgp pdalrpakyl slaldeppcg qfalpgggag
 241 gpglctcavc kfphlvpasl glaavqaqfs k

[0098] By “oligodendrocyte O1 nucleic acid molecule” (or oligodendrocyte marker O1; oligodendrocyte transcription factor 1; olig1) is meant a polynucleotide encoding an

oligodendrocyte O1 polypeptide. An exemplary oligodendrocyte O1 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_138983.

(SEQ ID NO: 30)
 1 gttctagatc gtttccccgc ggcagggtcc gcgaaaaagg ggccgcctgcc gacccggccca
 61 ccccaggcg ttcctgaagg gctgtctcgcc ccggcccccac cgccctccacat atgtactatg
 121 cgggttccca ggcgcgcgtg aacgcgggtcc ccggggaccat gctgcggcca cagccggcccg
 181 gagacttgca gtcggggcc tccctctacg agctgggtgg ctacaggcag ccggccctcc
 241 cctccctctc ctccacactcc tccacactct ccacttcctcc ctccctccacg acggccccc
 301 tcctcccaa ggctgcgcgc gagaagccgg aggccgcgcgc cgagcctcca ggcccccggc
 361 ccgggtcagg cgccgcaccccg ggccgcagcg cccggccggc cgccaaaggag gaggcagcagc
 421 agcagctcgcc ggcgcacatc aacagccgcg agccggaaagcg catgcaggac ctgaaacctgg
 481 ccatggacgc cctgcgcgcg gtcatcctgc cctactcagc ggccgcactgc caggccgcgc
 541 ccggccgc aa gtcctccaaat atgcacgc tgctgcgcgc ccgcactac atcctactgc
 601 tggcagctc gtcgcaggag ctgcgcgcg cgctggcgca gggccggccccc cccggccgc
 661 cgccgcctgc gtcggggcc ctgcgcgcgc tcgcgcgcgc gcccggctcc gtgcgtctgg
 721 cggccggccgc cgtaggaccc cccgcgcgc tgccgcgcgc caagtacctg tcgcgtggcgc
 781 tggacgcgcg gccgtgcggc cagttcgctc tcccgccggc cggccgcaggc ggcccccggc
 841 tctgcacctg cggcgtgtgc aagttccgc acctggtccc ggccagccctg ggccctggccg
 901 ccgtgcaggc gcaattctcc aagtggggc gggctggccctc ctggggccgc acctccggcc
 961 ggccctccctt cgctcagctt ctccgcgcgc ctgcctccctg cgtctggag agcgaggccg
 1021 agcaaggaaa gcaattcgaa cttccagtc cagaggaagg gactgtcgcc caccggcc
 1081 cccggcccca cccctggac gttaaagtga ccagagccgaa tggtcgatgg cgcctcgcc
 1141 cagttttgggg ttctgggtcg gttccagccg ctttaggcag aaagtgcctcg ctctcaccca
 1201 gcaatatctt ctccctgtcc ctggagttgc ggcgttcggc gggccgatgt agaactttag
 1261 ggccttcgcg gtcggggccgc cggccggggc gcagccggag gccatccccg agcgctaccc
 1321 cccggagcg gagcacgcgg gtcggccatc ctggggctgc cgctcgagca gtgggggggg
 1381 cgggggggtg gttttttcc ttcttcctccg ccagaggccg cggccgcgcct tggtccggcc
 1441 ggccagggtcc tatcaaagga ggctgcgcgc actcaagagg cagaaaaaga ccagtttag
 1501 ggtgcaggacg gtcggggacg tggcagacgg acggaccctc ggcggcagg tggcggggc
 1561 cgggggtgcgg tgggtagggg cgaggacaac gcagggtgcg ctgggttggg acgtgggtcc
 1621 acttttttag accagctgtt tggagagctg tatttaagac tgcgtatcc agtgttttgt
 1681 cgcagagact tttcactctt aaatcctggg ggtttcttag aaagcaactt agaactcgag
 1741 attcacctt cgtttccctt tcccaaaag tagcgttaacc aacatthaag cttgcttaaa
 1801 aacgaaaacc aaccgccttg catccagtttgc tcccgattta ctaaaatagg taaccaggcg
 1861 tctcacagtc gccgtctgtt caagagccgt aatgaacgtt ctcattaaca cgcaggagta

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1921 ccgggagccc tgaaccgccc gctgtcgcc ggatcccaga tgccgtggcg acggcgggaa
1981 ggcgccttcc gctgttcctc agcgggccgg gcccggacc agcgcggccc gcaggcttc
2041 cttctcgccg tcttgagtt gaagagctac atacgttagtc agtttcgatt ttgttacagac
2101 gttaacaaaat tccttaccc aaggttatgc tatgaccttt cccgagttt ctggatattt
2161 ctatgtttaa gggtttgggtt gttggtagta gcccggatata actggcactt tattttactt
2221 ctaaccttgt ttccgtacgg tgtacagaat caacaaaata aaacatattaa agtctgattt
2281 tttaaaaaaa aaaaaaaaaa

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[0099] By “oligodendrocyte O2 polypeptide” (or oligodendrocyte marker O2; oligodendrocyte transcription factor 2; olig2) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q13516.

```

(SEQ ID NO: 31)
1 mdsdaslvss rpsspepddl flparskgss gsaftggtvss stpsdcppe lsaelrgamg
61 sagahpgdkl ggsgfkssss stssstssaa asstkkdkkq mtepelqqlr lkinsrerkr
121 mhdlniamdg lrevmpyahg psvrklksia tlllarnyil mltnsleemk rlvseiyggh
181 hagfhpsacg glahsaplpa atahpaaaah aahhpavhlp ilppaaaaaa aaaaaaaavss
241 aslpgsrlps vgsirpphgl lkspaaaaa plggggggsg asggfqhwgg mpccpcsmcqv
301 ppphhhvssam gagslprlts dak

```

[0100] By “oligodendrocyte O2 nucleic acid molecule” (or oligodendrocyte marker O2; oligodendrocyte transcription factor 2; olig2) is meant a polynucleotide encoding an

oligodendrocyte O2 polypeptide. An exemplary oligodendrocyte O2 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_005806.

```

(SEQ ID NO: 32)
1 gggtgcttat tataatcgaa cgccgacacca gcccgggtt ccaggcttc ccctgaggct
61 ttccggagcg agtcctcaa atcgcatcca gagtaagtgt ccccgccccca cagcagccgc
121 agecttagatc ccagggacag acttcctca actccgtgt gaccggaaat gctccgatac
181 agggggtctg gatccctact ctgcgggcca tttctccaga gcgactttgc tcttctgtcc
241 tccccacact caccgtgca tctccctca caaaagcgag aagtccggagc gacaacagct
301 ctttctgccc aagccccagt cagctggta gctccccgtt gtctccagat gcagcacatg
361 gactctgggc cccgcgcgg ctctgggtgc atgtcggtgt gctgtgttt gctgtgtgtt
421 gtccatggag ataagggtgga tccgtttgag gaaccaaatac attagttctc tatttagatc
481 tccattctcc ccaaagaaag gcccactt cccactcggtt tattccagcc cgggggctca
541 gttttccac acctaactga aagccccaaag cctctagaat gcccacccgca ccccgagggt
601 caccaacgcg ccctgaaata acctgttgc tgagagcaga ggggagatag agagagctta
661 attataggtt cccgcgtgca gctaaaagga gggccagaga tagtagcgag ggggacgagg
721 agccacgggc cacctgtgcc gggaccccgca gctgtggatc tgccgtgcag gccccggcgg
781 cttttctgtc tctcaactgac tcactcttc tctctctccc tctctcttc tctcatttctc
841 tctctttctt cctccctctcc tggaaagttt cgggtccggag ggaaggagga ccctgcgaaa
901 gctgcgacga ctatctccc ctggggccat ggactcgac gcccggctgg tgcgtccggcc
961 cccgtcgctcg ccagagcccg atgacctttt tctgcggcc cggagtaagg gcagcagcgg

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1021 cagcgccttc actggggca ccgtgtcctc gtccaccccg agtgaactgcc cgccggagct
1081 gagcgccgag ctgcgcggcg ctatggctc tgccggcgcg catcctgtgg acaagctagg
1141 aggcaagtgc ttcaagtcat cctcgccag cacctcgctc tctacgtcgt cggccggctgc
1201 gtcgtccacc aagaaggaca agaagcaa at gacagagccg gagctgcage agctgcgtet
1261 caagatcaac agccgcgagc gcaagcgcat gcacgaccc aacatcgcca tggatggcct
1321 ccgcgaggtc atgcgcgtacg cacacggccc ttccggtgccg aagcttcca agatcgccac
1381 gctgctgtc ggcgcgaaact acatccat gtcaccaac togtggagg agatgaagecg
1441 actgggtgagc gagatctacg ggggcacca cgcgtggcttc cacccgtcg cctgcggccgg
1501 cctggcgacac tccgcgcggcc tgcggccgcg caccgcgcac cccgcgcgac cagcgcacgc
1561 cgcacatcac cccgcgggtgc accacccat cctgcgcggcc ggcgcgcag cggctgtgc
1621 cggcgctgcgca ggcgcggctg tgccagcgcc ctctctgcgg ggcgcggcc tggcgctcggt
1681 cggctccatc cgtccaccgc acggctact caagtctccg tctgctgcgg cggccggcccc
1741 gctggggggc gggggggggc gcagtggggc gagcggggggc ttccagact gggggggcat
1801 gcccgtcccc tgcagcatgt gccaggtgcc gcccgcgcac caccacgtgt cggctatggg
1861 cgcggcagc ctgcgcgcgc tcaccccgca cgcacgtga ggcgtactggc gcccgcgcgt
1921 tctggcgaca ggggagccag gggccgcggg gaagcgagga ctggcctgcg ctggcctcg
1981 gagctctgtc gcgaggaggg gcgcaggacc atggactggg ggtggggcat ggtggggatt
2041 tcagcatctg cgaacccaag caatggggc gcccacagag cagtgggag tgaggggatg
2101 ttctctccgg gacctgatcg agcgctgtct ggcttaacc tgagctggc cagtagacat
2161 cgttttatga aaaggtaccg ctgtgtgcatt tcctcactag aactcatccg acccccgacc
2221 cccacccctcg ggaaaagatt ctaaaaactt cttccctga gagcgtggcc tgacttgca
2281 actcggcttg ggcagcaattt cggggggggc ggggggttta tggggggggg acacattggg
2341 gccttgctcg ttctctctt ttcttggcg gtggggact cgggttagcc gcactgcaga
2401 agcaacagcc cgaccgcgc ctcacgggtc gtcctggcc caaggccagg gcccacaagt
2461 tagttggaa cccgcgttcg gtatcagaag cgcgtatgtt cttatccat ctcataatct
2521 gggtaatcc acaccctttt agaactgtgg cgttccctt ctgtctctcg ttgatgggg
2581 agaatatggt ttcttaataa atctgtggat gttccctttt caacagtatg agcaagttt
2641 tagacattca gagtagaacc acttgtggat tggataacc caaaactgcc gatttcagg
2701 cgggggtgcatt tgtagttt attttaaaat agaaactacc ccacccactc atctttccctt
2761 ctctaagcac aaagtattttt ggttattttt gtacactgaga acgttaacaga attaaaaggc
2821 agttgtgtg gaaacagttt gggttattttt ggggttctgt tggctttta aaattttctt
2881 ttgtgtgtt gtaaaattttt caatgtatgatgatgatgatgatgatgatgatgatgat
2941 cgtgactgcc agcccatcg gagtcataac cggcttcctt ctatgggtt ttatgggtt
3001 cacgttaac acaaatggta aactccctcca cgtgtttccctt ggttccgtg caagccgcct
3061 cggcgctgc tgcgttgcac actggggctt gtacccgttgc cccgttgcac cccttcctt
3121 gatcgccaccc cccctcgac agatgtatc atctgttttta tttttgtaaa aacaaagtgc
3181 taaaataat ttattactt tttgggttgc aaaaacggaaat aaatgtactga gtgtttagat
3241 tttaaataaa atttaagca aaaaaaaaaaaaaaaa

[0101] By “oligodendrocyte O4 polypeptide” (or oligodendrocyte marker O4; oligodendrocyte transcription factor 4; olig4) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. Q05586.

[0102] By “oligodendrocyte O4 nucleic acid molecule” (or oligodendrocyte marker O4; oligodendrocyte transcrip-

tion factor 4; olig4) is meant a polynucleotide encoding an oligodendrocyte O4 polypeptide. An exemplary oligodendrocyte O4 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_007327.

[0103] By “GFAP” (or Glial fibrillary acidic protein) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P14136.

```
(SEQ ID NO: 33)
1 merrritsaa rrsyvssgem mvgglapgrr lpgptrlsla rmppplptrv dfslagalna
61 gfketraser aemmelndrf asyiekvrfl eqqnkalaae lnqlrakept kladvyqael
121 relrlrlrdql tansarleve rdnlaqddlat vrqklqdets lrleaennla ayrqeadeat
181 larldlerki esleeeirfl rkiheeevre lqeqlarqqv hveldvakpd ltaalkeirt
241 qyeamassnm heaewyrsk fadltdaaar naellrqakh eandyrrqlq sltcleslr
301 gtneslerqm requeerhvre aasyqealar leeeggqslkd emarhlqeyq dllnvklaed
361 ieiatyrkll egeenritip vqtfsonlqir etsldtksvs eghlkrnivv ktvemrdgev
421 ikeskqehkd vm
```

[0104] By “GFAP nucleic acid molecule” (or Glial fibrillary acidic protein) is meant a polynucleotide encoding an GFAP polypeptide. An exemplary GFAP nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_002055.

```
(SEQ ID NO: 34)
1 gcaggatgga gaggagacgc atcacctccg ctgtcgccg ctccctacgtc tcctcagggg
61 agatgatggc ggggggcctg gctctggcc gccgtctggg tcctggacc cgccctctccc
121 ttggctcaat gccccctcca ctcggaccc gagttgattt ctccctggct gggcactca
181 atgctggcattt caaggagacc cgggocagtg agcgggcaga gatgatggag ctcaatgacc
241 gcttgcacg ctacatcgag aagttcgct tcctggaaaca gcaaaaacaag gcgctggctg
301 ctgagctgaa ccagctgcgg gccaaggagc ccaccaagct ggcagacgtc taccaggctg
361 agctgcgaga gctgcggctg cggctcgatc aactcaccgc caacagcgcc cggctggagg
421 ttgagagggca aatctggca caggacctgg ccactgttag gcagaagctc caggatggaa
481 ccaacacctgag gctgaaagcc gagaacaacc tggctgcata tagacaggaa gcagatgaag
541 ccacccctggc cctgtctggat ctggagagga agattgagtc gctggaggag gagatccgg
601 tcttggagaa gatccacgag gaggaggttc gggactcca ggagcagctg gcccacacgc
661 aggtccatgtt ggagcttgac gtggccaagc cagacccatc cgcageccctg aaagagatcc
721 gcacgcagta tgaggcaatg gctgtccagca acatgcata agccgaaagag tggtaccgct
781 ccaagttgc acacctgaca gacgctgctg cccgcaacgc ggagctgctc cgccaggcca
841 agcacgaagc caacgactac cggcgccagt tgcagtcctt gacctgcac ctggagtctc
901 tgccggcoac gaacgagtcc ctggagaggg agatgcgcga gcaggaggag cggcacgtgc
961 gggaggccgc cagttatcag gaggcgctgg cgccgctgg ggaagagggg cagagcccta
1021 aggacgagat ggccccccac ttgcaggagt accaggacct gctcaatgtc aagctggccc
1081 tggacatcga gatcgccacc tacaggaagc tgctagaggc cgaggagaac cggatcacca
1141 ttccctgtca gaccttctcc aacctgcaga ttcgagaaac cagcctggac accaagtctg
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1201 tgtcagaagg ccacctaag aggaacatcg tggtaagac cgtggagatg cgggatggag
 1261 aggtcattaa ggagtccaag caggagcaca aggtgtat gtgaggcagg acccacctgg
 1321 tggcctctgc cccgtctcat gaggggcccg agcagaagca ggatagttgc tccgcctctg
 1381 ctggcacatt tccccagacc tgagtcctcc accaccccg ctgtccccct cccctctctg
 1441 tcccttaggtc agcttgcgc cctaggctcc gtcagtatca ggctgtcc

[0105] By "s100b" (or S-100 protein beta chain; S-100 protein subunit beta; S100 calcium-binding protein B) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P04271.

[0106] 1 msele kamva lidvfhqysg regdkhklkk selkelinne Ishfleeike qevvdkvmet

[0107] 61 ldndgdgecd fqefmaf vttacheffe he (SEQ ID NO: 35)

[0108] By "s100b nucleic acid molecule" (or S-100 protein beta chain; S-100 protein subunit beta; S100 calcium-binding protein B) is meant a polynucleotide encoding an s100b polypeptide. An exemplary s100b nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_006272.

[0109] By "SOX10 polypeptide" (or SRY-related HMG-box transcription factor) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_008872.1.

(SEQ ID NO: 37)
 MAEEQDLSEVELSPVGSEEPRCLSPGSAPSLGPDGGGGSGLRASPGPE
 LGKVKKEQDGEADDDKFPVCIREAVSQVLSGYDWTLVPMPVRVNGASKS
 KPHVKRPMNAFMVWAQAARRKLADQYPHLHNELSKTLGKLWRLLNESDK
 RPPFIEEAERLRMWHKKDHDPDYKYQPRRRKNGKAAQGEAECPGGEAEQGGT
 AAIAQAHYKSAHLDHRHPGEGPSMSDGNPEHPSGQSHGPPTPPTPKTELQ
 SGKADPKRDGRSMGEGGKPHIDFGNVDIGEISHEVMSNMETFDVAELDQY

(SEQ ID NO: 36)
 1 gggcagaggg aataagaggc tgcctctgcc caccagtctt gcccggcagg accccgacca
 61 gagacgacgc ctgcaccaag gagaccagga aggggtgaga caaggaagag gatgtctgag
 121 ctggagaagg ccatggtggc cctcatcgac gttttccacc aatattctgg aagggaggg
 181 gacaagcaca agctgaagaa atccgaactg aaggagctca tcaacaatga gctttccat
 241 ttcttagagg aaatcaaaga gcaggagggt gtggacaaag tcatggaaac actggacaat
 301 gatggagacg gcgaatgtga cttccaggaa ttcatggcct ttgttgccat gtttactact
 361 gctgcacacg agtttttga acatggatgt gattagaaag cagccaaacc ttccctgtaa
 421 cagagacggt catgcaagaa agcagacagc aagggttgc agcctagtag gagctgagct
 481 ttccagccgt gttgtatgta attaggaagc ttgatggct ttgtgattga aaaattgaaa
 541 acctcttcc aaaggctgtt ttaacggcct gcatttcattt ttctgtata ttggcctgt
 601 gtgtaagctg actggccca gggactctt gtaacagtaa cttaggagtc aggtctcagt
 661 gataaagcgt gcacccgtca gcccggcatg gccgtgtaga ccctaaccgg gagggaaccc
 721 tgactacaga aattaccccg gggcacccctt aaaacttcca ctacctttaa aaaacaaagc
 781 cttatccagc attatttgc aacactgtcg ttctttaat gcttcctca tccatgcaga
 841 taacagctgg ttggccgggt tgccctgtca agggcgtgtt ggcttggcc tgcttcccg
 901 gatgcgcctg atcaccaggta gaacgctcg cgctggcagc gtcctggaa aaagcaactc
 961 catcagaact cgcaatccga gccagctctg ggggctccag cgtggccctcc gtgacccatg
 1021 cgatccaagt cgccggctgca ggatccttgc ctccaaacgtg ctccagcac atgcccattc
 1081 cgagggact accggggct ctgagccacc gcgagggcct gcttcaata aaaaag

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LPPNGHPGHVSSYSAAGYGLGSALAVASGHSWISKPPGVALPTVSPPGV
DAKAQVKTETAGPQGPPHYTDQPSTSQIAYTLSLPHYGSAFPSISRPQF
DYSDHQPSGPYYGHSGQASGLYSAFSYMGPSQRPLYTAISDPSPSG
PQSHSPTHWEQPVYTTLSRP

[0110] By "SOX10 nucleic acid molecule" (or SRY-related HMG-box transcription factor) is meant a polynucleotide encoding an SOX10 polypeptide. An exemplary SOX10 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_006941.3.

(SEQ ID NO: 38)
 1 gtccggccag ggtggtttgt ggtaaggatt caggctcggt cctaaccagg ccgtggcctg
 61 aggctcaggc ccccccggcc ctccttccca gcccaccagg gtcacccccc agccccggac
 121 tggaccgcac accttggac acggttttc acttcctaag gacgagccccc agactggagg
 181 agaggtccga ggaggtgggc gttggactct ttgcgaggac cccggggct ggcccggggg
 241 aggccggccga ggccggccgg gccggccggc ggggcgacat ggccggaggag caggacatat
 301 cggaggtggaa gctgagccccc gtgggctcg aggagccccc ctgcctgtcc ccggggagcg
 361 cgcctcgct agggcccgac ggccggccggc gcggatcggt cctgcgagcc agcccgggc
 421 caggcgagct gggcaaggc aagaaggcgc agcaggacgc cgaggcgac gatgacaagt
 481 tccccgtgtg catccgcgag gccgtcagecc aggtgctcag cggctacgac tggacgctgg
 541 tgcccatgcc cgtgcgcgctc aacggcgcca gcaaaagcaa gccgcacgctc aagcggccca
 601 tgaacgcctt catgggtgtgg gctcaggcag cgccgcaggaa gctcgcggac cagtaaccgc
 661 acctgcacaaa cgcttagcgc agcaagacgc tggcaagct ctggaggctg ctgaacgaaa
 721 gtgacaagcg ccccttcatac gaggaggctg agcggctccg tatgcagcac aagaaagacc
 781 acccggaacta caagtaccag cccaggccgc ggaagaacgg gaaggccgc cagggcgagg
 841 cggagtgccc cgggtggggag gcccggcaag gtgggaccgc cgccatccag gcccactaca
 901 agagcgccca cttggaccac cggcacccag gagagggctc cccatgtca gatgggaacc
 961 ccgagcaccc ctcaggccag agccatggcc cacccacccc tccaaccacc ccgaagacag
 1021 agctgcagtc gggcaaggca gacccgaaggc gggacgggcg ctccatgggg gagggcggg
 1081 agccctcatac cgacttcggc aacgtggaca ttgggtgatg cagccacgag gtaatgtcca
 1141 acatggagac cttttagtgg gctgagttgg accagtagctt gcccggccat gggcaccagg
 1201 gccatgttag cagtagtactca gcagccggct atgggctggg cagtgccctg gccgtggcca
 1261 gtggacactc cgccctggatc tccaagccac caggcgtggc tctgcccacg gtctcaccac
 1321 ctgggtgtggaa tgccaaagcc caggtgaaga cagagaccgc gggggcccaag gggggccca
 1381 actacaccga ccagccatcc acctcacaga tcgcctacac ctccctcagc ctgccccact
 1441 atggctcagc cttccctcc atctccgcgccc cccagtttg ctaactctgac catcggccct
 1501 caggacccta ttatggccac tggggccagg cctctggctt ctaactcggcc ttctccata
 1561 tggggccctc ccaagggccc ctctcacagg ccatctctga ccccaagccccc tcaggggcccc
 1621 agtccccacag ccccacacac tggggccaggc cagttatatac gacactgtcc cggccctaaaa
 1681 gggggccctg tggccaccac ccccccggccca gcccctgcggcc ccaagcctgtg tgccctgttc
 1741 cttggccacc tcaaggctgg tgggtggcagt ggaggaggct gaggaggctg aagaggctg
 1801 caggtcgggg ggctttctgt ctggctcaact gcccgtatgc cccacccggcc ccatccaggc
 1861 tccagcagca aagccccagg agaacaggct ggacagaggaa gaaggagggtt gactgttgc
 1921 cccacactga aagatgaggg gctgcaccc ccccccaggaa tgaccctcta tcccaggacc

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1981 tgagaaggcc ctgctcaccc tccctggggc ggggaagcac cagggttgtt ggcacatggag
2041 gccttaccac tcctatgact cctgtttct ctctcacaga tagtgagggt ctgacatgcc
2101 catgccacct atgcccacgt gcctaaggcc taggccaccc agagactgtg cccggagctg
2161 gccgtgtctc ccactcaggc gctgagagta gettgagga gcctcattgg ggagtggggg
2221 gttcgagggc ctttagggag ttctcatccc ttcaatgccc cttcccttc tgaaggcagg
2281 aaggagttgg cacagaggcc ccctgatcca attctgtgcc aataacctca ttctttgtct
2341 gagaaacagc ccccaagtccct cctccactac aacccatcg accttgagac gcatccccagg
2401 aggtgacgag gcaggggctc cagggaaagga atcagagaca attcacagag ccccccctcc
2461 tgggctctt cccagctccc tttccctta ctaggctcta tggccctgc tcaagtccagcc
2521 ccactccctg ggcttccctg agagtgcacag ctgctcaggc cctaaaccctt ggctccagga
2581 gacacaggcc ccagcaccca gggtgctgc ggccggctga agacactaga atccgtaccc
2641 gtacattctg cccttgcctc ttacccttg cctcccaagtgt gtatttgaat aaagtatgtt
2701 gctatatctg cccctatccc cctgttctgc ageccccca atccacatgt aactcattac
2761 tgtctcctgt tatttatctc agtagtcccc tctccctagcc actctagccc ctattaactc
2821 tgcattaaagc attccacata ataaaattaa aggtcccggt taaaaaaaaaaaaaaaa
2881 aa

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[0111] By "SYN1 protein" (or Synaptin I protein) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to GenBank: AH006533.2.

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(SEQ ID NO: 39)
MNYLRRRLSDSNFMANLPNGYMTDLQRQPQPPPPGAHSPGATPGPGTAT
AERSSGVAPAASPAAPSPGSSGGGFSSLNAVKQTTAAAATFSEQVG
GGSGGAGRGGAAASRVLLVIDEPHTDWAKYFKGKKIHGGIDIKVQEAFSD
LNLAHANGGFSVDMEVLRNGVKVVRSLKPDFVLIQHAFSMARNGDYRS
LVIGLQYAGIHSVNSLHSVYNPCDKPWVFAQMVRLLHKKLGTEEFPLIDQT
FYPNHKEMLSSTTYPVVVKMGHAHSGMGKVVDNQHDFQDIASVVALTKT
YATAEFPFIDAKYDVRVQKIGQNYKAYMRTSVGNWKTNTGSAMLEQIAMS

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DRYKLWVDTCSIEFGGLDICAVEALHGKDGRDHIEEVVGSSMPLIGDHQD
EDKQLIVEVVNKMAQALPRQRQRDASPGRGSHGQTPSPGALPLGRQTSQ
QPAQPPAQQRPPPQGGPPQPGPQRPQGPQPLQQRPPQGQQHLSGLGPPA
GSPLPQRLPSPTSAPQQPASQAAPPTQGQGRQSRPVAGGPQGAPPARPPA
SPSPQRQAGPPQATRQTSVSGPAPPKASGAPPGGQQRQGPQKPPGPAGP
TRQASQAGPVPRTPGPPTTQOPRPSGPGPAGAPKPKQLAQKPSQDVPPPATA
AAGGPPHPQLNKSQSLTNAFNLPEPAPPRPSLSQDEVKAETIRSLRKSFA
SLFSD

```

[0112] By "SYN1 nucleic acid molecule" (or synapsin I gene) is meant a polynucleotide encoding an SYN1 polypeptide. An exemplary SYN1 nucleic acid molecule (e.g., mRNA) is provided at GenBank: AH006533.2.

```

(SEQ ID NO: 40)
1 ctgcagagag aaggagagga cattcctggc agaagttaca acacatgcaa aggtacagag
61 gttggccctt tcctaccctt ctcccttagag gtgggttaga gatgtatcct ttttacagat
121 gaggaaacca aatctcagaa agattaagtc acttcccaa gtgtatggtg gaggccccac
181 ttgaacccag gcactgtgtc tccagacccc acactattac tgccttgtt aaaccagcca
241 actgatttaa tgaataaagg atgaacaaat gaataagtgg atgagtccacc tgaaaattct
301 gcaggcaaag agactccata tctacttact tcttgcctat ctctccttagt
361 ccaccatcac tgctcaactat ggtcaaggcc ctacccaaatc tggccctgc taccacaacc
421 cccttcacgt tggccagcc acattggcac tggatgttcc ctcttcctgg cacattctta
481 aaaaaatgtt ttgatcataa agtgaacatg accctttggg aatataactgg agttttgtt
541 ttccctcatac tgtaaaatag acattatattt atccacccca ctggattgtt gtgagggtgg

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601 gatgaaatga tgcataataaa cacgcttagc ttaagagttt ggtacaatca gtgaacaaat
661 gattatgaat tagtgctttt attgttagtca gaatcataaa gatttgacag gttcccatat
721 cccacctctg cttggactac ctcatttgc cataatgcaaa gattatttgg tacctactgt
781 gtgtgcacca tggatgggc ctgcctctgt ggaaagtctt tgggtgcagg gggagacagc
841 catgggact gatgacatca ggttagttatc gtgagtttg ggggtgtcca gagcaaagg
901 atggtgccgt atataccaag tgtgttctgg tgtgggggtt gacacgcacc agggctagg
961 ctgcagagaa tgtctgtgtt gcagatctag gtttctccat gatcatcggt gggaatgtgt
1021 tttgtctgca agtgtatgct cataatgagtt tccctgggtc tctgtgtgtc agtgtgttac
1081 ctgtgtgtt ggggttatgg gtgtatgcat gcatgtatgtt aacatgccc tttgtgttac
1141 tctggacttg tatgtctgttata tttttttttt gtttctgtct gtacatgccc
1201 tcgtatgtttt cctcaatttt gtgtgtgtt atatgtgtt cattttttt gtgccttcca
1261 ggccccctt gccaccccttgg gcaagggtgt gtacaccacc caagtgtcca cctccgcttgg
1321 tctgtatgttgc tctgtgacgc ccccgctctc tgccttagtgc agcctgtgtg gatgtggag
1381 actaatctcc ccgcgggcac tgcgtgtgac ctcacccccc tctgtgaggg ggttatttct
1441 ctactttcggtt gtctctgagg tgccttcag tgcccccttcc ccccaaaaaa atgccttctg
1501 agttgaatat caacactaca aaccgagttt ctgcagactg cagagggccc tgcgtatgag
1561 tgcgtatgttggg ttttaggacc aggttggggc ggggtggggg tgcctaccc tgcgtatgttgg
1621 ccgacccact ggacaaggcac ccaacccca ttcccaaat tgcgtatccc ctatcagaga
1681 gggggggggg aaacaggatg cggcgaggcg cgtcgcgcact ggcagcttca gcaccgcgg
1741 cagtcgttcc gccccccctt ggcggcgccg gcaaccgcgg cctcagactt gatggcgcc
1801 tgcgtatgttgggg ttttttttttcc cccggcccttcc cccggcccttcc cccggcccttcc
1861 cccggccggg cccaggccggg cccggccggg cccggccggg cccggccggg cccggccggg
1921 accatctcgcc tgcggcgcc ggcgacttcc cgcgttccat gtcgtgggtt ggcagcgag
1981 gagtcgtgttgc tgccttgaga ggcgagctgtt gtcctggggc accgcgcagt ccgcggcc
2041 ggctcctggc cagaccaccc ctggggggcc tgcggccat gtcgtatgttgg
2101 cggcgccggcc tgcggacag caactttatg gcaatctgc caaatgggtt catgacagac
2161 ctgcagcgcc cccggccggcc cccggccggcc cccggccggcc cccggccggcc cccggccggcc
2221 ggtccccggg cccggccactgc cggggggcc tccgggggtcc cccggccggcc cccggccggcc
2281 gcccctggcc cccggccggcc gggggggggg gggggggggg gggggggggg gggggggggg
2341 aaggcagacca cggcgccggc agctggccacc ttccggccggc aggtgggggg cggctctggg
2401 ggcgcggcc cccggggggcc cccggccggcc tgcgtgttgc tcatcgacga ggcgcacacc
2461 gactggtaag

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[0113] By "SYP protein" (or synaptophysin protein) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Reference Sequence: NM_003179.2.

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(SEQ ID NO: 41)
MLLLADMDVVNVQLVAGGQFRVVKEPLGFVVKVLQWVFAIFAFATCGSYSGE
LQLSVDCANKTESDLSIEVEFEPFRLHQVYFDAPTCRGTTKVFLVGDY

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SSSAEFFVTAVFAFLYSMGALATYIPLQNKYRENNKGPMFLATAVFA
FMWLVSAAA WAKGLSDVKMATDPENIIKEMPVCRTGNTCKELRDPVTSG
LNTSVVFGFLNLVWVGNLWFVFKETGWAAPPLRAPPGAPEKQPAPGDAY
GDAGYGQGPGGYGPQDSYGPQGGYQPDYGPQAGSGGSGYGPQGDYQQGY
GPQGAPTSFSNQM

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[0114] By "SYN nucleic acid molecule" (or synaptophysin gene) is meant a polynucleotide encoding an SYN1 polypeptide. An exemplary SYN nucleic acid molecule (e.g., mRNA) is provided at NCBI Reference Sequence: NM_003179.2.

(SEQ ID NO: 42)

```
1 gccccctgca ttgctgatgc tgctgctggc ggacatggac gtggtaatc agctggtggc
61 tgggggtcag ttccgggtgg tcaaggagcc cctcggttt gtgaagggtgc tgcaatgggt
121 cttcgcacc tcgcctttc ccacatgcgg cagctacagt ggggagctcc agctgagcgt
181 ggattgtgcc aacaagaccg agagtgcacct cagcatcgag gtcgagttcg agtaccctt
241 caggctgcac caagtgtact ttgatgcacc cacctgcccga gggggcacca ccaagggtctt
301 ctttagttggg gactactcct cgtcagccga attctttgtc accgtggccg tgggtgcctt
361 cctctactcc atgggggctc tggccaccta catcttcctg cagaacaagt accgagagaa
421 taacaaaaggg cccatgtctgg actttctggc cacggctgtg ttcgccttca tgggtgttagt
481 tagctcatcg gcatgggcca aggggctgtc agatgtgaag atggccacag acccagagaa
541 cattataaag gagatgcctg ttcgcgcacc gacagggAAC acatgcagg agctgagaga
601 ccctgtgacc tcgggactca acacccgtt ggtgttcggc ttctgaacc tggtgctctg
661 ggtcggaac ctgtgggtcg tggtaagga gacaggctgg gggccccgt tcctgcgcgc
721 gctcccgcc gccccccgaga aacaacccggc accccggggac gctacggcg atgcaggctt
781 cgggcaggcc cccgggggtt acggggccca ggattccatc gggcctcagg ggggttacca
841 gctgtactat ggtcaaccag cggcagcgg tggcagtggc tacgggctc agggcacta
901 tgggcagcaa ggctacggcc cgcagggtgc acccacctcc ttctccaatc agatgttagt
961 tggtcagtga agcccaggag gacctggggg gggcaagagc tcaggagaag gctgtcccc
1021 cttccccaccc ctatacccta ggtctccacc cctcaagccca ggagaccctg tctttgtgt
1081 ttatatatat atatattata tataaatatc tatttatctt tctgagccct gcccctactc
1141 cactccctc atccactagg tgcccagtct tgagtggcc ccctcttta ccccgccct
1201 ttccctgcatt cccttggccc ctctctgttt accctccctt tccctgagg ttaaggggat
1261 ctaaaaaggag gacagggagg gaacagaccc cggctgtgtg gggagggtgg gctgtactt
1321 agactcttc ctctctctcc ctccactctt cccaaactctt gcttgggttc ctccagcaat
1381 gcctgcctga acaaaggccg ttaggaaat ccaactccag ggttaaagaa aggccagagat
1441 tgggggggtt tgggttagag aggacagttt aggacccaaag gtggcttgg agaggaggtg
1501 tggagtgag gggtcagcag ggggttggg ttccagacag agtggatctg gagtctgaag
1561 gagaggaggc cgcttagagca ttctgggttg gggcttggaa gggcgctgag ggcagggttc
1621 tagaaggggc gaggtttaa gcttggcaga atggtgggtt ccagagtagg tgggtcttgg
1681 atgggttacca gacccatgg aaagggtgtg gcttggaaac tttggagac ttaggtttagt
1741 tctaaagggg acagatcttgc agcaaggcaa gaagtggat tcaggaatgg gccaaggccag
1801 ggttccagac aggggtgggc tttagaatggg gcttccatgg tggtttccaga aaggccagcc
1861 cttccccatg gtgcagtgaa gaaaatgttt tacaatggct ggggttggc agtggagagg
1921 ggacttggat aggagcttcc agatgggttt tggtaggggtt gggggagaat ggctctggct
1981 acgacttggg acggaaagtgg cctgagaaga gtcgagtgtat tggcttgcata gggtgaggcg
2041 tgggatccag agagaagcac cccaccacac acacccttcc ccactccctt gatgaaacag
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2101 ctaggttaat aggaggacag aaccaacggg tctgtggac tggcccaccc ctcttcccc
2161 ttcccctgcg ccctccctcc ctccacacct ccaccctgtcc tggggtggtt ggaggcctgg
2221 tctggagccc ctatccgtca ccctctgtca tgtctgtat gtcaagtatgt cctgtatcg
2281 tgtgttgcca ttttgtctgg ctgtggcccc tccttctccc ctccagaccc ctacccttc
2341 ccaaaccctt cggattttgtt caaaagaaccc ccctcccca ggaagaacaa atatgattct
2401 cctctccaa ataaaactcct taaccaccta gtcaaaaaaa aaaaaaaaa

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[0115] By "NOGOA polypeptide" (or neurite outgrowth inhibitor A; neurite outgrowth inhibitor isoform A; human reticulon-4; human reticulon-4 isoform A) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_065393.

