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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.

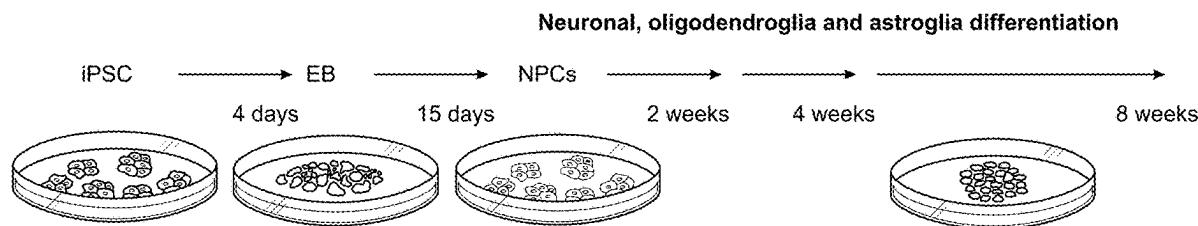
**Publication Classification**

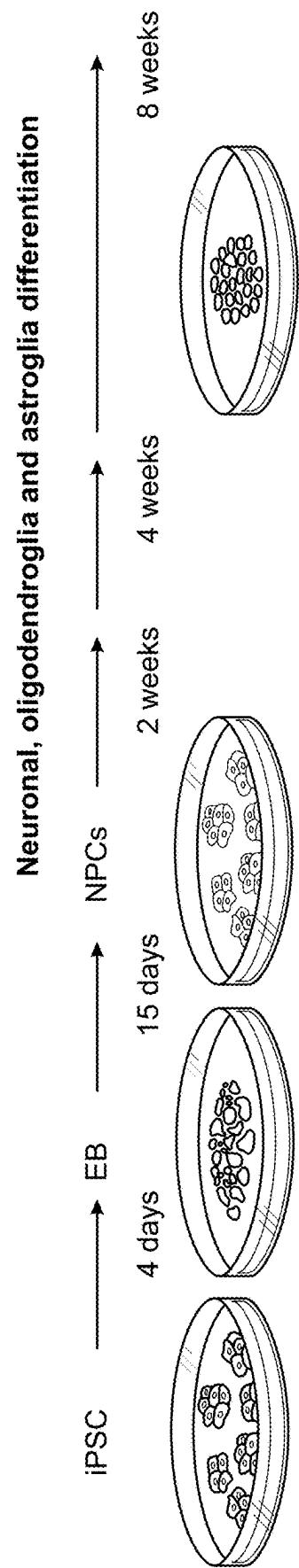
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C12N 5/074	(2010.01)

*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**

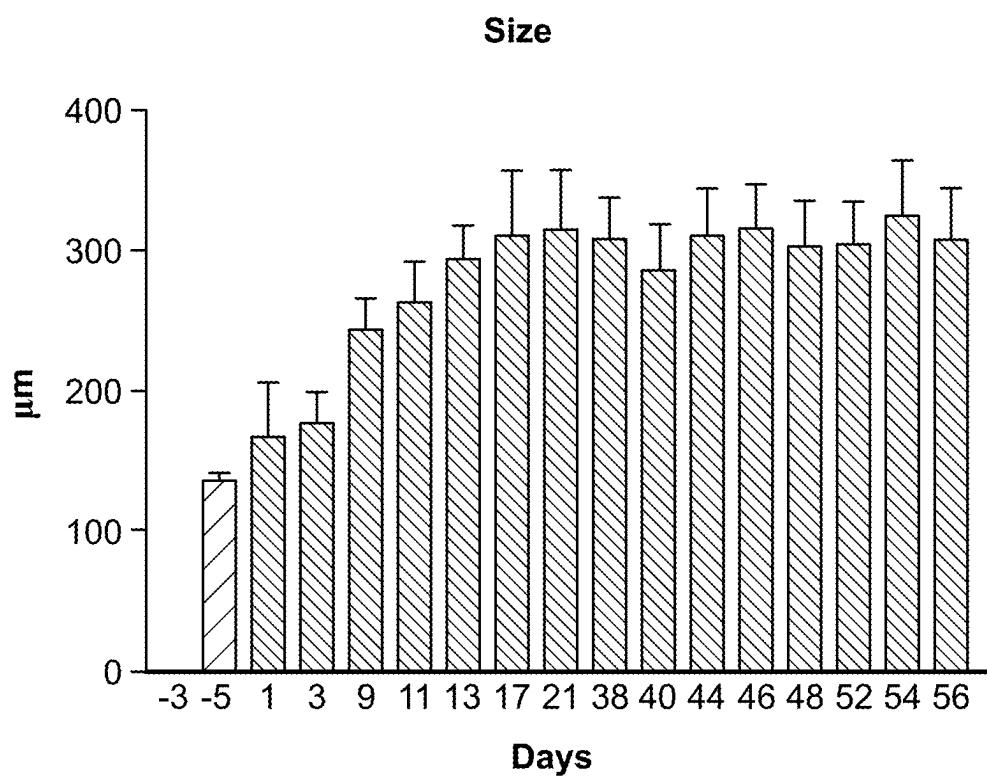


FIG. 1B

Proliferation and stem cell markers

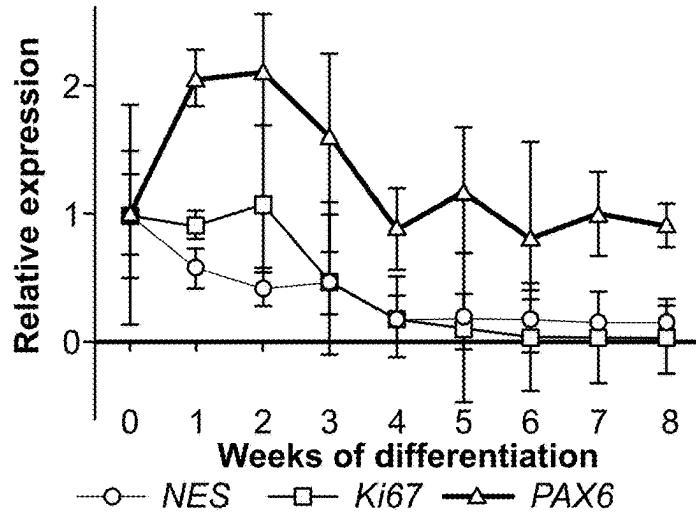


FIG. 1C1

Astroglia and oligodendroglia

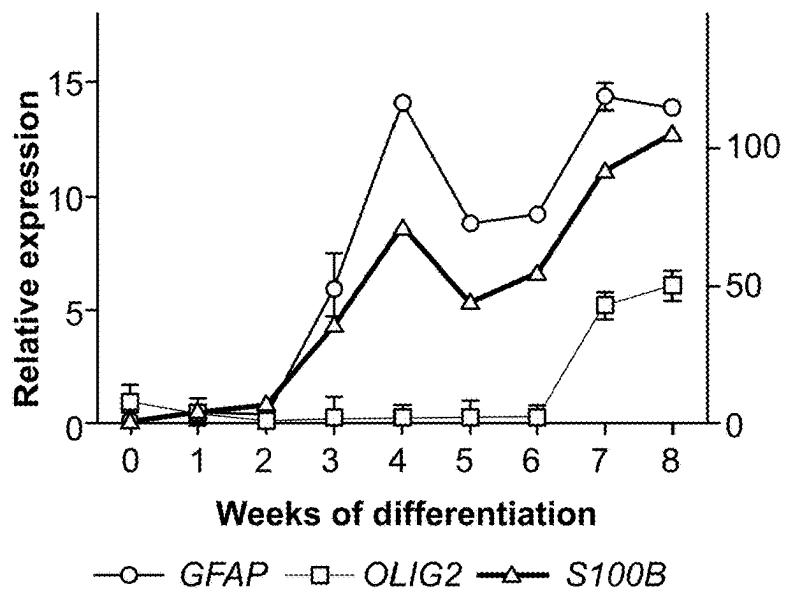
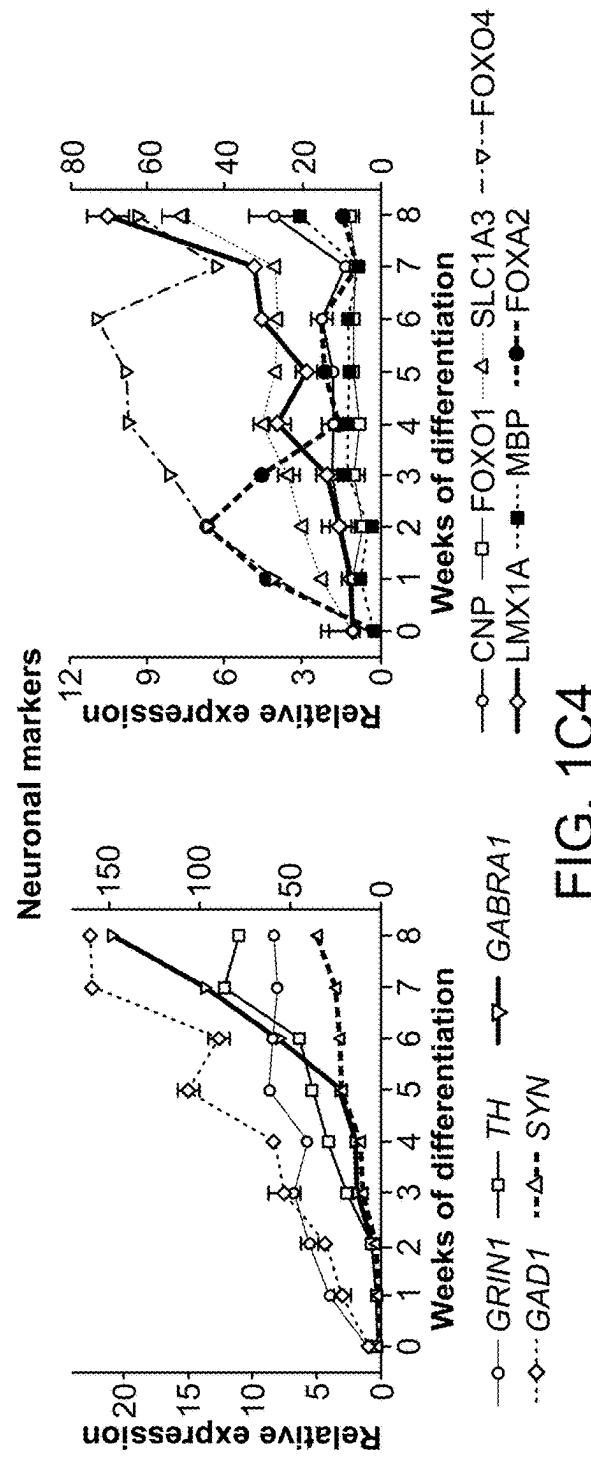
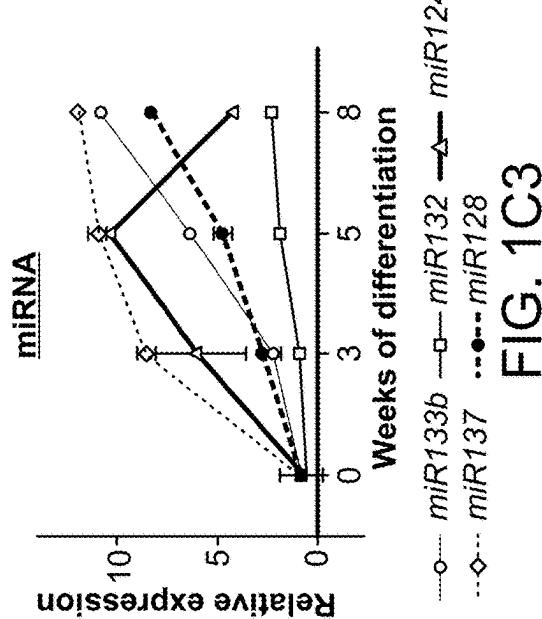