```

(SEQ ID NO: 43)
1 medldqplv sssdspprpq pafkyqfvre pedeeeeeee eeeddededle elevlerkpa
61 aglsaaapvt apaagaplmd fgndfvppap rgplpaappv aperqpswdp spvsstvpap
121 splsaaavsp sklpedddepp arpppppas vspqaepvwt ppapapaapp stpaapkrrg
181 ssgsvdetlf alpaasepvi rsssaenmdlk eqpgntisag qedfpsvlle taaslpsslsp
241 lsaasfkehe ylgnlstvlp tegtlqenvs easkevseka ktllidrdlt efseleysem
301 gssfsvspka esavivanpr eeiivknde eeklvsnnil hnqgelptal tklvkedevv
361 ssekakdsfn ekrvaveapm reeyadfkpf ervwevkdsk edsdfaagg kiesnleskv
421 dkkcfadsle qtnhekdses snndtsfpst pegikdrsga yitcapfnpa atesiatiif
481 pllgdptsen ktdekkieek kaqivteknt stkt.snpflv aaqdsetdyv ttdnltkvte
541 evvanmpegl tpdlvqeace selnevtgtk iayetkmdlv qtsevmqesl ypaaqlcpsf
601 eeseatpspv lpdivmeapl nsavpsagas viqpsssple assvnyesik hepenpppye
661 eamsvslkkv sgikeeikep eninaalqet eapyisiacd liketklsae papdfsdyse
721 makveqvpvd hselvedssp dsepvdlfsd dsipdvpqkq detvmlvkes ltetsfesmi
781 eyenkeklsa lppeggkpyl esfklsldnt kdtilpdevs tlkkekipl qmeelstavy
841 snndlifiske aqiretetfs dsspieiide fptlissktd sfsklareyt dlevshksei
901 anapdgagsl pctelphdls lknipkvee kisfsddfsk ngsatskvll lppdvsalat
961 qaeiesivkp kvlvkeakk lpsdtekdr spsaifsael sktsvvdlly wrdikktgvv
1021 fgaslfllls ltvfsivsvt ayialallsv tisfriykgv iqaiqksdeg hpfraylese
1081 vaseelvqk ysnsalghvn ctikelrrlf lvddlvdslk favlmwvfty vgalfngl1
1141 lilalislfs vpviyerhqa qidhylgan knvkdamaki qakipglkrk ae

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[0116] By "NOGOA nucleic acid molecule" (or neurite outgrowth inhibitor A; neurite outgrowth inhibitor isoform A; human reticulon-4; human reticulon-4 isoform A) is

meant a polynucleotide encoding an NOGOA polypeptide. An exemplary NOGOA nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_020532.

```

(SEQ ID NO: 44)
1 agtcccctgcc ctccccctggg gagggtgagt cacgccaac tggggcgagaa gtccgctggc
61 ctcaactcta gctcatctgg gccgcggcgaa caagtggggc cagggcggtt ggccgcataac
121 cggcgccggag gcaggaggag cagtcattt gttccggggag ccgtcaccac agtaggtccc
181 tcggctcagt cggcccagcc cctctcagtc ctccccaaacc cccacaaccc cccggggctc

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241 tgagacgogg ccccgccggc ggccgcagca gctgcagcat catctccacc ctccagccat
301 ggaagacctg gaccagtctc ctctggtctc gtcctcgac agcccacccc ggccgcagcc
361 cgcgttaag taccaggctcg tgaggggagcc cgaggacgag gaggagaag aggaggagga
421 agaggaggac gaggagaag acctggagga getggaggtg ctggagagga agccccccgc
481 cgggctgtcc gggccccag tgcacccccc ccctgcggcc ggccgcgcgc tgatggactt
541 cggaaatgac ttctgtccgc cggegcggc gggacccctg cggccgcgtc ccccggtcg
601 cccggagcgg cagccgtctt gggaccccgag cccgggtgtcg tgcacccgtc ccgcgcacat
661 cccgctgtct gtcgcgcag tctgcgcctc caagctccct gaggacgacg agccctccgc
721 cggccctccc cctccctccc cgccgcgcgt gagcccccag gcagagcccg tggatggacccc
781 gecagccccg gtcgcgcgcg cgccccccctc cacccggcc gggcccaagc gcaggggctc
841 ctccggctca gtggatgaga cccttttgc tcttcctgtc gatctgtgc ctgtgatacg
901 ctccctcgca gaaaatatgg acttgaagga gcagccaggt aacactattt cggctggtca
961 agaggatttc ccatctgtcc tgcttgcac tgctgcttct ctcccttctc tgccttcctct
1021 ctcagccgct tcttcaaag aacatgaata ctttgtaat ttgtcaacag tattaccac
1081 tgaaggaaca cttcaagaaa atgtcagtga agcttctaaa gaggtctcag agaaggcaaa
1141 aactctactc atagatagag atttaacaga gtttcagaa tttagataact cagaaatggg
1201 atcatcggttc agtgcgtctc caaaagcaga atctgcgtc atagtagcaa atccctaggaa
1261 agaaataatc gtgaaaaata aagatgaaga agagaagttt gtttagtaata acatccttca
1321 taatcaacaa gagttaccta cagctttac taaattggtt aaagaggatg aagttgtgtc
1381 ttcagaaaaaa gcaaaagaca gttttatga aaagagatgt gcagtggaaat ctcctatgag
1441 ggaggaatgc cagacttca aaccatttgc gcgcgttatgg gaagtggaaat atgtagatgg
1501 agatagtatgt atgttggctg ctggaggtaa aatcgagacg aacttggaaa gtaaagtgg
1561 taaaaaatgt tttgcagata gccttgcac aactaatcac gaaaagata gtgagatgt
1621 taatgtatgt acttcttcc ccagtcgc aagatgtata aaggatgtt caggagcata
1681 tatcacatgt gtcctttta acccagcagc aactgagacg attgcaacaa acattttcc
1741 tttgttaga gatcctactt cagaaaataa gaccgtgaa aaaaaatag aagaaaagaa
1801 ggcccaata gtaacagaga agaataactg caccaaaaca tcaaaccctt ttcttgtagc
1861 agcacaggat tctgagacag attatgtcac aacagataat ttaacaaagg tgactgagga
1921 agtcgtggca aacatgcctg aaggcctgac tccagattt gtacagggaaat catgtgaaag
1981 tgaattgaat gaagttactg gtacaaagat tgcttatgaa aaaaaatgg acttgggtca
2041 aacatcgaaat gttatgcac agtcaactcta tcctgcacca cagcttgc catcatgt
2101 agagtcgaaat gctactcctt caccaggatgtt gcgtgacatt gttatggaaat caccattgaa
2161 ttctgcgtt ccttagtgcgt gtgcgtccgt gatacagcc agctcatcac cattagaagc
2221 ttcttcgtt aattatgaaa gcataaaaaca tgacgtgaa aaccccccac catatgaa
2281 ggccatgatgt gtatcactaa aaaaagtatc aggaataaaag gaagaaatta aagagcctga
2341 aaatattaaat gcagcttcc aagaaacaga agctccctat atatctattt catgtgattt
2401 aattaaagaa acaaagcttt ctgtgtacc agctccggat ttctctgattt attcagaaat
2461 ggccaaatgtt gaacagccag tgcctgtatca ttcttgatca gttgaagatt cctcacctga

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2521 ttctgaacca gttgacttat ttatgtatga ttcaataacct gacgttccac aaaaacaaga
2581 taaaaactgtg atgcattgtga aagaaagtct cactgagact tcatttgagt caatgataga
2641 atatgaaaat aaggaaaaac tcagtgcctt gccacctgag ggagggaaagc catatttgg
2701 atcttttaag ctcagtttag ataacacaaa agataaccctg ttacctgatg aagtttcaac
2761 attgagcaaa aaggagaaaa ttcccttgca gatggaggag ctcagtactg cagtttattc
2821 aaatgtatgc ttatTTTTT ctaaggaagc acagataaga gaaactgaaa cgTTTcaga
2881 ttcatctcca attgaaatta tagatgagtt ccctacattt gcagttcta aaactgattc
2941 attttctaaa ttagccaggg aatatactga cctagaagta tcccacaaaa gtgaaattgc
3001 taatgcggcg gatggagctg ggtcattgcc ttgcacagaa ttgcggccatg acctttcttt
3061 gaagaacata caacccaaag ttgaagagaa aatcagtttc tcagatgact tttctaaaaa
3121 tgggtctgct acatcaaagg tgctcttattt gcctccagat gtttctgctt tggccactca
3181 agcagagata gagagcatag ttaaacccaa agttcttgcg aaagaagctg agaaaaaaact
3241 tccttccgat acagaaaaag aggacagatc accatctgct atatTTTcag cagagctgag
3301 taaaacttca gttgttgcacc tcctgtactg gagagacatt aagaagactg gagttgggtt
3361 tggtgccagc ctattctgc tgctttcattt gagagtattc agcattgtga gctgtacagc
3421 ctacattgcc ttggccctgc tctctgtgac catcagcttt aggatataca agggtgtgat
3481 ccaagctatc cagaatcag atgaaggcca cccattcagg gcatatctgg aatctgaagt
3541 tgctatatct gaggagttgg ttcaagaagta cagtaattct gctttggc atgtgaactg
3601 cacgataaag gaactcagggc gccttttctt agttgatgat ttagttgatt ctctgaagtt
3661 tgcagtttg atgtgggtat ttacctatgt tgggccttg ttatggc tgacactact
3721 gatTTTggc ttcatttcac tttcattgt tccattttt tatgaacggc atcaggcaca
3781 gatagatcat tatctaggac ttgcaataa gaatgtaaa gatgctatgg ctaaaatcca
3841 agcaaaaatc cctggattga agcgc当地 tgaatgaaa cgc当地 aatttagtgg
3901 agttcatctt taaagggat attcatttga ttatacgggg gagggtcagg gaagaacgaa
3961 ctttgacgtt gcagtgcaat ttcacagatc gtttttagat ctttatTTT agccatgcac
4021 tgggttggg aaaaatttacc tgcattgtact gccatgtgtt catcatctt agtattgtaa
4081 gctgctatgt atggatttaa accgtaatca tttttttt ctatctatct gaggcactgg
4141 tggaaataaa aacctgtata ttttacttg ttgcagatag tcttgcggca tcttggcaag
4201 ttgcagagat ggtggagctt gaaaaaaaaa aaaaaaagcc ctttcagtt tgcactgt
4261 gatgggtccg tggatttgc tgcagatTTT ctgaaatgaa atgtttttt agacgagatc
4321 ataccggtaa agcaggaaatc acaaagcttgc ctttctgtt atgttctagg tgcattgtga
4381 cttttactgt tatattaaatt gccaatataa gtaaatatag attatataatg tatagtgttt
4441 cacaaagctt agacctttac cttccagcca ccccacatgt ctgtatattt cagagtcgt
4501 cattgggtt acatgtgttag ttccaaagca cataagctg aagaagaaat atttcttagga
4561 gcactaccat ctgttttcaa catgaaatgc cacacacata gaactccaac atcaatttca
4621 ttgcacagac tgactgttagt taatTTTgc acagaatctt tggactgaat ctaatcttc
4681 caaaaatgtt gtttgggttgc aaatataaa cattgtttagt caagaaatta ttaattacaa
4741 aatgaagatt tataccatttgc tggtttaagc tgtactgaac taaatctgtg gaatgcatttgc

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4801 tgaactgtaa aagcaaagta tcaataaagc ttatagactt aaaaaaaaaaaa aaaaaaaaaaa

4861 aaaaaaaaaa a

[0117] By "GFAP" (or Glial fibrillary acidic protein) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P14136.

(SEQ ID NO: 45)
 1 merrritsaa rrsyvssgem mvgglapgrr lpgptrlsla rmpplptrv dfslagalna
 61 gfketraser aemmelndrf asyiekvrfl eqqnkalaae lnqlrakept kladvyqael
 121 relrlrlldql tansarleve rdnlaqdlat vrqklqdett lrleaennla ayrqeadeat
 181 larldlerki esleeeirfl rkiheevre lqeqlarqqv hveldvakpd ltaalkeirt
 241 qyeamassnm heaeewyrsk fadltdaar naellrqakh eandyrrqlq sltcleslr
 301 gtneslerqm requeerhvre aasyqealar leeeggqslkd emarhlqeyq dllnvklaed
 361 ieiatyrkll egeenritip vqtfnsnlqir etsldtksvs eghlkrnivv ktvemrdgev
 421 ikeskqehkd vm

[0118] By "GFAP nucleic acid molecule" (or Glial fibrillary acidic protein) is meant a polynucleotide encoding an GFAP polypeptide. An exemplary GFAP nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_002055.

(SEQ ID NO: 46)
 1 atgcccgagtc tagcccactc cttcataaaag ccctcgcattt ccaggaggcga gcagagccag
 61 agcaggatgg agaggagacg catcacctcc gctgctcgcc gctcctacgt ctccctcaggg
 121 gagatgtatgg tggggggcct ggctcttggc cgccgtctgg gtccctggcac ccgcctctcc
 181 ctggctcgaa tgccccctcc actcccgacc cgggtggatt tctccctggc tggggactc
 241 aatgctggct tcaaggagac ccggggccagt gagggggcag agatgtatgg gctcaatgac
 301 cgctttgcca gtcacatcga gaagggttcgc ttccctggAAC agcaaaacaa ggccgtggct
 361 gctgagctga accagctgcg ggccaaggag cccaccaagc tggcagacagt ctaccaggct
 421 gagctgcgag agctgcggct gccggctcgat caactccaccc ccaacagcgc ccggctggag
 481 gttgagaggc acaatctggc acaggacctg gccactgtga ggcagaagct ccaggatgaa
 541 accaacatcga ggcttggaaac cgagaacaac ctggctgcct atagacaggg agcagatggaa
 601 gccaccctgg cccgtctgg tctggagagg aagattgagt cgcttggagga ggagatccgg
 661 ttcttgagga agatccacga ggaggagggtt cgggactcc aggagcagct ggccgcacag
 721 caggtccatg tggagcttga cgtggccaaag ccagacctca ccgcagccct gaaagagatc
 781 cgcacgcagt atgaggcaat ggcgtccacg aacatgcatg aagccgaaga gtggtaaccgc
 841 tccaagtttgcagacactgac agacgctgct gcccgcacg cggagctgct ccggcaggcc
 901 aagcacgaag ccaacgacta ccggcgccag ttgcagtcct tgacactgcga octggagtc
 961 ctgcgcggca cgaacgagtc cctggagagg cagatgcgcg agcaggaggaa gcggcacgt
 1021 cgggaggccgg ccagttatca ggaggcgctg ggcggctgg aggaagaggg gcagagcctc
 1081 aaggacgaga tggcccgcca cttgcaggag taccaggacc tgctcaatgt caagctggcc
 1141 ctggacatcg agatcgccac ctacaggaag ctgcttagagg gcggaggaa ccggatcacc

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1201 attcccggtgc agacacctc caacctgcag attcgagaaa ccagcctgga caccaagtct
1261 gtgtcagaag gccacactaa gaggAACatc gtggtaaga cCGTGGAGAT gCGGGATGGA
1321 gaggtcatta aggagtccaa gcaggAGCAC aaggatgtga tGTGAGGGAG gaccCACCTG
1381 gtggcctctg ccccgctctca tgagggggccc gageagaAGC aggatAGTTG ctccgeetct
1441 gctggcacat ttccccagac ctgagctccc caccACCCCA gctgctcccc tccctctct
1501 gtccttaggt cagcttgctg ccctaggctc cgtcagtatac aggctgcca gacggcacc
1561 acccagcacc cagcaactcc aactaacaag aaactcaccc ccaaggGGCA gtctggaggg
1621 gcatggccag cagcttgcgt tagaatgagg aggaaggaga gaaggggagg agggcgggggg
1681 gcacctaacta catcgccctc cacatccctg attctgttg ttatggaaac ttttgcaga
1741 gatggaggtt ctctcgagt atctggAAC ttttgccttgg agtttccctca ggctgtgg
1801 ggaaaactga gactcagaca ggaaaggAA gggcccacAG acaaggTAGC cttggccaga
1861 ggcttgggtt gtctttgggt ttttatgagg tggatatacc ctatgtGCC taggtgtacc
1921 ttgaactctt gggctcaAGC agtctacccA cctcagccTC ctgtgtAGC gggattatAG
1981 attggagCCA ccatGCCAG ctcagaggGT ttttctccta gactgaccCT gatcAGtcta
2041 agatgggtgg ggacgtcctG ccacctgggg cagtCACCTG cccAGATCCC agaaggACCT
2101 cctgagcgt gactcaagtG ttcAGtcca cctgagctGc catccaggGA tgccatctgt
2161 gggcacgtG tggcagggtG ggaggttGat ttcAGcact tgggggatct gttgttacG
2221 tggagaggGA tgaggtgtG ggagggatAG agggggGCTG cttggccccC agctgtgggt
2281 acagagaggT caagcccAGG aggACTGCC cgtcAGact ggagggGACG ctggtagAGA
2341 tggaggaggGA ggcaattGGG atggcgctAG gcatACAAGT aggggttGtG ggtgaccAGt
2401 tgcacttggc ctctggattG tggaaattAA ggaAGTgact catccttG aAGATGCTGA
2461 aacaggAGAG aaaggGGGAtG tatccatGGG ggcaggGCat gactttGtCC catttctAAA
2521 ggccttcc ttgctgtgtc ataccaggCC gccccAGCCT ctgagccccCT gggactGtG
2581 cttcttaacc ccagtaAGCC actGCCACAC gtcAGACCt CTCCACCCCA tagtGaccGG
2641 ctgtttcc ctaAGCCAAG ggcccttGc ggtcccttCT tactcacaca cAAAtGtAC
2701 ccagtattct aggtAGTGCC ctatTTACA attgtAAAAC tgaggcAcGA gcaaAGtGAA
2761 gacactGGtC catattCCTG cagcctGGAG gcccGGtGtC caggGtGAC acgtCCACCC
2821 cagtGcACCC actctGtTT GactGAGCAG actGGtGAGC agactGGtGG gatctGtGCC
2881 cagAGatGGG actGGGAGGG CCCACTTCAG gtttctcCTC tcccctctAA gGCCGAAGAA
2941 gggcccttcc ctctccccAA gactGGtGTG ctttccctc CactccttCC tgccacCTGc
3001 tgctgtgtC gctgctaAtC ttcaGGGAcC tgctgtGCC tttAGtGtGtC gagaaaaAA
3061 aaAGACAAAt gctGCGCCt tccccAAAAA aaaaaAA

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[0119] By “s100b” (or S-100 protein beta chain; S-100 protein subunit beta; \$100 calcium-binding protein B) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. P04271.

(SEQ ID NO: 47)
1 mselekaMva lidvfhQySg regdkhklkk selkelinne lshfleeike qevvdkvmet
61 ldndgdgecd fqefmafVam vttacheffe he

[0120] By “s100b nucleic acid molecule” (or S-100 protein beta chain; S-100 protein subunit beta; S100 calcium-binding protein B) is meant a polynucleotide encoding an s100b polypeptide. An exemplary s100b nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_006272.

(SEQ ID NO: 48)

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1 gggcagaggg aataagaggc tgcctctgcc caccagtccct gcccggccagg accccgacgc
61 gagacgacgc ctgcaccaag gagaccagga aggggtgaga caaggaagag gatgtctgag
121 ctggagaagg ccatggggc cctcatcgac gtttccacc aatattctgg aagggagggaa
181 gacaaggcaca agctgaagaa atccgaactg aaggagctca tcaacaatga gctttccat
241 ttcttagagg aaatcaaaga gcaggagggtt gtggacaaag tcatggaaac actggacaaat
301 gatggagacg gcgaatgtga cttccaggaa ttcatggccct ttgttgccat ggtaactact
361 gctgcacacg agtttttga acatgagtga gattagaaag cagccaaacc ttccctgtaa
421 cagagacggt catgcaagaa agcagacagc aaggggcttc agcctagtag gagctgagct
481 ttccagccgt gtttagctta attaggaagc ttgatttgc ttgtgattga aaaattgaaa
541 accttttcc aaaggctgtt ttaacggccctt gcatcattct ttctgtata ttggcctgt
601 gtgtaaagctg actggccccca gggactcttg ttaacagtaa cttaggagtc aggtctcagt
661 gataaagcgt gcaccgtgca gcccggccatg gccgtgtaga ccctaaccgg gagggaaccc
721 tgactacaga aattaccccg gggcacccctt aaaacttcca ctacctttaa aaaacaaagc
781 cttatccagc attatttgaa aacactgctg ttctttaat gcttcctca tccatgcaga
841 taacagctgg ttggccgggtg tggccctgca agggcgtggg ggttccggcc tgcttccgg
901 gatgcgcctg atcaccaggt gaacgctcag cgctggcagc gtcctggaa aaagcaactc
961 catcagaact cgcaatccga gccagctctg ggggctccag cgtggccctcc gtgaccatcg
1021 cgatccaagt cgccgtgca ggatcctgc ctccaaacgtg ctccacgcac atgcggcttc
1081 cgagggcact accggggct ctgagccacc gcgaggggct ggttcaata aaaaag

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[0121] By “PAX6 polypeptide” (or paired box protein PAX6) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAK95849.1.

(SEQ ID NO: 49)

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MQNSHSGVNQLGGVFVNGRPLPDSTRQKIVELAHSGARPCDISRILQVSN
GCVSKILGRYYETGSTRPRAIGGSKPRVATPEVVSKIAQYKRECPHSIFAW
EIRDRLLSEGVCTNDNIPSVSSINRVRLNLASEKQQMGADGMYDKLRLMN
GQTGSWGTRPGWYPGTSPVGQPTQDGCCQQQEGGGENTNSISSNGEDSDEA

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QMRLQLRKLRQRNRTSFTQEIQIEALEKEFERTHYHPDVFARERLAAKIDLP
EARIQVWFNSNRRAKWRREEKLRNQRQRASNTPSHIPISSSFSTSVDQPIP
QPTTPVSSFTSGSMLGRDTALTNTYSALPPMPSFTMANNLPMQPPVPSQ
TSSYSCMLPTSPSVNGRSYDTYTPPHMQTHMNSQPMGTSGETSTGLISPG
VSVPVQVPGSEPDMSSQYWPRQLQ

```

[0122] By “PAX6 polynucleotide” (or paired box protein PAX6) is meant a polynucleotide encoding an PAX6 polypeptide. An exemplary PAX6 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. AY047583.

(SEQ ID NO: 50)

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1 agggggaaaga cttaactag gggcgccgcg atgtgtgagg ctttttatgc tgagagtgaa
61 cagacatccg agatttcaga gccccatatt cgagccccgt ggaatccgc ggcggccgc
121 cagagccgcg atgcagaaca gtcacagcgg agtgaatcag ctcgggtggg tctttgtcaa
181 cggccggcca ctgcccggact ccacccggca gaagattgtaa gagctagctc acagccgggc
241 cccggccgtgc gacatttccc gaattctgc ggtgtccaaac ggtgtgtga gtaaaattct

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301 gggcaggtat tacgagactg gctccatcg acccaggca atcggtggta gtaaaccgag
361 agtagcgact ccagaagttg taagcaaaat agcccagtat aagcgggagt gcccgccat
421 ctttgcttgg gaaatccgag acagattact gtccgagggg gtctgtacca acgataacat
481 accaagcggt tcatcaataa acagagttct tcgeaacctg gctagcgaaa agcaacagat
541 gggcgccagac ggcacgtatg ataaactaag gatgttgaac gggcagaccg gaagctgggg
601 cacccgccct ggttgtatc cggggacttc ggtgccaggg caacctacgc aagatggctg
661 ccagcaacag gaaggagggg gagagaatac caactccatc agttccaacg gagaagattc
721 agatgaggct caaatgcgac ttcaagctgaa gcggaaagctg caaagaaata gaacatcatt
781 tacccaaagag caaatttgggg ccctggagaa agagttttag agaaacccatt atccagatgt
841 gtttgcggca gaaagactag cagccaaaat agatctacct gaagcaagaa tacaggtatg
901 gtttctaat cgaaggccca aatggagaag agaagaaaaa ctgaggaatc agagaagaca
961 ggcacagcaac acacccatgc atattccatc cagcagtagt ttcaagcacca gtgtctacca
1021 accaattcca caacccacca caccggtttc ctccctcaca tctggctcca tggtggcccg
1081 aacagacaca gcccacaa acacccatcag cgctctgccc cctatgccc gtttccccat
1141 ggcaataaac ctgcctatgc aaccccccagt ccccaagccag acctccatc atccctgcatt
1201 gctgcccacc agcccttcgg tgaatggcg gagttatgtt acctacaccc ccccacatat
1261 gcagacacac atgaacagtc agccaatggg cacctcgggc accacttcaa caggactcat
1321 ttccccctggt gtgtcagttc cagttcaagt tcccgaaagt gaaacctgata tgtctcaata
1381 ctggccaaga ttacagtaa

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[0123] By "Nestin polypeptide" is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_006608.1.

(SEQ ID NO: 51)

```

MEGCMGEESFQMWEFLNRLEAYLARVKALEEQNELLSAELGGLRAQSADT
SWRAHADDELALRALVDQRWREKHAEEVARDNLAAELEGVAGRCCQQLRL
ARERTTEEVARNRRAVEAEKCARAWLSSQVAELERELEALRVAHEEERVG
LNAQAAACAPRCPPAPPRGPPAPAPEVEELARRLGEAWRGAVRGYQERVAHM
ETSLGQARERLGRAVQGAREGRLELQQLQAERGGLLERRAALQRLGRW
QERLRATEKFQLAVEALEQEKGQLQSQIAQVLEGRQQLAHLKMSLSLEVA
TYRTLLEAENSRLQTPGGGSKTSLSFDPKLELQFPRTPEGRRRLGSLLPV
LSPTSLPSPLPATLETPVPAFLKNQEFLQARTPTLASTPIPPTPQAPSPA
VDAEIRAQDAPLSLLQTQGGRKQAPEPLREARVAIPASVLGPPEEPGGQ
RQEASTGQSPEDHASLAPPLSDHSSLREAKDGSGSRVFSICRGECEGEGQ
IWGLVEKETAIEGVVVSSLQQEIQWEEEIDLNRKEIQLSQVPLEKETLKSLG
EEIQESLKTLENQSHETLERENQECPRSLEEDLETLSLEKENKELLKD
EVVRPLEKEAVGQLKPTGKEDTQLSQLQKENQELMKSLEGNLETFLFPG
TENQELVSSLQENLESLTALEKENQEPLRSPEVGDEEALRPLTKENQEPL
RSLEDENKEAFRSLEKENQEPLKTLEEEDQSVIRPLETENHKSLRSLEEQ
DQETLRTLEKETQQRRLSLGEQDQMTLRPPEKVDLEPLKSLDQEARIPL

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NENQEFLKSLKEESVEAVKSLETEILESLKSAGQENLETILKSPETQAPLW
TPEEEINQGMNPLEKEIQEPLESVEVNQETFRLLEEEENQESLRLSGAWNWL
ENLRSPEEVDKESQRNLEEEENLGKGEYQESLRSLEEEQELPQSADVQR
WEDTVEKDQELAESPPGMAGVENEDAEALNLREQDFTGKEEVVEQGEL
NATEEVWIPEGHPPESPEPKERQGLVVEGASVKGGAEGLQDPPEGQSQVGA
PGLQAPQGLPEAIEPPLVEDDVAPGGDQASPEVMLGSEPMGESAAGAEPG
PGQGVGLGLDPGHLTREEVMEPPLLEESLEAKRVQGLEGPRKDLEEAGGL
GTEFSELPGKSRDPWEPREGRESESEAAPRGAAEAPPATLGHGTGSDAP
SPWPPLGSEEAEEDVPPVLVSPSPTYTPILEDAPGPQPQAEQSGQEASWGVQ
GRAEALGKVESEQEELGSGEIPEGPQEEGEESREEESEDELGETLPDSTP
LGFYLRSPSPRWDPTGEQRPPPQGETGKEGWDPAVLASEGLEAPPSEKE
EGEEGEEECGRDSLSEEFEDLGTEAPFLPGVGEVAEPLGQVPQLLDP
AAWDRDGESDGFADEEESGEEGEEDQEEGREPGAGRWGPSSVGSLOALS
SSQRGEFLESDSVSVSPWDDSLRGAVAGAPKTALETESQDSAEPSGSEE
ESDPVSLEREDKVPGPBLEIPSGMEDAGPGADIIGVNGQGPNLEGKSQHVN
GGVMNGLEQSEEVGQGMPLVSEGDRGSPFQEEEGSALKTSWAGAPVHLGQ
GQFLKFTQREGDRESWSSGED

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[0124] By "Nestin polynucleotide" is meant a polynucleotide encoding an Nestin polypeptide. An exemplary Nestin nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_006617.

(SEQ ID NO: 52)

1 gctactccca ccccggcccg ccccgtcatt gtccccgtcg gtctctttc tttccgtcc
61 taaaagctct gcgagccgc cccttctccc ggtgccccgc gtctgtccat cctcagtggg
121 tcagacgagc aggtggagg gctgcatggg ggaggagtcg tttcagatgt gggagctcaa
181 tcggcgctcg gaggccctacc tggccgggt caaggcgctg gaggagcaga atgagctgct
241 cagcgcggag ctcggggggc tccgggacaca atcccgccgac acctcctggc gggcgcatgc
301 cgacgacgag ctggcgcccc tgccggccct cggtgaccaa cgctggcggg agaagcacgc
361 ggccgaggtg ggcgcgacaca acctggctga agagctggag ggcgtggcag gccgatgcc
421 gcagctgcgg ctggcccccgg agcggacgac ggaggaggta gcccgcacacc ggcgcgcccgt
481 cgaggcagag aaatgcgcacc gggcctggct gaggtagccag gtggcagcgc tggagcgcga
541 gctagaggct ctacgcgtgg cgacacgagga ggagcgcgtc ggctgaacg cgcaggctgc
601 ctgtgcccccc cgctgcccccc cgccgcccccc cggccctccc gcccggcccc cggaggtaga
661 ggagctggca aggcaactgg gcgaggcgtg gcgcggggca gtgcgcggct accaggagcg
721 cgtggcacac atggagacgt cgctggggca ggcggcgag cggctggggcc gggcggtgca
781 ggggtggccgc gagggccgc tggagctgca gcagctccag gctgagcgcg gaggcctcc
841 ggagcgcagg gcagcggtgg aacagaggaa ggaggggccgc tggcaggagc ggctgcgggg
901 tactgaaaag ttccagctgg ctgtggaggc cctggagcag gagaacacagg gcctacagag
961 ccagatcgct caggtccctgg aaggcggca gcagctggcg cacctaaga tgcctccat
1021 cctggagggtg gccacgtaca ggaccctccct ggaggcttag aactcccgcc tgcaaacacc
1081 tggcggtggc tccaagactt ccctcagctt tcaggacccc aagctggagc tgcaattcccc
1141 taggacccca gagggccggc gtcttgatc tttgtccca gtcttgagcc caactccct
1201 cccctcaccc ttgcctgtata cccttgagac acctgtgcca gccttttta agaaccacaa
1261 atccctccat gcccgtaccc ctaccttggc cagaacccca atccccccca cacctcaggc
1321 accctctctt getgttagatc cagagatcag agccaggat gctcctctt ctctgtccca
1381 gacacagggt gggagggaaac aggtccaga gcccctgcgg gctgaagcca gggtggccat
1441 tccctggcgc gtcctgtgtc gaccagagga gcctggggcc cagcggcaag aggccagtag
1501 aggccagttcc ccagaggacc atgcctccctt ggaccacccc ctcagccctg accactccag
1561 ttttaggggt aaggatgggg aatccgggtgg gtcttagatgt ttccat ggcgggggg
1621 aggtgaaggg caaatctggg ggttgtttaga gaaagaaaca gccatagagg gcaaaatgg
1681 aagcagcttg cagcaggaaa tatggaaaga agaggatcta aacacggagg aaatccagg
1741 ctcccaggtt ctttggaaa aagaaaccct gaagtctctg ggagaggaga ttcaagagtc
1801 actgaagact ctggaaaacc agagccatga gacactagaa agggagaatc aagaatgtcc
1861 gaggtcttta gaagaagact tagaaacact aaaaagtcta gaaaaggaaa ataaagagct
1921 attaaaggat gtggaggtag tgagacatct agaaaaagag gctgttagcc aacttaagcc
1981 tacaggaaaa gaggacacac agacattgca atccctgcaa aaggagaatc aagaactaat
2041 gaaatctttt gaaggtatac tagagacatt ttatccca ggaacggaaa atcaagaatt
2101 agtaagttct ctgcaagaga acttagagtc attgacatgt ctggaaaagg agaatcaaga
2161 gccactgaga tctccagaag tagggatgtc ggaggactg agacactctga caaaggagaa
2221 tcaggaaccc ctgaggtctc ttgaagatgtc gaacaaagag gccttagat ctctagaaaa
2281 agagaaccag gagccactgaa agactctaga agaagaggac cagagtatttgc tgagacatct

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2341 agaaacagag aatcacaaat cactgaggc tttagaagaa caggaccaag agacatttag
2401 aactcttcaa aaagagactc aacagcgacg gaggctctca ggggaacagg atcagatgac
2461 attaagaccc ccagaaaaag tggatctaga accactgaag tctcttgacc aggagatagc
2521 tagaccttta gaaaatgaga atcaagagtt cttaaagtca ctcaaagaag agagcgtaga
2581 ggcagtaaaa tcttagaaa cagagatcct agaatcactg aagtctgcgg gacaagagaa
2641 cctggaaaca ctgaaatctc cagaaactca agcaccactg tggactccag aagaaataaa
2701 tcagggggca atgaatctc tagaaaagga aattcaagaa ccactggagt ctgtggaaagt
2761 gaaccaagag acattcagac tccttggaga ggagaatcag gaatcattga gatctctgg
2821 agcatggAAC ctggagaatt tgagatctcc agaggaggt gacaaggaaa gtcaaaggaa
2881 tctggaaagag gaagagaacc tggaaaggg agagtagccaa gagtcactga ggtctctgg
2941 ggaggaggaa caggagctgc cgcaagtctgc agatgtgcag aggtggaaag atacgggtgg
3001 gaaggacca gaactggc tcctggatg gctggagtg aaaatgagga
3061 tgaggcagag ctgaatctga gggagcagga tggcttcaact gggaggagg aggtggtaga
3121 gcaggagag ctgaatgccaa cagaggaggt ctggatccc ggcgaggggc acccagagag
3181 ccctgagccc aaagagcaga gaggcctgg tggaggagcc agtgtgaagg gaggggctga
3241 gggcctccag gacccttgaag ggcaatcaca acaggtgggg gccccaggcc tccaggctcc
3301 ccaggggctg ccagaggcga tagagccccct ggtggaaat gatgtggccc cagggggctga
3361 ccaagectcc ccagaggctca tggggggctc agagcctgc atgggtgagt ctgctgcggg
3421 agctgagcca gggccggggc aggggggtggg agggctgggg gacccaggcc atctgaccag
3481 ggaagagggtg atgaaaccac cccttggaga ggagagttt gaggcaaaga gggttcagg
3541 cttggaaaggg cctagaaaagg accttagagga ggcagggtgt ctggggacag agttctccga
3601 gctgcctggg aagagcagag acccttggga gcctcccagg gagggttaggg aggagttaga
3661 ggctgaggcc cccaggggag cagaggaggc gttccctgtc gagaccctgg gccacactgg
3721 aagtgtatgcc cttcacctt ggctcttggg gtcagaggaa gctgaggagg atgtaccacc
3781 agtgcgtggc tccccccagcc caacgtacac cccgtacgtc gaagatggcc ctgggcctca
3841 gcctcaggct gaaggaggc tagagggtgt ctgggggggtg cagggggagg ctgaaggccc
3901 gggggaaatgtc gagagcgcgc agggaggatgtt ggggtctggg gagatccccg agggccccca
3961 ggaggaaggg gaggagagca gagaagagag cgaggaggat gagctgggg agacccttcc
4021 agactccact cccctgggtc tctacccatg gtccccacc tccccccaggt gggaceccac
4081 tggagagcag aggcaccccc ctcacggggaa gactggaaag gagggtgttgg atccctgtgt
4141 cctggctcc gaggcccttgg agggccacc ctcagaaaag gaggagggggg aggaggggaga
4201 agaggagtgt ggccgtgact ctgacccgtc agaagaattt gaggacctgg ggactgaggc
4261 accttttctt cctgggggtc ctggggagggt ggcaggacacct ctggggccagg tgccccagct
4321 gctactggat ctcacggcc gggatcgaga tgggggtgtc gatgggtttt gcatgtgg
4381 agaaaatgtggg gaggaggaggag aggaggatca ggaggagggggg agggaggccag gggctgggg
4441 gtggggggccaa ggggtttctgt ttggcaggccctg agtagctccc agagagggg
4501 atccctggag tctgattctg tgagtgtcag tggccctgg gatgacagct tgagggg
4561 agtggctgtgtt gcccccaaga ctggccctggaa aacggaggcc caggacactg ctgaccc
4621 tggctcagag gaagagtctg accctgtttc ctggagagg gaggacaag tccctggccc

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4681 tctagagatc cccagtggga tggaggatgc agggccaggg gcagacatca ttgggtttaa
4741 tggccagggt cccaaacttgg aggggaagtc acagcatgtg aatgggggg tgatgaacgg
4801 gctggagcag tctgaggaag tggggcaagg aatgccgcta gtctctgagg gagaccgagg
4861 gagcccttt caggaggagg aggggagtg tctgaagacc tcttggcgag gggctctgt
4921 tcacctggc cagggtcagt tcctgaagtt cactcagagg gaaggagata gagagtctg
4981 gtcctcaggg gaggactagg aaaagaccat ctgccccggca ctggggactt aggggtgcgg
5041 ggaggggaag gacgcctcca agcccgctcc ctgctcagga gcagcactct taacttacga
5101 tctcttgaca tatggtttgc ggctgagagg cctggcccgc taaggtgaaa aggggtgtgg
5161 caaaggagcc tactccaaga atggaggctg taggaatata acctccacc ctgcaaagg
5221 aatctttgc ctgctccatc tcataggcta agtcagctga atcccgatag tacttaggtcc
5281 cttccctcc gcatcccgta agctggaaaa ggcctgtggc ccagaggctt ctccaaagg
5341 agggtgacat gctggctttt gtgcccaga tcaccagccc tgcccacct cactgcagta
5401 gtgcaccatc tcactgcagt agcacgcctt cctggggcgt ctggcctgtg gctaattggag
5461 gtgacggcac tccatgtgc tgactcccc catccctgccc acgctgtggc cttgcctggc
5521 tagtccctgc ctgaataaag taatgcctcc gcttcaaaaa aaaaaaaaaa aaaaaaaaaa
5581 aaaaaaaaaa a

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[0125] By “LHX6 polypeptide” (or LIM homeobox 6) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAI03937.1.

(SEQ ID NO: 53)
MAQPGSGCKATTRCLEGTAPPAMAQSDEALAGALDKDEGQASPCTPSTP
SVCSPPSAASSVPSAGKNICSSCGLEILDRLYLLKVNNLIWHVRCLECSV
RTSLRQQNSCYIKNKEIFCKMDYFSRGTKCARCGRQIYASDWVRARGN

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AYHLACFACFSCKRQLSTGEEFLVEEKVLCRHYDTMIENLKRAAENG
GLTLEGAVPSEQDQPQPKPAKRARTSFTAEQLQVMQAQFAQDNNPDAQTLQ
KLADMTGLSRRVIQWVFQNCRARHKHPTQHPVPPSGAPPRLPSALSDD
IHYTPFSSPERARMVTLHGVIESHPFSLTLPALPHLPVGAPQLPLSR

[0126] By “LHX6 polynucleotide” (or LIM homeobox 6) is meant a polynucleotide encoding an LHX6 polypeptide. An exemplary LHX6 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC103936.

(SEQ ID NO: 54)
1 cccgcccaccc accaggtgat ggcccagcca gggccggct gcaaagcgac caccgcgtt
61 ctgtggggg cccgcgcgc cccatggct cagtcgtaccc cccggccctt ggcaggagct
121 ctggacaagg acgggggtca ggcctccca tgcacgcacc tcgtctgtca
181 cccgcctctg cccgcctctc cgtggcgat gcaggcaaga acatctgtcc cagctggcc
241 ctgcagatcc tggaccgata tctgtcaag gtcaacaacc tcacatggca cgtgggggtc
301 ctgcagatgtcc cctgtgtcg cacgtcgctg aggccggcaga acagctgtca catcaagaac
361 aaggagatct tctgcaagat ggactacttcc agccgattcg ggaccaagtg tgccgggtc
421 ggccgcacaga tctacgcccag cgactgggtg cggagagctc gcccgcacgc ctaccaccc
481 gcctgcgtcg cctgcgtctc gtgcacgcgc cagctgtcca ctgggtggaa gttccggctg
541 gtgcaggaga aggtgtctg ccgcacccac tacgacacca tgattgagaa cctcaagagg
601 gcccggaga acggggacgg cctcaacgttg gagggggcag tgccctcgga acaggacagt
661 caacccaaagc cggccaaagcg cggccggacgc tccttcacccg cggaaacagct gcaggttatg

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721 caggcgcagt tcgcgcagga caacaacccc gacgctcaga cgctgcagaa gctggggac
781 atgacgggcc tcagccggag agtcatccag gtgtggttc aaaactgccc ggcgcgtcat
841 aaaaagcaca cggccacaaca cccagtggcg ccctcgaaaa cggccccgtc cggccttccc
901 tccgcctgt cegacgacat ccactacacc ccgttcagca gccccgagcg ggcgcgcatt
961 gtcacccctgc acggctacat tgagagtcat ccttttcag tactaacgct gccggcactt
1021 ccgcacatctgc ccgtggggcgc cccacagctg cccctcagcc gctgagatcc agtgtccaag
1081 ctgcggccag gagtccaccc acctccgcat ccacccctgt ccgcacatctt gcccacccacc
1141 aggtcgggttc cggaggectg gccttccct ctctgctga gaaccagaac ccaccaggag
1201 caccacagag tcctcctt ggaaggcaga actccctgaa atctggaatc agggtggaaa
1261 cagccgttt ttccattta aacaggagtc ctcttcaact tcagctgatt acaataacaa
1321 aaggcgaat tgaattgtgc gatgccaacg gccttctcat ttacaggttt tttcccca
1381 cattggcctt tatttactac ttccctggaa ccacatctgt attctgaata gtcgacaacc
1441 cccaaatgtta tccactctgt tgctttgtc tgaaaaactc tacagtgttt gtgggatgtc
1501 cccaaaggta agctatgttc taattttatc attccatct gtctggttat gtcaagttaa
1561 ttcagaaaga gaagagacag tgaccaaccc tgagaggcct aatagggcag agatggaggc
1621 ctgcccacac taggaggcag cggggataga cagggatgg ggagaagaaa gaccccccatt
1681 ggtttgaaa tcaaggagag ggcggtgaca tattggacca gaagaggcac tagccattt
1741 aaggagagga aagagaaaac tctggggtca gggagagacc ctaccccccac ctaattatcc
1801 agcatatatg taagaaacat agcagcgatg gtattcgatc tgtccatga ctcttctgaa
1861 tgtttgaca ggtagagtt ggggacccct gttggccact ttttgacccct tcatagtgg
1921 gcttggccca ggtcttctca atggagggg aatcccttat aggggagagg gaacagagcc
1981 cagtgaaatg gcagtcagaa ttttacccct ggatccatct ctaagtagag agaggggtgcc
2041 cattgccttag gtgagtgtc caagctcagg attccactg gtgcctctga gttcccaat
2101 caatacttcc tggagccacccc cctgagaaca gaggtcagac acagctgcgt
2161 aacatccatc ctgctacaac tcttccaccc caaacaagg ggctcaggct acacacgacc
2221 atgattttatg ttttcagggg atgcccattt gtcccaagct ttttctgtaa ttcttagatt
2281 acctgggtgc ctgatgcatt ttccactaga ggttgctaatt cagcatgttt tagcccaagt
2341 ccaccccttctt gtttttttttttgg aaggagactc taagacagg
2401 aaagcaagtt catggatcat acgcagccat ttttccatg gcaagacattt
2461 ctaatcaatg gcagctctat ttcaactgagt ctggataagg tttcagagtt caaatgctt
2521 acgttggcac ttaacatgaa agcttatagg tcattcttc tctggatct acaggcagg
2581 taggcacagg tgcagcctaa gaagggaaacc tgcccttccaa gacagtgaca
2641 gctgactgag ggcaaaagac aggcaccact cagaacgtgg tgagtagcgc tcagctcagc
2701 actcagtcag tggtaacttg tgcccaagccc ttttttttttttttttttgg gctgacatca
2761 ccaggggccca attccctggcc ttggagctca aatcccttctt ttttttttttttttttttttttgg
2821 tcaaggcccc agtgg

[0127] By "LHX8 polypeptide" (or LIM homeobox 8) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAH40321.1.

(SEQ ID NO: 55)
 MQILSRCQGLMSEECRTTALAAGRTRKGAGEEGLVSPPEGAGDEDSCSSS
 APLSPSSSPRSMASGSGCPPGKVCNSCGLEIVDKYLLKVNDLCWHVRCL
 SCSVCRTSLGRHTSCYIKDKDIFCKLDYFRRYGTCSRGRHIHSTDWVR

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 RAKGNVYHLACFACFSCKRQLSTGEEFALVEEKVLCRVHYDCMLDNLKRE
 VENGNGISVEGALLTEQDVNHPKPAKRARTSFTADQLQVMQAQFAQDNNP
 DAQTLQKLAERTGLSRRVIQVWFQNCRARHKHVSPNHSSTPVTAAPPS
 RLSPPMLEEMAYSAYVPQDGTMITALHSYMDAHSPTTLGLQPLLPHSMTO
 LPISHT

[0128] By "LHX8 polynucleotide" (or LIM homeobox 8) is meant a polynucleotide encoding an LHX8 polypeptide. An exemplary LHX8 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC040321.

(SEQ ID NO: 56)
 1 agcgccaaga ggcttagggc tggaccactt gtgtggagt ggtaaagAAC tatcatgaat
 61 ccatttaactg aaagtgtcca ttctctaact caccctaaAG aggacAAACA ccgcaaaAGTA
 121 gttaaaaAGTC aggcatTCGC gtcggacGTC tgggtttGAAG ttctgcCTG gcttgactGG
 181 aaacgcTTCC CCTATTCTT ccgtacGGGA ccggggAGAGC ttactggcGC tctgcGAACC
 241 ggctggAAAG aaacaccGAG tcactcgtAC agactcttGG tcgcAGAACT tggctttCCG
 301 ctattggTC CTCAGAACCG CTTGAACAA CTGGCCCCAG CTGGCGCATC agaccgcAGT
 361 gagGAATGCC GCGGGGGCGGG TGGCGAAGGC AGGGTCTGCC CGCCAGTGGA TTCCCGGGTG
 421 tcccgcgtgg agcaggcttGCCCAGCTGGG aAGCCCATCA AACCTCAGTC ttggcccaca
 481 gtgggagaga gaccagtggg tcccagacGG aggccatcGC ccgcTTTGG cgacccTCCAC
 541 tggcgtGAAT AAAAGCACCC CTCTTCTTACc CTCAGAAACT gtgggtAGCA aggtataaaaa
 601 cggagtctgg gaccggtaAG tcccAGGTG AGCCCGTATA cagctctGCC atctctgagg
 661 ggttatgcAG ATTCTGAGCA ggtgtcAGGG GCTCATGTCA gaggAGTGCG ggcggactac
 721 agccctggcg GCGGGGAGGA CTCGCAAAGG CGCCGGGGAA gagggactGG tgagccccGA
 781 gggagcGGGG gacgaggact cgtgcTCTC CTCGGCCCCG CTGTCCCCGT CGTCCTCGCC
 841 ccggTCCATG GCTCGGGCT CGGCGTCCC TCCTGGCAAG TGTGTGTGCA acagttgcGG
 901 CCTGGAGATC GTGGACAAAT ACCTTCTCAAG GGTGAATGAC CTATGTGGC ATGTCGGTG
 961 tctctcCTGC AGTGTGGCA GAACTCCCT AGGAAGGCAC ACCAGCTGTT ATATTAAGA
 1021 caaaAGACATT TTCTGAAAC TTGATTATTT CAGAAGGTAT GGAACCTCGCT GCTCTCGATG
 1081 tgggagacac ATCCATTCTA CTGACTGGGT CGGGAGAGC AAGGGGAATG TCTATCACTT
 1141 ggcATGCTTT GCTGTCTTT CCTGAAAAG GCAACTTCC ACAGGGAGGG AGTTTGTCTT
 1201 ggtggaaAGAG AAAGTCTCT GCAGAGTACA TTATGACTGC ATGCTGGATA ATTTAAAAAG
 1261 agaaaggaca GGCTTGAGCA GACGTGTGAT ACAGGTGTGG TTTAGAGCAGC
 1321 taaccatCCA AAACCAGCAA AAAGAGCTCG GACCAGCTT ACAGCAGATC AGCTTCAGGT
 1381 tatGCAAGCA CAATTGCTC AGGACAACAA CCCAGATGCA CAGACACTCC AGAAATTGGC
 1441 agaaaggaca GGCTTGAGCA GACGTGTGAT ACAGGTGTGG TTTAGAGCAGC
 1501 ccacaAGAAA CACGTCACTC CTAATCACTC ATCCTCCACC CGAGTCACAG CAGCCCCACC
 1561 CTCCAGGCTG TCTCCACCCA TGTAGAAGA ATGGCTTAT TCTGCCTACG TGCCCCAAGA
 1621 tggAACGATG TTAACTGCGC TGCGATAGTTA TATGGATGCT CATTCAACCA AAACCTCTGG
 1681 ACTCCAGCCC TTGTTACCCC ATTCAATGAC ACAACTGCCA ATAAGTCATA CCTAATTCTT
 1741 TTTTCAGGGA TAGACTTGAT TAAGGATATA AATTGTCT ATATTATGTA TAAAATACCA

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1801 ttgaaaagat attactgtta attttttatt taacacctaa agcatttcca acatcacttt
1861 gctgccagg tatgtatcta tagttggcct gcaagacact tttattaatt cttcatttt
1921 tgtaaaacctt atgtttaca gaagaaaaca aatcaaaaca tttttgtat tgtctggaaa
1981 tagttcaactc tagtgtgtat ctgttaattt atttgtcattc aaaagagcac tttgcctaaa
2041 agaaaggact gacaagtgtg caaaatgttt acaatcttt gtgaaattgt agtttatcat
2101 tagtttgtat ctgttaagtta ttgtataaaa tattacctgt atttttgtt atatacaact
2161 ttatacttgc aagcttgtat ctgtgaattt gcaactgaaa ttatattgc caatgtttc
2221 tgaatgaact gaataaagct tctgttgtag catgocatgc aaacacatta ttgtgtttgt
2281 gggtgatgaa ttatggctgt aaataaacact atagtttaat aagccccacca ttctgagttt
2341 attaaacatt ttccatttgc ttgaaaattt caaaaaaaaaaaaaaa aaagaaaaaaaaaaaa
2401 aaaaaaaaaa a

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[0129] By “TBR1 polypeptide” (or T-box, brain 1 (TBR1)) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_006584.1.

(SEQ ID NO: 57)

```

MQLEHCLSPSIMLSKKFLNVSSSYPHSGGSSELVLDHPIISTTDNLERSS
PLKKITRGMTNQSDTDNFPSDKSPGDVQRSKLSPVLDGVSELRLHSFDGS
AADRYLLSQSSQPQSAATAPSAMFPYPGQHGPAPAFSIGSPSRYMAHH
VITNGAYNSLLSNSSPQGYPTAGYPYPQQYGHYSQGAPFYQFSSSTQPGLV
PGKAQVYLCNRPLWLKPHRHQTEMIITKQGRRMFPLSFNISGLDPTAHY
NIFVDVILADPNHWRFQGGKWVPCGKADTNVQGNRVMHPDPNTGAHW
RQEISFGKLKLTNNKGASNNNQMVVLQSLHKYQPRLHVVEVNEDGTEDT

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SQPGRVQTFTFPETQFIAVTAYQNTDITQLKIDHNPFAGFRDNYDTIYT
GCDMDRLTPSPNDSPRSQIVPGARYAMAGSFLQDQFVSNYAKARPHPGAG
AGPGPGTDRSVPHTNGLLSPQQAEDPGAPSPQRWFVTPANNRLDFAASAY
DTATDFAGNAATLLSYAAAGVKALPLQAAGCTGRPLGYYADPSGWGARSP
POYCCTKSGSVLPWPNSAAAARMAGANPYLGEEAEGLAAERSPLPPGA
AEDAKPKDLSWIETPSSIKSIDSSDSGIYEQAKRRRISPADTPVSES
SSPLKSEVLAQRDCEKNCAKDISGYGFYSHS

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[0130] By “TBR1 polynucleotide” (or T-box, brain 1 (TBR1)) is meant a polynucleotide encoding an TBR1 polypeptide. An exemplary TBR1 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_006593.

(SEQ ID NO: 58)

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1 gtcgctacca ggagccaggt gattatccta attaatgtct atctaattaa attactgtca
61 gcagctaacc aatggcagga gccgttcat cggctgcaca agcagcaaga tcaaaagtga
121 gcctttctg attgctgcat agtgtcaatt ggccaatctc ttctcccagg gaaaaaaaaaa
181 agtaaatcaa acctttgaga agcatttgc ggttgaagtg ctttctgtct agtgagggggg
241 tctgtggatt tcttagttat gataaatagg actttaaaaa ccagggacgg gagggcggagt
301 gttcagggttc tagagctatc cagctggagc actgccttc tccttctatc atgctctcca
361 agaaatttct caatgtgagc agcagctacc cacattcagg cggatccgag cttgtctgc
421 acgatcatcc cattatctcg accactgaca acctggagag aagttcacct ttgaaaaaaaaaa
481 ttaccagggg gatgacgaaat cagtcagata cagacaattt tcctgactcc aaggactcac
541 cagggggacgt ccagagaagt aaactctctc ctgtcttggc cggggctctc gagcttcgtc
601 acagtttgcg tggctctgcgct gcagatcgct acctcctctc tcagtcgcagc cagccacagt
661 ctgcggccac tgctcccagt gccatgttcc cgtaccccg ccagcacgg ccggcgcacc
721 ccgccttctc catcgccagc cctagccgt acatggccca ccacccggc atcaccaacg
781 gagcctacaa cagcctcctg tccaaactcct cggccgcaggg atacccacg gccggctacc
841 cctacccaca gcagtaacggc cactcctacc aaggagctcc gttctaccag ttctcctcca

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901 cccagccggg gctgggtgcc ggc当地acac aggtgtacct gtgcaacagg ccccttggc
961 tgaatttca ccggcaccaa acggagatga tc当地accaa acaggaaagg cgc当地tttc
1021 ctttttaag ttttaacatt tctggctcg atcccacggc tc当地acaat atttttgtgg
1081 atgtgatTTT ggccggatccc aatcactgga ggTTTcaagg aggcaaATgg gttccttgcg
1141 gcaaAGCggA caccaatgtg caaggAAATC gggTctataT gcatccggat tcccccaaca
1201 ctggggctca ctggatgcgc caagaaATCT ctTTTggAAA attaaaACTT acgaacaaca
1261 aaggagCTTC aaataacaat gggcagatgg tgTTTtaca gtc当地tgcac aagtaccagc
1321 cccgcctgca tgtggTggAA gtgaacgagg acggcacggA ggacactagc cagccccggcc
1381 gcgtgcagac gttcacttC cctgagactc agttcatcgC cgtcaccggc taccagaaca
1441 cggatattac acaactgaaa atagatcaca acccTTTgc AAAaggattt cgggataatt
1501 atgacacgat ctacaccggc tgtgacatgg accgcctgac cccctcgccc aacgactcgC
1561 cgc当地tcgca gatcgtggcc gggggccgct acggccatggc cggctcttC ctgcaggacc
1621 agttcgtgag caactacgCc aaggcccgct tccacccggg cgc当地ggcg ggggggggg
1681 cgggtacggA cgc当地cgTg cgc当地cacca acgggctgct gtc当地ggcag caggccgagg
1741 acccggggcgc gccc当地cgcc caacgc当地gtt tgTgacgCc ggccaacaac cggctggact
1801 tc当地ggcctc ggc当地tatgac acggccacgg acTTcgccggg caacgc当地ggcc acgctgctct
1861 cttacgc当地ggc ggc当地ggcgtg aaggccgctc cgc当地cgaggc tgccaggctgc actggccgccc
1921 cgctcggcta ctacgc当地gc acgc当地ggcgtt gggggccccc cagtc当地cccg cagtaactgC
1981 gc当地ccaaggC gggc当地gggtg ctgc当地ctgct gggccaaacag cgc当地ggggcc ggc当地ggc
2041 tggccggcgc caatccctac ctggggcagg aggccgaggg cctggccgccc gagc当地ctc
2101 cgctgc当地cc gggccggcc gaggacgCc agggcaaggA cctgtccgat tccagctggA
2161 tc当地gacgCc ctacctegate aagtccatcg actccagega ctccgggatt tacgagcagg
2221 ccaagcggag gggatctcg cggccgacA cgc当地ctgC cagagatTC tcccccgetca
2281 agagc当地gggt gtc当地ggccag cgggactgC agaagaactg cgc当地aggac attagcggct
2341 actatggcTT ctactcgac acgttagggcc cccctgccc cccggccccc cgc当地ggcc
2401 gaccccccagc cagccctca cagcttcc ccaagctccgc ctccccacac tccctcttgc
2461 gc当地ccactc attttatttgc accctcgatg gccgtctgca gcaataagt gcaaggctcc
2521 gagc当地gtgatt ttaacccttt ttgc当地cagca gtc当地tgc当地 ttagctcacc gaccttca
2581 tttgc当地tggaa acctttggT ttccctactt actcttctc tggaggtaa tccctctaca
2641 atccccctcc cccctcgTtt tctcttacct cctacttctc tttttgtaa tggaaactt
2701 cacctttagg agacctgggc agtc当地gtca ggc当地cageg attc当地ggcc gcaaggctc
2761 ggc当地ccaca ttaaccatag gatgttgact ct当地aacctg gacccaccca ggc当地tcc
2821 tcttatcccc gagttggg atggatggat ggtggtagg gatgttaata attttagtgg
2881 aacaaggct gt当地aaatgtat tgc当地atgtt gt当地aacgtat ggctagttt
2941 tattctcgCt aaggc当地aaa accaggctcat gctt当地acctt ttttccctt cccctt
3001 cttttcttC tctctctca tacttctct tctctctt ttaatttct tgc当地gata
3061 tattcttaaga ggctctagaa acatgaaata ctc当地tagtgc atgggTTcc cacttct
3121 caatccgttG catgaaataa ttactatgtg cc当地aatgca cacaatagc taaggagaat
3181 ccacccaaac acctttaaag gatagggtgc tggcatagg caagtc当地gatt aagtggcatg

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3241 atgcctgcaa agcaaagtca actggagttg tatgttcccc ccacccatc aatagaatag
3301 ctcgacatca gcaatattat tttgccttat ttgttttcc ccaaagtgc aaatccatta
3361 ctggctgtg caggtgcca atatgtgac aaactgttc tgaatatctt tcagtaccc
3421 ttcaccta tatgtctgaa atcttgtaa tgaatactct attaatgata tagatgactg
3481 aattgttgt aactatagt tagtctagt aagatgaatt gtgtgagttg tatattttac
3541 tgcattttag ttttggaaaat gacttccccca ccacccatgaa acagctgaaa tttgacttcc
3601 ttgggagaac actagcatta atgcaagtaa gactgattt cccctaagtc ttgttatatt
3661 tgataaggag catataatccc cctggaaata gattagtagg atttctaatg ttgtgttagca
3721 aacctatact ttttgtatt taaaaattaa tgtgaaatat gcatcataca caatattcaa
3781 tctagattcc agtccatggg gggattttc ctaataggaa ttcaagggtt aacgtgtgt
3841 atattttggc tcttctgtaa atctaatgtt gtgatttttta tatttgttcc gttttgtctg
3901 tgaactgaat aatttataca agaacacact ccattggaaa acgttttgc ttttgcgt
3961 ttgtatcgta tgtgtataac aagtaaaaata aacctggtaa aaacgc

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[0131] By "SLC1A3 polypeptide" (or solute carrier family 1; glial high affinity glutamate transporter member 3 (SLC1A3)) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. BAG35230.1.

(SEQ ID NO: 59)
MTKSNGEEPKMGRMERFQQGVRKRTLLAKKKVQNIKEDVKSYLPRNAF
VLLTVTAIVGTILGFTLRPYRMSYREVKYFSPGELLMRMLQMLVLPLI
ISSLVTGMAALDSKASGKMGRAVYYMMTTTIAVVIGIIIVIIIHPGKG
TKENMHREGKIVRVTAADAFLDLIRNMFPPLNVEACFKQFKTNYEKRSFK
VPIQANETLVGAVINNVSEAMETLTRITEELVPVPGSVNGVNALGLVVFS

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MCFGFVIGNMKEQQQALREFFDSLNEAIMRLVAVIMWYAPVGILFLIAGK
IVEMEDMGVIGGQLAMYTVTVIVGLLIHAVIVLPPLLFLVTRKNPWWFIG
GLLQALITALGTSSSSATLPIFKCLEENGVDKRVTFRVLPVGATINMD
GTALYEALAAIFIAQVNNEFLNFGQIITISITATAASIGAAGIPQAGLVT
MVIVLTSVGLPTDDITLIIAVDWFLDRLRTTNVLGDSLGAGIVEHLSRH
ELKNRDVEMGNVIEENEMKKPYQLIAQDNETEKPIDSETKM

[0132] By "SLC1A3 polynucleotide" (or solute carrier family 1; glial high affinity glutamate transporter member 3 (SLC1A3)) is meant a polynucleotide encoding an SLC1A3 polypeptide. An exemplary SLC1A3 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. AK312304.

(SEQ ID NO: 60)
1 gatagtaact tgcagttca gaggcacatgc acactgtcag ggctagccct cctgcttacg
61 cgcgctgcgg attgttgctc cgtgtacct gctggggat tcacccctgtt actgtttgtat
121 atcttccacc ccttacaaaa tcagaaaagt tgtgtttct aataccaaag aggagggttg
181 gctttctgtg ggtgattccc agacactgaa gtgcaaagaa gagaccctcc tagaaaagta
241 aaatatgact aaaagcaatg gagaagagcc caagatgggg ggcaggatgg agagattcca
301 gcagggagtc cgtaaacgca cactttggc caagaagaaa gtgcagaaca ttacaaagga
361 ggatgttaaa agttacctgt ttccggatgtc ttttgcgtt ctcacagtca ccgctgtcat
421 tgtgggtaca atccttggat ttaccctccg accatacaga atgagctacc gggaaagtcaa
481 gtacttctcc ttccctgggg aacttctgtat gaggatgtt cagatgtgg tcttaccact
541 tatcatctcc agtcttgtca caggaatggc ggcgtcatat agtaaggcat cagggaaagat
601 gggaaatgcga gctgttagtct attatatgac taccaccatc attgctgtgg tgattggcat
661 aatcattgtc atcatcatcc atcctggaa gggcacaag gaaaacatgc acagagaagg
721 caaaattgtt cagtgacag ctgcagatgc cttccctggac ttgatcagga acatgttccc

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781 tccaaatctg gtagaaggct gcttaaaca gttaaaacc aactatgaga agagaagctt
841 taaagtgcac atccaggcca acgaaacgct tgtgggtgt gtgataaaca atgtgtctga
901 ggccatggag actcttaccc gaatcacaga ggagctggtc ccagttccag gatctgtgaa
961 tggagtcata gcccctggtc tagttgtctt ctccatgtgc ttccgggttg tgattggaaa
1021 catgaaggaa cagggcagg cccttagaga gttttgtat tctcttaacg aagccatcat
1081 gagactggta gcagtaataa tgtggtatgc ccccggtgg attctttcc tgattgtgg
1141 gaagattgtg gagatggaa acatgggtgt gattgggggg cagcttgcac tgacaccgt
1201 gactgtcatt gttggcttac tcattcacgc agtcatcgcc ttgcactcc totacttctt
1261 ggtaaacacgg aaaaaccctt ggggtttat tggagggttg ctgcaagcac tcatcaccgc
1321 tctggggacc tttcaagtt ctgccaccct acccatcacc ttcaagtgc tggaagagaa
1381 caatggcgtg gacaagecg tcaccagatt cgtgtcccc gtaggagcca ccattaacat
1441 ggtatggact gcccctatag aggcttggc tgccatttc attgtcaag ttaacaactt
1501 tgaactgaac ttccggacaaa ttattacaat cagcatcaca gcccacagctt ccagtattgg
1561 ggcagctgga attcctcagg cggcctggt cactatggtc attgtgtga catctgtcg
1621 cctgcccact gacgacatca cgctcatcat cgcgggtggac tggttccctgg atcgccctcg
1681 gaccaccacc aacgtactgg gagactccct gggagctggg attgtggagc acttgtcactg
1741 acatgaactg aagaacagag atgttcaaattt ggttaactca gtgattgaag agaatgaaat
1801 gaagaaacca tatcaactga ttgcacagga caatgaaact gagaacccca tcgacagtga
1861 aaccaagatg tag

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[0133] By "TH polypeptide" (or tyrosine hydroxylase) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAI43612.1.

(SEQ ID NO: 61)
MPTPDATTPQAKGFRRAVSELDQQAEEAIMSPRFIGRRQSLIEDARKERE
AAVAAAAAAAVPSEPGDPLEAVAFEEKEKGKAVLNLLFSRATKPSALSRAV
KVFETFEAKIHHLETRPAQRPRAGGPHELYFVRLEVRGRDLAALLSGVRQ
VSEDVRSRSPAGPKVPWFPRKVSELDKCHHLVTKFDPLDLDWPGFSDQVYR

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QRRKLIAEIAFQYRHGDPIPRVEYTAEEIATWKEVYTLKGLYATHACGE
HLEAFALLERFSGYREDNIPQLEDVSRLKERTGFQLRPVAGLLSARDFL
ASLAFRVFQCTQYIRHASSPMHSPEPDCCHELLGHVPMLADRTFAQFSQD
IGLASLGASDEEIEKLSTLYWFTVEFLCKQNGEVKAYGAGLSSYGEELL
HCLSEEPEIRAFDPPEAAAVQPYQDQTYQSVPVSESFSDAKDKLRSYASR
IQRPFNSVFKDPYTLAIDVLDSPOAVRRSLEGVQDELDLTAHALSAIG

[0134] By "TH polynucleotide" (or tyrosine hydroxylase) is meant a polynucleotide encoding an TH polypeptide. An exemplary TH nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC143611.

(SEQ ID NO: 62)
1 acccagagg ggctttgacg tcagtcago ttataagagg ctgctggggcc agggctgtgg
61 agacggagcc cggacctcca cactgagcca tgcccacccc cgacgccacc acgccacagg
121 ccaagggtt cccgaggccc gtgtctgacg tggacgcca gcagggcagag gccatcatgt
181 ccccgccgtt cattgggcgc aggccagagcc tcattcgagga cgcccgcaag gageggggagg
241 cggcggtggc agcagccggcc gctgcagtc cctccggagcc cggggacccc ctggaggctg
301 tggcccttga ggagaaggag gggaaaggccg tgctaaacct gctcttccccc ccgaggggcca
361 ccaagccctc ggcgcgtgtcc cgagctgtga aggtgtttga gacgtttggaa gccaaaatcc
421 accatctaga gaccggccc gcccagagcc cgccagctgg gggcccccac ctggagact
481 tcgtgcgcct cgaggtgcgc cgaggggacc tggccgcctc gtcagtggt gtgcgcagg

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541 tgcagagga cgtgcgcgac cccgcggggc ccaaggccc ctggttccca agaaaagtgt
601 cagagctgga caagtgtcat cacctggtca ccaagttcgac ccctgacactg gacttggacc
661 acccggtt ctccggaccag gtgtaccgcc acgcgcaggaa gctgattgtc gagatcgcc
721 tccagtagac gcacggcgc cccatcccc gtgtggagta caccgcgcgag gagattgcca
781 cctggaaaggaa ggtctacacc acgtgtacggg gcctctacgc caccgcacgc tgccggggagc
841 acctggggc ctttgcttg ctggagcgct tcagggctta ccgggaagac aatatcccc
901 agctggggg cgtctccgc ttctgtacggg agcgcacggg ctccagctg cggcctgtgg
961 ccggcctgtgt gtccgcgggg gacttctgg ccagccctggc ctccgcgtg ttccagtgtca
1021 cccagttat cccgcacgcg tcctgcacca tgcactcccc tgagccggac tgctgcacg
1081 agctgtggg gcacgtgtccc atgtggccg accgcaccc cgcgcgttc tgcaggaca
1141 ttggcctggc gtccctgggg gcctcgatg agggaaattgtaa gaagctgtcc acgctgtact
1201 ggttcacggg ggagttgggg ctgtgtaaagc agaacggggg ggtgtggcc tatgggtggc
1261 ggctgtgtc ctcttacggg gagcttctgc actgtgtgtc tgaggaggct gagattgggg
1321 ctttcgaccc tgaggctgcg gccgtgcgc cctaccaaga ccagacgtac cagtcgtct
1381 acttcgtgtc tgagaggttc agtgcacgca aggacaagct caggagctat gcctcacgca
1441 tccagcgccc ctttcgggt aagtgcgacc cgtacacgtt ggcacatcgac gtgtggac
1501 gccccaggc cgtggggcgc tccctgggg gtgtccggaa tgagctggac acccttggcc
1561 atgcgttag tgccattggc taggtgcacg gctgtccctga gggcccttcc caacctcccc
1621 tggtcctgc

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[0135] By "Neurofilament 200 polypeptide" (or neurofilament heavy (NEFH)) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_066554.2.