FIG. 1C2



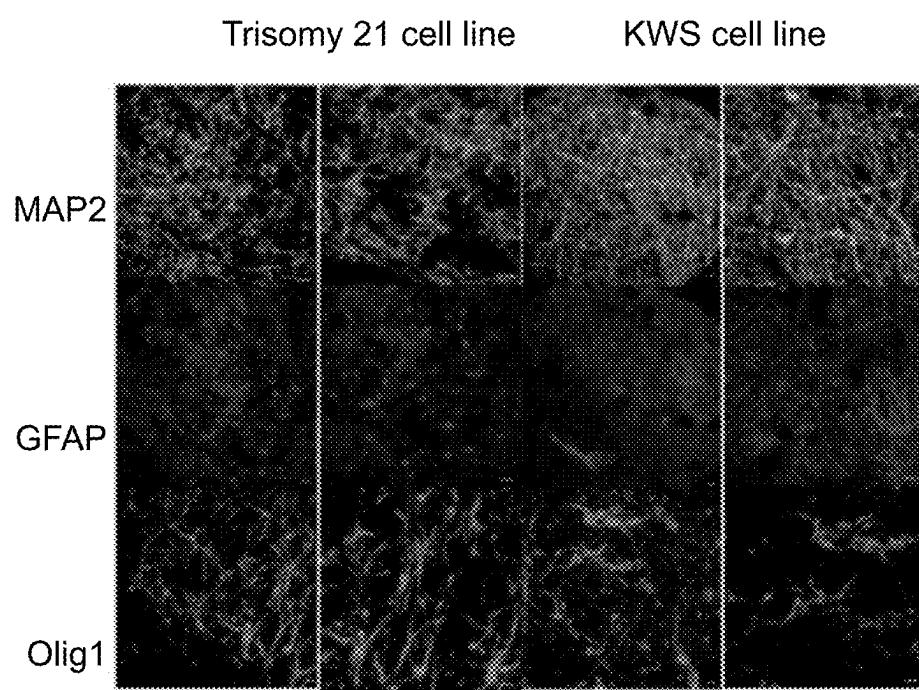
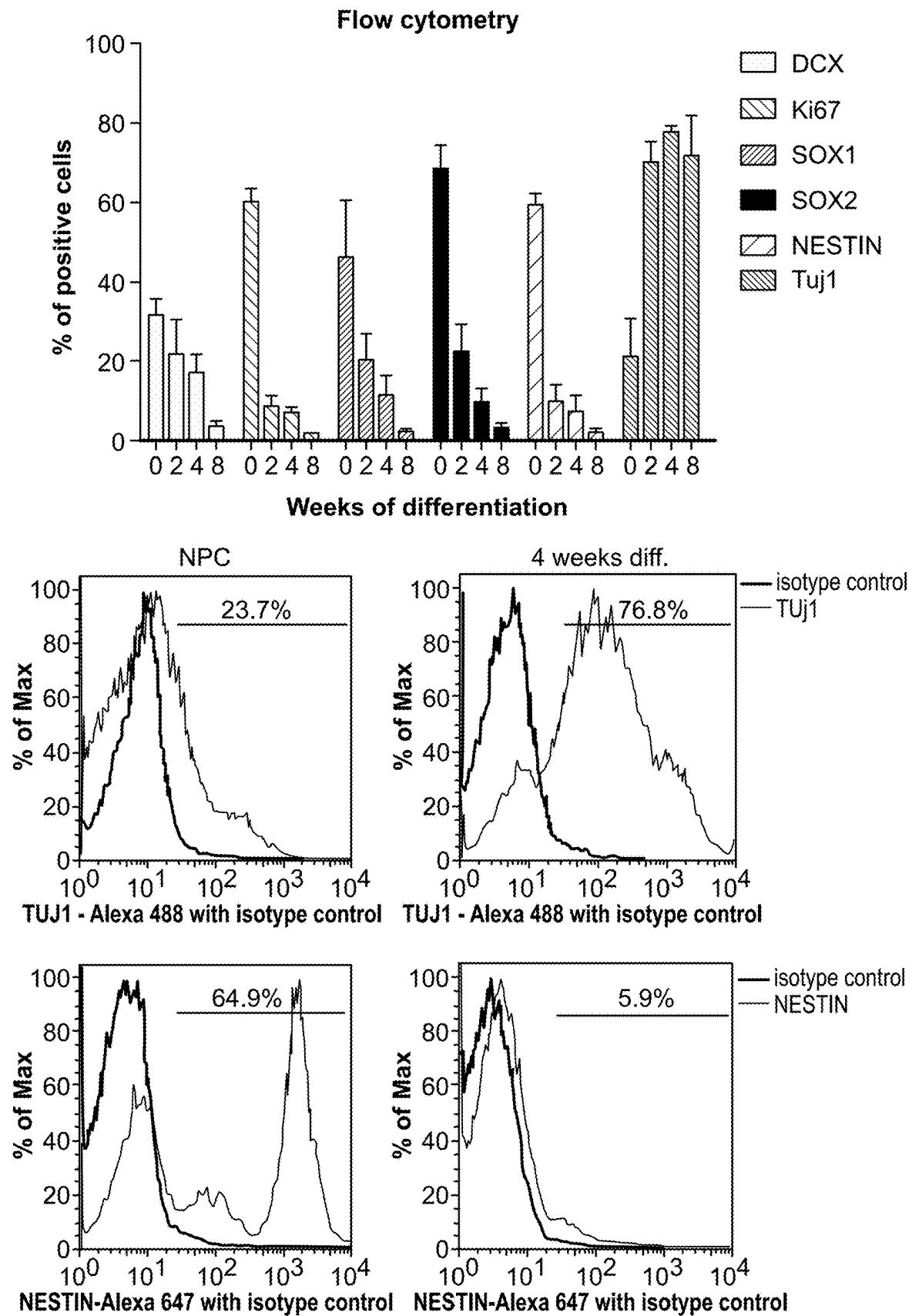