(SEQ ID NO: 63)
MMSFGGADALLGAPFAPLHGGGLHYALARKGGAGGTRSAAGSSGFHSW
TRTSVSSVSASPSRFRGAGAASSTDSDLTLSNGPEGMVAVATRSEKEQ
LQALNDRFAGYIDKVRQLEAHNRSLEGEAAALRQQQAGRSAMGELYEREV
REMRGAVLRLGAARGQLRLEQEHLLEDIAHVRQRLLDDEARQREEAEEAAR
ALARFAQEAEARVDLQKKAQALQEECGYLRRHHQEEVGELLGQIQGSGA
AQAOQMQAETRDALKCDVTSALREIRAQLEGHAVQSTLQSEEWFRVRLDRL
SEAAKVNTDAMRSAQEEITEYRQLQARTTELEALKSTKDSLTERQSELE
DRHQADIASYQEAQQLDAELRNTKWEAAQLREYQDLLNVKMAVDIEIA
AYRKLLGEEECRIGFGPIPFSLPEGLPKIPSVSTHKVKSEEKIKVVEKS
EKETVIVEEQTEETQVTEEVTEEEEKEAKEEEKGEEEGGEEEEAEGGEEE

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TKSPPAEEAASPEKEAKSPVKEEAKSPAEAKSPEKEAKSPAEVKSPEKA
KSPAKEAKSPPEAKSPEKEAKSPAEVKSPEAKSPAKEEAKSPAAEAKS
PEAKSPVKEEAKSPAEAKSPVKEEAKSPAEVKSPEAKSPTKEEAKSPE
KAKSPEKEEAKSPEAKSPVKAEEAKSPEAKSPVKAEEAKSPEAKSPVKE
EAKSPEAKSPVKEEAKSPEAKSPVKEEAKTPEAKSPVKEEAKSPEKA
KSPEAKTLDVKSPEAKTPAKEARSPADKFPEAKSPVKEEVKSPEAK
SPLKEDAKAPEKEIPKKEEVKSPVKEEKPQEVKVKEPPKKAEEEKAPAT
PKTEEKDKSKKEEAKPKVKEAPKPKVKEEKKEPAVEKPKESKVEAKKEAEDK
KKVPTPEKEAPAKVEVKEAKPKEKTEVAKKEPDDAKAKEPSKPAEKKEA
APEKKDTKEEKAKKPEEKPKTEAKAKEDDKTLSKEPSKPKAEEAKSSST
DQKDSKPPEKATEDKAAGKG

[0136] By "Neurofilament 200 polynucleotide" (or neurofilament heavy (NEFH)) is meant a polynucleotide encoding an Neurofilament 200 polypeptide. An exemplary Neurofilament 200 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_021076.

(SEQ ID NO: 64)
1 aaaagggcgc ggcgcctggc gctgcgcgc tgcctccgc cccgtccggc cctcgccac
61 ctgctcaggc catgtgcgc ttcggggggc cggacgcgc gctggggc cccgtccgc
121 cgctgcgtgg cggcgccgc ctccactacg cgctagcccg aaagggtggc gcaggcgaa

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181 cgcgtccgc cgctggctc tccagggct tcactcggt gacacggacg tccgtgatct
241 ccgtgtccgc ctgcggccagc cgcttccgtg gcgcaggcgc cgccctaagc accgactcgc
301 tggacacgt gagcaacggg ccggagggtc gcatgggtgc ggtggccacc tcacgcagt
361 agaaggagca gtgcaggcg ctgaacgacc gcttcggcg gtacategac aaggtggggc
421 agctggaggc gcacaacccgc agcctggagg gcgcaggctgc ggccgtgcgg cagcagcagg
481 cggccgcctc cgatatgggc gagctgtacg agcgcgaggt ccgcgagatg cgcggcgagg
541 tgctgcgcctt gggcgccggc cgccgtcagc tacgccttgc gcaggaggac ctgctcgagg
601 acatcgccca cgtgcgcacag cgcttagacg acgaggcccg gcagcgagag gaggccgagg
661 cggcgccccc cgccgtggcg cgcttcgcgc agggaggccga ggccgcgcgc gtggacactgc
721 agaagaaggc gcaggcgctg caggaggagt gcccgtaccc gcccgcac caccaggaag
781 aggtggcgca gtgcgtcgcc cagatccagg gctccggcgc cgcgcaggcg cagatcgagg
841 ccgagacgcg cgacgcctg aagtggacg tgacgtcgcc gctgcgcgag attcgcgcgc
901 agcttgaagg ccacgcggtg cagacacgc tgcaagtccga ggagtggttc cgagtggaggc
961 tggaccgact gtccggaggca gccaaaggta acacagacgc tatgcgtca ggcaggagg
1021 agataactga gtacccggcgt cagctcgagg ccaggaccac agagctggag gactgaaaa
1081 gcaccaagga ctcactggag aggacgcgtc ctgagcttgc ggaccgtcat caggccgaca
1141 ttgccttcata ccaggaaggc attcagcagc tggacgcgtga gctgaggaa accaagtgggg
1201 agatggccgc ccagctgcga gaataccagg acctgctcaa tgtcaagatg gctctggata
1261 tagagatgc cgcttacaga aaactcctgg aaggtaaga gtgtcgatt ggctttggcc
1321 caattccctt ctcgccttca gaaggactcc cccaaattcc ctctgtgtcc actcacataa
1381 aggtgaaaag cgaagagaag atcaaagtgg tgagaagtc tgagaaagaa actgtgattt
1441 tggaggaaca gacagaggag accaaagtga ctgaagaagt gactgaagaa gaggagaaag
1501 aggccaaaga ggaggaggc aaggaggaag aagggggtga agaagaggag gcagaagggg
1561 gagaagaaga aacaaagtct cccccagcag aagggctgc atccccagag aaggaagcca
1621 agtcaccagt aaaggaagag gcaaaagtac cggctgaggc caagtcccc gagaaggagg
1681 aagccaaatc cccagccgaa gtcaagtccc ctgagaaggc caagtcttca gcaaaggaag
1741 aggccaaagtcc accgcctgag gccaagtccc cagagaagga ggaagcaaaa tctccagctg
1801 aggtcaagtcc ccccgagaag gccaagtccc cagcaagga agaggcaag tcaccggctg
1861 aggccaaagtcc tccagagaag gccaagtccc cagtgaaaggc agaagcaag tcaccggctg
1921 aggccaaagtcc cccagtgaag gaagaagcaa aatctccagc tgaggtcaag tccccggaaa
1981 aggccaaagtcc tccaaacgaa gaggaaaggca agtccccgtga gaaggcaag tccccagaga
2041 aggaagaggc caagtccccctt gagaaggccca agtccccagt gaaggccagaa gcaaagtcccc
2101 ctgagaaggc caagtccccca gtgaaggcag aagcaagtc ccctgagaag gccaagtccc
2161 cagtgaaaggc agaagcaag tccccgtgaga aggcaagtcc cccagtgaag gaagaagcaa
2221 agtccccgtga gaaggccaa gccaagtgc aggaagaagc aaagaccccc gagaaggccca
2281 agtccccagt gaaggaaaggc gccaagtccc cagagaaggc caagtccccca gagaaggccca
2341 agacttgc tgtaagtctt ccagaagcca agactccagc gaaggaggaa gcaagggtcccc
2401 ctgcagacaa attccctgaa aaggccaaa gcccgtcaag ggaggaggc aagtccccag
2461 agaaggcgaa atctccctg aaggaggatg ccaaggcccc tgagaaggag atcccaaaaa

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2521 aggaagaggt gaagtccca gtgaaggagg aggagaagcc ccaggaggtg aaagtcaaag
2581 agccccaaa gaaggcagag gaagagaaag cccctgccac accaaaaaca gaggagaaga
2641 aggacagcaa gaaagaggag gcacccaaga aggaggctcc aaagcccaag gtggaggaga
2701 agaaggaacc tgctgtcgaa aagcccaaag aatccaaagt tgaagccaag aaggaagagg
2761 ctgaagataa gaaaaaaatc cccacccag agaaggaggc tcctgccaag gtggaggtga
2821 aggaagacgc taaacccaaa gaaaagacag agtagccaa gaaggaacca gatgatgcca
2881 aggccaaagga acccagcaa ccagcagaga agaaggaggc agcacccggag aaaaaagacaa
2941 ccaaggagga gaaggccaag aaggctgagg agaaacccaa gacagaggcc aaagccaaagg
3001 aagatgacaa gaccctcta aagagccta gcaaggctaa ggcagaaaaag gtcgaaaaat
3061 cctccagcac agacaaaaaa gacagcaagc ctccagagaa ggccacagaa gacaaggccg
3121 ccaagggaa gtaaggcagg gagaaggaa catccggAAC agccaaagaa actcagaaga
3181 gtccggagc tcaaggatca gagtaacaca atttcactt ttctgttt tatgtaaagaa
3241 gaaactgctt agatgacggg gcctcttct tcaaacagga atttctgtta gcaatatgtt
3301 agcaagagag ggcactccca ggccctgccc cccaggccct cccaggcga tggacaattt
3361 tgatagctt ttagtgcata tggatacat gccaatgcc acacgtaaac acttgactat
3421 aaaaactgcc cccctcctt ccaaataagt gcatttattt cctctatgtt caactgacag
3481 atgaccgca taatgaatgca gcaatggaa atacattatg cttgagatgt cttaacctat
3541 tccaaatgc cttctgttt ccaaaggagt ggtcaagccc ttgcccagag ctctcttattt
3601 tggaaagacg gtccagggtgg ggccgggac tggccactga attatgccag ggccacttt
3661 ccactggagt tcacttcaa ttgctctgt gcaataaaac caagtgttta taaaatgaaa
3721 a

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[0137] By "Map2" (or microtubule-associated protein 2) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAH38857.1.

(SEQ ID NO: 65)
MADERKDEAKAPHWTSAPlTEASAHSHPPEIKDQGGAGEGLVRSANGFPY
REDEEGAFGEHGSQGTYNSNTKENGINGELTSADRETAEEVSARIVQVVTAA
EAVAVLKGEQEKEAQHKDQTAALPLAAEETANLPPSPPPSPASEQTVTVE
EAAGGESALAPSVFQAKDKVSNSTLSKIPALQGSTKSPRYSSACPSTTK
RATFSDSLLIQPTSAGSTDRLPYSKSGNKDGVTKSPEKRSSLPRPSSILP
PRRGVSGDRDENFSLNSSISSSARRTRSEPIRRAGKSGTSTPTTPGST

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AITPGTPPSYSSRTPGTPGTPSYPRTPHTPGTPKSAILVPSEKKVAIIRT
PPKSPATPKQLRLINQPLPDLKNVKSIGSTDNIKYQPKGGQVRILNKKI
DFSKVQSRCGSKDNIKHSAGGGNVQIVTKKIDLSHVTSKGSLKNIRHRP
GGGRVKIESVKLDFKEKAQAKVGSLDNAHHVPGGGNVKIDSQKLNPREHA
KARVDHGAEIITQSPGRSSVASPRLSNVSSSGSINLLESPQLATLAEDV
TAALAKQGL

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[0138] By "Map2 polynucleotide" (or microtubule-associated protein 2) is meant a polynucleotide encoding an Map2 polypeptide. An exemplary Map2 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC038857.

(SEQ ID NO: 66)
1 ggcgcgtcggtt ctgcgcgggc tctggggcago agcagcagca gcagcagcat cctctttcc
61 tttaacttccc ttcccgcttct ttctcttctt ttcctttttt tttccccccc ctcccccttct
121 tccccctaacc cttctacccc tctcctttttt ctccggaggg cgctaagtcc gtgagcggtg
181 gcagtcgoga ccgcgggtgc atccagtttc tggccccaga ttttattgtt ctaatccaaa
241 gtatcttata acttctggct ggaattaaga ttcttcagct tgcgttcaac cgaggaagca
301 ttgattggga gctactcatt cagaaaaatta aaagaaagaa gccagaaaaat attatcaacc

-continued

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361 ctttggaaac acgacacaac gaacttata ttttaccact tccttgaata gttgcaggag
421 aaataacaag gcattgaaga atggcagatg aacggaaaga cgaagcaaag gcacccact
481 ggacctcagc accgctaaca gaggcatctg cacactcaca tccacctgag attaaggatc
541 aaggccggagc aggggaagga cttgtccgaa ggcgcataatgg attccctatac agggaggatg
601 aagagggtgc ctttggagag catgggtcac agggcaccta ttcaaatacc aaagagaatg
661 ggtcaacgg agagctgacc tcagctgaca gagaacacgc agaggaggatg tctgcaagga
721 tagttcaagt agtcactgct gaggctgttag cagtcctgaa aggtgaacaa gagaaagaag
781 ctcaacataa agaccagact gcagctctgc ctttagcagc tgaagaaaaca gctaattctgc
841 ctccttctcc acccccatca cctgcctcag aacagactgt cacagtgagc gaagcagcag
901 gtgggaaatc agctctggct cccagtgtat ttaaacaggc aaaggacaaa gtctctaatt
961 ctacccgtc aaagattctt gctttacagg gtacgcacaaa gtcggcaaga tacagctcag
1021 cctgccttag cacgactaaa agggctacat tttctgacag tttattaata cagcccaccc
1081 cagcaggctc cacagaccgt ttgcctact caaaatcagg gaacaaggac ggagtaacca
1141 agagccaga aaagcgctc tctctccaa gacccctc cattctccct cctcgccgag
1201 gtgtgtcagg agacagagat gagaattcct tctctctcaa cagttctatc tcttcttcag
1261 cacggcggac caccaggctc gagccaattc gcagagcagg gaagagtggt acctcaacac
1321 ccactacccc tgggtctact gccatcaactc ctggcaccccc accaagttat tcttcacgca
1381 caccaggcac tccttggaaacc cctagctatc ccaggaccccc tcacacacca ggaacccca
1441 agtctgccat cttgggtggc agtgcgaaaga aggtcgccat catacgatc cctccaaat
1501 ctcctgcgac tcccaaggcag ctccggctta ttaaccaacc actgccagac ctgaagaatg
1561 tcaaattccaa aatcgatca acagacaaca tcaaatacca gcctaaaggg gggcaggat
1621 ggattttaaa caagaagatc gattttagca aagttcagtc cagatgtggt tccaaggata
1681 acatcaaaca ttccggctggg ggccggaaatg tacaattgt taccacaaaa atagacctaa
1741 gccatgtgac atccaaatgt ggctctctga agaacatccg ccacaggcca ggtggggac
1801 gtgtgaaaat tgagagtgtaa aacttagatt tcaaagaaaa ggcccaagct aaagttggtt
1861 ctcttgataa tgctcatcat gtacctggag gtggtaatgt caagattgac agccaaaagt
1921 tgaacttcag agagcatgt aaagcccggt tgaccatgg ggctgagatc attacacagt
1981 ccccaaggcag atccagcggtg gcatcacccca gacgactcag caatgtctcc tctgtggaa
2041 gcatcaacccct gctcgatct cctcagcttgc ccactttggc tgaggatgtc actgctgcac
2101 tcgctaaagca gggcttgtga atatttctca tttagcatttggaa aataataat atttaggcatt
2161 gagcttggc caggagtggg ctctgagcag ttgttatatt cattctttat aaaccataaa
2221 ataaataatc tcatcccaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2281 aaaaaa

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[0139] By "DCX" (or doublecortin) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. NP_835366.1.

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(SEQ ID NO: 67)
MELDFGHFDERDKTSRNMGRSMNGLPSPTHSAHCSFYRTRTLQALSNEK
KAKKVRFYRNGDRYFKGIVYAVSSDRFRSFALLADLRSLSDNINLPQG

VRYIYTIDGSRKIGSMDELEEGESYVCSSDNFFKKVEYTKNVNPNSVNV
KT SANMKAPQSLASSNSAQARENKDFVRPKLVTIIIRSGVKPRKAVRVLLN
KKT AHSPEQVLTDITEAIKLETGVVKLYTLDGKQVTCLHDFFGDDDVFI
ACGP EKFRYAQDDFSLDENECRVMKGPNPSATAGPKASPTPQKTSAKSPGP

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MRRSKSPADSANGTSSSQLSTPKSKQSPISTPTSPGSLRKHKDLYLPLSL
DDSDSLGDSM

[0140] By "DCX polynucleotide" (or doublecortin) is meant a polynucleotide encoding an DCX polypeptide. An exemplary DCX nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. NM_178153.

(SEQ ID NO: 68)

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1 ctggcaggaa tttcttgctt ggagctcaga caacaaaggc atagagagat tggtttctt
61 tctctcagca tctccaccca accagcagaa aaccggcttc tgaggttcca cccaaaatcg
121 gaacttgcatt ttggacactt tgacgaaaga gataagacat ccaggaacat gcgaggcgtcc
181 cggatgaatg ggttgcctag ccccactcac agcgccccact gtagcttcata ccgaaccaga
241 accttgcagg cacttagtaa tgagaagaaa gccaagaagg tacgtttcta ccgcaatggg
301 gaccgctact tcaagggat tgggtacgt gtgtcctctg accgtttcg cagcttgcac
361 gccttgcctgg ctgacctgac gcgcacatctg tctgacaaca tcaacctgcc tcagggagtg
421 cgttacattt acaccattga tggatccagg aagatcgaa gcatggatga actggaggaa
481 ggggaaagct atgtctgttc ctcagacaac ttctttaaaa aggtggagta caccaagaat
541 gtcaatccca actggctctgt caacgtaaaa acatctgcca atatgaaagc ccccccagtcc
601 ttggctagca gcaacagtgc acaggccagg gagaacaagg actttgtcg ccccaagctg
661 gttaccatca tccgcgttgg ggtgaaggct cggaggctg tgcgtgtgtc tctgaacaag
721 aagacagccc actctttga gcaagtcctc actgatatac cagaagccat caaactggag
781 accgggggttgc tcaaaaaact ctacactctg gatggaaaac aggttaacttgc tctccatgt
841 ttctttgggttgc atgatgtatgt gtttattgtc tgggtccttgc aaaaatttgc ctatgtcag
901 gatgattttt ctctggatga aaatgaatgc cgagtcatga agggaaacccc atcagccaca
961 gctggcccaa aggcatcccc aacacctcg aagacttcag ccaagagccc tggcctatg
1021 cggccgaagca agtctccagc tgactcagca aacggaaacct ccagcagcaca gctctctacc
1081 cccaaatctca agcagtctcc catctctacg cccaccagtc ctggcagcct ccggaaagcac
1141 aaggacatgt acctgcctct gtcctggat gactcgact cgcttggatg ttccatgtaa
1201 agggggggag agtgcgtcaga gtccagagta caaatccaaatgc cttatcatgt tagtagggta
1261 ctctgtctca agtgcgtcaac agggctattt gtcgtttcaatgc gtttttttttgc tgggttgc
1321 gttatatttgc aaaaacacatt gtaatatgtt gggtttattt ttcgtgtattt ttcctcttgc
1381 gccactgtac cacatgttacc aattatgaga gatagattgttgc taaccatcct ttggggcagc
1441 attccaggaa tgcaaaatgt gctagtcacat gaccttcaatgc tggaaagctt aggtgcctgc
1501 gtttatatttgc cctgtctcaatgc ttttgccttac acgtcttcac ttctgttagag ggctgtttac
1561 atatacagca cttaaaatgt ttgtgtggaa aaaaaaaaaac tcaattggcag atccaagaat
1621 gacaaacaca agtgccttgc ttctctggat ctcaagaatgc gtggaggacc ctggaaaggac
1681 agcaaggcag ctccccagcc tcactcttca ctctgtatttgc agggccgggt ttgtgttca
1741 gcaccaattc tggctgtcaatgc tggggagaaa taaaccaaca acttataatttgc gtgcacccag
1801 atgcatttagga ttcgtgtgttgc gggtagtcaatgc agagaataga cagaatttgc aataactgca
1861 gacatttccg aagagtttat aaagcacatgttgc gatccctgg tcaatcttc cactgaggca
1921 atttggaaatc aataagcaat tgataatagt ttggtagtgc gggacttcata tacctgttgc
1981 ctctagaagg ctgtctcaaca taccacatgttgc tttacatgttgc tttatgttgc tttatgttgc
2041 ctgttctattt gatgccttgc ttaacagcaca acactgaaa cactgtgaga atttgtttc

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2101 aggtctgaca ctttcagtc tcttttata gcaagaaatc aatatcctt ttataaaaat
2161 tcatgtctgt atttcaggag caaactctc aggctcctt ttataaaact ggtgatttt
2221 ctttgtcta aaaaacacat gaagaaaatt taccaaaaaa aaaaaaaaaa gcagaagaat
2281 aatgttagttt agaaattatg ctgtcactgc caaacagtaa cctccaggag aaaacaagat
2341 gaatagcaga ggccaattca atagaatcag tttttgata gcttttaac agttatgctt
2401 gcattaataa ttcaatgtg gaccagacat tctaattata tttaaatgaa aatgttacag
2461 catatttaa gcaactctt ttatctataa tcctaattatt tcatactgaa gacacagaaa
2521 tcttcactt gtcttaaca ttagaaagga tttctctta ctaaggactg atcatttgaa
2581 atagtttca gtcttttagt atacaggttt ataacactgc tttttttttt ctgtaatcat
2641 agccataat ggcaaaagaca actaaattta agtgaaggc atgcattgcca attctgtgtt
2701 tgcttttagc agatatgaag atttccttat ttctttgtaa ttgtgcagat attttgaag
2761 gcacagcatt cgaagccaag ctgctgtttg gctactgaat ggcttcagt tgttcccca
2821 ctctaaatgg aatgagcttgc tgggtgtgt gtgtgggtt ggtgggggg ggtgggtcat
2881 gtgtgtgtgt gtgtgtgc ctgcagctgc ttcaaaatta ggaataacta caggacaccc
2941 ctgtaatgga ttggggca ctgggtggca ctgctgatgt gcaactgtgta ggggggaacc
3001 cagtgggtggt ggggtagtc agatgcccct agacaagctt cagatgtctg tagtaccag
3061 aaacattttc ggttcaggaa aagttagatg atggtagtac tgggttctgg tgaaattgaa
3121 gaaccccaa tgatgaggat ctcttttgc cccctctcct tttttgttag acccattcaa
3181 aaccattaaat aagccccatt tactaagccc ctatctttt ctagaagctc agggttttct
3241 tagtgcctcc cagaacattt ttagttaat tggaaaaag tgataacttgg attaggggt
3301 gtgggcataa agaatgggg gaggcctgat tttaaacttc aggccagaac ccccaatgac
3361 tccacccata gtctcaattt aggttcatt tagtccatca cttttatattt aagttgagga
3421 agtggaggct ggtaaagagc aggaccagag gaagaatcca gatttcctta tgcttggcc
3481 tcacactagc tctctgagta ttctttgat tgccgtatata gtactactag aaaataccaa
3541 atggatataat ttcttttagg ataaccctt aaccaacaat ctcaataac aatagtacat
3601 ctccatctt actttaatc gagtataagg aaatgtttct ttatggccat tttgggggaa
3661 gcaggggatg aggcttggca tagtccaaaa tttaagtctc caataattaa ttgcattttt
3721 aattggccca cttaaggc aattttttt gtgtgtctgt aactgagctc ctccacccct
3781 gtcattcaacttccaatttccaatccaa tttagcact caagttccat tgggttaatt
3841 tctgcacggt caacaaacat caagtcagca agcatttgc accactccct atacttc
3901 ctccttcata cacacacaca cacacacaca cacacaatcc atctcttgct tggtccacc
3961 tcctgatttt ttcccatac agaaatagaa atagggacaa agaagggaa aatgtatata
4021 ttggggctgg gctgaacaac taacttcata agtagtattt actaggggtt aattggagaga
4081 aaagctcctt ttcttcac tggggggaa aggatagcca ttagcatgac tgcttgggt
4141 ccttatggac tttagtattt gccttagattt aattatagcg tttcttagct ggaaggaaacc
4201 ttaagatcac atcatctact cctctactcc aaatttctca ttcttcaggc caggaaaccc
4261 agacacagag gtaaagtaat ttcccaagg tcacacagct ggctggggca ggattgggtt
4321 tacaacccac atctcctggc tcttattcca gggcttttc ccactaagta gtattgc
4381 ccattaggct cctgagagtt atttctcagg gtcattgtgc atcttggagc cacaatgtgc

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4441 tgccctgatc tcagtgaa atccacccag caacctaata cagcccatt tccctgcatt
4501 cacctggtc ccatccacat ggggtgcaga tgtccttga gagagtgagg cattgaggc
4561 caataggagc aatggggtcc ctggccttgt ccatctgatt caggagatca ctgctccatc
4621 gtgaggagcc ctctgaatag ccccccaactg aatgttgc ttgcccaaata ggaatggagg
4681 aagattgatt ttctccatca gttcaccttgc tgcacatctca taatggttgg tctttccagg
4741 ctgagggaaa tgttcttgtt ttccagagta gaaaaagaaa gagtggaaaca atagcttgc
4801 tcatcctaacc ttctcgatgg ggctttcaaa cattttaaaaaa aacttagtgc ggctaccatt
4861 cactggcaat gattctttt agaatatggg agtaagatga gctagagaaa ataacctgg
4921 ctcactgtgg ttgcctcat ccacaatgtc cccaaagcca tcctgctctg atgaggacaa
4981 ttccaggtta taagcaaggg gctttgtac aaaaatgtac cctggctgtat gttaaacatt
5041 ggccctgtgtt tttgcaccaaa aatagcaagc tgcgtgtctt atacactt cccatcgatc
5101 tgcgtacact gctcctgtgg ccttccacag cagaaaccag ggccaaagg tccaaacaca
5161 tggttttctt tgctgcaagg ctcttcctgg gaactaaggg ggtatattttt agttcagttc
5221 taagagaccc cttctgggc ttacccact cctcaggatc ttctctctcc ttctcttcc
5281 tcctccacag tcacaagtaa ccaaggaaacc tgaaaagtgg tgcgttagcta ttgaaagaag
5341 gcaaggaacc ctgagattct tcttgaatc ctctagtc agtcttagac cagtgattgg
5401 tgcttaccc tttttttttt ttgtctgtgt tcttaatccc ttcataactc tgggtacaat
5461 gctcccaatc accctgcaca tttgattcta aatggctttt attttttaaa aatccatatac
5521 ccttaggacaa gagaacacgg tgcctatatac cccaaatgtc gctccaggac actgatgg
5581 atgatccaa agatcaccacc acctcagaaaa cgtctgtgc aagagacttc cccagataga
5641 aacactggga cagtggtttt aacgacttct tttatgggtt tccagtttgc tatggaaata
5701 aaaggcattt attttttaaa aagatgatttgc gaaacctgtt tggccacat agggccactt
5761 ggatccattt ccaggcccta ctcataattt gccttcactg aagggttttgc gtttaagtc
5821 ccagactggc ctcccaagtg aaccataagt gtttggagc tcatctgggg tgaggcatga
5881 gaatgttgc ccatctatcc ctccaggaaaa aggtgccttc ctccttcc tccctaaagcc
5941 tgggtccccag aaattgtttt tgcgtccaaa agtcttagat ggtctttata caccctgact
6001 cttagtgc tgcgtccatc tttttttttt tttttttttt tttttttttt
6061 cttagctgc gtgacattgg ctatcatttgc acaagactaa cttttttttt tttttttttt
6121 tgactgatc tccctctgtc acctaggctg gactgcgtgc gcacaatctt ggctcgatgc
6181 aaccttcacc ctacacccatcc caggtcgaag cgattctctt gcctcgtctt cccgatgc
6241 tgggattaca ggctgtgcacc accaaatctg gctattttttt tattttttt atttttttagta
6301 gagatgggggt ttcaccatgt tggccagact ggtcttgcac tcttggcttc aaattatctg
6361 cccacccatgg ctccttccaaag tgctggattt acaggcatgc gcccacatgc ccagctgaca
6421 agactaattt tttatccctt ggtttattgg ctcaacatc ttctggatc agaggtgatt
6481 ttttcttacc ttggatgcctt gagaactaggg gactatagaa ttccaaattgg taattaaggc
6541 atctttctgc tccctgtatc aagggcaggat gtttggag ggtctcgtatc gcacaacaga
6601 agtcacccatgg taagtaaggc aagacttgc aggcttgc ttttcttcattt actaggatcaa
6661 taacctgagg gaatcaatgg ctttttgcgc ctctacccatc tgcgtatctc tttgactttt
6721 ctccatctgtt ctatccatc ttttttgcgc ctctacccatc tgcgtatctc tttgactttt

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6781 cacagtacaa acatccatcc ttctcctgt gcaattctgt ctctccctct tattatcttt
6841 atttgactt ttcccttcct ccctgtctag gcattggca tgtgccttctt cttagcctgt
6901 gatttgcct tggactgat gataaattat ttccagattc aatcagccct ggtcctaccc
6961 cagtc当地 agaagtatgt tggtggaaat caacgtatc ctggcccttt cttcttc
7021 atttcattc gtaatcccc tcagcagatc ttacaagca gtttccttat agctcatgta
7081 tcttagtgc ttgcctcc aagactgta cagaataactt tgggttctt ttttagtctg
7141 acattttgtg gagcagtgaa gcgtgtcg agacataatc agctgaagag aaaaatcca
7201 cccatggatt tatacagct aaatactaattt aattgatttt gttgatgtg cccataattt
7261 ttaaagctgc aataataat aatgaggac cacaggtatc ttctcctgtc atttgtttt
7321 gctggatggg ggtgggggaa taattgctta aagtttacc attacacatt aaactctcta
7381 taataatctt gttggggct tgctactgt tgagctgtt taactaaact ggtaggcaat
7441 cggagttgtat ttaaatgaaa agataattt acaaatttatc actataaaaa gagacattt
7501 ctttaatttgc atgtatcccc tccttcgtat tcacctaaac atttactttt gacaccaact
7561 gttcatgata ctgaatagac agtccatata agagaaattt gttggaccaa agaagccaga
7621 ttgttaggtgt taatttatta aacagagtgc aaagccctt gaaatgtcac tgcttggcaa
7681 taccatatgg aatgccaaaa ttacaatga ctttcttta taagttatcc aaaagggatt
7741 tgaacaagta agaggttatg ccaaattgtc tccatgtat ggctgttaa tatattgcag
7801 cttgaagcca atgatccctt atgacttgta tacaactaat gcatgttttta ttgaattttt
7861 cattttccac gtgtggtaag ttctttaaaa tgggtttgtat caccctttt tgccattaaa
7921 cttgtacaga aaatgtttt atggccattt tcaaaggagaa aaagtttaaa atggaaacag
7981 cccacccctt ctgcctata gctgtatgta gaattgagta cctgttagca aacagctgt
8041 attgggtgtt gtagtgttag aggtgttagc ttgtgtatc ctagctttgg agagtaatg
8101 catggattt tacatcacat ttcttaactc gtttaacct ctgaaaagaa tatattctt
8161 tttgttagtcc ttcttccac ccccttgccc tctccctctc cctgctccca gttgttttac
8221 agttgtaat atctgatttggg aggccaaata actcttgcca agtaaagtca gcaaacaaca
8281 aacaaaccaa aatgtggggaa aaggccattt ctcaaccatc tctcagcagt tattgtatcat
8341 ttcttaaggaa acagcattgt gatcaaagac tcaactttac gtaaaaatca gtggtaatt
8401 ggggtgtat ttggccattt gattacattt caggattgaa tagttttcag aatcacatgt
8461 aatccaaaga cagtaggttag tgatgtccct tateccctgca gctgtttaa gatagagacc
8521 tcagaagact ctgcttgacc gatgaccaat aattatttga aaaaaaaaaa gaaaatgaga
8581 gaaataaaac agatatttaa gaactttgc cacctatttta gaatagttt agccagaaaa
8641 aaaaacaagg gcatgagttc aaatgcatta ctatcgtgt cctaggcaat acctaaccata
8701 ctctgaaattt gtgattcaaa agcagtattt caagaggcat tctccctttt tgggttgc
8761 accccacttgc gactggtagg ttgggtgagg ccccccataaa ccagctggag cagacccttt
8821 tcatctcctg tgcctgtaaac accccttccccc ccccaaaaaa tccgcaattc aatgagggt
8881 ttcttgggtc agaggacttc aagggtgtct agagaagttt gccatgtgtg taaggtgt
8941 tgaactgtga gtgctgaaga ttgcgcagcat tcaataccag gcagccaaag agctgtctt
9001 gcaatttattt tggctctcaa gctctgttct tcatcgatt ctcatttctg tgcacatttgc

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9061 caagatgtgt gtaatgtcat tttccaaaaaa taaaatttga tttcaataaa aaaaaaaaaa
9121 aaaaaaaaaa aaaaa

[0141] By "GABRA1" (or gamma-aminobutyric acid (GABA) A receptor) is meant a polypeptide or fragment thereof having at least about 85% amino acid identity to NCBI Accession No. AAH30696.1.

(SEQ ID NO: 69)
MRKSPGLSDCLWAWILLSTLTGRSYGQPSLQDELKDNTTVFTRILDRLL
DGYDNRLRPGLGERVTEVKTDIFVTSFGPVSDHDMETYIDVFVFRQSWKDE
RLKFKGPMTVLRLNNLMASKIWTPDTFFHNGKKSVAHNMTPNKLLRITE
DGTLLYTMRLTVRAECPMHLEDPMDAHACPLKFGSYAYTRAEVYYEWTR
EPARSVVVAEDGSRLNQYDLLGQTVDGIVQSSTGEYVVMTHFHLKRKI

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GYFVIQTYLPCIMTVILSQVSFWLNRESPARTVFGVTTVLMTTLSISA
RNSLPKVAYATAMDWFIAVCYAFVFSALIEFATVNYFTKRGYAWDGKSVV
PEKPKKKDKPLIKKNNTYAPTATSYTPNLARGDPGLATIASKSATIEPKEV
KPETKPPPEPKTFNSVSKIDRLSRIAPELLFGIFNLVYWATYLNRPQLK
APTPHQ

[0142] By "GABRA1 polynucleotide" (or gamma-aminobutyric acid (GABA) A receptor) is meant a polynucleotide encoding an GABRA1 polypeptide. An exemplary GABRA1 nucleic acid molecule (e.g., mRNA) is provided at NCBI Accession No. BC030696.