FIG. 1C5

**FIG. 1D**

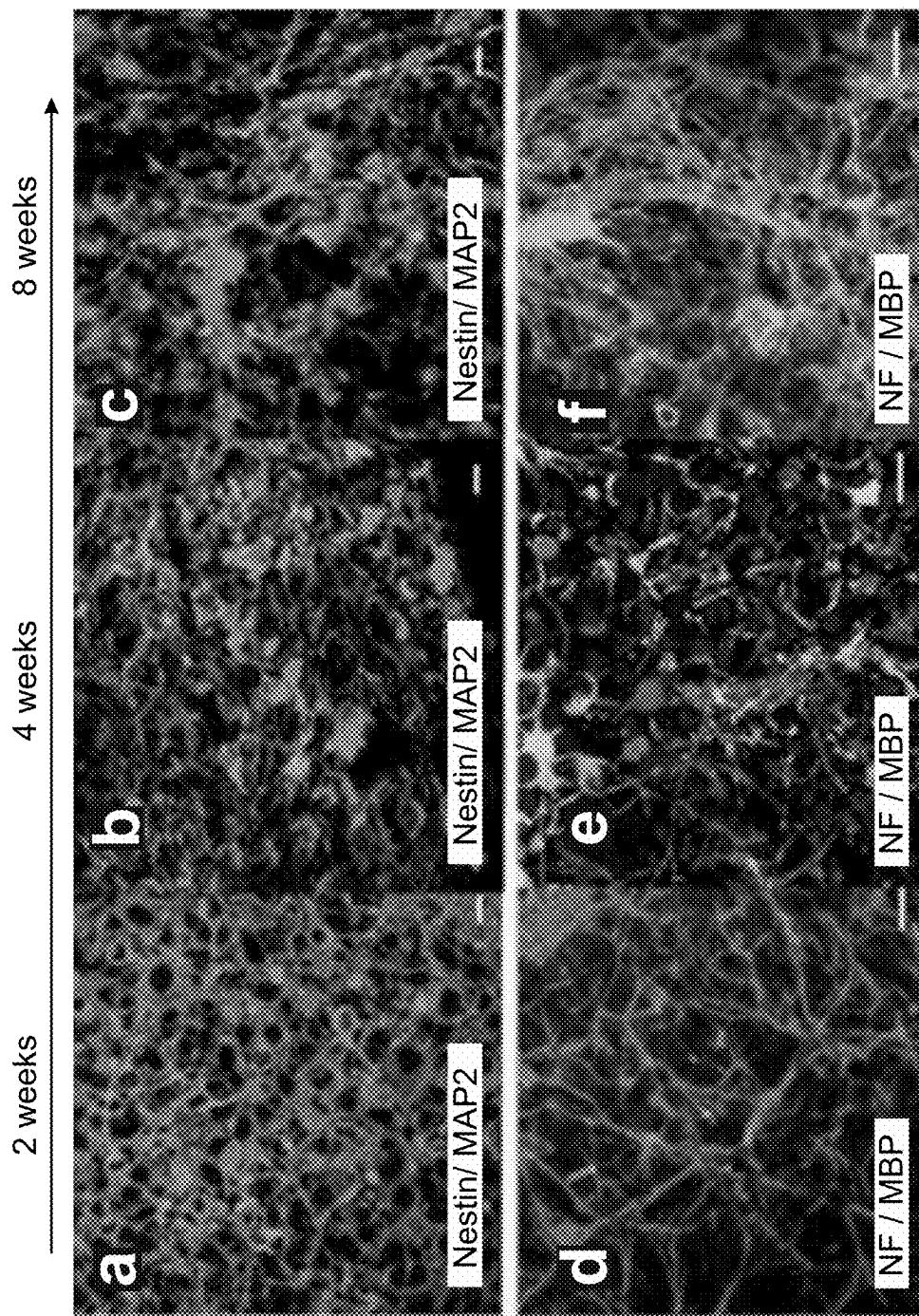


FIG. 2A

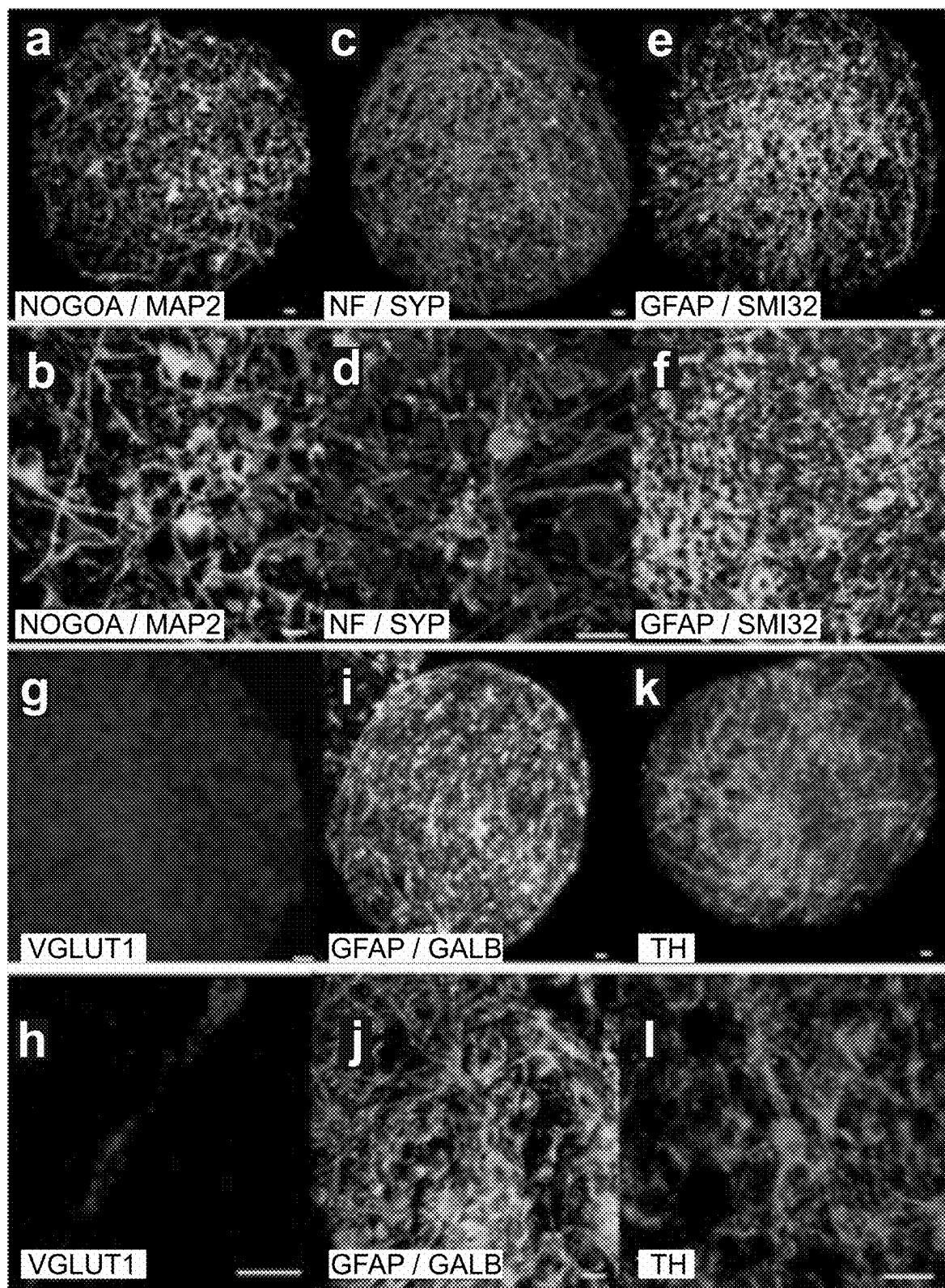


FIG. 2B

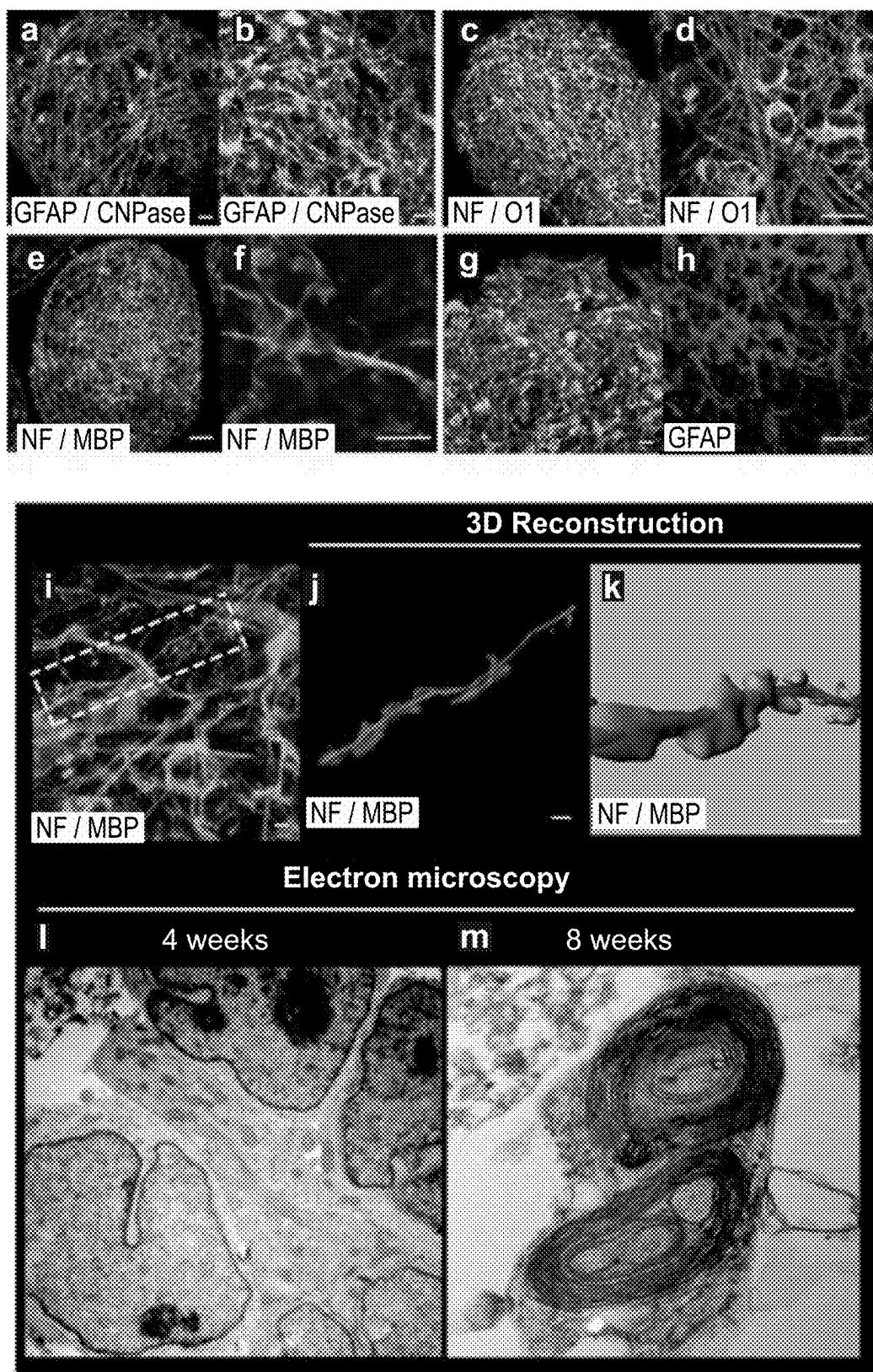


FIG. 2C

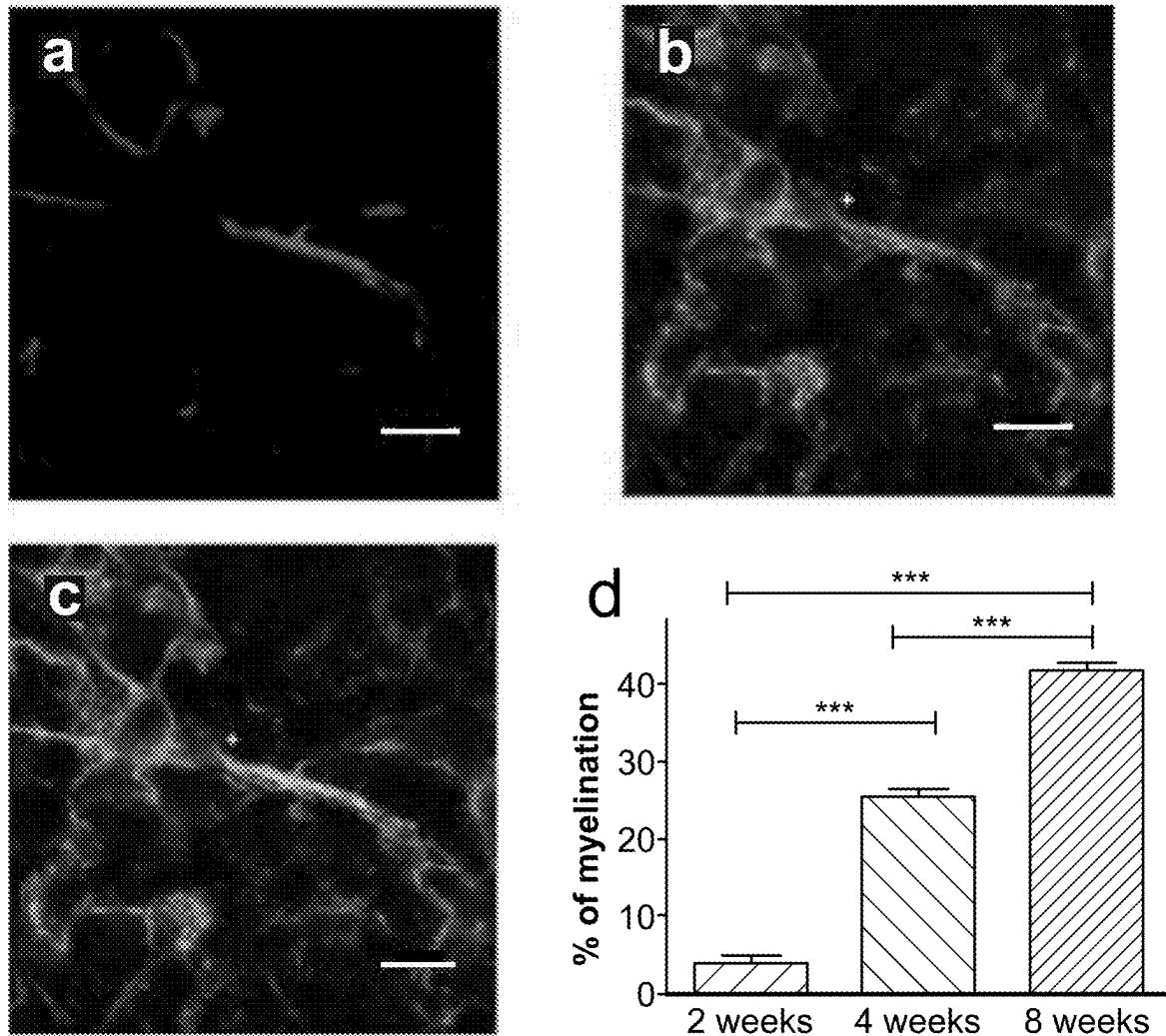


FIG. 2D

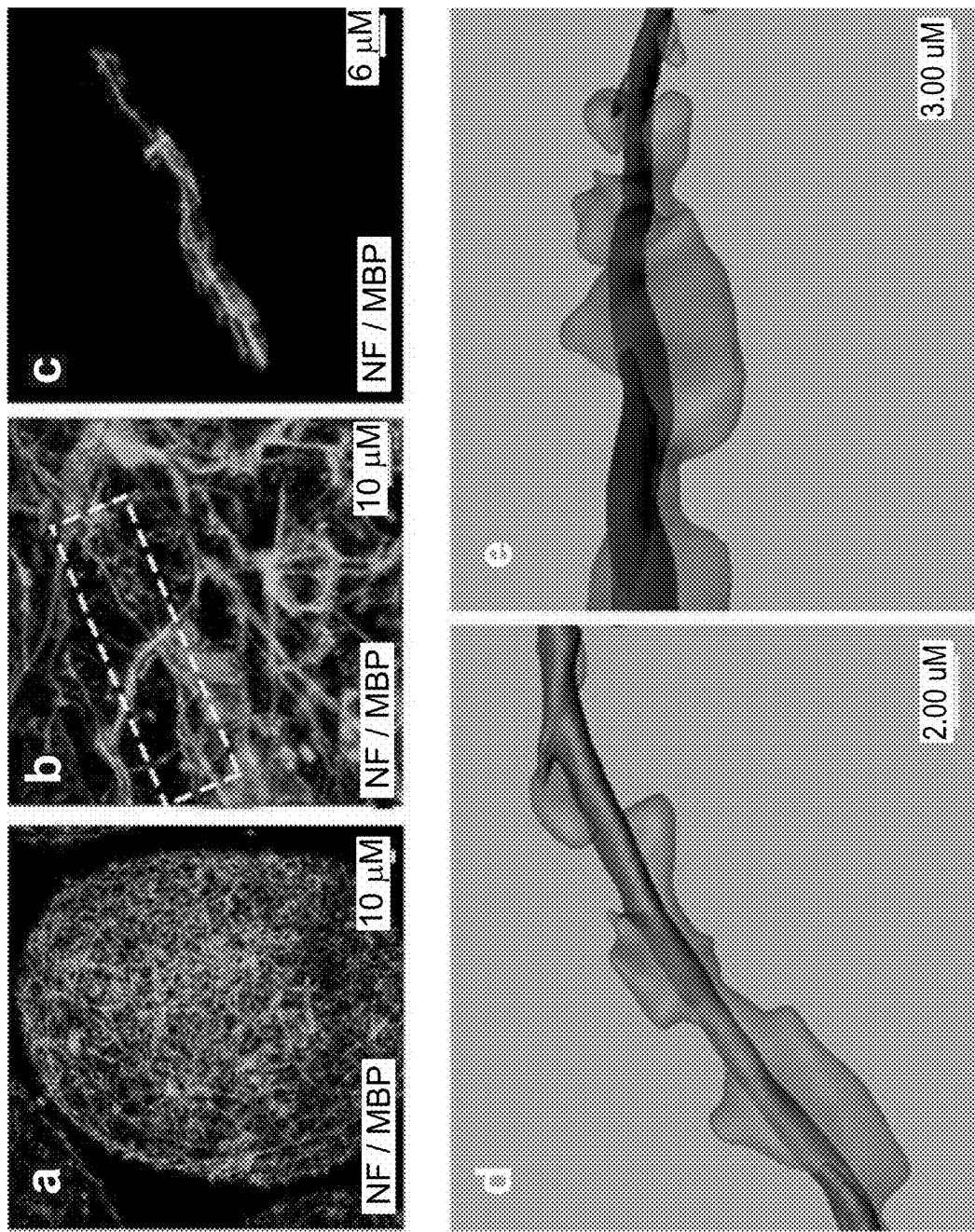


FIG. 2E

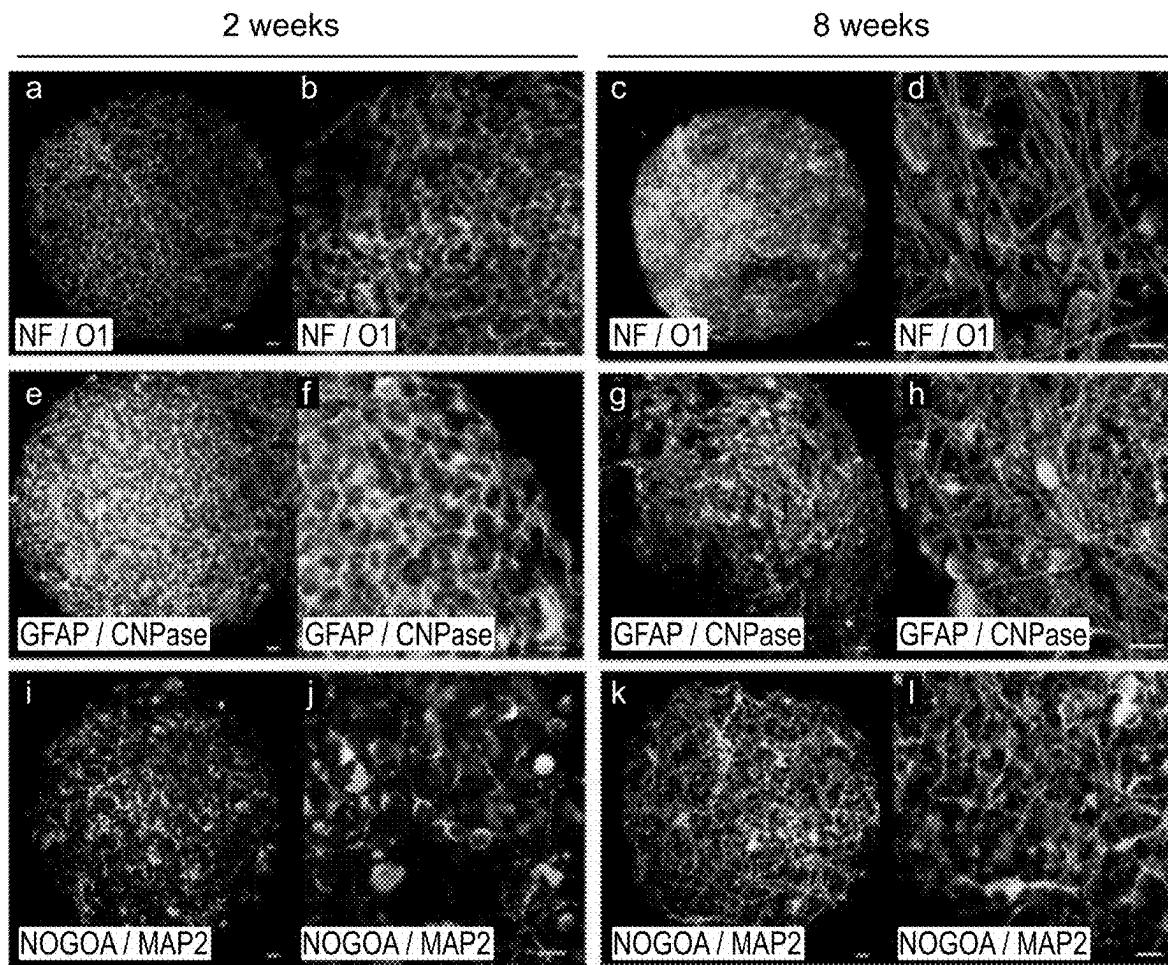


FIG. 2F

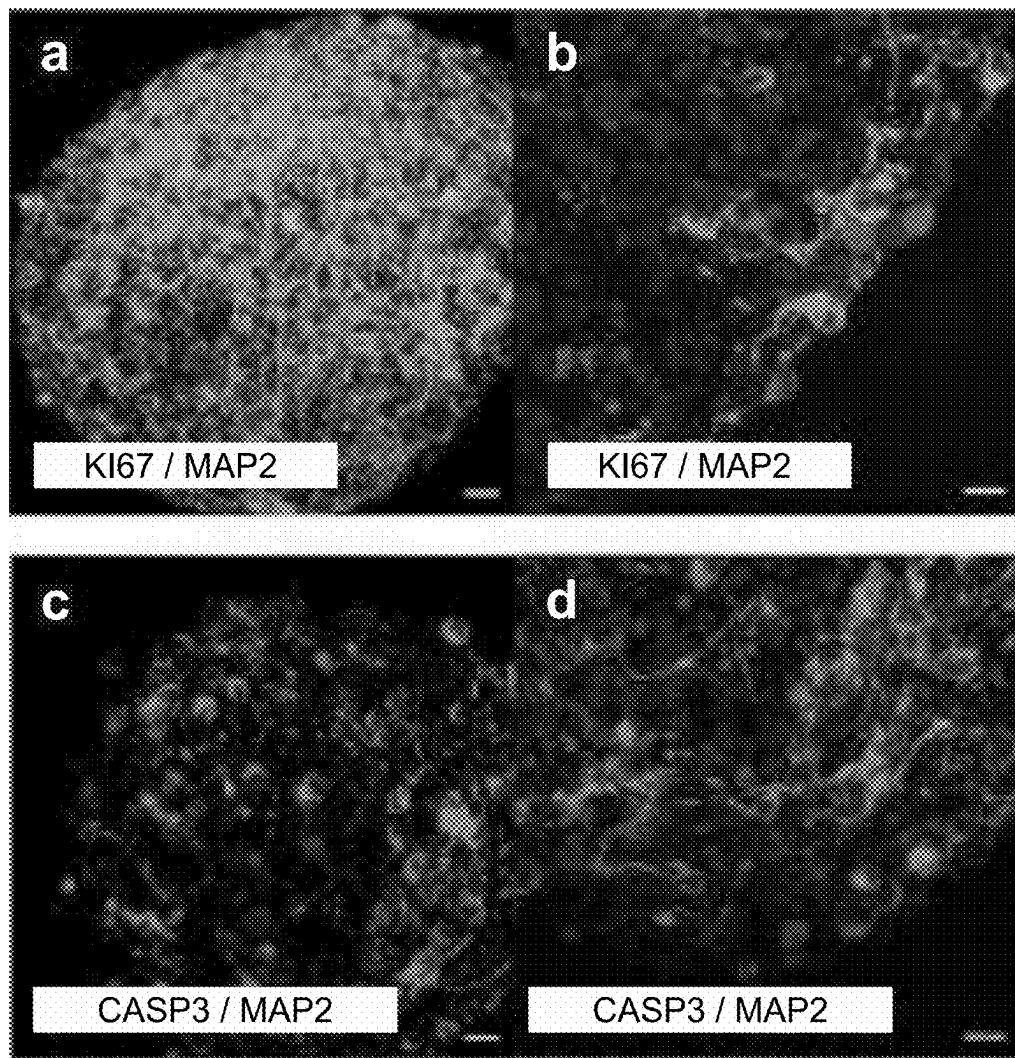


FIG. 2G

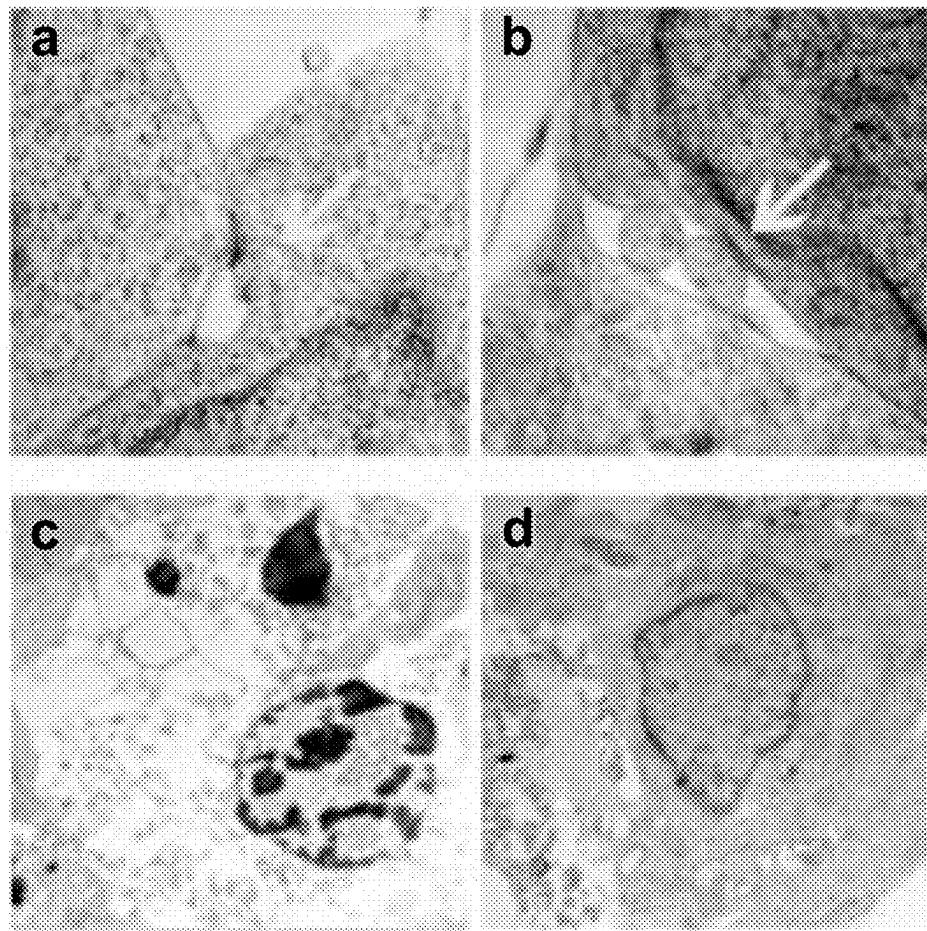


FIG. 2H

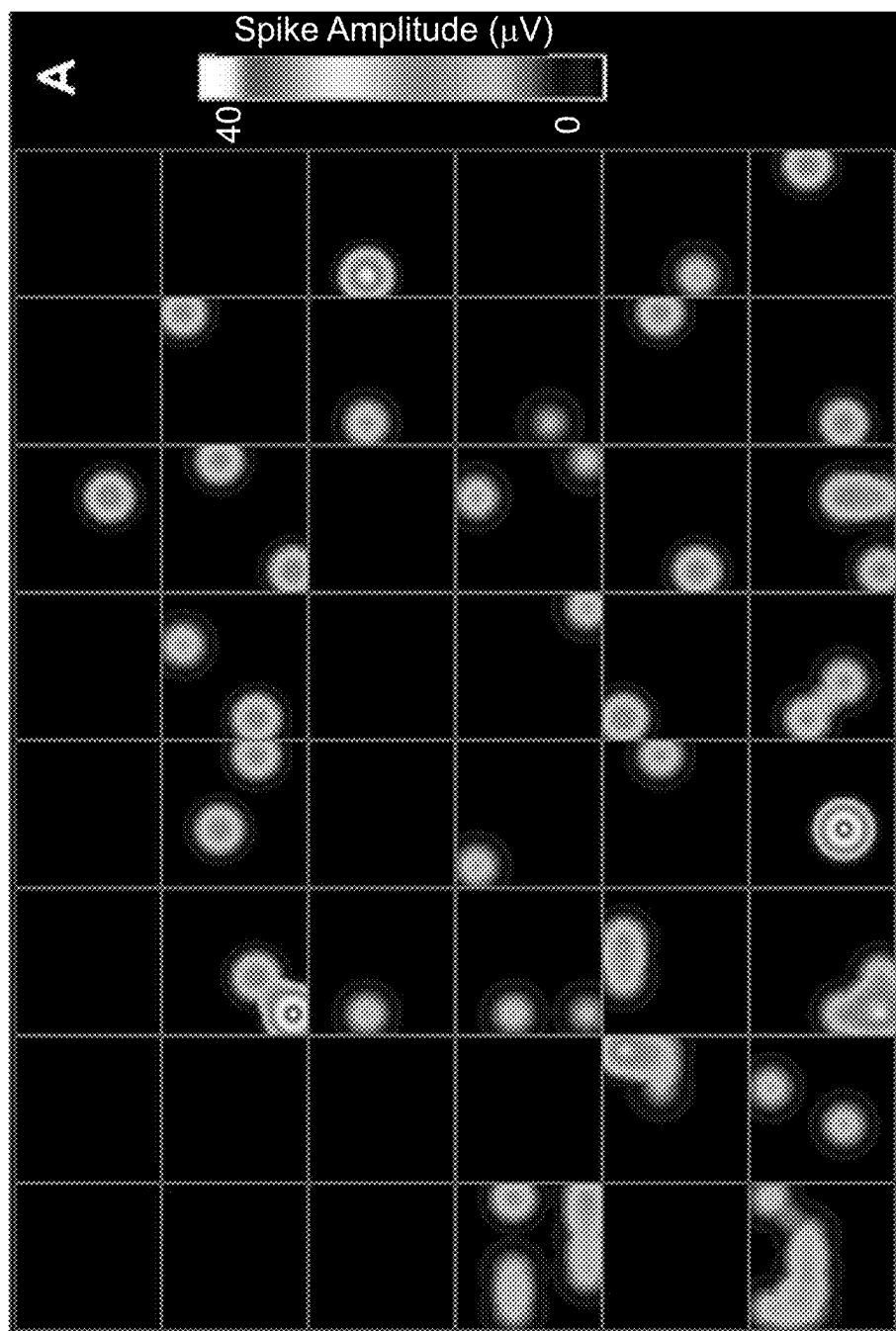


FIG. 3A

FIG. 3B

FIG. 3C

FIG. 3D

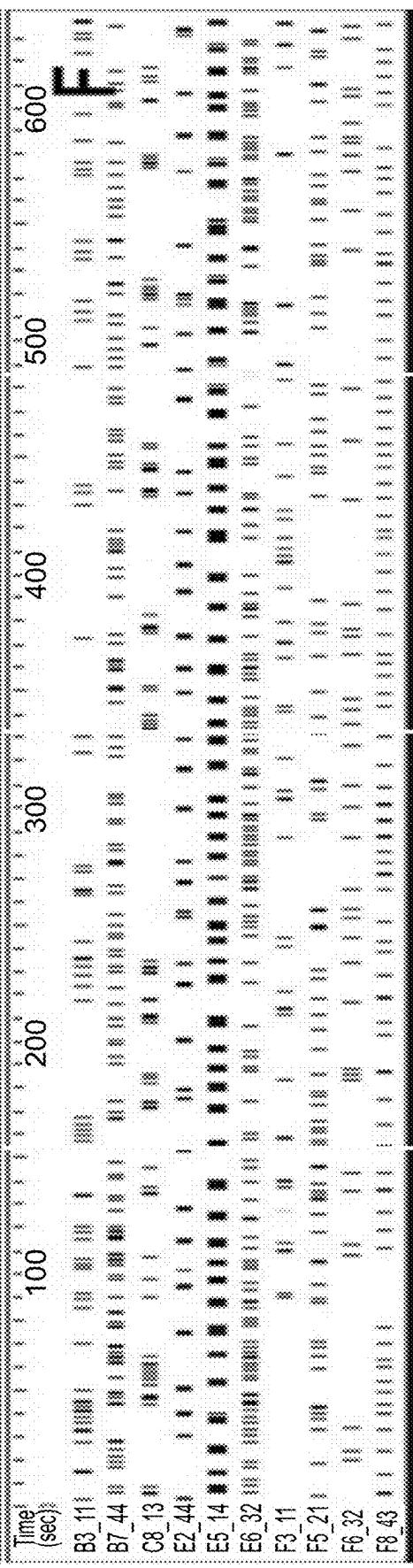
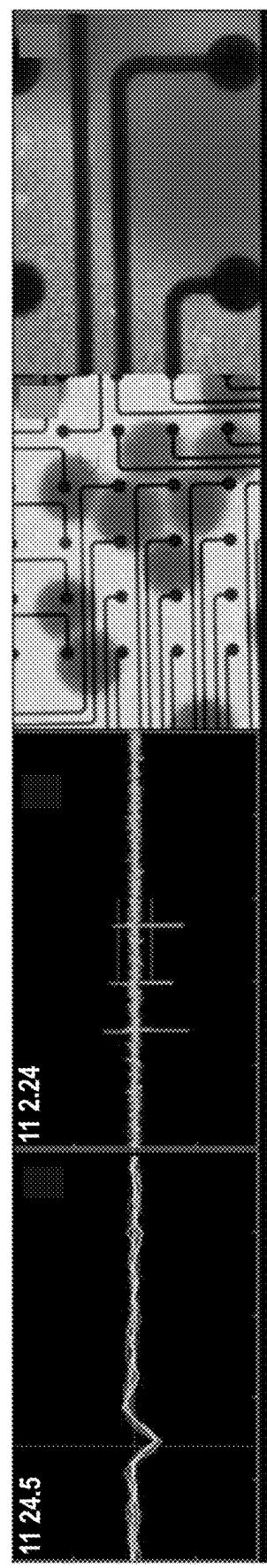