(SEQ ID NO: 70)
1 agcggagcgg gcgagcaagg gagcgagcag gacaggagcc tgatcccaca gctgtgctc
61 cagccccgcga tgaggaaaag tccaggtctg tctgactgtc tttgggcctg gatcctcctt
121 ctgagcacac tgactggaag aagctatgga cagccgtcat tacaagatga acttaaagac
181 aataccactg tcttcaccag gatttggac agactcctag atggttatga caatgcctg
241 agaccaggat tggggagagcg tgtaaccgaa gtgaagactg atatcttcgt caccagttc
301 ggaccgcgtt cagaccatga tatgaaatat acaatagatg tattttccg tcaaagctgg
361 aaggatgaaa ggttaaaatt taaaggacct atgacagtcc tccggttaaa taacctaattg
421 gcaagtaaaa tctggactcc ggacacattt ttccacaatg gaaagaagtc agtggccac
481 aacatgacca tgcccaacaa actcctgcgg atcacagagg atggcacctt gctgtacacc
541 atgaggctga cagttagagc tgaatgtccg atgcatttgg aggacttccc tatggatgcc
601 catgcttgc cactaaaatt tggagttat gcttatacaa gacgacaatg tggatgaa
661 tggaccagag agccagcacg ctcagtggtt gtagcagaag atggatcacg tctaaaccag
721 tatgacccctc ttggacaaac agtagactct ggaattgtcc agtcaagtac aggagaatatt
781 gttgttatga ccactcattt ccacttgaag agaaagattt gctactttgt tattcaaaca
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901 tctgtaccag caagaactgt ctttggagta acaactgtgc tcaaccatgac aacattgagc
961 atcaatgtccca gaaactccct ccctaagggt gcttatacgaa cagctatggaa ttggtttatt
1021 gccgtgtgtc atgcctttgt gttctcagct ctgatttgatg ttgccacagt aaactatssc
1081 actaagagag gttatgtcatg ggatggccaa agtgtggttc cagaaaagcc aaagaaagta
1141 aaggatcctc ttattaagaa aaacaacact tacgctccaa cagcaaccag ctacaccct
1201 aatttggcca gggcgaccc gggcttagec accattgcta aaagtgcac acatgaaacct
1261 aaagagggtca agcccgaaac aaaaccacca gaacccaaga aaacctttaa cagtgtcagc
1321 aaaattgacc gactgtcaag aatagccttc ccgctgtcat ttggatctt taacttagtc
1381 tactgggcta cgtatataaa cagagaccc cagctaaaag ccccccacacc acatcaatag
1441 atcttttact cacattctgt tggtcagtc tctgcactgg gaatttattt atgttctcaa

-continued

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1501 cgcgtaatt cccatctgct ttattgcctc tgcgtttaag aatttggaaag ttcccttatt
1561 ttccataattc atttaaaac aagagacccc tgcgttggcag tctggagcaa agcagactat
1621 gcaggcttgg aacaggattc tgacagagca agcgaagag caaaagtcatg tcagaaggag
1681 acagaatgg agagaaaaaaga gggggaaagat ggttcaaaga tacaagaaaa agtagaaaaa
1741 aaaataaacac ttaactaaaa cccttaggtc atttgttagat atatattcc aaatattcta
1801 aaaaagatac tgcgttatgtc aaaaatattt ttatgtgaag gtgtttcaaa gggttaaattt
1861 taaaatgttc atgaagaaaa aattttaaaa atctacgtct ttattacaca aactatggtg
1921 tgcttatgtt tttgtttgc tttttaaact gatgtatagc ttaacattt tgtttccaaa
1981 gctgaagatc cccattttt ctctttggaa aaaaaaaaaagg cctaatgcatt tattttgtca
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2101 gagcacattt agtccaatgtc agataaaatgc tttaaatagt ttacttcaact ttcatctgag
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2221 aaattttaaaat agttttaaaaa tattcccttt ttccaccctat ttccagatag cacatgagcc
2281 caacactcac ttaattctca ttatgtttagat gtttttagag gggcaaaaat attttgcag
2341 ctcttggaaatt gttgaatgtt ttcttttata taactacatt aaaaagcttta gattggaaatt
2401 tatgacttagc aaacaaaaat agaataatata aacgatataat gtaaatatac agcatgagat
2461 tgcgttacattt ttactttttt aaaaattgtgt tctttttata ttgtgtttaa atcactgcac
2521 ttatgtgtt gaaatgtt gaaatgtt gaaatacatt tagaacctgc atttaaaac
2581 agaacagcaa gtatgttacca catggaaacctt aaaaacatgtt ggtgtttagt ccacttatgt
2641 agacaaaaact tataatttcc aactgttgc ctgtatatac gtgttgcgtt gtcattttttttt
2701 caagtccattt cacacatttc cctttagt gcttataa tataaaaaa aatggggaaag
2761 cattatgttgg agcttagaaaaa tgaactgtat attttgttata tatttgcataa taccaactat
2821 ttcaataatgtt gttgttccat atgttagcatt aataaaaaa tacataaaag aatgtacaga
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3001 tctgtttcat tactgcccag atgttttgcataa gataatattt tatgcagaag gtatgtttttt
3061 agtctccctt tgcgttgcataa agttaacag atattttaaat ttatgttgcataa gaatccacaa
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3181 aagacagtttgg ggttccaaac ccaagtcttgc agcaatgtttt ttctcaaaaaa gctgttgcataa
3241 aatgtatagataa gaaaatatacat tgcgttttcc taaaacacactt ttttttttataa atgtgttgc
3301 attgtttgtt gttgttgcataa caagcttaggc caatgttgcataa gaaatcaag
3361 acatttccatc caccaatatac atgtgttagat attatgttata gaaaataaaaa taaattatgg
3421 ctccaaaaaaa aaaaaaaaaaaa

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[0143] Other features and advantages of the invention will be apparent to those skilled in the art from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0144] FIGS. 1A-1D depict characterization of BMPS during differentiation. FIG. 1A depicts a diagram of a differentiation protocol. FIG. 1B depicts size of aggregates measured during the 3D neuronal differentiation. Negative

days on the x-axis represent 3D cells cultured in NPC medium while positive days represent 3D cells cultured in differentiation medium. FIG. 1C1-C5 depicts BMPS mRNA and miRNA expression of different markers during differentiation. FIG. 1D depicts flow cytometry population analysis of BMPS at different stages of differentiation.

[0145] FIGS. 2A-2C depict morphological characterization of BMPS. FIG. 2A depicts co-immunostaining of neurons with markers. MAP2+ neurons were co-immunostained with the maturation marker Nestin at 2, 4, and 8 weeks of

differentiation, which showed progressive increase of MAP2+ neurons and decrease of Nestin+ cells over time (panels a, b, c), demonstrating neuronal maturation. Co-immunostaining of neurons (NF-H) with the myelin marker MBP at 2, 4, and 8 weeks of differentiation (d,e,f, respectively) showed progressive increase of MBP+ cells in association with axonal processes. An increasing number of MBP+ cells (oligodendrocytes) was observed in association with axons (panels d, e, f). FIG. 2B depicts neuronal and glial cell diversity was evaluated at 8 weeks. Neurons (MAP2, NF, SYP and SMI32) were visualized interacting with glia (GFAP and NOGOA). Neurons disclosed characteristic perikarya, dendrites (MAP2, panels a, b) and axons (NF, SMI32, panels c-f) associated with glia. Neurons exhibited diverse neurotransmitter identities shown by identification of glutamatergic VGLUT1+ (panels g, h), GABAergic CALB+ (panels i, j) and dopaminergic TH (panels k, l) neurons. FIG. 2C depicts that GFAP+ astroglia and CNPase+, O1+ and MBP+ oligodendroglia were identified. Oligodendroglia appeared mixed among astrocytes (panels a, b). O1+(panels c, d) and MBP+(panels e, f) oligodendrocytes were associated with axonal processes. Astrocytes established relationships with oligodendrocytes and exhibited characteristic multipolar processes (panels g, h). MBP+ oligodendrocytes issued processes in association with axons (panel i) 3D-reconstruction demonstrated myelinating processes resembling human myelination (panels j, k). Electron microscopy analysis of BMPS at 4 and 8 weeks of differentiation identified morphology of axonal structures and cells (e.g., oligodendrocytes) (panel l). Myelinating-like processes, which closely resembled cross-sections of myelinated axons of the CNS were identified at 8 weeks of differentiation (panel m). FIG. 2D depicts MBP+ oligodendrocytes issued processes in close association with axons and seemed to enwrap them at 8 weeks (a,b,c). Myelination calculated as the mean percentage MBP positive oligodendrocyte processes coverage of NF-H-positive axons (a,b,c) at 2, 4 and 8 weeks in at least 2 independent experiments showed significant increase of myelination observed with time of differentiation ($p < 0.001$) (d). FIG. 2E depicts 3D-reconstruction based on confocal z-stacks at 8 weeks demonstrating a “wrapping” myelinating process, which resembled the myelination of axons in human CNS. FIG. 2F depicts a comparison of expression of neuronal and glial markers at 2 and 8 weeks. At 2 weeks, oligodendrocytes (O1, CNPase, NOGOA) were identified without a preferential localization (a,b,e,f,i,j), later they resemble human oligodendrocytes and localize in close proximity with axons (c,d, g,h, k,l). At 2 weeks there are few MAP2-positive cells without identifiable neuronal shape (l,j) whereas at 8 weeks, the MAP2+ cells acquire a well-defined dendritic network (k,l). The amount of astrocytes and density of the astroglial network increases with time of differentiation (GFAP, g,h). FIG. 2G depicts variation in the nuclear morphology. Co-immunostaining of neurons (MAP2) with cell-division marker Ki67 showed that some cells are dividing (a,b), there was also a small degree of apoptosis demonstrated by positive staining with CASP3 (c). CASP 3-positive nuclei did not co-localize with mature neurons (d). FIG. 2H depicts ultrastructure analysis by electron microscopy of 4 week BMPS showed evidence of cell to cell junctions demonstrating functional interactions between the cells (arrows, a,b). Nuclear variation was confirmed by the presence of a few apoptotic nuclei (c) and normal healthy nuclei (d). NF: Neurofilament-

heavy-chain, MAP2: Microtubule-associated-protein 2, MBP: myelin-basic-protein, VGLUT1: Vesicular-glutamate-transporter 1, GFAP: Glial-fibrillary-acidic-protein, CALB: Calbindin, NOGOA: Neurite-outgrowth-inhibitor, SYP: Synaptophysin, SMI32: Nonphosphorylated-neurofilament, TH: Tyrosine-hydroxylase, O1: Olig1, CNPase: 2',3'-Cyclic-nucleotide-3'-phosphodiesterase. Scale Bar: 10 μ m.

[0146] FIGS. 3A-3F depict electrical activity of BMPS. Cells were cultured in 3D for 8 weeks and then cultured in 12-well and 48-well MEA plates for 4 more weeks. FIG. 3A depicts heat map recordings from a 48-well plate. FIG. 3B depicts illustration of an active well showing spike morphology and FIG. 3C depicts spike activity. FIGS. 3D and 3E depicts phase-contrast imaging of the mini-brains on MEAs, electrode diameter is 40-50 μ m and inter-electrode space is 350 μ m. FIG. 3F depicts activity pattern recordings over 0.05 spikes/sec of the electrode over 10 min.

[0147] FIGS. 4A-4G depict Parkinson's disease (PD) application of BMPS. BMPS were differentiated for 4 weeks and exposed to rotenone and MPP+ for 12 and 24 hours. FIG. 4A depicts viability (resazurin assay) of BMPS after 24 hours rotenone exposure. FIG. 4B depicts ROS (OxiSelectTM In Vitro ROS/RNS Assay Kit) production of BMPS after 12 and 24 hours rotenone exposure. FIG. 4C depicts viability (resazurin assay) of BMPS after 24 hours MPP+ exposure. FIG. 4D depicts ROS (OxiSelectTM In Vitro ROS/RNS Assay Kit) production of BMPS after 12 and 24 hours MPP+ exposure. FIGS. 4E and 4F depict confocal images of BMPS exposed to different concentrations of rotenone and MPP+ for NF200 (Red), TH (Green) and Hoechst nucleus staining (Blue). FIG. 4G depicts expression of genes associated with oxidative stress and PD by real time RT-PCR. Graphs represent the relative expression of different markers compared to control (cells not treated) after 24 hours exposure to 5 μ M rotenone and 1 mM MPP+. Genes of interest: mitochondrial complex 5 (ATP50, ATP5C1), mitochondrial complex 1 (NDUFB1), oxidative stress (KEAP1) and genes related to PD (TH, SNCA, TBR1, CASP1). Data are presented as mean \pm SD, of 3 independent experiments performed in 3 replicates. * $P < 0.05$ comparing to control (untreated).

[0148] FIGS. 5A-5D depict Down's Syndrome application of BMPS. BMPS were produced with iPSCs derived from a patient with Down's Syndrome. FIG. 5A depicts morphological characterization with immunostaining of neurons (MAP2, Syn1, TH, SYP), neural precursor cells (nestin) and glial cells (GFAP) at 8 weeks of differentiation. FIG. 5B depicts expression of genes in healthy BMPS vs. Down's Syndrome BMPS before and after treatment with 5 μ M rotenone, after 24 hours exposure. Genes of interest include CNS markers (TH, OLIG2, NEFH), mitochondrial markers (ATP5C1, ATP5J, ATP50) and ROS markers (NFE2L2, SOD1) which were measured by comparing control with exposed cells to rotenone on both healthy and Down syndrome derived mini-brains. FIGS. 5C and 5D depict karyotyping of iPSCs derived from the patient with Down's Syndrome. aCGH+SNP results for Down syndrome iPSC line are shown.

[0149] FIG. 6 depicts viability of pre-frozen NT2 human teratocarcinoma cell line and iPSC derived mini-brains. Fmedium corresponds to 95% FBS and 5% DMSO. NPC fmedium corresponds to STEMdiffTM Neural Progenitor Freezing Medium. Viability was measured by resazurin cell

viability assay. Non-frozen cells at the same stage of differentiation were used as control aggregates.

[0150] FIG. 7 depicts an example of a BMPS covered with other cell types. LUHMES fluorescent cells (red) were incorporated to a BMP using gravity systems to cover the surface of the aggregate.

[0151] FIGS. 8A-8E depict morphologic characterization of mature human BMPS. FIG. 8A shows at 8 weeks, neuronal populations exhibited a diversity of neurotransmitter identities as shown by identification of dopaminergic TH+ (a,b), glutamatergic VGLUT1+ (c,d) and gabaergic calbindin+ (e,f) neurons. Neurons disclosed characteristic axons (NF) and synaptic proteins (SYN) (g,h). FIG. 8B depicts two distinctive glial populations were identified in close interaction with neuronal populations, GFAP+ astroglia and CNPase+, O1+, NOGOA+ oligodendroglia. O1+ oligodendrocytes were closely associated with axonal processes (NF) (a,b), CNPase+ oligodendroglia appeared mixed among GFAP+ astroglia (c,d) and exhibited the characteristic multipolar glial processes, which extended from the perykaria (e,f). NOGOA+ cells were associated with MAP+ neurons (g,h). FIG. 8C depicts example of custom algorithm created using the Cellomics Target Activation image-analysis software package to study astrocytes and oligodendrocytes (a,b,c,d). Quantification of cell populations as a percentage of the total nuclei count showed 3% NOGOA+ positive cells, 9% CNPase+ cells and 19% GFAP+ cells at 8 weeks (e). FIG. 8D shows Co-expression of mature oligodendroglia markers (MBP and O2). FIG. 8E shows expression of neuronal markers (VGLUT, TUJ1, SYN). Scale Bar: 10 μm.

DETAILED DESCRIPTION OF THE INVENTION

[0152] The present invention is based, at least in part, upon the discovery that brain microphysiological systems (BMPS) can be produced from induced pluripotent stem cells (iPSCs). Furthermore, the invention provides for reproducible BMPS that differentiate into mature neurons and glial cells (astrocytes and oligodendrocytes) in the central nervous system. This model is spontaneously electrophysiological active and may be reproduced with patient or genetically modified cells. The derivation of 3D BMPS from iPSCs has applications in the study and treatment of neurological and neurodevelopmental diseases. In some embodiments, the present disclosure provides for compositions and methods to study and/or treat neurodevelopmental and neurodegenerative disorders. In some cases, the neurodevelopmental and neurodegenerative disorders treated and/or studied by the present disclosure include, but are not limited to, autism, encephalitis, trauma, brain cancer, stroke, Amyotrophic lateral sclerosis, Huntington's Disease, muscular dystrophy, neurodegenerative disorder, neurodevelopmental disorder, Multiple Sclerosis, infection, Parkinson's Disease and Alzheimer's Disease.

[0153] As described herein, the present disclosure provides for the derivation of a multitude of identical brain microphysiological systems (BMPS) from stem cells, preferably of human origin, but including stem cells from animal origin. The preferred starting material are human induced pluripotent stem cells or embryonic stem cells, although other pluripotent stem cells such as, for example, neuronal precursor cells and mesenchymal stem cells may also be employed. Human in-vitro models of brain neurophysiology

are needed to investigate molecular and cellular mechanisms associated with neurological disorders and neurotoxicity. The techniques herein provide a reproducible iPSC-derived human 3D BMPS that includes differentiated mature neurons and glial cells (astrocytes and oligodendrocytes) that reproduce neuronal-glial interactions and connectivity. BMPS mature over about eight weeks and show the critical elements of neuronal function including, but not limited to, synaptogenesis and neuron-to-neuron (e.g. spontaneous electric field potentials) and neuronal-glial interactions (e.g. myelination). Advantageously, the BMPS described herein include mature neurons (e.g., glutamatergic, dopaminergic and GABAergic neurons) and glial cells (e.g., astrocytes and oligodendrocytes). Quantification of the different cell types exhibited high reproducibility between experiments. Moreover, the BMPS disclosed herein present neuron and glial functions such as spontaneous electrical activity and axon myelination. The BMPS described herein are able to mimic the microenvironment of the central nervous system, which is a significant advance in the field of neurobiology as this ability has not been achieved at this level of functionality, reproducibility, and consistency in prior art in vitro systems.

[0154] In particular, the high amount of myelination of axons (up to 40%) in the disclosed BMPS represents a significant improvement over the prior art. Myelin pathology is a rather frequent condition in demyelinating and inflammatory disorders such as multiple sclerosis and post-infection diseases as well as other neurological diseases such as acute and post-traumatic brain injury, stroke and neurodegenerative disorders (see e.g., Fumagalli et al., 2016; Tse and Herrup, 2016). Moreover, the myelination process can be perturbed by exposure to chemicals and drugs (see e.g., Garcia et al., 2005; Brubaker et al., 2009; Creeley et al., 2013) during brain development and adulthood. For example, the BMPS disclosed herein show 40% overall myelination after 8 weeks of differentiation. Myelin was observed by immunohistochemistry and confirmed by confocal microscopy 3D reconstruction and electron microscopy. These findings are of particular relevance since myelin is crucial for proper neuronal function and development. The ability to assess oligodendroglia function and mechanisms associated with myelination in this BMPS model provide an excellent tool for future studies of neurological disorders such as multiple sclerosis and other demyelinating diseases. Thus, the BMPS provides a suitable and reliable model to investigate neuron-neuroglia function in neurotoxicology or other pathogenic mechanisms that has heretofore not been available in the prior art.

[0155] The method disclosed combines gyratory shaking or regular stirring and the addition of growth factors to obtain the basic model. Suitable conditions as to how to achieve reproducible brain composition are disclosed herein. In contrast to earlier models, identical units of BMPS are produced, which allow comparative testing for the purpose of product development or safety assessments.

[0156] According to the techniques herein, a number of additional measures complement the basic BMPS to increase their completeness in modeling the human brain and improve its usefulness for such testing, for example:

[0157] 1. The addition of microglia: All stem-cell-derived brain models described so far lack micro-glia. The techniques herein provide that the addition of micro-glia precursor cells and suitable growth factors may allow microglia to be added to the model. Suitable cells may be monocytes

(e.g., human monocytes), hematopoietic stem cells, respective (pro-)monocyte cell lines, and isolated microglia.

[0158] 2. The addition of a blood-brain-barrier: The human brain is protected by a tight blood-brain-barrier that excludes many substances from the brain. For the first time, the techniques herein provide a method to form a blood-brain-barrier to the BMPS via cells such as, for example, human endothelial cells.

[0159] 3. Addition of reporter and reporter cells: During the generation of the BMPS, cells carrying reporter for testing purposes may be used or added. These include, but are not limited to, fluorescent or luminescent markers to indicate a certain cell lineage or cell response. Genetic transient or permanent transfections are the primary, but not only, method of choice.

[0160] 4. The BMPS may also be produced, entirely or in its components, from cells from a specific genetic background, e.g. from patients with a specific disease or after selective genetic manipulation of the cells.

[0161] 5. The versatility of the BMPS may be improved by combining it with electrodes including, but not limited to, micro-electrode arrays (MEA).

[0162] 6. The versatility of the BMPS may be improved by combining it with other MPS (organ models) platforms such as, for example, microfluidic human-on-chip systems, perfusion chambers and others.

[0163] 7. Transportability of BMPS: Methods to cryopreserve BMPS were developed, which allow transport to other laboratories and testing or integration into multi-MPS platforms.

[0164] Simplified neural in vitro systems do not reflect physiology, interactions between different cell types, or human genetics. Induced pluripotent stem cells (iPSC)-derived human-relevant microphysiological systems (MPS) better mimic the organ level, but are too complex for chemical and drug screening. As described herein, a reproducible 3D brain MPS (BMPS) that differentiates into mature neurons and glial cells (astrocytes and oligodendrocytes), which reproduces the topology of neuronal-glial interactions and connectivity in the central nervous system was developed. BMPS from healthy donors or patients evolve from a period of differentiation to maturity over about 8 weeks, including synaptogenesis, neuron-neuron interactions (e.g. spontaneous electric field potentials) and neuronal-glial interactions (e.g. myelination of axons), which mimic the microenvironment of the central nervous system. Effects of substances on neurodevelopment may be studied during this phase of BMPS development. In an exemplary embodiment, the techniques herein were used to study Parkinson's disease (PD) by evaluating neurotoxicants with a link to PD pathogenesis. Exposure to 5 µM rotenone or 100 µM 1-methyl-4-phenylpyridinium (MPP+) (or 1 mM 1-methyl-4-phenylpyridinium (MPP+) for gene expression studies) disrupted dopaminergic neurons, as observed by immunohistochemistry and altered expression of PD-related genes (TH, TBR1, SNCA, KEAP1, NDUFB1, ATP5C1, ATP50 and CASP1), thus recapitulating hallmarks of PD pathogenesis linked to toxicant compounds in the respective animal models. The BMPS, as described herein, provide a suitable and reliable model to investigate neuron-neuroglia function in neurotoxicity or other pathogenic mechanisms.

[0165] There is growing concern about the continuing increase in neurodevelopmental and -degenerative disorders such as autism [1, 2], Parkinson's [3] and Alzheimer disease

[4]. Although genetic factors play an important role, environmental factors such as pesticides, air pollution, cigarette smoke, and dietary toxicants appear to contribute [5, 6, 7]. Due to a lack of mechanistic understanding, it is difficult to study their contributions and interactions with respect to neurotoxicity and neurological disorders. The complexity of the CNS makes it challenging to find appropriate in vitro human-relevant models, ideally from different genetic backgrounds, that are able to recapitulate the relevant pathophysiology. The poor predictive ability of animal-based models for human health, which may fail to mimic human pathology as outlined in the costly and time-consuming current developmental neurotoxicity (DNT) guidelines, contributes to the lack of reliable information on DNT mechanisms [8]. At the same time, more than 90% of all drugs fail clinical trials after extensive animal testing [9] due, in part, to the fact that animal studies often do not reflect human physiology and inter-individual differences. Simple in vitro systems do not represent physiology and organ function [10], which creates a critical demand for better models in drug development, study of disease mechanisms and progression, bioengineering and toxicological testing.

[0166] Attempts to generate more complex organotypic cultures or microphysiological systems (MPS) [11, 12, 13, 14] have resulted in more physiological multicellular 3D co-culture models able to simulate a functional part of the brain [15, 16]. 3D MPS have shown increased cell survival, differentiation, cell-cell interactions and can reproduce the complexity of the organ more closely [18]. Recent US research programs by NIH, FDA, DARPA, and DTRA have initiated the systematic development of MPS, including the model presented here, and their combinations to human-on-a-chip technologies to assess the safety and efficacy of countermeasures to biological and chemical terrorism and warfare [19].

[0167] The discovery of induced pluripotent stem cells (iPSC) and new protocols to differentiate them into various cell types have boosted the development of human in vitro models [20, 21]. iPSC from healthy or patient donors with a specific disease [22, 23, 24, 12] used in MPS promise more human-representative models, e.g. the brain organoids by Lancaster et al. and Kadoshima et al., have been able to recapitulate features of human cortical development [15, 16]. These complex systems present novel tools to study biological mechanisms in the CNS, however, they have certain limitations: 1) an elaborate and complex protocol, 2) size differences between organoids, 3) necrosis in the center of the organoid, 4) low reproducibility in cell differentiation. The human BMPS described herein overcomes these limitations. The reproducible in vitro iPSC-derived human 3D brain microphysiological system (BMPS) is comprised of differentiated and mature neurons and glial cells (astrocytes and oligodendrocytes).

[0168] The techniques herein provide a reproducible BMPS that contains several different cell types of the human brain, such as glutamatergic, dopaminergic and GABAergic neurons, astrocytes and oligodendrocytes. Moreover, the system has shown neural functionality as observed by spontaneous electrical activity and myelination of axons. Furthermore, the BMPS is reproducible from batch to batch and displays differences between healthy and patient donors. In addition, the obtained results demonstrate the application of such BMPS to the study of neurological disorders such as, for example, Parkinson's Disease (PD).

[0169] The brain MPS described herein is a versatile tool for more complex testing platforms and strategies as well as research into neurotoxicity (e.g., developmental), CNS physiology and pathology. Some stem cell-derived brain microphysiological systems have been developed in the latest years showing the capability to recapitulate some of the *in vivo* biological process [36, 37, 38]. These models have an enormous advantage over the classical *in vitro* models to study various differentiation mechanisms, developmental processes and diseases [15]. However, they are mostly based on human embryonic stem cells raising ethical concerns and not allowing the use of patient cells. Moreover, they require complicated protocols that may reduce the reproducibility of the system and make it difficult to use in other fields such as chemical and drug screening. Some of these complex organoids have a large diameter, which can lead to extensive cell death, visible in the core of these tissues [15]. This may be due to insufficient diffusion of nutrients and oxygen in these non-vascularized systems, which may generate artifacts in toxicological and disease measurements and make it difficult to study different endpoints in a medium- to high-throughput manner. In addition, it will be challenging to adapt endpoints, established for relative simple 2D cultures, to such complex models. In the study described herein, the ability to generate a high number of viable (about 800 per batch), BMPS that are homogeneous in size (e.g., about 300 µm) and shape using iPSC by applying a constant or regular gyration shaking or stirring technique as described earlier for rat re-aggregating brain cell cultures [40] is shown. Control of the size using specific shaker speed allowed the aggregates to be maintained below 350 µM in diameter (FIG. 1B) and avoid disparate morphology and/or necrosis in the middle of the organoids. Moreover, a spherical homogeneous shape facilitates fluorescent quantification and further imaging-based endpoints as well as reproducibility between aggregates. The BMPS had reproducible cell composition by immunomorphological quantification, assessment of imaging-based endpoints and neurophysiological testing.

[0170] The 3D differentiation protocol described herein covered stages from neuronal precursors to different cell types of the mature CNS. After 2 weeks, BMPS consisted of an immature population of cells, showing minimal neuronal networks, low percentage of mature astrocytes and oligodendrocytes, with no myelin basic protein expression (FIG. 1C). Cell populations in the BMPS were further differentiated and matured over time (FIG. 2A). Evidence of iPSC differentiation into mature BMPS was supported by decreased Nestin expression over time. Nestin is normally expressed in embryonic tissue and its expression decreases with age in humans, therefore its decrement is a sign of maturation towards the adult phenotype [41, 42]. Also, the increasing presence of mature neuronal and glial markers such as MAP2, GFAP, Olig1 and MBP corroborate differentiation of the system. Different markers of pluripotency and proliferation decreased during the differentiation process, indicating maturing of the *in vitro* system (FIGS. 1C and 1D). Neuronal precursor markers such as Nestin, SOX1, SOX2 and the proliferation marker Ki67 decreased at the gene expression level and in flow cytometry measurements during the differentiation process (FIGS. 1C and 1D). Gene expression studies, flow cytometry, image analysis, immunostaining and miRNA studies have demonstrated an increase of cell maturation markers, which follows the

BMPS differentiation (FIGS. 1A-1D, 2A-2H and 9A-9C). Obtained data demonstrate that this simple protocol is sufficient to generate representative CNS cell phenotypes that can reproduce various stages of differentiation. The presence of GABAergic neurons, dopaminergic neurons and glutamatergic neurons was observed by immunohistochemistry and real-time-PCR data (FIG. 1C and FIG. 2B). In addition, miRNAs such as mir-124, mir-132, mir-128, mir-137 and mir133b with a role in nervous system differentiation and neuronal degeneration [43, 44] increased during differentiation in patterns consistent with the *in vivo* situation. Moreover, the BMPS described herein produced spontaneous electrical activity (FIG. 3) confirming neuronal functionality of the system. However, further optimizations of the electrophysiological measurements using MEAs in 3D systems are needed.

[0171] Most of the brain MPS published so far are entirely focused on neurons and not glia populations [45, 46]; the brain MPS described herein is the first 3D model with fully characterized mature human oligodendrocytes, astrocytes and neurons, derived from iPSC. Astrocytes and oligodendrocytes play an important role during neuronal development, plasticity and neuronal injury. Astrocytes have a role in protecting neurons, increasing neuronal viability and mitochondrial biogenesis from both exogenous (e.g. chemicals) or endogenous (such as glutamate-induced excitotoxicity or the Alzheimer related Aβ1-42) toxicity [47, 48, 49, 50]. Astrocytes have an especially important role in neuroprotection from oxidative stress. Oxidative stress is known to be involved in a number of neuropathological conditions (such as neurodegenerative diseases) [51, 52, 53]. Thus, the presence of astrocytes in a biological system to study disease is crucial due to their role in detoxification and neuronal protection. Immunohistochemistry results from the iPSC-derived BMPS showed low numbers of astrocytes (GFAP-positive cells) at 2 weeks of differentiation, which increased continuously throughout differentiation (FIG. 2F-2H, and FIG. 2A). Real-time RT-PCR data supports these findings, as a continuous increase in both s100b and GFAP mRNA levels could be observed from 2 weeks up to 8 weeks old BMPS. Immunohistochemistry and RT-PCR data results showed increasing numbers of astrocytes (GFAP-positive cells) in the BMPS model, reaching 19% astrocytes of the total cell population at 8 weeks. After 4 weeks of differentiation, astrocytes demonstrated increased positive staining for GFAP and the presence of glial network was observed (FIG. 2C, panels g, h). At the same time, the presence of oligodendrocytes and myelination of axons could be observed in the system described herein. This process is highly important, since it is known to be involved in many degenerative diseases such as multiple sclerosis [54], congenital hypomyelination [55], progressive multifocal leukoencephalopathy caused by JC virus infection [56], periventricular leukomalacia (PVL) [57] and Alzheimer's disease [58]. Moreover, several chemicals such as ethanol [59], tellurium [60] and lead [(61, 62, 63, 64, 65] have shown to have an effect on the myelination process.

[0172] The presence of astroglia and oligodendroglia in the model described herein brings the system closer to the *in vivo* brain physiology, which is a crucial component to study neurodegeneration and neurotoxicity. In addition, the system has shown functionality as seen by imaging of cell-cell junctions, myelination, a rich astroglial network and electrical activity (FIG. 3). These characteristics make the

BMPS described herein a promising tool to study interactions between human neuronal cells in neurological diseases. The use of iPSCs makes it possible to study genetic factors and gene/environment interactions.

[0173] An assessment of the myelination process by quantification of MBP immunostaining along axons showed an increase over time reaching 42% of myelinated axons at 8 weeks (FIG. 2D). 3D reconstruction of confocal z-stacks images (FIGS. 2C and 2E) and electron microscopy confirmed the wrapping of axonal structures after 8 weeks of differentiation (FIG. 2C). These findings are of particular relevance since myelin is a critical element for proper neuronal function and development, the ensheathment of axons by myelin allows faster action potential transmission, reduces axonal energy consumption and protects the axons from degeneration[79]. Furthermore, recent evidence suggests that oligodendrocytes and myelin have a role in the metabolic support of axons independent of their role in action potential conduction, highlighting their importance in neuronal survival[80]. The ability of assessing oligodendroglia function and mechanisms associated with myelination in the BMPS model provide an excellent tool for future studies of neurological disorders such as multiple sclerosis and other demyelinating disorders.

[0174] In one embodiment, the model described herein is useful for studying Parkinson's disease (PD). Traditionally, PD has been described as a pre-synaptic degenerative process that affects dopaminergic neurons and induces a fundamental motor disorder [66], however, non-motor symptoms can also be present [67]. Research in Parkinson's disease is experiencing an upswing at the moment, owing to a lack of curative drugs for the large number of patients. Drug testing is nearly exclusively performed *in vivo* in the so-called MPTP (the parent compound to the metabolite MPP+ used here), rotenone, methamphetamine and 6-hydroxydopamine models requiring tens of thousands of animals [68, 69, 70]. These model toxins are mainly used in mice and primates (and less in cell cultures) to model a disease state resembling PD. Human neurons, which would be most relevant, are not usually available and existing cell lines are only very poor substitutes. The model described herein shows that treatment with MPP+ or rotenone induced specific degeneration of dopaminergic neurons in agreement with Parkinson patients and current animal models of the disease (FIGS. 4E and 4F). The BMPS PD model has shown to recapitulate some of the molecular mechanisms of the human disease, e.g. increase in ROS production (FIGS. 4B and 3D) and changes in genes related to PD (FIG. 4G). BMPS treated with rotenone or MPP+ had decreased TH gene expression compared to controls, supporting the results presented in FIGS. 4E and 4F where the dopaminergic neuronal phenotype is altered after treatment with the two chemicals. TBR1 encodes a transcription factor involved in the regulation of developmental processes. It also plays a role in major neurological diseases such as Alzheimer Disease and PD [71]. This gene was down-regulated after treatment with non-cytotoxic concentrations of MPP+ and rotenone. At the same time, mRNA levels of SNAC were altered. α -Synucleinopathy (common in Parkinson) is a neurodegenerative disease, which consists of the abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers or glial cells [72]. Alpha-synuclein plays regulatory roles such as synaptic maintenance, mitochondrial homeostasis, proteasome function, dopamine

metabolism [73]. Reduction of SNCA (the alpha-synuclein encoding gene) after treatment with 5 μ M rotenone and to a lesser extent after 1 mM MPP+ exposure could be explained by the alteration of alpha-synuclein protein metabolism. However, it may be that longer exposure times are required to produce an increase in gene expression. Caspase-1 (CASP1) expression increased significantly after 24 h exposure to 1 μ M MPP+. Recently, some studies have identified human enzyme caspase-1 as the protease that cleaves α -synuclein *in vivo* [74]. This cleavage generates α -synuclein fragments that are prone to toxic aggregate formation. Finally, effects upon genes related with mitochondrial function (such as NDUFB1, ATP5C1 and ATP50) were down-regulated, more strongly in BMPS treated with MPP+ than rotenone. Changes in NDUFB1, indicate an alteration in mitochondrial function, agreeing with the phenomena already described in Parkinson's disease. This downregulation is linked to the increase in KEAP1 expression (oxidative stress marker) after 24 h exposure to 1 mM MPP+. The high variability in some of the genes may be explained by the selective effects of these chemicals (especially MPP+) to dopaminergic neurons, which represent only a subpopulation within the BMPS. While rotenone and MPP+ alter gene expression of this cell population, the other populations presented in BMPS appear not to be affected. Further studies using cell sorting could identify cell-specific effects.

[0175] This disclosure provides for a description of a brain microphysiological system aiming to study various aspects of brain development, pathophysiology and disturbance by genetic and environmental factors. The possibilities to study developmental and neurodegenerative disorders, infections, toxicity and trauma are emerging with such a system. Furthermore, the potential to use iPSC from different donors adds a personalized component to these studies. The high reproducibility and relatively easy protocol, enables future higher throughput testing of chemicals, and drugs and their potential to induce or treat diseases.