FIG. 3F

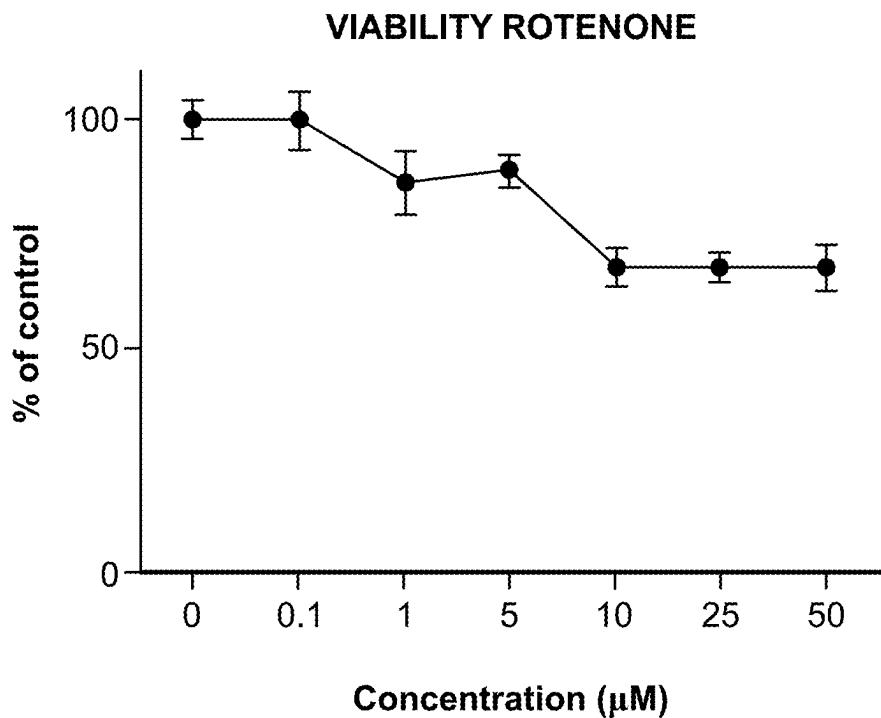


FIG. 4A

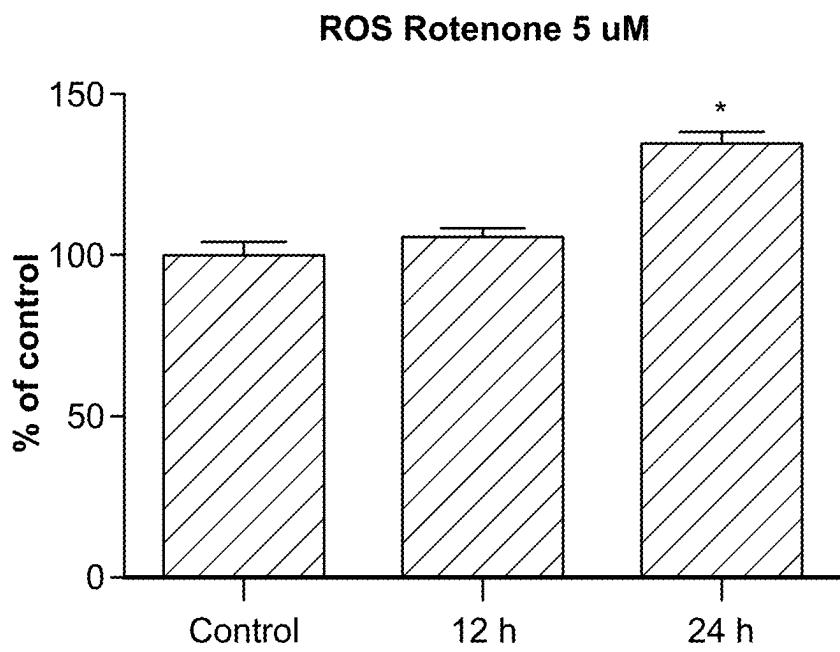


FIG. 4B

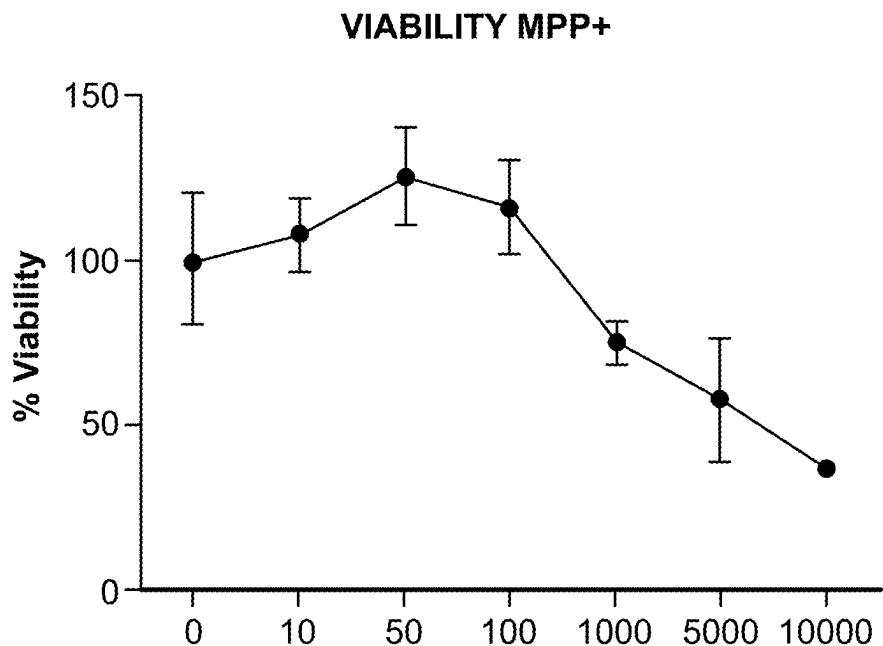


FIG. 4C

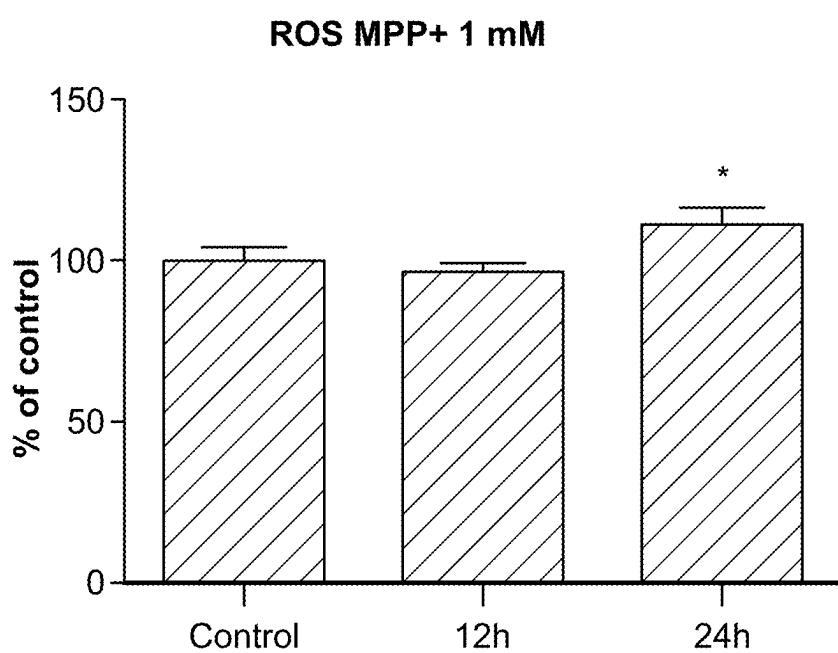


FIG. 4D

FIG. 4E

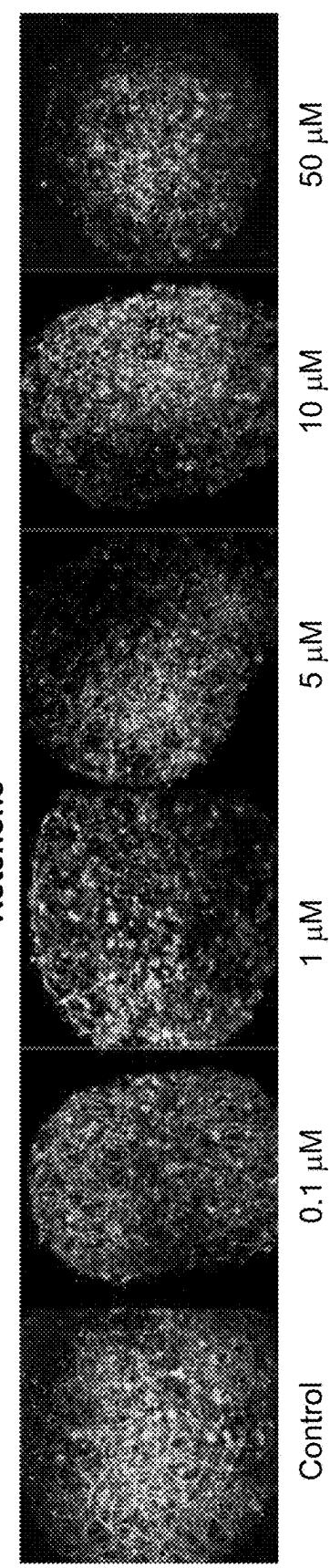
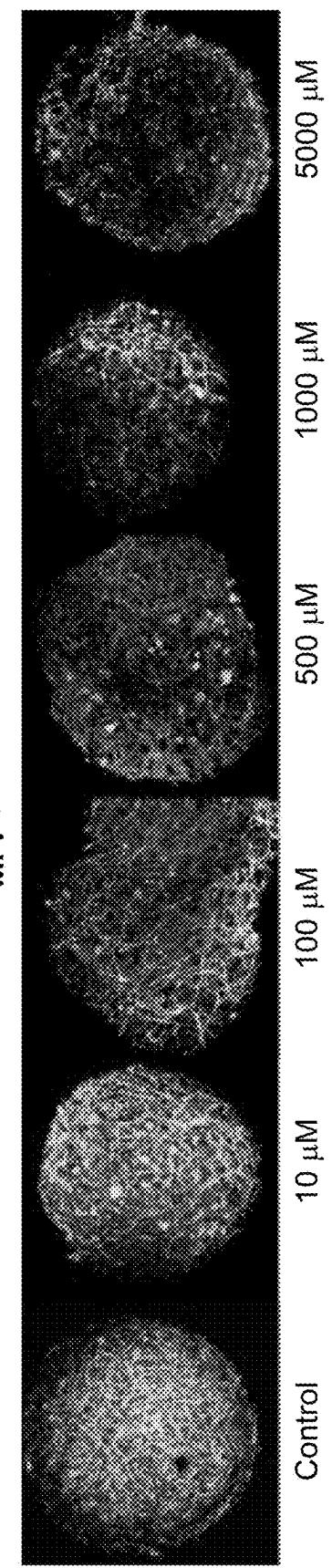


FIG. 4F



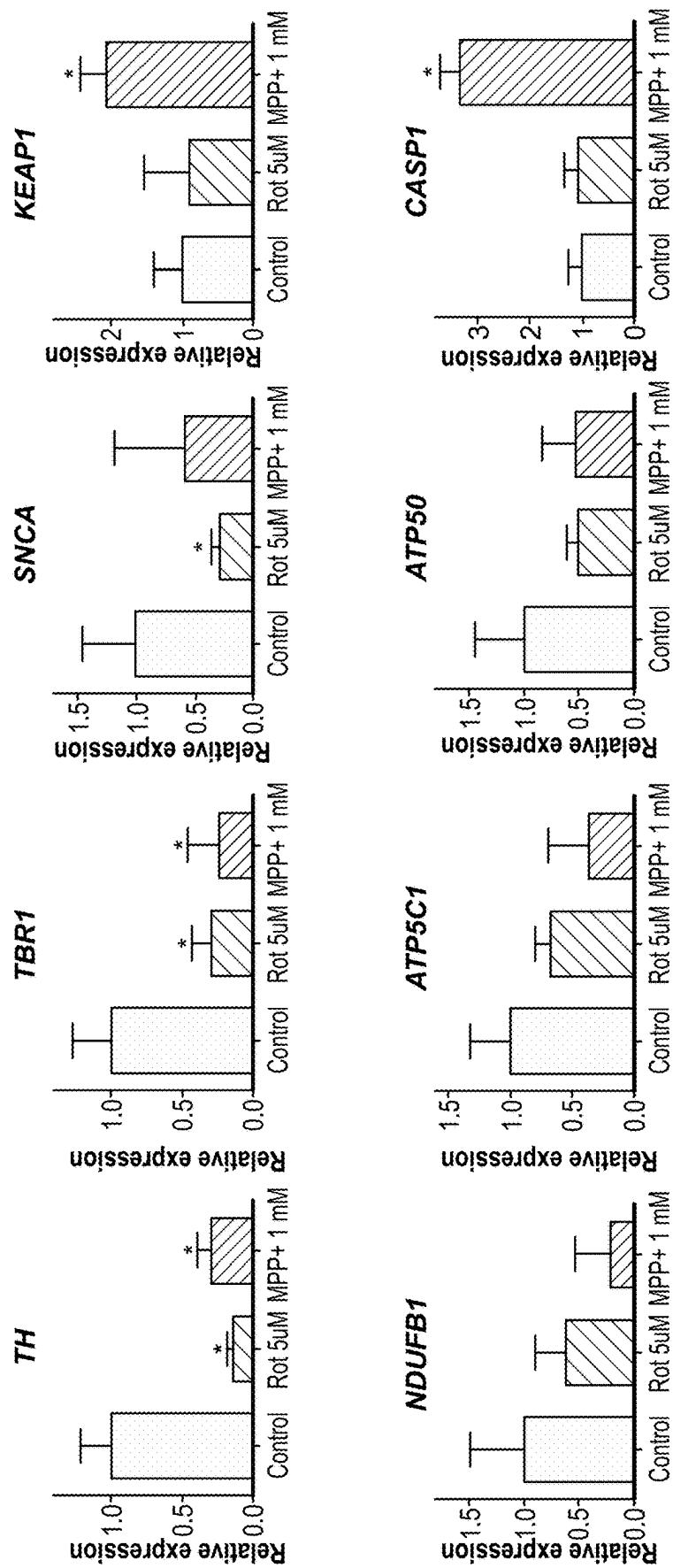


FIG. 4G

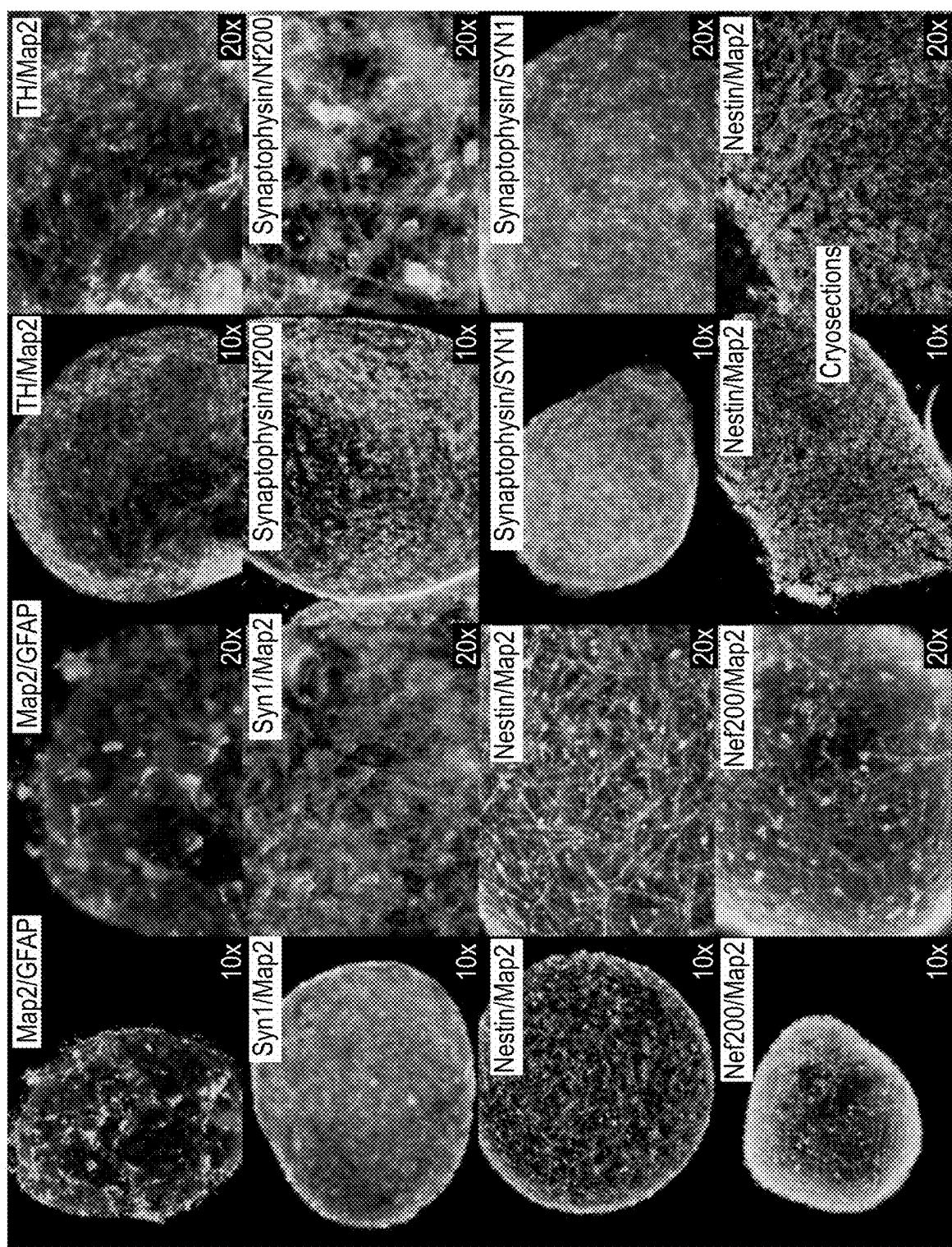


FIG. 5A

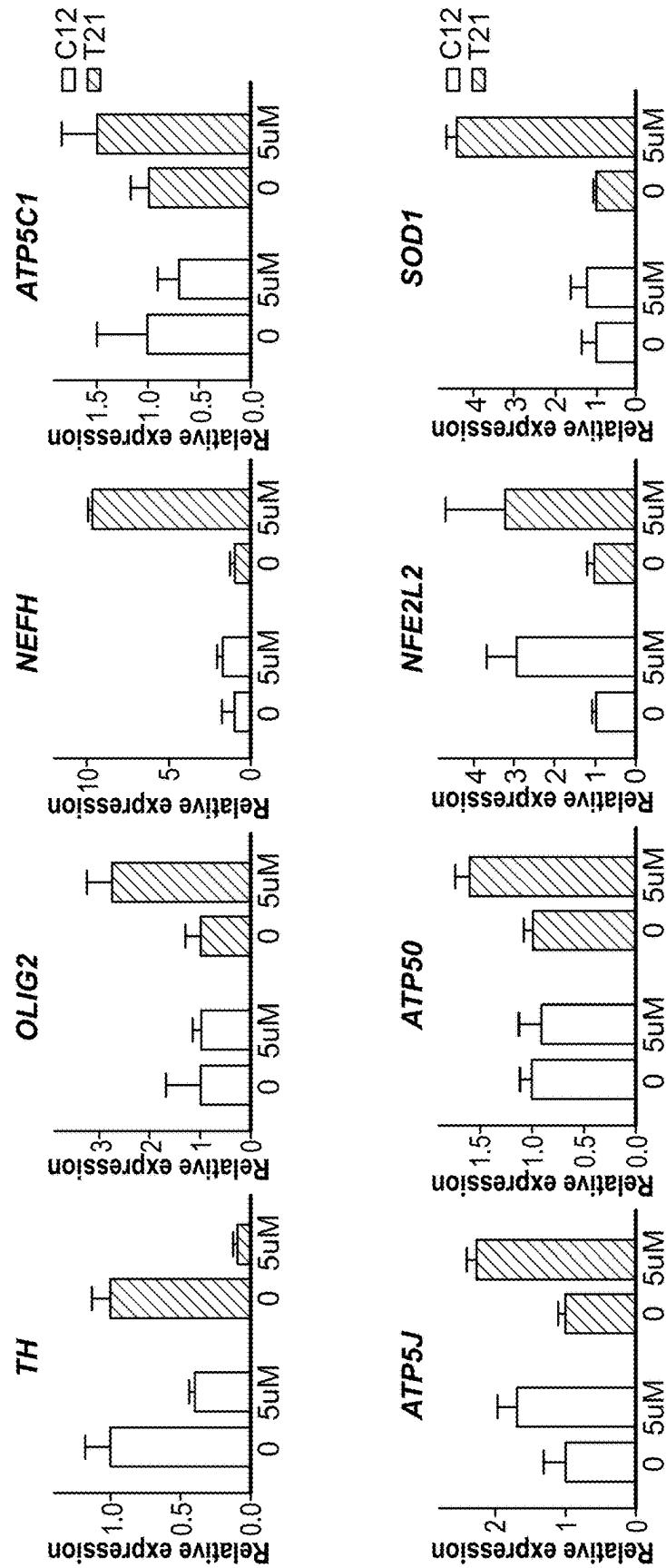


FIG. 5B

Amp/Deletion Table							Overlap Normal CNVs? $\beta$
Chr	Amp/Del	Start-Stop (bp)	Size (kb)	Chr Band	# Probes	Log2 Ratio	Genes $\alpha$
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, CRIP1, 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, POTE1G, 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

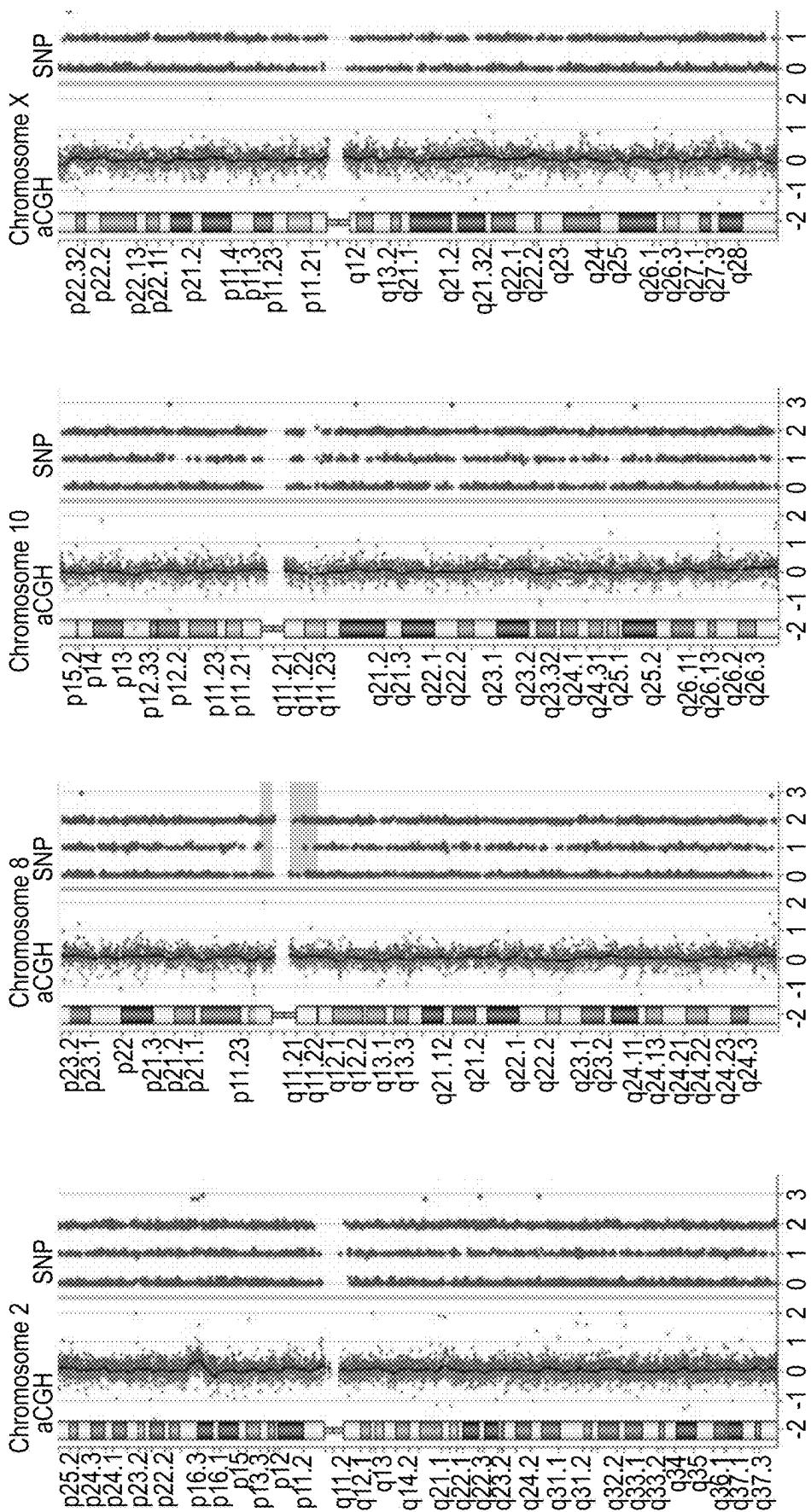
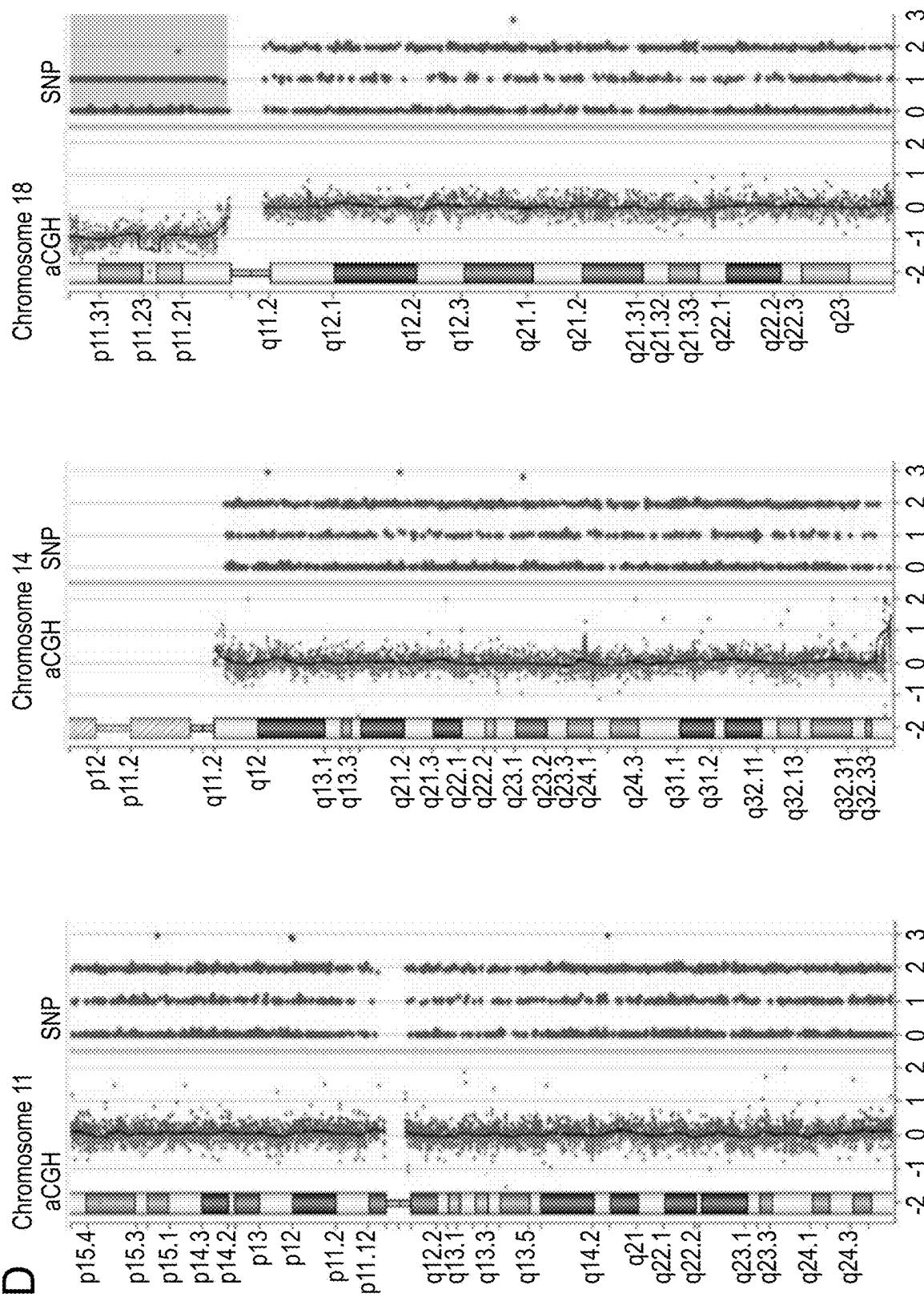


FIG. 5C (CONTINUED)