Autism

[0176] Autism is a highly variable neurodevelopmental disorder that first appears during infancy or childhood, and generally follows a steady course without remission. Patients with autism may be severely impaired in some respects but normal, or even superior, in others. Overt symptoms gradually begin after the age of six months, become established by age two or three years, and tend to continue through adulthood, although often in more muted form. It is distinguished not by a single symptom, but by a characteristic triad of symptoms: impairments in social interaction; impairments in communication; and restricted interests and repetitive behavior. Other aspects, such as atypical eating, are also common but are not essential for diagnosis. Autism's individual symptoms occur in the general population and appear not to associate highly, without a sharp line separating pathologically severe from common traits.

[0177] While autism is highly heritable, researchers suspect both environmental and genetic factors as causes. In rare cases, autism is strongly associated with agents that cause birth defects. Controversies surround other proposed environmental causes; for example, the vaccine hypotheses have been disproven. Autism affects information processing in the brain by altering how nerve cells and their synapses connect and organize; how this occurs is not well under-

stood. It is one of three recognized disorders in the autism spectrum (ASDs), the other two being Asperger syndrome, which lacks delays in cognitive development and language, and pervasive developmental disorder, not otherwise specified (commonly abbreviated as PDD-NOS), which is diagnosed when the full set of criteria for autism or Asperger syndrome are not met.

[0178] Globally, autism is estimated to affect 21.7 million people as of 2013. As of 2010, the number of people affected is estimated at about 1-2 per 1,000 worldwide. It occurs four to five times more often in boys than girls. About 1.5% of children in the United States (one in 68) are diagnosed with ASD as of 2014, a 30% increase from one in 88 in 2012. The rate of autism among adults aged 18 years and over in the United Kingdom is 1.1%. The number of people diagnosed has been increasing dramatically since the 1980s, partly due to changes in diagnostic practice and government-subsidized financial incentives for named diagnoses; the question of whether actual rates have increased is unresolved.

[0179] Autism has a strong genetic basis, although the genetics of autism are complex and it is unclear whether ASD is explained more by rare mutations with major effects, or by rare multigene interactions of common genetic variants. Complexity arises due to interactions among multiple genes, the environment, and epigenetic factors which do not change DNA but are heritable and influence gene expression. Studies of twins suggest that heritability is 0.7 for autism and as high as 0.9 for ASD, and siblings of those with autism are about 25 times more likely to be autistic than the general population. However, most of the mutations that increase autism risk have not been identified. Typically, autism cannot be traced to a Mendelian (single-gene) mutation or to a single chromosome abnormality, and none of the genetic syndromes associated with ASDs have been shown to selectively cause ASD. Numerous candidate genes have been located, with only small effects attributable to any particular gene. The large number of autistic individuals with unaffected family members may result from copy number variations-spontaneous deletions or duplications in genetic material during meiosis. Hence, a substantial fraction of autism cases may be traceable to genetic causes that are highly heritable but not inherited: that is, the mutation that causes the autism is not present in the parental genome.

[0180] Several lines of evidence point to synaptic dysfunction as a cause of autism. Some rare mutations may lead to autism by disrupting some synaptic pathways, such as those involved with cell adhesion. Gene replacement studies in mice suggest that autistic symptoms are closely related to later developmental steps that depend on activity in synapses and on activity-dependent changes. All known teratogens (agents that cause birth defects) related to the risk of autism appear to act during the first eight weeks from conception, and though this does not exclude the possibility that autism can be initiated or affected later, there is strong evidence that autism arises very early in development.

[0181] Exposure to air pollution during pregnancy, especially heavy metals and particulates, may increase the risk of autism. Environmental factors that have been claimed to contribute to or exacerbate autism, or may be important in future research, include certain foods, infectious diseases, solvents, diesel exhaust, PCBs, phthalates and phenols used in plastic products, pesticides, brominated flame retardants,

alcohol, smoking, illicit drugs, vaccines, and prenatal stress, although no links have been found, and some have been completely disproven.

[0182] Autism does not have a clear unifying mechanism at either the molecular, cellular, or systems level; it is not known whether autism is a few disorders caused by mutations converging on a few common molecular pathways, or is (like intellectual disability) a large set of disorders with diverse mechanisms. Autism appears to result from developmental factors that affect many or all functional brain systems, and to disturb the timing of brain development more than the final product. Neuroanatomical studies and the associations with teratogens strongly suggest that autism's mechanism includes alteration of brain development soon after conception. This anomaly appears to start a cascade of pathological events in the brain that are significantly influenced by environmental factors. Just after birth, the brains of children with autism tend to grow faster than usual, followed by normal or relatively slower growth in childhood. It is not known whether early overgrowth occurs in all children with autism. It seems to be most prominent in brain areas underlying the development of higher cognitive specialization. Hypotheses for the cellular and molecular bases of pathological early overgrowth include the following: an excess of neurons that causes local over connectivity in key brain regions, disturbed neuronal migration during early gestation, unbalanced excitatory-inhibitory networks, and abnormal formation of synapses and dendritic spines, for example, by modulation of the neurexin-neuroligin cell-adhesion system, or by poorly regulated synthesis of synaptic proteins.

[0183] The immune system is thought to play an important role in autism. Children with autism have been found by researchers to have inflammation of both the peripheral and central immune systems as indicated by increased levels of pro-inflammatory cytokines and significant activation of microglia. Biomarkers of abnormal immune function have also been associated with increased impairments in behaviors that are characteristic of the core features of autism such as deficits in social interactions and communication. Interactions between the immune system and the nervous system begin early during the embryonic stage of life, and successful neurodevelopment depends on a balanced immune response. It is thought that activation of a pregnant mother's immune system such as from environmental toxicants or infection can contribute to causing autism through causing a disruption of brain development. This is supported by recent studies that have found that infection during pregnancy is associated with an increased risk of autism.

[0184] The relationship of neurochemicals to autism is not well understood; several have been investigated, with the most evidence for the role of serotonin and of genetic differences in its transport. The role of group I metabotropic glutamate receptors (mGluR) in the pathogenesis of fragile X syndrome, the most common identified genetic cause of autism, has led to interest in the possible implications for future autism research into this pathway. Some data suggests neuronal overgrowth potentially related to an increase in several growth hormones or to impaired regulation of growth factor receptors. Also, some inborn errors of metabolism are associated with autism, but probably account for less than 5% of cases.

[0185] The mirror neuron system (MNS) theory of autism hypothesizes that distortion in the development of the MNS

interferes with imitation and leads to autism's core features of social impairment and communication difficulties. The MNS operates when an animal performs an action or observes another animal perform the same action. The MNS may contribute to an individual's understanding of other people by enabling the modeling of their behavior via embodied simulation of their actions, intentions, and emotions. Several studies have tested this hypothesis by demonstrating structural abnormalities in MNS regions of individuals with ASD, delay in the activation in the core circuit for imitation in individuals with Asperger syndrome, and a correlation between reduced MNS activity and severity of the syndrome in children with ASD. However, individuals with autism also have abnormal brain activation in many circuits outside the MNS and the MNS theory does not explain the normal performance of children with autism on imitation tasks that involve a goal or object.

[0186] The under connectivity theory of autism hypothesizes that autism is marked by under functioning high-level neural connections and synchronization, along with an excess of low-level processes. Evidence for this theory has been found in functional neuroimaging studies on autistic individuals and by a brainwave study that suggested that adults with ASD have local over connectivity in the cortex and weak functional connections between the frontal lobe and the rest of the cortex. Other evidence suggests the under connectivity is mainly within each hemisphere of the cortex and that autism is a disorder of the association cortex.

[0187] From studies based on event-related potentials, transient changes to the brain's electrical activity in response to stimuli, there is considerable evidence for differences in autistic individuals with respect to attention, orientation to auditory and visual stimuli, novelty detection, language and face processing, and information storage; several studies have found a preference for nonsocial stimuli. For example, magnetoencephalography studies have found evidence in children with autism of delayed responses in the brain's processing of auditory signals.

[0188] Relations have been found between autism and schizophrenia based on duplications and deletions of chromosomes; research showed that schizophrenia and autism are significantly more common in combination with 1q21.1 deletion syndrome. Research on autism/schizophrenia relations for chromosome 15 (15q13.3), chromosome 16 (16p13.1) and chromosome 17 (17p12) are inconclusive.

[0189] Diagnosis is based on behavior, not cause or mechanism. Under the DSM-5, autism is characterized by persistent deficits in social communication and interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities. These deficits are present in early childhood, typically before age three, and lead to clinically significant functional impairment. Sample symptoms include lack of social or emotional reciprocity, stereotyped and repetitive use of language or idiosyncratic language, and persistent preoccupation with unusual objects. The disturbance must not be better accounted for by Rett syndrome, intellectual disability or global developmental delay. ICD-10 uses essentially the same definition. A pediatrician commonly performs a preliminary investigation by taking developmental history and physically examining the child. If warranted, diagnosis and evaluations are conducted with help from ASD specialists, observing and assessing cognitive, communication, family, and other factors using standardized tools, and taking into

account any associated medical conditions. A pediatric neuropsychologist is often asked to assess behavior and cognitive skills, both to aid diagnosis and to help recommend educational interventions.

[0190] Clinical genetics evaluations are often done once ASD is diagnosed, particularly when other symptoms already suggest a genetic cause. Although genetic technology allows clinical geneticists to link an estimated 40% of cases to genetic causes, consensus guidelines in the US and UK are limited to high-resolution chromosome and fragile X testing. Metabolic and neuroimaging tests are sometimes helpful, but are not routine.

[0191] Many medications are used to treat ASD symptoms that interfere with integrating a child into home or school when behavioral treatment fails. More than half of US children diagnosed with ASD are prescribed psychoactive drugs or anticonvulsants, with the most common drug classes being antidepressants, stimulants, and antipsychotics. Antipsychotics, such as risperidone and aripiprazole, have been found to be useful for treating some conditions associated with autism, including irritability, repetitive behavior, and sleeplessness. A person with ASD may respond atypically to medications, the medications can have adverse effects, and no known medication relieves autism's core symptoms of social and communication impairments. Experiments in mice have reversed or reduced some symptoms related to autism by replacing or modulating gene function, suggesting the possibility of targeting therapies to specific rare mutations known to cause autism. Although many alternative therapies and interventions are available, few are supported by scientific studies. Some alternative treatments may place the child at risk. A 2008 study found that compared to their peers, autistic boys have significantly thinner bones if on casein-free diets; in 2005, botched chelation therapy killed a five-year-old child with autism. There has been early research looking at hyperbaric treatments in children with autism.

Parkinson's Disease

[0192] Parkinson's disease (PD, also known as idiopathic or primary parkinsonism, hypokinetic rigid syndrome (HRS), or paralysis agitans) is a degenerative disorder of the central nervous system mainly affecting the motor system. The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain. The causes of this cell death are poorly understood. Early in the course of the disease, the most obvious symptoms are movement-related; these include shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, thinking and behavioral problems may arise, with dementia commonly occurring in the advanced stages of the disease, and depression is the most common psychiatric symptom. Other symptoms include sensory, sleep and emotional problems. Parkinson's disease is more common in older people, with most cases occurring after the age of 50; when it is seen in young adults, it is called young onset PD (YOPD).

[0193] The main motor symptoms are collectively called "parkinsonism," or a "parkinsonian syndrome." The disease can be either primary or secondary. Primary Parkinson's disease is referred to as idiopathic (having no known cause), although some atypical cases have a genetic origin, while secondary parkinsonism is due to known causes like toxins. The pathology of the disease is characterized by the accu-

mulation of a protein into Lewy bodies in neurons, and insufficient formation and activity of dopamine in certain parts of the midbrain. Where the Lewy bodies are located is often related to the expression and degree of the symptoms of an individual. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used for confirmation.

[0194] Diagnosis of Parkinson's disease involves a physician taking a medical history and performing a neurological examination. There is no lab test that will clearly identify the disease, but brain scans are sometimes used to rule out disorders that could give rise to similar symptoms. People may be given levodopa and resulting relief of motor impairment tends to confirm diagnosis. The finding of Lewy bodies in the midbrain on autopsy is usually considered proof that the person had Parkinson's disease. The progress of the illness over time may reveal it is not Parkinson's disease, and some authorities recommend that the diagnosis be periodically reviewed. Other causes that can secondarily produce a parkinsonian syndrome are Alzheimer's disease, multiple cerebral infarction and drug-induced parkinsonism. Parkinson plus syndromes such as progressive supranuclear palsy and multiple system atrophy must be ruled out. Anti-Parkinson's medications are typically less effective at controlling symptoms in Parkinson plus syndromes. Faster progression rates, early cognitive dysfunction or postural instability, minimal tremor or symmetry at onset may indicate a Parkinson plus disease rather than PD itself. Genetic forms are usually classified as PD, although the terms familial Parkinson's disease and familial parkinsonism are used for disease entities with an autosomal dominant or recessive pattern of inheritance.

[0195] The PD Society Brain Bank criteria require slowness of movement (bradykinesia) plus either rigidity, resting tremor, or postural instability. Other possible causes for these symptoms need to be ruled out prior to diagnosis with PD. Finally, three or more of the following features are required during onset or evolution: unilateral onset, tremor at rest, progression in time, asymmetry of motor symptoms, response to levodopa for at least five years, clinical course of at least ten years and appearance of dyskinesias induced by the intake of excessive levodopa. Accuracy of diagnostic criteria evaluated at autopsy is 75-90%, with specialists such as neurologists having the highest rates. Computed tomography (CT) and conventional magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal. These techniques are nevertheless useful to rule out other diseases that can be secondary causes of parkinsonism, such as basal ganglia tumors, vascular pathology and hydrocephalus. A specific technique of MRI, diffusion MRI, has been reported to be useful at discriminating between typical and atypical parkinsonism, although its exact diagnostic value is still under investigation. Dopaminergic function in the basal ganglia can be measured with different PET and SPECT radiotracers. Examples are ioflupane (123I) (trade name DaTSCAN) and iometopane (Dopascan) for SPECT or fluorodeoxyglucose (18F) and DTBZ for PET. A pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD.

[0196] Treatments, typically the medications L-DOPA and dopamine agonists, improve the early symptoms of the disease. As the disease progresses and dopaminergic neurons continue to be lost, these drugs eventually become ineffective at treating the symptoms and at the same time

produce a complication marked by involuntary writhing movements. Surgery and deep brain stimulation have been used to reduce motor symptoms as a last resort in severe cases where drugs are ineffective. Although dopamine replacement alleviates the symptomatic motor dysfunction, its effectiveness is reduced as the disease progresses, leading to unacceptable side effects such as severe motor fluctuations and dyskinesias. Furthermore, there is no therapy that will halt the progress of the disease. Moreover, this palliative therapeutic approach does not address the underlying mechanisms of the disease.

[0197] The term parkinsonism is used for a motor syndrome whose main symptoms are tremor at rest, stiffness, slowing of movement and postural instability. Parkinsonian syndromes can be divided into four subtypes according to their origin: primary or idiopathic, secondary or acquired, hereditary parkinsonism, and Parkinson plus syndromes or multiple system degeneration. Usually classified as a movement disorder, PD also gives rise to several non-motor types of symptoms such as sensory deficits, cognitive difficulties or sleep problems. Parkinson plus diseases are primary parkinsonisms which present additional features. They include multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and dementia with Lewy bodies.

[0198] In terms of pathophysiology, PD is considered a synucleopathy due to an abnormal accumulation of alpha-synuclein protein in the brain in the form of Lewy bodies, as opposed to other diseases such as Alzheimer's disease where the brain accumulates tau protein in the form of neurofibrillary tangles. Nevertheless, there is clinical and pathological overlap between tauopathies and synucleinopathies. The most typical symptom of Alzheimer's disease, dementia, occurs in advanced stages of PD, while it is common to find neurofibrillary tangles in brains affected by PD. Dementia with Lewy bodies (DLB) is another synucleinopathy that has similarities with PD, and especially with the subset of PD cases with dementia. However, the relationship between PD and DLB is complex and still has to be clarified. They may represent parts of a continuum or they may be separate diseases.

[0199] Mutations in specific genes have been conclusively shown to cause PD. These genes encode alpha-synuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2. In most cases, people with these mutations will develop PD. With the exception of LRRK2, however, they account for only a small minority of cases of PD. The most extensively studied PD-related genes are SNCA and LRRK2. Mutations in genes including SNCA, LRRK2 and glucocerebrosidase (GBA) have been found to be risk factors for sporadic PD. Mutations in GBA are known to cause Gaucher's disease. Genome-wide association studies, which search for mutated alleles with low penetrance in sporadic cases, have now yielded many positive results.

[0200] The role of the SNCA gene is important in PD because the alpha-synuclein protein is the main component of Lewy bodies. The histopathology (microscopic anatomy) of the substantia nigra and several other brain regions shows neuronal loss and Lewy bodies in many of the remaining nerve cells. Neuronal loss is accompanied by death of

astrocytes (star-shaped glial cells) and activation of the microglia (another type of glial cell). Lewy bodies are a key pathological feature of PD.

Alzheimer's Disease

[0201] Alzheimer's disease (AD) accounts for 60% to 70% of cases of dementia. It is a chronic neurodegenerative disease that often starts slowly, but progressively worsens over time. The most common early symptom is short-term memory loss. As the disease advances, symptoms include problems with language, mood swings, loss of motivation, disorientation, behavioral issues, and poorly managed self-care. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years. The cause of Alzheimer's disease is poorly understood. About 70% of the risk is believed to be genetic with many genes involved. Other risk factors include a history of head injuries, hypertension, or depression. The disease process is associated with plaques and tangles in the brain.

[0202] Alzheimer's disease is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Alzheimer's disease has been hypothesized to be a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain. Plaques are made up of small peptides, 39-43 amino acids in length, called beta-amyloid (also written as A-beta or A β). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair. In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis. One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques.

[0203] A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes. Initial symptoms are often mistaken for normal ageing. Examination of brain tissue is needed for a definite diagnosis. Alzheimer's disease is diagnosed through a complete medical assessment. There is no one clinical test that can determine whether a person has Alzheimer's. Usually several tests are performed to rule out any other cause of dementia. The only definitive method of diagnosis is examination of brain tissue obtained from a biopsy or autopsy. Tests (such as blood tests and brain imaging) are used to rule out other causes of dementia-like symptoms. Laboratory tests and screening include: complete blood cell count; electrolyte panel; screening metabolic panel; thyroid gland function tests; vitamin B-12 folate levels; tests for syphilis and, depending on history, for human immunodeficiency antibodies; urinalysis; electrocardiogram (ECG); chest X-ray; computerized tomography (CT) head scan; and an electroencephalogram (EEG). A lumbar puncture may also be informative in the overall diagnosis.

[0204] There are no known medications or supplements that decrease risk of Alzheimer's. Additionally, no known treatments stop or reverse Alzheimer's progression, although some may temporarily improve symptoms.

[0205] This invention is further illustrated by the following examples, which should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application, as well as the figures, are incorporated herein by reference.

EXAMPLES

Example 1: Characterization of BMPS by Expression of Neural Specific Genes During Differentiation

[0206] According to the techniques herein, the BMPS model established herein follows a stepwise differentiation protocol (FIG. 1A). In the final step, cells were differentiated into various neuronal and glial cell types during constant gyratory shaking. Briefly, the BMPS were established as follows: cells were differentiated, by addition of B27, GDNF and BDNF and withdrawal of stempro, basic FGF and EGF, into different neuronal and glial cell types with CNS functions during constant gyratory shaking. Advantageously, the techniques herein provide that the BMPS that were produced were of a spherical shape and a consistent size. For example, the BMPS showed spherical shapes and controlled sizes that were below 350 μm after 17 days in culture, a size that avoids necrosis in the center of the aggregate (FIG. 1B) that occurs in larger spheroids (e.g., >350 μm) due to nutrient and oxygen deprivation. Nutrient and oxygen deprivation-induced necrosis could produce artifacts in the different endpoints measured, especially in disease and toxicity studies. Five days after initiation of aggregation in NPC medium, spheres were on average 130 \pm 5 μm in diameter; the size increased to 300 \pm 40 μm during the first 17 days in differentiation medium. From day 17 onwards size remained constant around 310 μm . Advantageously, this technique significantly increases throughput of BMPS production by allowing simultaneous production of several batches with different conditions. Without the shaking condition, aggregates tend to stick together, grow in different shapes, attach to the bottom and in some point get necrotic in the middle of the sphere. Thus, constant gyratory shaking technology is a suitable method to control the shape and size of BMPS.

[0207] In order to characterize different stages of the differentiation and maturation process, BMPS were collected every week up to 8 weeks of differentiation (FIGS. 1C1-C5). Analysis of different neuronal and glial cell-specific genes by real-time reverse transcription polymerase chain reaction (RT-PCR) was performed to characterize the presence of neurons, astrocytes, oligodendrocytes and neural precursor cells (NPC). NPC are self-renewing and proliferating multi-potent cells able to generate different cell types of the central nervous system. The differentiation of NPC in 3D was initiated by changing the medium to differentiation medium. Gene expression of the cell proliferation marker Ki67 decreased 95% after 2 weeks of differentiation (FIG. 1C1, proliferation and stem cell markers). The remaining Ki67 expression appears to be due to the presence of a small population of NPC and other proliferating cell types such as oligodendrocytes and astrocytes (FIG. 1C2, astrogli and oligodendroglia). Astrocyte-specific genes (S100B and GFAP) showed a constant increase after two weeks, while, differentiation of oligodendrocytes was induced later, after six weeks of differentiation as shown by OLIG2 gene expression (FIG. 1C2).

[0208] Gene expression of specific neurotransmitters or their receptors was used to characterize the identity of different neuronal populations and the differentiation patterns of the human iPSC derived BMPS (FIG. 1C4, neuronal markers; right y-axis relative quantification of GRIN1 and GABRA1; MBP, FOXA2, and SLC1A3). GRIN1 encodes the essential Glutamate [NMDA] receptor subunit zeta-1 [25] was increased at very early stages of differentiation (one week after induction of differentiation) and continued to increase up to 5 weeks when it reached a plateau (FIG. 1C4). Similarly, GAD1, a GABAergic neuronal gene marker which encodes the Glutamate decarboxylase 1, and catalyzes decarboxylation of glutamate to GABA, showed an increase in expression during the first 4 weeks of differentiation, reaching a plateau thereafter (FIG. 1C4). The expression of tyrosine hydroxylase (TH) a gene, which identifies dopaminergic neurons, was observed first after three weeks, showing delayed differentiation compared to glutamatergic neurons. The expression of TH increased constantly thereafter reaching an 86-fold increase at seven weeks compared to NPC (week 0; FIG. 1C4). GABRA1, which encodes the gamma-aminobutyric acid (GABA) receptor, showed a steady increase of expression after 2 weeks and reached its maximum increase of a 150-fold change at 8 weeks compared to week 0 (FIG. 1C4). Moreover other markers for specific part of the brain, such as ventral midbrain neuron marker LMX1A, FOXO1 and FOXA2 (Hedlund et al., 2016; Stott et al., 2013), cerebral cortex marker FOXO4, or markers for myelination CNP and MBP (Li and Richardson, 2008; Agrawal et al., 1994) and L-glutamate transport SLC1A6 (Sery et al., 2015) has been studied (FIG. 1D d). Based on the patterns of expression of neuronal genes, the iPSC-derived BMPS model closely represents the different neuronal populations of different cortical and subcortical areas of the human CNS, suggesting that some of the mechanisms implicated in the early stages of nervous system development are reflected.

[0209] To prove that BMPS can be generated from different iPCs, another healthy line (IPS IMR90) and Down syndrome line (DYP0730) were used (FIG. 1C5). Both lines were able to generate BMPS and differentiated to neurons (MAP2 marker), astrocytes (GFAP marker) and oligodendrocytes (OLIG1 marker).

Example 2: Characterization of BMPS by Flow Cytometry Analysis Shows Neuronal Maturation of the Human Induced Pluripotent Stem Cells Over Time

[0210] In order to quantify cell populations in the iPSC-derived BMPS and verify the reproducibility between

experiments and batches of the cell line (C1, CRL-2097), flow cytometry was performed using CNS-specific antibodies for identification of neural markers (Table 1). Flow cytometry allowed quantifying 60% of cells with proliferation marker (Ki67) at the NPCs stage (week 0), which was reduced during differentiation down to 9% at 2 weeks, 7% at 4 weeks and 1% at 8 weeks (FIG. 1D), indicating a fast reduction of proliferating cells after induction of differentiation. This confirms the gene expression data and indicates a fast reduction of proliferating cells after induction of differentiation. This result was confirmed by further analysis of NPC markers such as SOX1, SOX2 and Nestin. SOX1 and SOX2 are known to be involved in the maintenance of neural progenitor cell identity. The number of SOX1-, SOX2- and NES-positive (NPC marker) cells in the NPC population (week 0) was 46%, 68% and 60%, respectively. SOX1, SOX2 and NES expression was reduced dramatically with differentiation, showing very low positive populations at eight weeks (2%, 3% and 2%, respectively). This loss in the NPC population during differentiation was corroborated by Doublecortin (DCX), a microtubule-associated protein expressed in neuroblasts and immature neurons: the number of DCX-positive cells in NPC (week 0) was around 30%, which reduced to 22% at two, 17% at four and 4% at eight weeks, respectively. On the other hand, the marker for mature neurons, Tuj1 (Neuron-specific class III beta-tubulin) presented the opposite pattern. Analysis showed low levels of Tuj1-positive cells at the NPC stage (week 0). The expression of this marker in the cell population increased to 70% after 2 weeks of differentiation and remained constant up to 8 weeks. These flow cytometry experiments indicate differentiation and maturation of the BMPS over time.

[0211] Quantification of the cell population in at least three independent experiments showed low variability between cultures, demonstrating the reproducibility of the system. The variation (standard deviation, SD) between experiments decreased with the cell differentiation process and was very small at the latest maturation stage (eight weeks); DCX SD 0.9%, Ki67 SD 0.2%, SOX1 SD 0.7%, SOX2 SD 1.2%, NES SD 0.7% and Tuj1 SD 9.8% (FIG. 1E). These results indicate that after eight weeks of differentiation the cellular composition is similar and shows high reproducibility between different BMPS experiments.

TABLE 1

Gene and miRNAs Taqman Assays. List of the primers used for the experiments.				
Assay ID	Assay Type	Availability	Catalog Number	Assay Name
Gene Expression Taqman Primers				
Hs01060665	TaqMan ® Gene Expression Assay	Inventoried	4331182	BACT
Hs99999901	TaqMan ® Gene Expression Assay	Inventoried	4331182	18S
Hs04187831	TaqMan ® Gene Expression Assay	Inventoried	4331182	NES
Hs01032443	TaqMan ® Gene Expression Assay	Inventoried	4331182	Ki67
Hs01088112	TaqMan ® Gene Expression Assay	Inventoried	4331182	PAX6
Hs00909233	TaqMan ® Gene Expression Assay	Inventoried	4331182	GFAP
Hs00300164	TaqMan ® Gene Expression Assay	Inventoried	4331182	OLIG2
Hs00902901	TaqMan ® Gene Expression Assay	Inventoried	4331182	S100B
Hs00609557	TaqMan ® Gene Expression Assay	Inventoried	4331182	GRIN1
Hs00165941	TaqMan ® Gene Expression Assay	Inventoried	4331182	TH

TABLE 1-continued

Gene and miRNAs Taqman Assays. List of the primers used for the experiments.				
Assay ID	Assay Type	Availability	Catalog Number	Assay Name
Hs00971228	TaqMan ® Gene Expression Assay	Inventoried	4331182	GABRA1
Hs01065893	TaqMan ® Gene Expression Assay	Inventoried	4331182	GAD1
Hs00199577	TaqMan ® Gene Expression Assay	Inventoried	4331182	SYN1
Hs00232429	TaqMan ® Gene Expression Assay	Inventoried	4331182	TBR1
Hs01003383	TaqMan ® Gene Expression Assay	Inventoried	4331182	SNCA
Hs01003430	TaqMan ® Gene Expression Assay	Inventoried	4331182	KEAP1
Hs00929425	TaqMan ® Gene Expression Assay	Inventoried	4331182	NDUFB1
Hs01101219	TaqMan ® Gene Expression Assay	Inventoried	4331182	ATP5C1
Hs00919163	TaqMan ® Gene Expression Assay	Inventoried	4331182	ATP5O
Hs00354836	TaqMan ® Gene Expression Assay	Inventoried	4331182	CASP1
Hs00263981	TaqMan ® Gene Expression Assay	Inventoried	4331182	CNP
Hs01054576	TaqMan ® Gene Expression Assay	Inventoried	4331182	FOXO1
Hs00188193	TaqMan ® Gene Expression Assay	Inventoried	4331182	SLC1A3
Hs00936217	TaqMan ® Gene Expression Assay	Inventoried	4331182	FOXO4
Hs00892663	TaqMan ® Gene Expression Assay	Inventoried	4331182	LMX1A
Hs00232764	TaqMan ® Gene Expression Assay	Inventoried	4331182	FOXA2
miRNA Taqman Assays				
1182	TaqMan ® microRNA Assay	Inventoried	4427975	mmu-miR-124a
2216	TaqMan ® microRNA Assay	Inventoried	4427975	hsa-miR-128a
457	TaqMan ® microRNA Assay	Inventoried	4427975	hsa-miR-132
2247	TaqMan ® microRNA Assay	Inventoried	4427975	hsa-miR-133b
1129	TaqMan ® microRNA Assay	Inventoried	4427975	mmu-miR-137
1094	Control miRNA Assay	Inventoried	4427975	RNU44

Example 3: MicroRNAs as Neuronal Differentiation Markers in Human iPSC-Derived BMPS

[0212] MicroRNAs (miRNA), known as posttranscriptional regulators of developmental timing, have recently been established as markers to study the differentiation process [26]. Expression of neural-specific miRNAs showed strong induction of miRNAs involved in neurogenesis (FIG. 1C3, miRNA). mir-124, the most abundant brain miRNA, was strongly induced in the earlier stages of differentiation, then slightly down-regulated at eight weeks of differentiation. This finding correlates with previous studies, where mir-124 was shown to promote neuronal lineage commitment at earlier stages of neural stem cells specification by targeting anti-neuronal factors [26]. mir-128, a modulator of late neural differentiation, was strongly up-regulated after 5 weeks of differentiation. mir-137, the most induced miRNA over time in the system described herein, is known as a regulator of neural differentiation of embryonic stem cells (ESCs) [27]. mir-132 and mir-133b which are involved in regulation of dopaminergic neuron maturation and function, were induced in week three of differentiation, a finding which correlates with the expression pattern of TH. Moreover, mir-132 is involved in dendritic spine formation [28]. These results support the view of a coordinated mechanism of neuronal differentiation as reflected by the patterns of neuronal gene and miRNA expression and neuronal and neurotransmitter identity.

Example 4: Characterization of Human BMPS by Immunohistochemistry and Electron Microscopy Shows Evidence of Differentiation into Mature Brain Cell Types

[0213] In order to assess the cellular composition and the process of maturation of the cells within the human BMPS, the expression of markers for different CNS cell populations including neurons and glial cells at 2, 4 and 8 weeks of

differentiation were evaluated using immunohistochemistry and electron microscopy techniques. A reproducible pattern of expression consistent with maturation of the BMPS towards mature neural phenotypes was found. After 4 weeks of differentiation, the BMPS showed positive staining for mature neuronal markers such as microtubule-associated protein 2 (MAP2), neurofilament-heavy chain (NF, SMI32) and synaptophysin (FIG. 2A, 2B). Furthermore, different neuronal subtypes in the BMPS including dopaminergic (TH-positive neurons), glutamatergic (VGLUT1-positive neurons) and GABAergic interneurons (calbindin-positive neurons) (FIG. 2B, FIG. 8A) were observed. Moreover, the BMPS matured over time of differentiation as seen by decreased NES-positive cells (FIG. 2A) and increased cell-cell interactions (neuron-neuron and neuron glia) as subsets of neurons showed several processes, which resembled dendritic and axonal projections (FIG. 8A).

[0214] A subset of neuronal cells exhibited immunoreactivity for markers such as NOGOA, O1, O2, and CNPase (FIG. 8B, panels a-j; FIG. 1C5), which identifies the presence of mature oligodendrocytes in the BMPS [31, 33]. Automatic image quantification showed that oligodendrocytes (CNPase, NOGOA, and Olig1) comprised 3, 9, and 11% of the total cell population, respectively, at 8 weeks of differentiation (FIG. 8C; FIG. 1C5). Similar to the in vivo physiology, these cells were immunoreactive for myelin basic protein (MBP) (FIG. 2), which characterizes myelinating oligodendrocytes [32]. Moreover, they had morphological features of normal human oligodendrocytes in vivo and appeared in close contact with neuronal processes (FIG. 8a-b, FIG. 2C, 2D).

[0215] Similarly, populations of neuroglia such as astrocytes and oligodendrocytes were identified using specific antibody markers. A subset of neuroglial cells exhibit immunoreactivity for markers such as NOGOA, Olig1 and CNPase (FIG. 2C, panels a-f and 2C, panel i), which identify the presence of mature oligodendrocytes in the BMPS [29, 30, 31, 32]. This pattern of immunostaining suggests that

oligodendrocytes within the BMPS are functional and myelinate axons. Similar to the *in vivo* physiology, these cells were also immunoreactive for myelin basic protein (MBP) (FIG. 2C panel i and 2C panel j), which characterizes myelinating oligodendrocytes [33, 30]. These cells had morphological features of normal human oligodendrocytes and appeared in close contact with neuron processes, which resemble axonal structures (FIG. 2C, panels j-m). In addition, a high number of mature astrocytes (FIG. 2Ca, 2Cb, 2Cg, 2Ch and 2F) at 4 and 8 weeks of differentiation were observed. Morphometric studies of neuronal processes identified by immunostaining with NF antibodies and MBP markers were used to estimate the percentage of myelinated axons within the BMPS with an average of 4% at 2 weeks, 25% at 4 weeks and 42% at 8 weeks of differentiation ($p<0.001$) (FIG. 2D). All analyzed BMPS showed similar extent of myelination at the same differentiation window. Percentages were calculated as the mean of at least 18 microscopy fields from at least 3 individual BMPS in 2 different experiments. Ultrastructural analysis by electron microscopy demonstrated cell projections, which enwrapped cell processes resembling axons after 8 weeks of differentiation (FIG. 2C).

[0216] GFAP-positive cells formed numerous cell processes organized in a network typical for human astrocyte glial processes *in vivo*, which established contacts with other glial cells and neurons (FIG. 2Cg, 2Ch, 2F, and FIG. 8B). Image quantification revealed 19% of astrocytes in the total population (FIG. 8C). Altogether, the patterns of cell morphology, immunostaining and cell-cell interactions shown by neuronal and glial cell populations demonstrates that the BMPS recapitulates the cellular types and pattern of interactions seen in the human CNS and is, therefore, considered organotypic.

[0217] The morphology of cell nuclei observed by immunocytochemistry and electron microscopy showed some variation in nuclear morphology attributed to (i) cell proliferation as seen by positive staining for Ki67 and Nestin markers, and (ii) nuclear fragmentation likely associated with apoptosis as indicated by caspase 3 staining (FIG. 2G, 2H) was observed. These observations were also confirmed by electron microscopy studies at 4 and 8 weeks of differentiation (FIG. 2H). The variation of nuclei morphology likely reflects the active stages of cell differentiation that BMPS exhibited during all stages of development. The presence of apoptotic nuclei likely resemble stages of cell death seen in normal neurodevelopment [34, 35]. Importantly, Caspase 3-positive nuclei did not concentrate in the center of the spheres and BMPS did not present necrosis in the center of the 3D structures (FIG. 2G). Thus, Caspase3-positive nuclei do not appear linked to deprivation of oxygen or nutrients. Caspase has been quantified at eight weeks in BMPS (FIG. 8C). Additionally, FIGS. 8D and 8E depict co-expression of mature oligodendroglia markers (MBP and O2) and expression of neuronal markers (VGLUT, TUJ1, SYN), respectively.