FIG. 5D



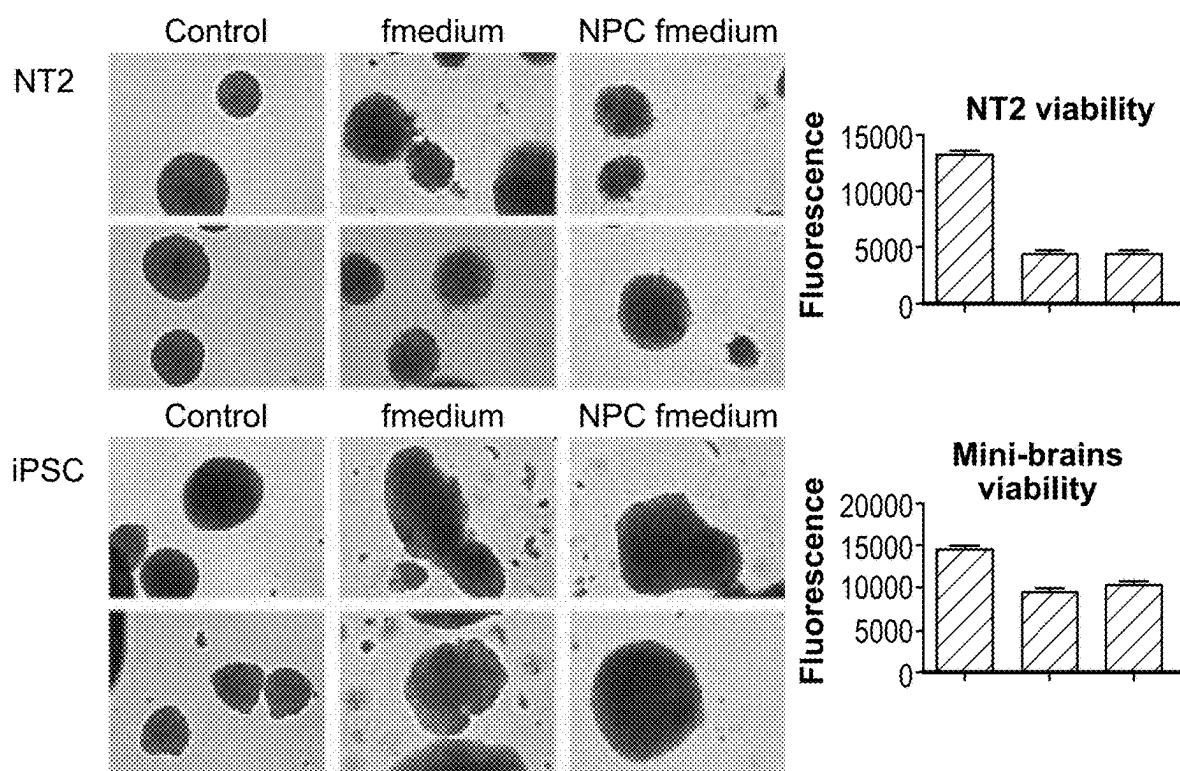


FIG. 6

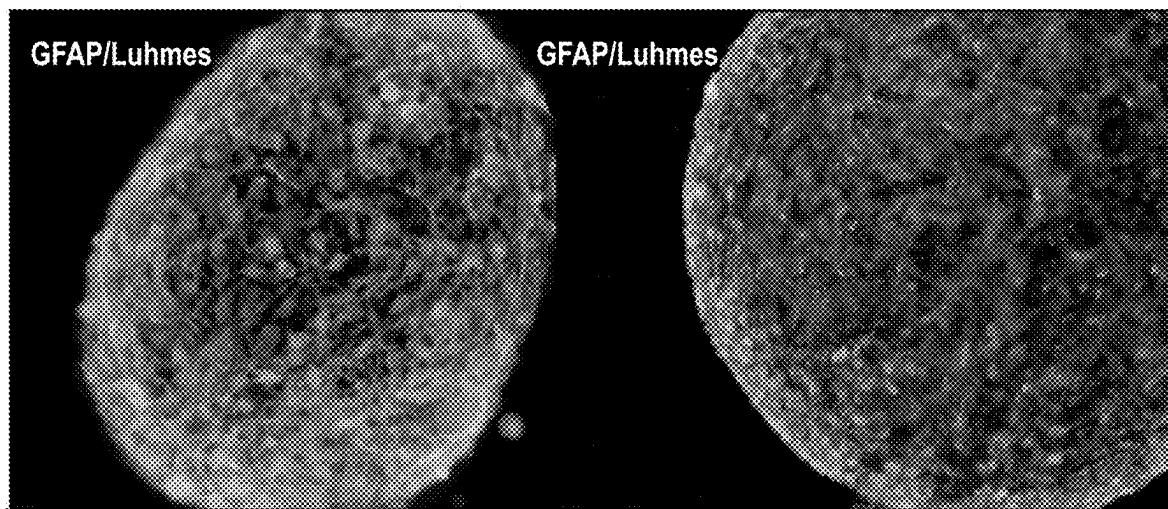


FIG. 7

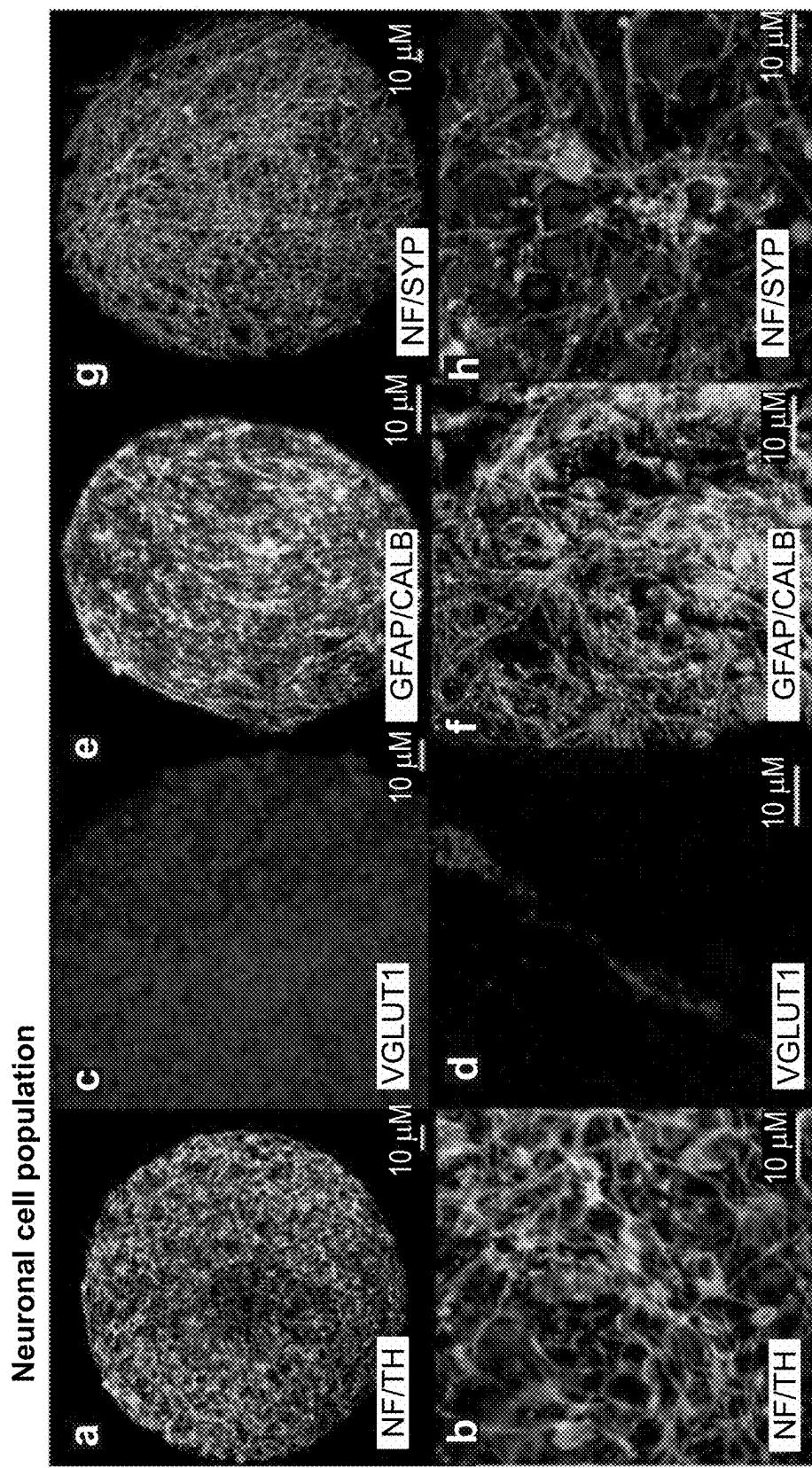


FIG. 8A

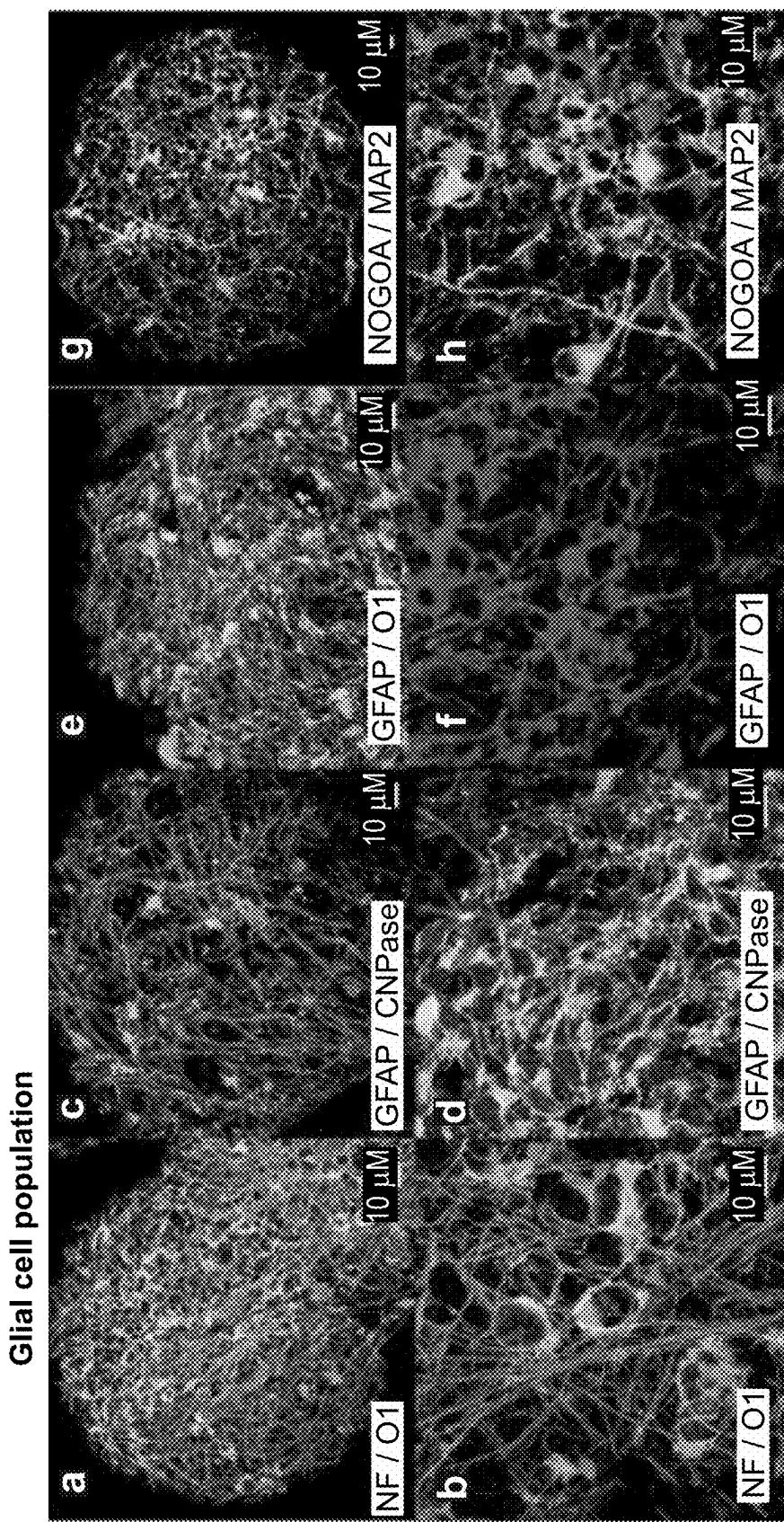


FIG. 8B

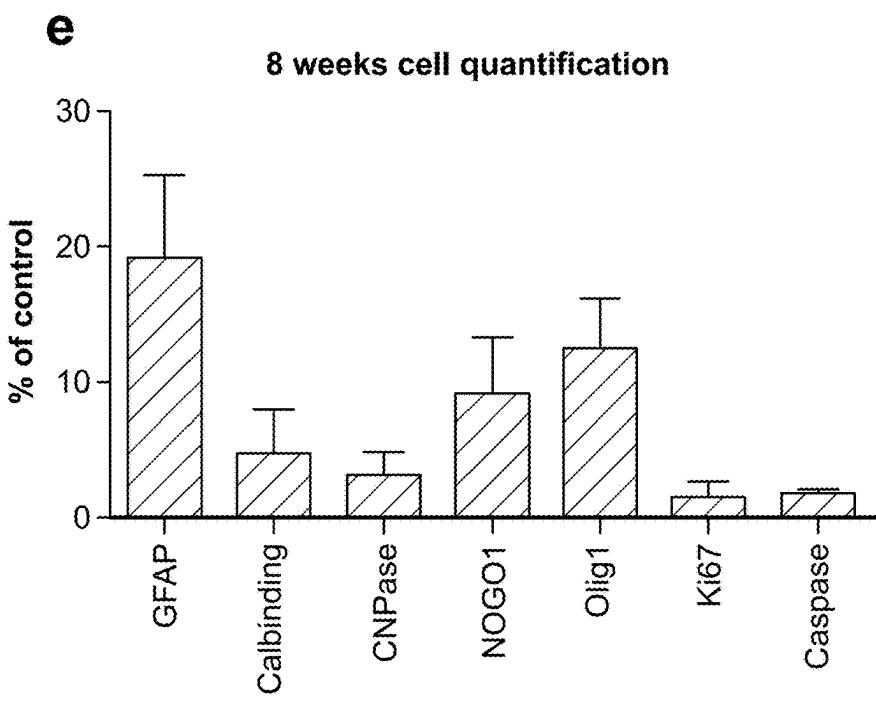
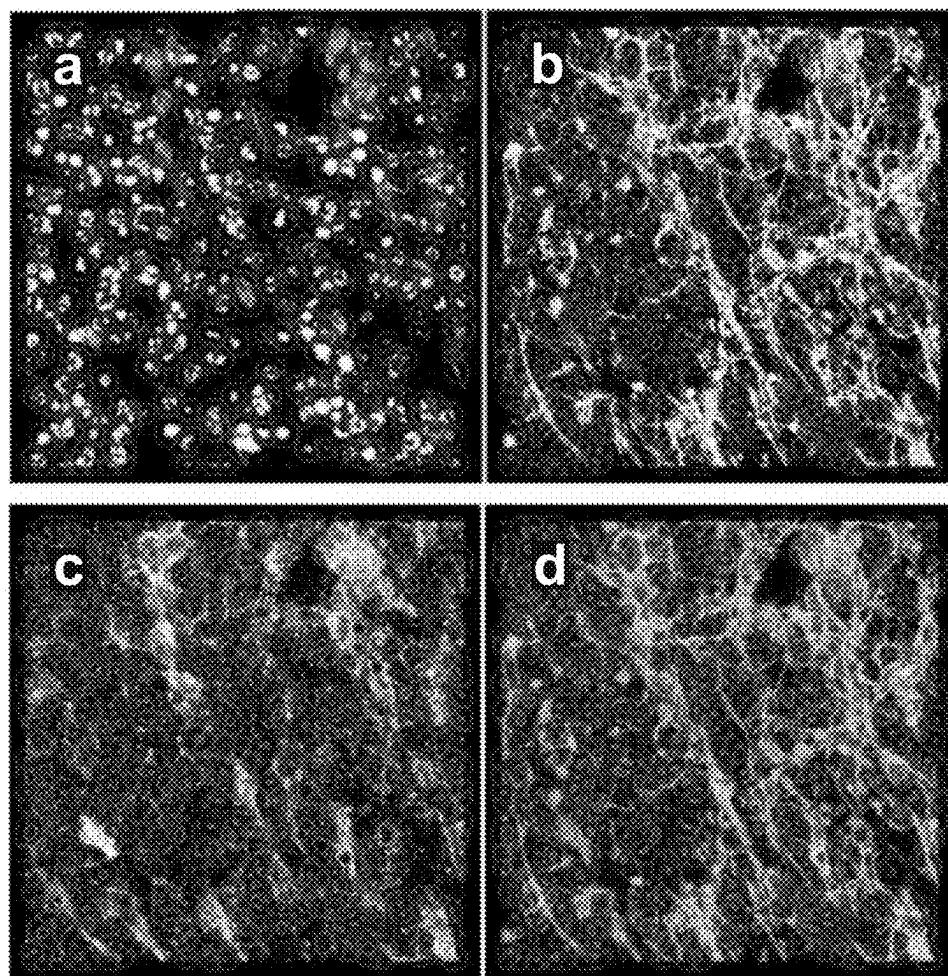
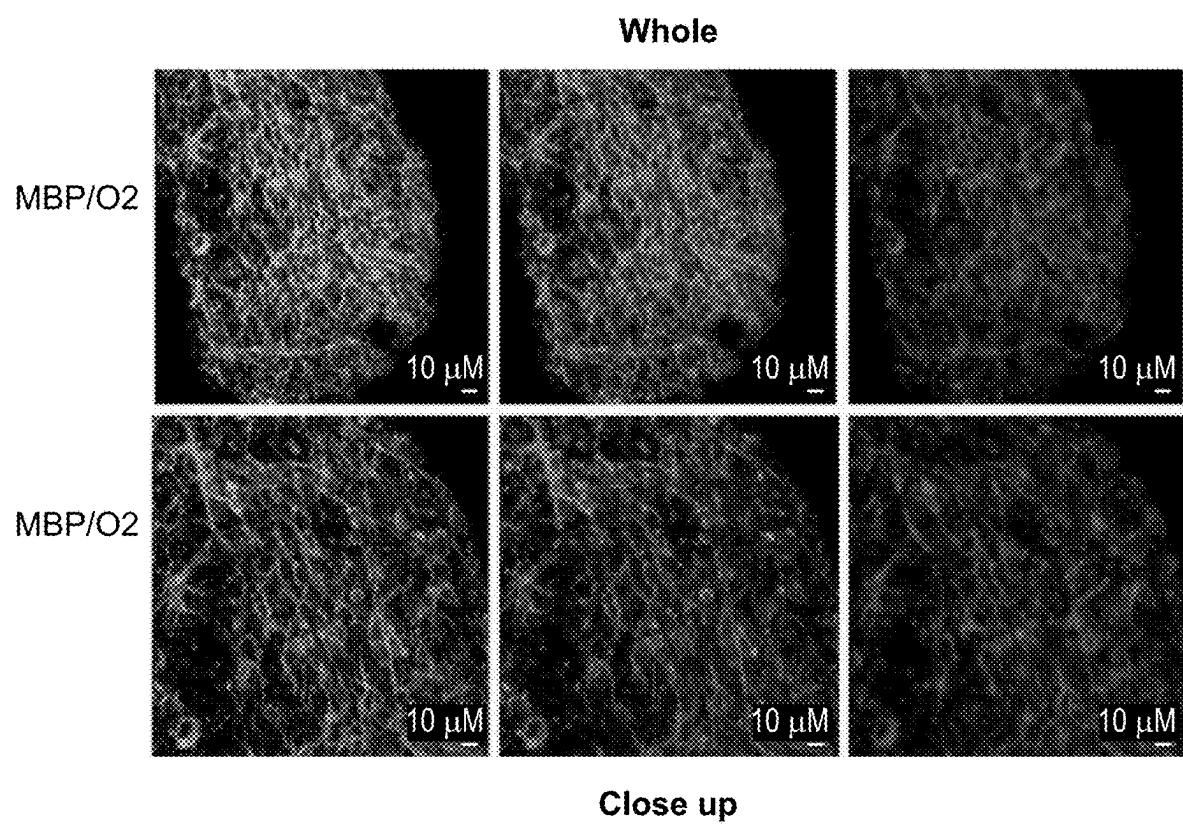