[0218] Further analysis of neuronal cell populations and morphology presented a pattern of evolution that suggests BMPS maturation as seen by Nestin-positive cells decreasing over time of differentiation while MBP expressing cells increased (FIG. 2A). There was also evidence of cell-cell interactions as subsets of neurons showed several processes, which resemble dendritic and axonal projections that interact with other neurons as well as glial cells (FIG. 2B, FIG.

2H). Furthermore, cells immunostained with myelin binding protein (MBP) antibodies issued projections, which appear to enwrap neuronal processes, which resemble axons (FIG. 2C, panels i-k, 2C, panel m). The pattern of immunostaining with MBP and its association with neuronal processes suggests that oligodendrocytes within the BMPS exhibit myelinating properties such as in the human CNS *in vivo*. Ultrastructural analysis by electron microscopy demonstrated cell projections, which enwrapped cell processes resembling axons (FIG. 2C, panel m).

Example 5: Microelectrode Array Recording of Spontaneous Electrical Activity of BMPS

[0219] To test the neurophysiological properties of the cells within the BMPS model, spontaneous electrical activity in BMPS was analyzed by micro-electrode array (MEA) (see FIG. 3 generally). BMPS were plated in 12-well or 48-well MEA plates at 8 weeks of differentiation. The aggregates were attached to the MEAs using Matrigel coating. Spontaneous electrical activity was measured starting one week after plating up to two weeks. The activity was measured for 20 minutes on 7 different days. Electrodes were considered active when the recorded activity was above 0.05 spikes/sec. FIG. 3A shows a representative heatmap of a 48-well MEA plate measurement from one 20 minute recording. The heatmap represents the spike amplitude (V) with a minimum of 0 μ V and maximum of 40 μ V (FIG. 3A). The spikes showed a common waveform between different electrodes and measurements (FIG. 3B) and neurons were repeatedly firing. 25 electrodes, distributed over 19 wells, were included after the first step of data analysis. 20 to 40% of these 25 electrodes reached the threshold of 0.05 spikes/sec during each recording. FIG. 3F shows the spike events of active electrodes from one representative 20 minutes recording. These data show potential for the use of MEA to measure electrical activity of the 3D BMPS. Further optimization of the protocol may increase the measurement of the neuronal activity on the electrodes.

Example 6: A Human 3D Model to Study Parkinson's Disease

[0220] Due to the presence of TH-positive dopaminergic neurons in the iPSC-derived BMPS (FIG. 2B, panels k, l, and FIG. 8), the possibility of using this model to study Parkinson's Disease (PD), a neurodegenerative disorder known to specifically affect dopaminergic neurons, was further explored. Two well-known neurotoxicants, which induce pathogenic processes resembling the mechanism associated with neurodegeneration in PD: the illicit drug MPTP's toxic metabolite MPP⁺ and the broadly used pesticide rotenone, were selected. Both MPP⁺ and rotenone interfere with oxidative phosphorylation in mitochondria by inhibiting complex I [36]. Initially, cytotoxicity experiments were performed to estimate sub-cytotoxic concentrations of these two compounds affecting only dopaminergic neurons (FIGS. 4A and 4C). Selective disruption of dopaminergic neurons but not of any other cell types in the systems described herein were observed with immunohistochemistry after exposure to 1 μ M rotenone and 100 μ M MPP⁺ for 24 h (FIGS. 4E and 4F). This effect was likely selective even at cytotoxic concentrations of 10 μ M rotenone and 1000 μ M MPP⁺ as these concentrations did not show any alterations in other neurofilament 200-positive neurons. Lower concentra-

tions of these compounds may induce effects in dopaminergic neurons, however, the effect was not as obvious by immunocytochemistry. Higher concentrations of rotenone and MPP+(up to 50 μ M and 5000 μ M, respectively) led to general cytotoxicity and affected also other neuronal types stained positive for neurofilament 200 (FIGS. 4E and F). 5 μ M of rotenone and 1000 μ M of MPP+ were selected for further studies as these concentrations induced clear and selective dopaminergic effects. Reactive oxygen species (ROS) were measured in the cellular medium using the OxiSelectTM In Vitro ROS/RNS Assay Kit (Cellbiolabs, San Diego, CA) as an indication of oxidative stress. Exposure to rotenone at 5 μ M and MPP+ at 1000 μ M showed an increase in ROS production after 24 hours exposure, while 12 hours showed no statistically significant changes. Real time RT-PCR was performed in order to determine effects of both chemicals on genes related to PD, mitochondrial dysfunction and oxidative stress. Tyrosine hydroxylase (TH, Dopaminergic neuronal marker) mRNA expression decreased by 84% \pm 11 after exposure to 5 μ M rotenone and 70% \pm 9 after exposure to 1000 μ M MPP+ for 24 hours. Additional genes related to PD also showed changes at sub-cytotoxic concentrations of MPP+ and rotenone. The expression of genes that encode T-box brain 1 (TBR1) and Alpha-synuclein (SNCA) protein decreased after 24 hours exposure. The reduction of TBR1 was 70 \pm 13% (rotenone) and 76 \pm 22% (MPP+) and the reduction of SNCA was 72 \pm 6% (rotenone) and 41 \pm 40% (MPP, however, BMPS exposed to 1 mM MPP+ led to no statistically significant changes in SNCA expression). Expression of genes related to mitochondrial function complex I (NDUFB1) or complex 0 (ATP5C1 or ATP5O) tended to decrease in expression but these changes were not statistically significant. Caspase-1 gene expression, which has been related to SNCA, increased after 24 hours exposure to MPP+. These results demonstrate the potential of BMPS for studies elucidating molecular mechanisms of PD, lending itself to PD drug and neurotoxicity screening.

Example 7: Addition of Microglia

[0221] Peripheral blood mononuclear cells (PBMCs) are isolated from fresh or commercially available cryo-preserved whole blood of pooled healthy donors by Ficoll or Percoll gradient centrifugation. Monocyte populations are obtained by negative magnet-antibody selection after Ficoll or Percoll gradient and then re-suspend in RPMI 1640. Monocytes are cultured in macrophage serum-free medium, stimulated with a cocktail of cytokines, GM-CSF and IL-34. Monocytes may also be obtained by differentiation of iPSCs, hematopoietic or other stem cells. The microglia-like cells are combined with neuronal precursor cells in shaker cultures to preferably arrive at a final concentration of 5-8% microglia.

[0222] Primary monocytes or iPSC-derived monocytes may be incorporated into the system, both at early and later stages of BMPS differentiation. For the early stages, a number of 2×10^6 NPCs mixed with 2×10^4 monocytes are plated per 1 well (6 well-plate). Gyrotatory shaking is used at 88 rpm to generate spheres. After 2 days media are replaced with $\frac{1}{2}$ CNS differentiation medial (Neurobasal[®]) electro Medium (Gibco) supplemented with 5% B-27[®] Electrophysiology (Gibco), 1% glutamax (Gibco), 10 μ g human recombinant GDNF (Gemini), 10 μ g human recombinant BDNF (Gemini) and $\frac{1}{2}$ macrophage differentiation media (Dulbecco's modified Eagle's medium (Invitrogen) supple-

mented with 10% FCS, 0.055 mM β -mercaptoethanol, M-CSF (50 ng/ml), and IL-3 (25 ng/ml) (R&D Systems). The medium is replaced every 3 days.

[0223] Monocytes can also be incorporated after BMPS differentiation. For that, BMPS are differentiated up to 8 weeks. BMPS spheres are separated in 500 μ l Eppendorf tubes. 2×10^4 monocytes are added to the Eppendorf with the BMPS. Tubes are shaking manually every hour, up to 8 hours. After that, BMPS-monocytes are collected and plated in 6 well plates. Cells are kept on constant shaking until use.

[0224] The characterization of the immune-competent human organoids can be carried out by immunocytochemically assessing the presence of markers such as HLA-DR, and the ionized calcium-binding adapter molecule 1 (Iba1), specific microglial markers. Measures of cytokines and chemokines release and expression of receptors associated with microglia function (e.g., CCL2 and CX3CL) demonstrates successful engrafting of the microglia cells. This modified model is more suitable to investigate the neuro-immunological component associated with many substance exposures and diseases.

Example 8: Addition of a Blood Brain Barrier

[0225] The blood brain barrier (BBB) has a crucial role in neurotoxicity, being the last barrier for substances before reaching the brain. Moreover, the BBB is the bottleneck in brain drug development and is the single most important factor limiting the future growth of neurotherapeutics [81]. Most of the in vitro models do not incorporate BBB.

[0226] Human brain microvascular endothelial cells (hBMVECs) from human iPSCs are incorporated into the BMPS by two techniques. In the first approach, mature BBB endothelial cells and neuronal precursors cells (NPCs) are combined in a single cells suspension in a ratio of 1:5, gyrotatory shaking or stirring are used to generated spheroids and aggregates are cultured up to 8 weeks. In the second technique, mature BMPS (8 weeks of differentiation) are covered by BBB endothelial cells using gravity systems (aggrewell, gravity well or hanging drops). Cells may be covered as well with other cell types, such as fluorescent LUHMES cells (FIG. 7).

Example 9: Addition of Reporters

[0227] The BMPS gives the opportunity to develop cell-based assays allowing for high-content imaging (HCI) that can be adapted to high-throughput platforms, to evaluate the effects of toxicants on key cellular processes of neural development and physiology in the culture system.

[0228] Example of establishing fluorescent iPSC cell line: Creation of reporter cells lines greatly assists imaging efforts by allowing us to avoid complications associated with staining 3D cultures, to image subsets of cells, and to perform functional assays. Differentiated 3D aggregates from iPSC cultures spiked with 1-2% of iPSCs ubiquitously expressing fluorescent protein allow visualizing individual cells within the aggregates aiding quantification of phenotypic parameters, including neurite outgrowth and migration. Lines expressing markers allow measurement of synapse formation (PSD95, Synapsin 1), proliferation (Ki67), glial maturation (GFAP), and calcium signaling (GCaMP). Clustered Regularly Interspaced Short Palindromic Repeats/Cas (CRISPR) were used to create the various lines. Similar in function to the well-established zinc-finger (ZFNs) and

TALEN nucleases, the Cas9-CRISPR system is a new entrant into the rapidly emerging field of genome engineering and has been quickly adopted and validated across a wide array of human stem cells. Gene-editing in hiPSCs has traditionally been a technically difficult task but with these advances it is now possible to generate reporter and mutant cell lines with genetically matched controls [83, 84, 85, 86]; essential tools not only for this project but also for the future success of using human iPSC-derived cells in quantitative live-cell phenotypic assays of toxicant testing.

[0229] Using the CRISPR-Cas9 system, fluorescent protein (FxP) reporter cell lines were generated by generating gRNAs targeting the gene of interest. In this system as described herein, an RNA guided Cas9 endonuclease is used in conjunction with customizable small guide RNAs (gRNAs) to target and cleave any DNA template with a GN21GG sequence; the first G is for the U6 polymerase promoter while the N21GG is for the protospacer adjacent motif (PAM) sequence requirement of Cas9 [86, 87, 89].

[0230] For reporter cell generation, homology-directed repair (HDR) guides the insertion of the appropriate DNA donor fragment into a target site at regions of homology between the donor fragment and the genomic DNA target. An ES line that ubiquitously expresses GFP was created by introducing CAG promoter-driven GFP into the AAVS1 safe harbor locus, and can use these constructs to transfect iPSC cells. For other reporters, constructs may be created that will direct the integration of a self-cleaving P2A peptide sequence [90] targeted fluorescent protein cassette in frame at the stop codon of the gene of interest. The P2A sequence engineered between the C-terminus of the endogenous protein and the fluorescent protein may minimize possible fusion protein functional defects. Plasmids encoding the Cas9 nuclease, the targeting gRNA, and appropriate donor DNA will be introduced by electroporation, recombinant hiPSC clones will be manually selected and screened for the desired insertion by PCR, and the genotype may be verified by sequencing. Reporter hiPSCs will be subjected to a differentiation protocol and expression of the reporter validated by examining expression patterns and through immunohistochemistry experiments where it may be determined whether the FxP expressing cells co-label with known markers.

Example 10: Using Cells with Specific Genetic Backgrounds

[0231] The use of iPSCs, as described herein, has created new opportunities to study human diseases and gene/environment interaction [20, 21]. Fibroblasts or other somatic cells from healthy and diseased individuals can be reprogrammed into iPSCs, and subsequently be differentiated into all neural cell types. Similarly, iPSC can be genetically modified before creating the BMPS. As a proof-of-principle, iPSCs were obtained from patients with Down's syndrome (FIGS. 1C5 and 5A-D), Rett Syndrome and from individuals with mutations in disrupted in schizophrenia 1 (DISC1). DISC1 may have some functional overlap with TSC-iPSCs as both are involved in the mTOR cell signaling pathway.

[0232] The Down's syndrome model is further characterized (see FIGS. 5A-5D). Down's syndrome iPSCs have been successfully differentiated into neural precursor cells (NPCs). Currently the cells are differentiated in 3D and characterization by gene expression and immunohistochemistry is being performed. The Down's syndrome model has

been exposed to compounds that induce oxidative stress (rotenone and paraquat). The response was compared to the model from healthy donors, which were more sensitive to these compounds than the healthy model.

Example 11: Combining the BMPS with Other Organoids

[0233] In some embodiments, BMPS may be combined with other organs and/or organ model systems. Several groups have been developing organ-on-a-chip platforms for different organs by using microfluidic techniques. Those platforms are designed to mimic in-vivo fluidic flows in the organs by separating cell culture chambers and perfusion channels, and successfully demonstrate recapitulation of iPSC-based organ functions. Together with other organ models on these platforms, the BMPS can be integrated, which allow us to untwine the complex toxicology from organ interactions. Such platforms allow (1) in-situ and high-throughput production of mini-brains on chip, (2) in-vivo like fluidic flow around mini-brains with enough supply of nutrient and small molecule through diffusion, (3) a large number of parallel test of toxic materials, and (4) a real-time monitoring of electrophysiological activities from BMPS with integrated electrodes. Companies such as TissUse GmbH have designed microfluidics platform that allow culture of floating spheres like the BMPS as described herein.

Example 12: Cryopreservation and Other Modes of Transportability

[0234] In order to e.g. incorporate the BMPS into platforms or enable any use in other laboratories, transportability of the system was optimized. Preliminary studies have shown possible recovery of the neuronal 3D aggregates after cryopreservation (FIG. 6). A human embryonal carcinoma stem cell line, (hNT2), and iPSC derived-aggregates were differentiated into mature neurons (8 weeks of differentiation for each cell line) and then cryopreserved with regular cryopreservation medium (95% FBS and 5% DMSO) or STEMdiff™ Neural Progenitor Freezing Medium (Stem cells technologies). After 2 days in liquid nitrogen, cells were thawed. Freezing media was removed and fresh media was added. One day later, viability was measured using the resazurin cell viability assay. hNT2 aggregates presented a 70% decrease in viability in both freezing medias while iPSC derived mini-brains showed a 20%-35% reduction in viability (FIG. 6). However, viability recovery of the 3D aggregates is currently optimized using other viability and functional assays. Optimization of this protocol will vary additives (DMSO, HES, glycerol, serum etc.), the cooling temperature gradient as well as thawing protocol.

[0235] Human iPSC derived mini-brains are kept in culture at 37° C. In order to transport the live mini-brains, temperature must be controlled. Different methods can be used to control temperature during transport. Heating pads combined with an insulated box have been used to transport live biological material. Disposable chemical pads employ a one-time exothermic chemical reaction such as catalyzed rusting of iron, or dissolving calcium chloride. The most common reusable heat pads are based on a chemical reaction that transforms a liquid into a solid thus releasing energy. Some new heating pads (such as Deltaphase Isothermal Pad 3SET, from Braintree Scientific, Inc.) have been able to

maintain 37° C. for more than 6 hours. 3D mini-brains cultured up to 8 weeks are sent in an insulated material box with heating pads. After transport, viability may be measured.

Example 13: Overview

[0236] The techniques herein provide a human BMPS model that is a versatile tool for more complex testing platforms, as well as for research into CNS physiology, mechanisms associated with (developmental) neurotoxicity, and pathogenesis of neurological disorders. Prior art stem cell-derived brain model systems developed in the past few years have shown the capability to recapitulate some of the *in vivo* biological processes (Juraver-Geslin and Durand, 2015; Nakano et al., 2012; Krug et al., 2014) and have an advantage over other classical *in vitro* models as they facilitate the study of various differentiation mechanisms, developmental processes and diseases (Lancaster et al., 2013). Unfortunately, these prior art systems require complicated protocols that reduce the reproducibility of the system and make it difficult to use in other fields such as chemical toxicity and drug screening. Additionally, these prior art models are also limited by large diameters, which lead to extensive cell death in the interior regions due to insufficient diffusion of oxygen and nutrients (Lancaster et al., 2013) and other artifacts.

[0237] The techniques herein overcome the limitations of the prior art by developing a human *in vitro* model by the gyratory shaking technique that enables reliable generation of a high number (about 500 per six-well plate) of viable BMPS that are homogeneous in size and shape. Control of size makes it possible to keep cell aggregates below 350 µM in diameter (FIG. 1C) and thereby avoid disparate morphology and/or necrosis in the center of the spheres. Moreover, the BMPS showed reproducible cell composition by immunomorphological quantification, assessment of imaging-based endpoints and flow cytometry analysis.

[0238] As described herein, the 3D differentiation protocol for the BMPS covers stages from neuronal precursors to different cell types of the mature CNS. As discussed in detail above, at two weeks, BMPS consisted of an immature population of cells, showing minimal neuronal networks, a low percentage of mature astrocytes and oligodendrocytes, and minimal but early stages of myelin basic protein (MBP) expression. iPSC differentiation into mature BMPS was indicated by decreasing NES expression over time and a progressive expression of mature neuronal and glial markers such as MAP2, GFAP, O1 and MBP. Gene expression studies, flow cytometry, image analysis, immunostaining and miRNA studies have shown increase of cell maturation markers, which follow the BMPS differentiation. The presence of GABAergic neurons, dopaminergic neurons and glutamatergic neurons was documented by immunohistochemistry and real-time PCR data. Moreover, the BMPS showed spontaneous electrical activity, indicating neuronal functionality of the system.

[0239] Since astrocytes and oligodendrocytes play important roles during neuronal development, plasticity and injury, the presence of glial cell populations in the presently disclosed BMPS model provides an excellent opportunity for the evaluation of neuronal-glial interactions and the role of glia in pathogenesis and toxicity processes. Astrocytes have an important role in protecting neurons, increasing neuronal viability and mitochondrial biogenesis from both

exogenous (e.g. chemicals) and endogenous toxicity (Shinozaki et al., 2014; Aguirre-Rueda et al., 2015), especially against oxidative stress (Shao et al., 1997; Schwab and McGeer, 2008). Thus, their presence in a biological system to study disease and neurotoxicity is crucial. Immunohistochemistry and RT-PCR results showed increasing numbers of astrocytes (GFAP-positive cells) in the BMPS model reaching 19% astrocytes of the total cell population at eight weeks, which is earlier than in previously described cortical spheroids, where similar proportions of GFAP-positive cells were observed first at day 181, at day 86 the number of GFAP+ cells was below 10% (Pasca et al., 2015).

[0240] The most novel element of this BMPS is the presence of mature human oligodendrocytes with myelination properties, which has not been achieved in the prior art. Immunocytochemical and ultrastructural studies confirmed the morphological identity of these cells (FIG. 2D) as multiple markers for mature oligodendrocytes were expressed by rounded cells with branching processes and membrane sheaths that are similar to the ones found in humans *in vivo*. The structure and morphology was further confirmed by electron microscopy. Quantitative assessment of the myelination process of MBP immunostaining along axons showed an increase over time of differentiation reaching 42% of myelinated axons at eight weeks (FIG. 2D). 3D reconstruction of confocal z-stacks images (FIG. 2A) and electron microscopy confirmed the wrapping of axonal structures after eight weeks of differentiation (FIG. 2C). These findings are of particular relevance since myelin is a critical element for proper neuronal function and development, and the covering of axons by myelin allows faster action potential transmission, reduces axonal energy consumption and protects the axons from degeneration (Nave, 2010). Furthermore, recent evidence suggests that oligodendrocytes and myelin have a role in the metabolic support of axons independent of their role in action potential conduction, highlighting their importance in neuronal survival (Saab et al., 2013). This is the first time that a 3D human microphysiological system, consisting of different types of neurons and glial cells, has achieved such a high percentage of myelination. The ability to assess oligodendroglia function and mechanisms associated with myelination in this BMPS model provides an excellent tool for future studies of neurological disorders such as multiple sclerosis and other demyelinating disorders. As an illustration it was recently discovered that astroglia cells could promote oligodendrogenesis via secreted molecules (Jiang et al., 2016). A human BMPS that consist of neurons, astrocytes and oligodendrocytes is essential to evaluate this mechanism further and to develop a potential therapy for demyelinating disorders.

[0241] In conclusion, the techniques herein provide a BMPS that replicates crucial aspects of brain physiology and functionality. The potential for studying developmental and neurodegenerative disorders, brain infections, toxicity and trauma with such a system is growing. Furthermore, the potential to use iPSCs from different donors adds a personalized component to these studies. The high reproducibility and relatively simple protocol, enables future medium-throughput (96-well format) testing of chemicals, drugs and their potential to induce or treat diseases.

Methods and Materials

Chemicals

[0242] Rotenone and MPP+ were supplied from Sigma-Aldrich (St. Louis, MO). A 10 mM rotenone stock was

prepared in DMSO Hybri-Max (Sigma) while MPP+ was diluted in water to a concentration of 30 mM.

iPSC Generation

[0243] CCD1079Sk (ATCC® CRL2097™), IPS IMR90 (WiCELL) and ATCCDYP0730 Human (IPS) Cells (ATCC® ACS1003™) fibroblasts were originally purchased from ATCC. All studies followed institutional IRB protocols approved by the Johns Hopkins University School of Medicine. Human fibroblasts and mouse embryonic fibroblasts (MEFs) were cultured in Dulbecco's modified Eagle's medium (DMEM, Mediatech Inc.) supplemented with 10% fetal bovine serum (FBS, HyClone) and 2 mM L-glutamine (Invitrogen). MEFs were derived from E13.5 CF-1 mouse embryos. Human iPSCs cells were generated with the EBV-based vectors as previously described [75]. iPSC from other sources were used as well. Colonies of iPSCs were manually picked after 3-6 weeks for further expansion and characterization. iPSCs (passage ≤20) were cultured on irradiated MEFs in human embryonic stem cell (hESC) medium comprising D-MEM/F12 (Invitrogen), 20% Knockout Serum Replacement (KSR, Invitrogen), 2 mM L-glutamine (Invitrogen), 100 μM MEM NEAA (Invitrogen), 100 μM β-mercaptoethanol (Invitrogen), and 10 ng/mL human basic FGF (bFGF, PeproTech). Media were changed daily and iPSC lines were passaged using collagenase (Invitrogen, 1 mg/ml in D-MEM/F12 for 1 hr at 37° C.). These iPSC lines have been previously fully characterized [75].

Neuronal Progenitor Cells (NPC) Production

[0244] NPC generation followed the previous published protocol [75]. Briefly, iPSC colonies were detached from the feeder layer with collagenase (1 mg/ml) treatment for 1 hr and suspended in EB medium, comprising of FGF-2-free hESC medium supplemented with Dorsomorphin (2 μM) and A-83 (2 μM), in non-treated polystyrene plates for 4 days with a daily medium change. After 4 days, EB medium was replaced by neural induction medium (hNPC medium) comprising of DMEM/F12, N2 supplement, NEAA, heparin (2 μg/ml) for 15 more days. The floating neurospheres were then dissociated to single cells in Accutase and plated in 175 mm flasks and were allowed to expand for 7 days. NPCs were expanded in poly-1-ornithine and laminin-coated 175 mm flask on StemPro® NSC SFM (Life Technologies). Half of the media was changed every day. Cultures were maintained at 37° C. in an atmosphere of 5% CO₂. After NPC generation, iPSCs colonies were detached and NPCs were expanded in poly-1-ornithine and laminin-coated 175 mm flask in StemPro® NSC SFM (Life Technologies). Half of the media was changed every day. Cultures were maintained at 37° C. in an atmosphere of 5% CO₂.

BMPS Differentiation

[0245] At 100% confluence NPCs were detached mechanically and counted. 2×10⁶ cells per well were plated in 2 ml of medium in non-treated 6 well-plates. Cells were grown in NPC media for two days under constant gyratory shaking. Subsequently, medium was changed to differentiation medium (Neurobasal® electro Medium (Gibco), 1% glutamax (Gibco), 0.02 μg/ml human recombinant GDNF (Gemini), 0.02 μg/ml human recombinant BDNF (Gemini)). Cultures were maintained at 37° C., 5% CO₂ under constant

gyratory shaking for up to 8 weeks. Differentiation medium was routinely changed every 2 days.

Size Measurement

[0246] Aggregates (n=20) from 3 independent experiments were randomly selected per time point for obtaining pictures and measuring size using SPOT software 5.0. Results were expressed as mean±SD. Cells were kept two days in NPC medium, indicated as NPC med. 2d in FIG. 1B. RNA and miRNA Extraction

[0247] Total RNA was extracted from aggregates every week up to 8 weeks of differentiation using Tripure (Roche, Switzerland) according to Chomczynski and Sacchi (1987) [76]. The same RNA extraction method was used to isolate RNA after toxicant treatment. RNA quantity and purity was determined using NanoDrop 2000c (Thermo Scientific). One microgram of RNA was reverse-transcribed using the M-MI V Promega Reverse Transcriptase (Promega) according to the manufacturer's recommendations. For miRNA reverse-transcription 60 ng of RNA were reverse transcribed using TaqMan microRNA Reverse transcription kit in combination with miRNA specific stem-loop primers, which are a part of TaqMAN microRNA expression assay. Up to eight stem-loop primers were multiplexed in one reaction.

Quantitative RT-PCR

[0248] The expression of genes was evaluated using specific Taqman® gene expression assays (Life Technologies). miRNA expression was analyzed using TaqMAN microRNA expression assay in combination with TaqMan miRNA Reverse Transcription kit using protocol described in [77]. Table 1 shows a summary of the genes assayed. Real time RT-PCRs were performed using a 7500 Fast Real Time system machine (Applied Biosystems). Fold changes were calculated using the 2(-ΔΔCt) method [78]. β-actin and 18 s were used as a housekeeping genes for mRNA and RNU44 for miRNA. There were no statistically significant differences in expression for β-actin, 18 s, and RNU44. Data were presented as mean±SD, normalized to housekeeping genes and week 0.

Immunocytochemistry of the BMPS

[0249] BMPS aggregates were collected at 2, 4 and 8 weeks. BMPS were fixed in 4% paraformaldehyde for 1 hour, washed 3 times in PBS, then incubated for 1 hour in blocking solution consisting of 5% normal goat serum (NGS) in PBS with 0.4% TritonX (Sigma). BMPS were then incubated at 4° C. for 48 hours with a combination of primary antibodies (Table 2) diluted in PBS containing 3% NGS and 0.1% TritonX. BMPS were washed in PBS 3 times after which they were incubated with the appropriate fluorophore-tagged secondary antibody for 1 hour in PBS with 3% NGS at room temperature. Double immunostaining was visualized using the proper combination of secondary antibodies (e.g., goat anti-rabbit secondary antibody conjugated with Alexa 594 and goat anti-mouse secondary antibody conjugated with Alexa 488 (Molecular Probes). Nuclei were counterstained with DRAQ5 dye (Cell Signaling; 1:5000 in 1×PBS) or NucRed Live (Molecular Probes) for 15 minutes before mounted on slides with coverslips and Prolong Gold antifade reagent (Molecular Probes); BMPS used as negative controls for immunostaining were processed omitting the primary antibody. Images were taken using a Zeiss

UV-LSM 510 confocal microscope. The experiments were performed in duplicates; at least three different fields of view were analyzed for each combination of antibodies. 3D reconstruction was done using Imaris 7.6.4 software for scientific imaging.

TABLE 2

Primary Antibodies.				
Antibody	Host	Type	Source	Dilution
NF-H	Rabbit	Polyclonal	Enzo	1:1000
GFAP	Rabbit	Polyclonal	Dako	1:500
Olig 1	Mouse	Monoclonal	Millipore	1:500
CNPase	Mouse	Monoclonal	Millipore	1:500
Calbindin	Mouse	Monoclonal	SIGMA	1:500
NOGO-A	Rabbit	Polyclonal	Santa Cruz	1:500
Map2	Mouse	Monoclonal	Chemicon	1:1000
MBP/SMI99	Mouse	Monoclonal	COVANCE	1:1000
SMI-32	Mouse	Monoclonal	Stenberger	1:2000
			Monoclonals	
Synaptophysin	Mouse	Monoclonal	SIGMA	1:500
VGLUT1	Rabbit	Polyclonal	Alpha Diagnostic	1:500
TH	Mouse	Monoclonal	Millipore	1:250
Nestin	Rabbit	Polyclonal	Millipore	1:200
Ki67	Rabbit	Polyclonal	abcam	1:100
Caspase3	Rabbit	Polyclonal	R&D	0.2 µg/ml
OLIG1	Mouse	Monoclonal	Millipore	1:200
TUJ1	Mouse	Monoclonal	Stemcell technologies	1:200
S100B	Rabbit	Polyclonal	Santa Cruz	1:200

Automated Quantitation of Cell Types

[0250] BMPS was differentiated for 8 weeks. Randomly selected pictures from three experiments were acquired by confocal imaging and then analyzed with a custom algorithm created with the Cellomics TargetActivation (Thermo Fisher Scientific, Pittsburgh, PA) image-analysis software package. With this algorithm, cells were identified based on DRAQ5 stained nucleus and quantified oligodendrocytes and astrocytes based on staining of CNPase, NOGO1 and GFAP.

Myelination Assessment and Quantification

[0251] To calculate the percentage of axonal myelination, a semi-automated computer platform was used, termed computer-assisted evaluation of myelin formation (CEM) [82], which uses NIH Image J built-in tools as well as a Math lab processing functions. The results were generated as pixel counts and percent values. The percent of myelinated axons was calculated by dividing the pixel count for myelin by the pixel count for axons after cell body removal and multiplying by 100. For each time point at least 18 fields from at least two independent experiments were analyzed.

Electron Microscopy

[0252] BMPS aggregates were collected at 2, 4 and 8 weeks and were fixed in 2% glutaraldehyde and 4% formaldehyde in 0.1M Sodium Cacodylate buffer (EMS, electron microscopy sciences) pH 7.4 with 3% sucrose and 3 mM CaCl₂. Post-fixation was done with 2% osmium for 2 hours. The BMPS aggregates were then stained en bloc with 2% uranyl acetate in distilled water for 30 min and subsequently dehydrated in graded ethanol. Embed 812 (EMS) was used as the embedding media. Thin sections (70-80 nm) were cut on a Reichert Jung Ultracut E microtome and placed on

formvar coated 100 mesh copper grids. The grids were stained with uranyl acetate and followed by lead citrate. All imaging was performed on a Zeiss Libra 120 electron microscope with a Veleta (Olympus) camera.

Treatment and Cytotoxicity Assay

[0253] BMPS was exposed to different concentrations of rotenone and MPP+ for 24 and 48 hours after 4 weeks of differentiation. Rotenone working solutions were prepared in differentiation medium from 10 nM or 100 µM stocks to reach final concentrations of 0.1, 1, 10, 25 and 50 µM. DMSO was used as vehicle control. MPP+ working solutions were prepared in differentiation medium from 30 mM stocks to reach final concentrations of 10, 50, 100, 500, 1,000, 5,000 and 10,000 µM. Four independent experiments in 3 replicates were performed for each experimental condition (control and toxicant exposure for the different time points). Resazurin reduction assay was performed in order to determine cell viability after rotenone and MPP+ treatment. Resazurin (7-Hydroxy-3H-phenoxazin-3-one 10-oxide) is a blue dye that is reduced into red fluorescent resorufin by redox reactions in viable cells. 100 µl Resazurin (2 mg/ml stock) were added directly to the 6 well plates (2 ml/well). Plates were incubated for 3 h at 37° C., 5% CO₂. Subsequently, 50 µl of medium were transferred from each well in triplicates to a 96-well plate and fluorescence was measured at 530 nm/590 nm (excitation/emission) using a multi-well fluorometric reader CytoFluor series 4000 (PerSeptive Bio-systems, Inc). Data were presented as mean±SD. Statistical analysis was performed using Dunnett's test.

Reactive Oxygen Species Measurement

[0254] Reactive oxygen species (ROS) were measured in cell media collected 24 hours after treatment with 5 µM rotenone or 1,000 µM MPP+ using the OxiSelect™ In Vitro ROS/RNS Assay Kit (Cell Biolabs, San Diego, CA). This is a fluorescence-based assay measuring the presence of total free radicals within a sample and was used according to the manufacturer's protocol. The quenched fluorogenic dye dichlorodihydrofluorescein-DiOxyQ (DCFH-DiOxyQ) which is similar to the popular 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) is first primed with a quench removal reagent. The resulted highly reactive non-fluorescent DCFH can react with present ROS species in the cell supernatant and is then oxidized to the highly fluorescent DCF (2',7'-dichlorodihydroxyfluorescein). At every time point, 50 µl of the cell supernatant was added to a 96-well plate in triplicates and was mixed and incubated with the DCFH-DiOxyQ for 45 minutes. The fluorescence intensity was measured with a fluorescence microplate reader at 480 nm/530 nm (excitation/emission) and was proportional to the total ROS/RNS levels within the sample.

Flow Cytometry

[0255] In order to quantify percentage of NPCs, and neurons within the aggregates, flow cytometry with NPC and neuronal markers was performed. Flow cytometry was performed according to previously published protocol [77] with some optimization steps for 3D cultures. Aggregates were washed once with PBS/1 mM EDTA and trypsinized directly in the well using TrypLE Express containing 4 units/ml DNase for 30 min at 37° C. on the shaker. Pipetting the aggregates up and down with a 1 ml syringe and a

26G3/8 needle ensured generation of single cell suspension. Cells were counted, washed once with PBS/1 mM EDTA, fixed with 2% PFA for 20 min at 4° C., washed twice with PBS/1% BSA (wash solution I, WS I) and blocked for 30 min in blocking solution (PBS/1% BSA/0.15% saponin/10% NGS). 1×10⁶ cells were stained for one hour at 4° C. with fluorochrome-conjugated antibodies dissolved in blocking solution (Table 3). Unstained cells as well as cells incubated with isotype controls were used as negative controls to set the gates for measurements. Cells were washed twice with PBS/1% BSA/0.15% saponin, once with PBS/1% BSA. Flow cytometry was performed using a Becton Dickinson FACSCalibur system by measuring 10⁴ gating events per measurement. Data was analyzed using FlowJo v10 software.

TABLE 3

Antibodies for flow cytometry analysis				
Antibodies	Host	type	Source	Dilution
Alexa Fluor ® 647 Nestin	Mouse	Monoclonal, clone 25	BD Pharmingen	1:05
Alexa Fluor ® 488 β-III-Tubulin	Mouse	Monoclonal, clone TUJ1	BD Pharmingen	1:05
PerCP-Cy™ 5.5 Sox2	Mouse	Monoclonal, clone 030-678	BD Pharmingen	1:20
PerCP-Cy™ 5.5 Sox1	Mouse	Monoclonal, clone N23-844	BD Pharmingen	1:20
PE Doublecortin	Mouse	Monoclonal, clone 30	BD Pharmingen	1:20
Alexa Fluor ® 647 Ki67	Mouse	Monoclonal, clone B56	BD Pharmingen	1:20

Microelectrode Array (MEA) Recordings

[0256] After 8 weeks of differentiation, BMPS were plated on 48-well MEA plates previously coated with Matrigel. During two weeks spontaneous electrical activity was recorded using the ‘Maestro’ MEA platform and Axion’s Integrated Studio (AXIS) software [Axion Biosystems inc.; Atlanta, US]. Each well of the 48-well MEA plate contains 16 individual microelectrodes (~40-50 µm diameter, center-to-center spacing 350 µm) with integrated ground electrodes, resulting in a total of 768 electrodes/plate. The ‘Maestro’ MEA platform has an integrated heating system, which can be controlled by AXIS software. All recordings were performed at a constant temperature of 37° C. Prior to a twenty minutes recording, the MEA plates were placed in the Maestro MEA platform and equilibrated for five min. AXIS software was used to control heating system and monitor the recordings, which includes simultaneously sampling of the channels at 12.5 kHz/channel with a gain of 1200× and a band pass filter of 200-5000 Hz. The recordings were converted into RAW files. After a recording the RAW-files were re-recorded with AXIS to convert the data into a spike file, which includes spike timing and profile information. A variable threshold spike detector was used for the spike-file, it was set at 6 times standard deviations of the rms-noise on each channel. The spike file was later used for data analysis with NeuroExplorer® [Nex Technologies, Madison (AL), US] to convert data into Microsoft Excel files. Using the function rate histogram, a summary of the spikes of all electrodes of one plate was put into one Excel sheet. Only electrodes that recorded activity higher than 0.05 spikes/sec at least once over the time measured were included for data analysis.

Statistical Analysis

[0257] Statistical analysis was performed using GraphPad InStat 3. The Dunnett’s test was applied to all the experi-

ments shown here that compare to a control group. Statistically significant values ($p < 0.01$) are marked with an asterisk (*). For myelination quantification at the different time points, a Kruskal-Wallis test was employed, statistical significance was considered for p values < 0.05 .

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EQUIVALENTS

[0348] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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tggacggccgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	840
tctgcacccgtc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	900
ccgtgcggccgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	960
ggccctccctt gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	1020
agcaaggaaa gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	1080
ccccctggccgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	1140
cgtttgggg ttcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	1200
gcacatcttc ttcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc gtcgttgcgc	1260

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gcgccttggc	gtggttggcg	cgcggccgggt	gcagcgagag	gccatccccg	agcgctacacct	1320
ccccgagcg	gagcactcgta	gctcccgacta	ctaggggctg	cgctcgagca	gtgggggggg	1380
cggagggttg	gttctttccc	ttcttcctcg	ccagggccca	cgggcgcct	tgttcccgcc	1440
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ggtgcagacg	gtctgggacg	tggeagacgg	acggaccctc	ggcggacagg	tggtcggcgt	1560
cgggggtggg	tgggttagggg	cgaggacaaad	gcaggggtcg	ctgggttggg	acgttggtcc	1620
actttttag	accagctttt	ttggagagctg	tatthaagac	tcgctatcc	agtgttttgt	1680
cgcagagagt	tttactctt	aatcctggg	ggtttcttag	aaagcaactt	agaactcgag	1740
attcacctt	ctttttctt	tcccaaaaag	tagcgttaacc	aacatttaag	cttgcttaaa	1800
aacgaaaaaa	aaccgttgc	catccagttt	tcccgattta	ctaaaaatagg	taaccaggcg	1860
tctcacagtc	ccggctcttg	caagagcgt	aatgaacgtt	ctcataaca	cgcaggagta	1920
cggggagccc	tgaacccccc	gctgtcg	ggatccccc	tgcgggtggg	acggcgggaa	1980
ggcgctttcc	gctgttcctc	agcggggccgg	gcccttgacc	agcgcggccc	gcaggcttcc	2040
cttctcgccg	tcttcgagg	gaagactac	atacgtagtc	agtttcgatt	tgttacagac	2100
gttacaaaat	tcttttaccc	aagggtatgc	tatgacattt	ccgcgttta	ctttgtat	2160
ctatgttta	gttgggttgg	ttgttagta	gccaatatta	actggcattt	tatttactt	2220
ctaaccctgt	ttcctgacgg	tgtacagaat	caacaaaata	aaacatttaa	agtctgattt	2280
ttaaaaaaaa	aaaaaaaaaa					2298

SEQ ID NO: 31 moltype = AA length = 323

FEATURE Location/Qualifiers

source 1..323

mol_type = protein

organism = Homo sapiens

SEQUENCE: 31

MDSDASLVSS	RPSSPEPDDL	FLPARSKGSS	GSAFTGGTVS	SSTPSDCPPE	LSEALRGAMG	60
SAGAHPGDKL	GGSGPKSSSS	STSSSTSSAA	ASSTKKDKKQ	MTEPELQQLR	LKINSRERKR	120
MHDLNIAAMDG	LREVMPYAHG	PSVRKLSKIA	TLLLARNYIL	MLTNSLEEMK	RLVSEIYGGH	180
HAGFHPSCAGC	GLAHSAPLPA	ATAHPAAAHH	AAHHPAVHPH	ILPPAAAAAA	AAAAAAAVSS	240
ASLPGSLPLPS	VGSIRPHGL	LKSPSAAAAA	PLGGGGGGSG	ASGGFQHWGG	MPCPCSMCQV	300
PPPHHHVSAM	GAGSLPRLTS	DAK				323

SEQ ID NO: 32 moltype = DNA length = 3275

FEATURE Location/Qualifiers

source 1..3275

mol_type = unassigned DNA

organism = Homo sapiens

SEQUENCE: 32

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tttccggagcg	agctccctaa	atcgcatcca	gagtaagtgt	ccccgcccc	cagcagccgc	120
agccttagatc	ccagggacag	actctccctca	actcggtgt	gaccacaaat	gctccgatac	180
aggggggtctg	gatccctact	ctgcccccca	tttctccaga	gcgacttgc	tcttcgtcc	240
tcccccaact	caccgtcg	tctccctcac	caaaaggcgag	aagtccggagc	gacaacagct	300
ctttctggccc	aagccccagt	catgtggta	gtccccccgt	gttcccgat	gcagcacatg	360
gactctggcc	cccgccggcg	ctctgggtgc	atgtgcgtgt	gcgtgtgtt	gtctcggtgt	420
gtcgatggag	ataagggtga	tccgttttag	gaaccaaatac	attagttctc	tatttagatc	480
tccattctcc	ccaaagaaag	gcctccactt	cccaactcggt	tattccagcc	cgggggctca	540
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caccaacgc	cccttggataa	acctgttgc	tgagagcaga	ggggagatag	agagagctt	660
attataggta	cccgcggtc	gctaaaagga	ggggccagaga	tagtagcgag	ggggacgagg	720
agccacggcc	caccctgtgc	ggggccccc	gtctgggtac	tgcgggtgc	ggggggagcg	780
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tctcttttct	ctccctctcc	tggaaatttt	cggttccgg	ggaaggagga	cccttcgcaaa	900
gtcgcgacga	ctatettccc	ctggggccat	ggacttggac	gccagcctgg	tgtccaggccg	960
cccgctcg	ccagagcccc	atgacatttt	tctgcggccc	cgaggttaagg	gcagcagccgg	1020
cagcgcttc	actggggcga	ccgtgtctc	gtccacccccc	agtgcactgg	cgccggagct	1080
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gtcgccacc	aagaaggaca	agaagcaat	gacagagccg	gagctgcagc	agctgcgtt	1260
caagatcaac	aggccggcgc	gcaagcgca	gcacgaccc	aacatcgca	tggatcgcc	1320
cccgcgagg	atgcgttacg	caacacccc	ttccgtgc	aaatcttca	agatcgccac	1380
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cctggccac	cccgccggccc	tgccggcc	cacccggccac	ccggcagcag	caggccacgc	1560
cgcacatcac	cccgccgggtc	accacccat	cctggccccc	ccggccggcc	cggtgtctgc	1620
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gcctctggcc	tgcagatgt	gcccgtcc	caccacgtgt	cggtatagg	1860	
cgcggccagc	ctggccggcc	tcacccctcg	cgcccaagtga	gcctactggc	gcggccgcgt	1920
tctggcaca	ggggggccgg	ggggccgggg	gaagcgagg	ctggccgtcg	ctggccgtcg	1980
gagctctgtc	gogaggaggg	gcccggggcc	atggacttgg	ggtggggcat	ggtggggatt	2040
tcagcatctg	caaacccaag	caatgggg	gcccacagag	cagtggggag	tgagggat	2100
ttctctccgg	gacctgtatcg	tgacgtgtt	ggctttaaacc	tgagctggtc	cagttagacat	2160
cgttttatga	aaaggatccg	ctgtgtc	tccacttag	aactcatcg	accccccgg	2220
ccacacccctcg	ggaaaaagatt	ctaaaaactt	ctttccctga	gagcgtggcc	tgacttgcag	2280

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actcggcttg	ggcagcaccc	cggggggggg	gggggtgtt	tggggaggggg	acacattggg	2340
gccttgcctcg	tcttcctcc	ttcttggcgg	gtggggagact	ccgggttagcc	gcactgcaga	2400
agcaacagcc	cgaccgcgc	ctccagggtc	gtcccctggcc	caaggccagg	ggccacaagt	2460
tagtttggaa	ccggcggtcg	gtatcagaag	cgtgtatggt	cataatcaat	ctcaatatct	2520
gggttcaatcc	acacccttcc	agaactgtgg	cggttccctcc	ctgtctctcg	ttgatttggg	2580
agaatataatgtt	tttctaataa	atctgtggat	gttccttctt	caacagtatg	agcaagtttta	2640
tagacattca	gagtagaaacc	acttggatgtt	tggataaaacc	caaactggcc	gatttcaggg	2700
gegggttcat	tgttagttt	atttttaaaat	agaaactacc	ccaccgactc	atctttctt	2760
ctctaaagcac	aaagtatgtt	ggtttattttt	gtacctgaga	acgtaaacaga	attaaaaggc	2820
agtgtgtgt	gaaacatgg	gggttattttt	gtacctgaga	acgtaaacaga	attaaaaggc	2880
ttttggatgt	gtaaatttat	caatgtatgg	gtaaatgtatgg	aatgtatgg	tgtttgtca	2940
cgtgactgcc	agccccatcg	gagttttaago	cggttccctc	ctattttgtt	ttatttttgc	3000
cacgtttaac	acaaatggta	aactcctcca	cgtgttcc	cggttccgtg	caagccgct	3060
ccggcgctgc	tgcgttgc	actgggttcc	gtacgttcc	ccgtgtaaaca	cccttccct	3120
gatgcacccg	ccccctcg	agatgtatcc	atctgtttta	aaaaaaatgtc	3180	
taaaaataat	tttattatgt	tttgggtca	aaaaacggat	aatgtactga	gtgttgagat	3240
tttaaaaataa	attnaaagca	aaaaaaaaaa	aaaaaa			3275

SEQ ID NO: 33 moltype = AA length = 432
 FEATURE Location/Qualifiers
 source 1..432
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 33
 MERRITSAARRSYVSSGEM MVGGLAPGRR LGPGTRLSA RMPPPLPTRV DFSLAGALNA 60
 GFKETRASER AEMMELNDRF ASYIEKVRLP EQQNKLAAE LNQLRAKEPT KLADVYQAEI 120
 REILRLRDQL TANSARLEVE RDNLQADLVR VRQKLQDETIN LRLEANNLA AYRQEADEAR 180
 LARLDLERKI ESELEEEVIRFL RKİHİEEVRE LQEQLARQVH VHELDVAKPD LTAALKEIRT 240
 QYEAMASSNN HEAEEWYRSK FADLTDAAR NAELLRQAKH EANDYRQLQ SLTCDLESLR 300
 GTNESLERQM REQEERHVRE AASYQEALAR LEEEGQSLKD EMARHLQEQYQ DLLNVKLALD 360
 IEIATYRKLL EGEENRITIP VQTFSNLQIR ETSLDTKSVS EGHLKRNIIVV KTVEMRDGEV 420
 IKESKQEHKD VM 432

SEQ ID NO: 34 moltype = DNA length = 1488
 FEATURE Location/Qualifiers
 source 1..1488
 mol_type = unassigned DNA
 organism = Homo sapiens

SEQUENCE: 34
 gcaggatggaa gaggagacgc atcacctccg ctgttcgcgg ctcctacgtc tcctcagggg 60
 agatgtatggt gggggggctg gctcttggcc gcgcgtctgg tcctggacc ccgcctctcc 120
 tggctcaat gccccctcca ctcccgaccg gagtggattt ctccctggct ggggcaactca 180
 atgctggccat ccaggcggacc cggggccatgtt agcggggcaga gatgtatggag ctcaatgacc 240
 gctttgcgcg cccatccatcgag aagggttcgtt tccttggaaat gcaaaaacaag ggcgttgcgt 300
 ctgagctgaa ccaggctgcgg gccaaggago ccaccaacgtt ggcagacgtc taccaggctg 360
 agctgcgaga gtcgtggctg cgggttcgttcc aacttcaccgc caacagccgc cggctggagg 420
 ttgagatggaa caatctggca caggacccgg ccactgttgat gcaaggatcc caggatggaa 480
 ccaacctggat gtcggaaacc gagaacaaacc tgggtgccta tagacaggaa gcaatgtatgg 540
 ccaccctggc ccgttgcgtt ctggagggaa agatgtatggc gtcggaggag gagatccgtt 600
 tcttggggaa gatccacggag gaggagggtt gggaaacttca ggaggcgttgc gcccgacacc 660
 aggtccatgtt gggatgttgc gttggccaaatc cagacatccac cgcacccctt aaagagatcc 720
 gcacgcgttgc tgaggcaatg gcttcgttgc acatgtatggat gcaaggatggatggatcc 780
 ccaacttgcg accatgttgc gacgttgcgtt ccgcacccgc gggatgttgc cggccaggcca 840
 agcacgaatcc acacgttgcgtt cggccgttgcgtt gacgttgcgtt gacgttgcgtt 900
 tgcgcggccac gaaatgttgcgtt cttggaggagc agatgtatggc gcaaggatggag cggcacgttc 960
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 aggacgatggat gggccggccatc ttggatgtatggat gcaaggatggatggatggatggatggat 1080
 ttggacatcgat gatccatcgat tacaggatggat tggatgtatggatggatggatggatggat 1140
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 tggatgtatggatggatggatggatggatggatggatggatggatggatggatggatggatggatggat 1260
 aggttcatggatggatggatggatggatggatggatggatggatggatggatggatggatggatggat 1320
 tggccctctgc cccatgttgcgtt gggatgtatggatggatggatggatggatggatggatggat 1380
 ctggcacatt tccccatgttgcgtt gggatgtatggatggatggatggatggatggatggatggat 1440
 tcccttaggttgcgtt gggatgtatggatggatggatggatggatggatggatggatggatggat 1488

SEQ ID NO: 35 moltype = AA length = 92
 FEATURE Location/Qualifiers
 source 1..92
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 35
 MSELEKAMVA LIDVFHQYSG REGDKHKLKK SELKELINNE LSHFLEEIKE QEVDVKVMET 60
 LDNDGDGECD PQEPMFVAM VTTACHEFFE HE 92

SEQ ID NO: 36 moltype = DNA length = 1135
 FEATURE Location/Qualifiers

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source	1..1135
	mol_type = unassigned DNA
	organism = Homo sapiens
SEQUENCE: 36	
gggcagaggg aataagaggc	tgcctctgcc caccagtccgt gcccggcagg acccgacga 60
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ctggagaagg ccatggtggc	cctcatcgaa gtttccacc aatattctgg aaggggaggga 180
gacaagcaca	agctaaagaa atccaaactg aaggagtc tcaacaatg gcttccat 240
ttcttagagg aaatcaaaga	gcaggaggtt gtggacaagaa tcatggaaac actggacaaat 300
atggagacgc	gatggatgttgc ttccaggaa ttcattggct ttgttgcata gtttactact 360
gcgtccacg	gcttcttgc acatgttgc gattaaatgc cagccaaacc tttctgtaa 420
catggacgtt	catgttgc acatgttgc gattaaatgc cagccaaacc tttctgtaa 480
ttccagecg	tttgcgtt attaggaagc ttgttgc ttgttgcataaaaattgaaa 540
actcttttc	aaagggttttgc ttaacggctt gcatttc ttttgcata ttggccctgt 600
gtgttgcgtt	actggggcca gggacttgc ttaacgttgc tttagggatc aggttgcgtt 660
gataaaaggcgt	gcacccgtca gccccccatg gccgttgc gcccttacccg gaggaaacc 720
tgactacaga	aatttccccg gggccaccctt aaaaacttccca ctacccataaa aaaaacaacc 780
cttatccagc	attatgttgc aacatgttgc ttctttaaat gcttccca tccatgcaga 840
taacatgttgc	ttggccgttgc tgccgttgc aggggcgttgc ggcttccgg tgcttccgg 900
gtatgcgttgc	atcaccatgttgc gaacgttgc cgttgc gcccttgc gaaaggaaactc 960
catcagaact	cgcaatccga gccagcttgc ggggcttccg cgttgc gtc 1020
cgattcaatgttgc	cgccgttgc gatccggccac atgcggcttc 1080
cgagggacttgc	accgggggttgc ctgagccaco gcttgc gtc 1135
SEQ ID NO: 37	moltype = AA length = 466
FEATURE	Location/Qualifiers
source	1..466
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 37	
MAEEQDLSEV ELSPGVSEEP RCLSPGSAPS LGPDGGGGGS GLRASPGPGE LGVKVKKEQQD 60	
GEADDKFPV CIREAVSQLV SGYDWTLVPM PVRVNGASKS KPHVKRPMNA FMVWAQARR 120	
KLADQYPLHL NAELSKTLGK LWRLLNESDK RPFIEEAERL RMQHKKDHPD KYQPRRRRN 180	
GKAQGEAEAC PGGEAEQGGT AAIQAHYKSA HLDHRHGPGE SPMSDGNPEH PSGQSHGPPT 240	
PPTTPKTELO SGKADPKRDG RSMGEGGKPH IDFGNVDIGE ISHEVMSNME TFDVAELDQY 300	
LPPNGHGPCHV SSYSAAGYGL GSALAVASGH SAWISKPPGV ALPTVSPPGV DAKAQVKTET 360	
AGPQGPPPHYT DQPSTSQIAY TSLSLPHYGS AFFPSISRPQF DYSDHQPSGP YYGHSGQASG 420	
LYSAFSYMGPS QSRPLYTAIS DPSPSPGPQSH SPTHWEQPVY TTLSRP 466	
SEQ ID NO: 38	moltype = DNA length = 2882
FEATURE	Location/Qualifiers
source	1..2882
	mol_type = unassigned DNA
	organism = Homo sapiens
SEQUENCE: 38	
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tggaccgcac accttggc	acgttccatcccttccaa gacgttgcggcc agactggagg 180
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cccccttcatac	atcccgccatcc aacccgttgc gcaaaaggca gcccacgttgc aacggggccca 600
tgaacgttgc	catgggttgc gtcggaggac cggccggaggac catggccgc 660
acotcgttgc	tcgttgc gtcggaggac cggccggaggac catggccgc 720
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cttggccatccatcc	tcgttgc gtcggaggac cggccggaggac catggccgc 1860
cagggttgcgttgc	tcgttgc gtcggaggac cggccggaggac catggccgc 1860

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tccagcagca	aagccccagg	agaacaggct	ggacagagga	gaaggagggtt	gactgttgca	1920
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tgagaaggcc	ctgctcaccc	tcctcgggga	ggggaaagcac	cagggttgtt	ggcatcgagg	2040
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catgccacct	atgcccacagt	gcctaagggc	taggccacc	agagactgtg	cccgagctg	2160
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aaggagttgg	cacagaggcc	ccctgatcca	attctgtgc	aataacccca	ttctttgtct	2340
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tgggtcttc	cccaagtc	tcttcctta	ctaggtctca	tggccctcgc	tcagtcagcc	2520
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gacacaggcc	ccagcaccca	gggtgctgc	ggcaggctga	agacactaga	atcctgaccc	2640
gtacattctcg	cccttgctc	ttaccctctg	cetcccaagtg	gtatattgtt	aaagtatgt	2700
gtatatatctg	ccctatctt	cetgttctgc	agecccccaa	atccacatgt	aactatattac	2760
tgtctctctgt	tatattatctc	agtgttcccc	tctctctac	actctagccc	ctattaactc	2820
tgcattaagc	attccacata	ataaaaattaa	aggttccgg	taaaaaaaaaa	aaaaaaaaaa	2880
aa						2882

SEQ ID NO: 39 moltype = AA length = 705

FEATURE Location/Qualifiers

source 1..705

mol_type = protein

organism = Homo sapiens

SEQUENCE: 39

MYLRRRLSD	SNFMANLPNG	YMTDLQRQP	PPPPPGAHSP	GATPGPGTAT	AERSSGVAPA	60
ASPAAPSPGS	SGGGGFFSSL	SNAVKQTTAA	AAATFSEQVG	GGSGGAGRGG	AASRVLLVID	120
EPHTDWAKYF	KGKKIHINGID	IKVEQAEFS	LNLVAHANGG	FSVDMEVLRN	GVKVVRSLKP	180
DFVLIQRQHAF	SMARNGDYRS	LVIGLQYAGI	PSVNSLHSVY	NFCDPWPVFA	QMVRHLKLG	240
TEEFPLIDQT	FYPNHKEMLS	STTYPPVVVM	GHASHGMGKV	KVDNQHDFQD	IASVVALTKT	300
YATAEFPIDA	KYDVRVQKIG	QNYKAYMRTS	VSGNWKTNTAG	SAMLEQIAMS	DRYKLWVDT	360
SEIFGGLDIC	AVEALHGKD	RDHIIEVVGS	SMPLIGDHQD	EDKQLIVEVL	VNKMAQALPR	420
QRQRDASPGR	GSHGQTPSPG	ALPLGRQTSQ	QPAGPPAQOR	PPPQGGPPQP	GPGPQRQGPP	480
LQRQRPPOGQ	QHLSGLGPRA	GSPLPQRLPS	PTSAPQQPS	QAAPPTQGQG	RQSRPVAGGP	540
GAPPAAARPRA	SPSPQRQAGP	PQATRQTSVS	GPAPPKASGA	PPGGQQRQGP	PQKPPGPAGP	600
TROASQAGPV	PRTGPPTQQ	PRPSPGPAG	APKQQLAQKP	SQDVPPPATA	AAGGPPHPQL	660
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SEQ ID NO: 40 moltype = DNA length = 2470

FEATURE Location/Qualifiers

source 1..2470

mol_type = unassigned DNA

organism = Homo sapiens

SEQUENCE: 40

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gcaggcaag	agactccata	tctacttact	tcttcctat	cttctgcac	ctctcctagt	360
ccaccatcac	tgctcaact	ggtaaagggt	ctacccaaatc	tggccctcgc	taccacaacc	420
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SEQ ID NO: 41	moltype = AA	length = 313				
FEATURE	Location/Qualifiers					
source	1..313					
	mol_type = protein					
	organism = Homo sapiens					
SEQUENCE: 41						
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TESDLSIEVE FEYPFRLHQV	YFDAPTCRGG	TTKVFLVGDY	SSSAEFFVT	AVFAFLYSMG		120
ALATYIFLQN KYRENNGP	LDFLATAVFA	FMWLVS	SSAW AKGLSDV	KMA TDPE	NIKEM	180
PVCRTGNTC KELRDPVTSG	LNTSVVFGL	NLVLWVG	NLW FVFKETGWAA	PFLRAPP	GAP	240
EKQPAPGDAY GDAGYGQGPG	GYGPQDSYGP	QGGYQPDYQQ	PAGSGGSGY	PQGDY	QQGY	300
GPQGAPTSFS NM						313

SEQ ID NO: 42	moltype = DNA	length = 2449				
FEATURE	Location/Qualifiers					
source	1..2449					
	mol_type = unassigned DNA					
	organism = Homo sapiens					
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SEQ ID NO: 43	moltype = AA	length = 1192
FEATURE	Location/Qualifiers	
source	1..1192	
	mol_type = protein	

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SEQUENCE: 43 organism = Homo sapiens

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SPLSAAAVSP SKLPEDDEPP ARPPPPPAS VSPQAEPVWT PPAPAPAAPP STPAAPKRRG 180
SSGSVDETFL ALPAASEPVT RSSAENMDLK EQPGNTISAG QEDFPSVLL TAASLPSLSP 240
LSAASFKEHE YLGNLSTVLP TEGTLQENVS EASKEVSEKA KTLLLIDRDLT EFSELEYSEM 300
GSSFSVSPKA ESAVIVANPE EEEIVKNKDE EEKLVVNINL HNQQUELPTAL TKLVKEDEVV 360
SSEKAKDSFN EKRAVEAPM REEYADFKPF ERVWEVKDSK EDSDMLAAGG KIESNLESKV 420
DKKCFADSLE QTNNHKDSES SNDDTSFPST PEGIKDRSGA YITCAFNPNA ATESIATNIF 480
PLLGDPTESEN KTDEKKIEEK KAQIVTEKNT STKTSNPFILV AAQDSETDYY TTDNLTKVTE 540
EVVANMPPEGL TPDLVQEACE SELNEVTGTK IAYETKMDLV QTSEVMQESL YPAAQCLCPSF 600
EESEATPSPV LPDIVMEAPL NSAVPSAGAS VIQPSSSPLS ASSVNYYESIK HEPENPPPYE 660
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MAKVEQPVVD HSELVEDDSSP DSEPVDFLFD DSIPDVPQKQ DETVMLVKES LTETSFESMI 780
EYENKEKLSA LPPEGGPYVL ESFKLSDLNT KDTLLPDEVS TLSKKEKIPL QMEEELSTAVY 840
SNDDLFISKE AQIRETETFS DSSPIEIIDE FPFTLISSKTQ SFSKLAREYT DLEVSHKSEI 900
ANAPDGAGSL PCTELPHDLS LKNIQOPKVEE KISFSDDFSK NGSATSKVLL LPPDVSALET 960
QAEIESIVKP KVVKVEAEKK LPSDTEKEDR SPSTAIFSAEL SKTSVVDLLY WRDIKKTGVV 1020
FGASLFLLILS LTVFSLVSVT AYIALALLSV TISFRYKGV QIAIQKSDEG HPFRAYLESE 1080
VAISEELVQK YNSNALGHVN CTIKELRRLF LVDDLVDSLK FAVALMWFTY VGALFNGLTL 1140
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SEQ ID NO: 44 moltype = DNA length = 4871

FEATURE Location/Qualifiers

source 1..4871

mol_type = unassigned DNA

organism = Homo sapiens

SEQUENCE: 44

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SEQ ID NO: 45 moltype = AA length = 432
FEATURE Location/Qualifiers
source 1..432
mol_type = protein
organism = Homo sapiens

SEQUENCE:	45	organism = Homo sapiens
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LARLTLERKI	EQQNKLAAE	DFSLAGALNA
QYBAMASSNM	LNQLRAKEPT	60
GTMESLERQM	KLADVYQAEL	120
IIEATYRKLK	REEQEERHVRE	180
IKESKQHEKD	AASYQEALAR	240
VM	LEEEGQSLSK	300
	EMARHIQEYQ	360
	DLLNVKLAID	420
	KTVEMRDGEV	480
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	KTVEMLDGEV	600
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SEQ ID NO: 46 moltype = DNA length = 3097
FEATURE Location/Qualifiers
source 1..3097
mol_type = unassigned DNA
organism = Homo sapiens

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SEQ ID NO: 47      moltype = AA  length = 92
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source           1..92
mol_type = protein
organism = Homo sapiens

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SEQ ID NO: 48      moltype = DNA  length = 1135
FEATURE          Location/Qualifiers
source           1..1135
mol_type = unassigned DNA
organism = Homo sapiens

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organism = Homo sapiens

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ERLAAKIDL	EARIQWFSN	RRAKWRREEK	LRNQRRQASN	TPSHIPISSS	FSTSVYQPIP	300
QPTTPVSSFT	SGSMLGRTDT	ALTNTYSALP	PMPMSFTMANN	LPMQPPVPSQ	TSSYSCMLPT	360
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LQ						422

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FEATURE	Location/Qualifiers

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 mol_type = protein
 organism = Homo sapiens

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mol_type = protein
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SEQ ID NO: 63      moltype = AA length = 1020
FEATURE          Location/Qualifiers
source           1..1020
mol_type = protein
organism = Homo sapiens

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HNRSLGEAAA ALRQQOAGRS AMGELYEREV REMRGAVLRL GAARGQLRLE QEHLLEDIAH 180
VRQRLLDDEAR QREEAEAAAAR ALARFAQEAE AARVDLQKKA QALQEECGYL RRHHQEEVGE 240
LILQIQGSGA AQAQMQAETR DALKCDVTSA LREIRAOLEG HAVQSTLQSE EWFRVRLDRL 300
SEAALKVNTDA MRSAAQEITE YRRQLQARTT ELEALKSTKD SLERQKSELE DRHQADIASY 360
QEAIQQLDAE LRNTKWEEMA RLREYQQLDLN VKMALDIEIA AYRKLEGEET CRIGEGPIP 420
SLPEGLPKIP SVSTHIKVKS EEKIKVVEKS EKETVIVEEQ TEETQVTEEV TEEEKEAKE 480
EEGKEEECEG EEEAEAGGEEE TKSPPAEEAA SPEKA KSEEAKSPAEE KSPEKEEAKS 540
PAEVKSEPEKA KSPAKEEAKS PPEAKSPEKE EAKSPA EAKSPA EAKSPA EAKSPA EAKS 600
PEKAKSPVKE EAKSPA EAKSPA EAKSPA EAKSPA EAKSPA EAKSPA EAKSPA EAKS 660
KSPEKA KSPAK EAKSPEKA KSPVKA EAKSPEKA EAKSPEKA EAKSPEKA EAKSPEKA 720
KAKSPVKEEA KTPEAKSPV KEEAKSPEKA KSPEAKTLD VKSPEAKTPA KEEARSPADK 780
FPEKAKSPVKE EEVKSPVKE SPLKEDAKAP EKETPKKEEV KSPVKEEEKP QEVKVKEPPK 840
KAEKEEKAPEK PKTEEKKDSK KEEAKPKEAP KPKVEEKKEP AVEKPKESKV EAKKEEAEKD 900
KVKPTPEKEA PAKVEVKEDA KPKEKTEVAK KEPDDAKAKE PSKPAEKKEA APEKKDTKEE 960
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SEQ ID NO: 64      moltype = DNA length = 3721
FEATURE          Location/Qualifiers
source           1..3721
mol_type = unassigned DNA

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SEQUENCE: 64 organism = Homo sapiens

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aagatgacaa	gacc	gtgg	aaat	gtgg	aaat	3060
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gaaatgtt	agat	gtgg	aaat	gtgg	aaat	3300
agcaaggag	ggcact	gtgg	aaat	gtgg	aaat	3360
tgatagctt	tgtgt	gtgg	aaat	gtgg	aaat	3420
aaaactgc	ccctt	gtgg	aaat	gtgg	aaat	3480
atgacc	taat	gtgg	aaat	gtgg	aaat	3540
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caactgg	tgact	gtgg	aaat	gtgg	aaat	3720
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SEQ ID NO: 65 moltype = AA length = 559
 FEATURE Location/Qualifiers
 source 1..559
 mol_type = protein
 organism = Homo sapiens

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GGNVQIVTKK	IDLSHVTSKC	GSLKNIRHRP	GGGRVKIESV	KLDFKEKAQA	KVGSLDNAHH	480
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SEQ ID NO: 66 moltype = DNA length = 2286
 FEATURE Location/Qualifiers
 source 1..2286
 mol_type = unassigned DNA
 organism = Homo sapiens
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SEQ ID NO: 67 moltype = AA length = 360
 FEATURE Location/Qualifiers
 source 1..360
 mol_type = protein
 organism = Homo sapiens
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 EGESYVCSSD NFFFKKVEYTK NVNPNSWVNV KTSANMKAPQ SLASSNSAQA RENKDFVRPK 180
 LVTIIRSGVK PRKAVERVLLN KKTAAHSFEQV LTDITEAIKL ETGVVKLYT LDGKVQVCLH 240
 DFFGDDDFVI ACGPEKFRYA QDDFSLDENE CRVMKGPNPSA TAGPKASPTP QKTSAKSPGP 300
 MRRSKSPADS ANGTSSSQLS TPKSQKSPIS TPTSPGSLRK HKDLYLPLSL DDSDSLGDMS 360

SEQ ID NO: 68 moltype = DNA length = 9135
 FEATURE Location/Qualifiers
 source 1..9135
 mol_type = unassigned DNA
 organism = Homo sapiens
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1-47. (canceled)

48. An in vitro brain microphysiological system (BMPS), comprising:

at least two neural cell types aggregated into a spheroid mass and endothelial cells capable of forming a blood brain barrier, wherein the spheroid mass has a diameter that is less than about 500 μm and the in vitro BMPS is electrophysiologically active in a spontaneous manner.

49. The BMPS of claim **48**, further comprising one or more microglia-like cells.

50. The BMPS of claim **49**, wherein the micro-glia like cells comprise microglia, microglia precursor cells, or a combination thereof.

51. The BMPS of claim **48**, wherein the in vitro BMPS has neural characteristics selected from the group consisting of synaptogenesis, neuron-neuron interactions, neuronal-glia interactions, axon myelination, and combinations thereof.

52. The BMPS of claim **48**, wherein at least one neural cell type comprises a mature neuron, a glial cell, or a combination thereof.

53. The BMPS of claim **48**, wherein at least one neural cell type comprises astrocytes, polydendrocytes, oligodendrocytes, or combinations thereof.

54. The BMPS of claim **481**, wherein the BMPS mimics the microenvironment of the central nervous system (CNS).

55. A synthetic neurological organ comprising a mature neuron, at least one glial cell aggregated into a spheroid mass, and a population of microglia-like cells, wherein the spheroid mass has a diameter that is less than 500 μm and the synthetic neurological organ is electrophysiologically active in a spontaneous manner.

56. The synthetic neurological organ of claim **55**, further comprising one or more endothelial cells capable of forming a blood-brain-barrier.

57. The synthetic neurological organ of claim **55**, wherein the micro-glia like cells comprise microglia, microglia precursor cells, or a combination thereof.

58. The synthetic neurological organ of claim **55**, wherein the mature neuron and glial cells further comprise cells selected from the group consisting of astrocytes, polydendrocytes, oligodendrocytes, and combinations thereof.

59. The synthetic neurological organ of claim **55**, wherein synthetic neurological organ further comprises neural characteristics selected from the group consisting of synaptogenesis, neuron-neuron interactions, neuronal-glia interactions, axon myelination, and combinations thereof.

60. The synthetic neurological organ of claim **55**, wherein the synthetic neurological organ mimics the microenvironment of the central nervous system (CNS).

61. A method of reproducibly producing an in vitro brain microphysiological system (BMPS) that is electrophysiologically active in a spontaneous manner, comprising:

exposing one or more NPC types to gyratory shaking or stirring; and

differentiating the one or more NPC types into one or more neural cell types aggregated into a spheroid mass.

62. The method of claim **61**, wherein the spheroid mass has a diameter that is less than about 450 μm , less than about 400 μm , less than about 350 μm , or less than about 300 μm .

63. The method of claim **61**, wherein gyratory shaking comprises constant or regular gyratory shaking or stirring for 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, or 8 or more weeks.

64. The method of claim **61**, further comprising adding one or more microglia-like cells.

65. The method of claim **64**, wherein the micro-glia like cells comprise microglia, microglia precursor cells, or a combination thereof.

66. The method of claim **61**, wherein at least one neural cell type comprises a mature neuron, at least one neuronal cell type comprises a glial cell, or a combination thereof.

67. The method of claim **61**, further comprising adding one or one or more endothelial cells capable of forming a blood-brain-barrier.

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