FIG. 8C



**FIG. 8D**

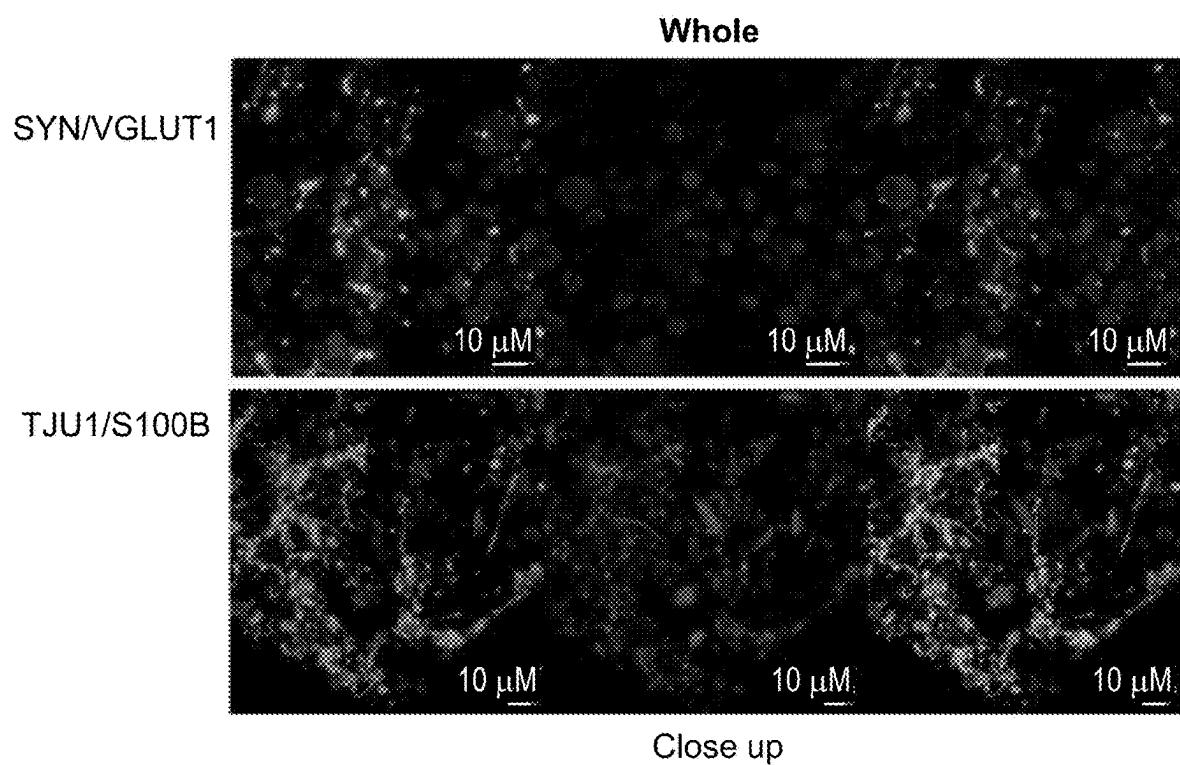


FIG. 8E

## 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 hvavamlyll drfspfgrfk vnseeeeeda  
 601 ltssamwfs wgvllnsgig egaprsfsar ilgmvwagfa miivasylan laafvlldr  
 661 eeritgindp rlrnpdsdkfi yatvkqssvd iyfrqrvels tmyrhmekhn yesaaeaiqa  
 721 vrdnklnhafi 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 agccgcccgc gccggccgccc  
61 ggccctttcc aagccggggcg ctcggagctg tgccggcccc cgcttcagca ccggggacag  
121 cgccggccgc gtggggctga gcggcggagcc cccgcgcacg cttagcgcgc ccttccctcg  
181 gcccacgtcc cggggccgc gctccggggg agacgtggcg tccgcagccc gggggccgg  
241 gcgagcgcag gacggcccg aagcccccg gggatgcgc cgaggggcccc gcgttcgcgc  
301 cgccgagcgc caggcccgcg gcccggagccc atgagcacca tgccgcctgct gacgctcgcc  
361 ctgcgtttct cctgcgtccgt cggccgtgcc gcgtgcgcacc ccaagatcgta caacattggc  
421 gcggtgtcgta gcacggggaa gcacgagcg atgtcccgcg aggccgtgaa ccaggccaac  
481 aaggccgcacg gtcctggaa gattcagctc aatgccaccc cggtcacgc caagcccaac  
541 gccatccaga tggctctgtc ggtgtgcgc gacctcatct ccagccaggt ctacgcacatc  
601 cttagttggcc atccacccatc ccccaacgc cacttcactc ccacccctgt ctccatcaca  
661 gccggcttct accgcatacc cgtgtgggg ctgaccaccc gcatgtccat ctactcgac  
721 aagagcatcc accttagctt cctgcgcacc gtggccccc actccacca gtccagcggt  
781 tggtttgaga tgatgcgtgt ctacagctgg aaccacatca tcctgcttgt cagcgacgac  
841 cacgaggggcc gggcggtctca gaaacgcctg gagacgctgc tggaggagcg tgagtccaa  
901 gcagagaagg tgctgcagtt tgacccagg accaagaacg tgacggccct gctgtatggag  
961 ggcggaaaggc tggaggcccg ggtcatcata ctttctgcca gcgaggacga tgctgcccact  
1021 gtataccgcg cagccgcgat gctgaacatg acgggtcccg ggtacgtgtg gctggcgcc  
1081 gagcgcgaga tctcgggaa cggccgtgcgc taacggccctc acggcatct cgggctgcgac  
1141 ctcataacg gcaagaacga gtcggccac atcagcgacg ccgtggcggt ggtggcccaag  
1201 gccgtgcacg agctccgtca gaaggagaac atcaccgacc cggccggggg ctgcgtgggg  
1261 aacaccaaca tctggaaagac cggggcgctc ttcaagagag tgctgtatgtc ttccaaagtat  
1321 gggatgggg tgactggcg cgtggagttc aatgaggatg gggaccggaa gttcgccaa  
1381 tacagcatca tgaacctgca gaaccgcag ctgggtgcag tggcatcta caatggcacc  
1441 cacgtcatcc ctaatgacag gaagatcata tggccaggcg gagagacaga gaaggccctcg  
1501 gggtaccaga tgtccaccag actgaagatt gtgacgatcc accaggagcc cttcggtgtac  
1561 gtcaagccca cgctgtgtga tgggacatgc aaggaggagt tcacagtcac cggcgacccca  
1621 gtcaagaagg tgatctgcac cggggccaaac gacacgtgc cgggcagccc cggccacacg  
1681 gtgcctcaatg gttgtacgg ctttgcata gacgtgtca tcaagctggc acggaccatcg  
1741 aacttcaccc acgaggtgca cctgggtggca gatggcaagt tcggcacaca ggagcgggtg  
1801 aacaacgcg acaagaagga gtggaatggg atgtatggcg agctgtcgac cggggcggcc  
1861 gacatgtatcg tggcgccgct aaccataaac aacgagcgcg cggcgtacat cgagtttcc  
1921 aaggccctca agtaccaggc octgactatt ctggtcaaga aggagattcc cgggagccacg  
1981 ctggactcgat tcatgcagcc gttccagagc acactgtggc tgctgggtgg gctgtcggtg  
2041 cacgtgggg ccgtgtgtgt gttacgtgtg gacccgttca gccccttcgg cgggttcgg

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2101 gtgaacagcg aggaggagga ggaggacgca ctgaccctgt cctcggccat gtggttctcc  
2161 tggggcgctcc tgctcaactc cgcatcgaa gaaggcgccc ccagaagctt ctcagcgcgc  
2221 atccctgggca tggtgtggc cggtttgcc atgatcatcg tggcctccta caccgccaac  
2281 ctggcggccct tccttggtct ggaccggccg gaggagcgca tcacggccat caacgaccct  
2341 cggctgagga acccctcgga caagtttatc taccccacgg tgaagcagag ctccgtggat  
2401 atctacttcc ggcgcaggt ggagctgagc accatgtacc ggcataatgga gaagcacaac  
2461 tacgagatgc cggcggaggc catccaggcc gtgagagaca acaagctgca tgccttcata  
2521 tgggactcgg cgggtgtggta ttctggagcc tcgcagaagt gogacctggt gacgactgg  
2581 gagctgtttt tccgctcggtt 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 gcctttgcgc cccgttaacgt gtggcggaaag aacctgcagg atagaaagag tggtagagca  
2941 gacccctgacc ctaaaaagaa agccacattt agggctatca cctccaccct ggcttccagc  
3001 ttcaagaggc gtaggtcctc caaagacacg agcacccggg gtggacgcgg cgctttgcaa  
3061 aacccaaaag acacagtgc gccgcacgc gctattgaga gggaggaggg ccagctgcag  
3121 ctgtgttccc gtcataaggaa gagctgagac tccccggccg ccctctctg cccctcccc  
3181 cgcagacaga cagacacacg gacgggacag cggccggcc cacgcagagc cccggagcac  
3241 cacggggtcg ggggaggagc accccacggc tccccggc tgcgcctgca cggccggccgg  
3301 ttggccggctt ggccggctca cccctggccg gccccggc tgcggccggc gtggggctaa  
3361 cggccgcctt gtctgtgtat ttctatttt cagcagtacc atcccactga tatcacgggc  
3421 ccgctcaacc tctcagatcc ctccggcagc accgtgggtt gaggccccgg gaggeggccca  
3481 cctgcccagt tagccggcc aaggacactg atgggtctcg ctgctcgaa aggcctgagg  
3541 gaagccacc cggcccccggc actgcccacc ctggccctcc cgtccggccg cccggccacc  
3601 ccgctgcctg gggggcagcc cctgcgtggc caaggtgcgg accggagcgg ctgaggacgg  
3661 ggcagagctg agtcggctgg gcagggccgc agggcgctcc ggcagaggca gggccctggg  
3721 gtctctgagc agtggggagc gggggctaac tggccccagg cggagggggct tggagcagag  
3781 acggcagccccc catccttccc gcagcaccag cctgagccac agtggggcccc atggccccag  
3841 ctggctgggtt cggcccttcc cggccgcctg cgtccctctg cagcctgagc tccaccctcc  
3901 cctcttcttgc cggcaccggcc caccacacc ccgtctggcc ctgcgtggcc cacggccgggg  
3961 ctggccctgc cccctccac ggccgtccct gacttccctg ctggcagcgc ctccggccgc  
4021 ctggggccgc ctcccttccaga ctgcggaggg ctgcggccctt cctctctcg tccggccctgc  
4081 agcccaacac gggcctcccc gggggctccc ggacgtggc tggggactgt cttaaccct  
4141 gccctgcacc ttgggcacgg gagagcgcca cccggccggc cccggccctcg ctccgggtgc  
4201 gtgaccggcc cggccacccctt tacagaacca gcactccag ggccggagcgc cgtgccttcc  
4261 ccgtgcggcc cgtgcgcagc cgcgcctgc ccctccgtcc ccagggtgc ggcgcgcacc  
4321 gcccaaccccc caccctccgg tggatgcagt ggtgtatgcct 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 yakiknreef 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 gcgttgcata ctggccttgg acccccaccc cgaccccgac  
 481 cccgcctcgat ctcggcgctt cactccaggat cgccgcgtat caccgcaga ctcgagagcg  
 541 gcccaggctt acgctccctg cgccccagta ccggagctag cgccgcacgtc tcctccgctg  
 601 ccccccacccc tgccgcacccc taccaggccg gctcgctgc ttccctccctt ctgtctctc  
 661 cagagccgga tcttcaaggg gagcctccgt gccccggct gtcagtccc tccggtgtgc  
 721 aggaccccccgg aagtccccc cgcacagctc tcgttctctt ttgcagectg tttctgcgcc  
 781 ggaccaggctg aggactctgg acagtagagg cccggggacg accgagctga tggcgtctc  
 841 gaccccatct tcgtccgcaa cctccctcgaa cgccggagcg gaccccaata ccactaacct  
 901 ggcgcacca acgtacgata cctgggtgcgg cgtggcccat ggatgcacca gaaaactggg  
 961 gctcaagatc tgccggcttct tgcggaaaggac caacagcctg gaagagaaga gtcgcctgt  
 1021 gagtgcccttc aaggagaggc aatccctccaa gaaacctgctt tcctgtgaaa acagcgcaccc  
 1081 ggatgcccgc ttccggcgca cagagactga cttctcta at ctgtttgcta gagatctgt  
 1141 tccggctaaag aacggtgagg agcaaaccgt gcaattcctc ctggaaagtgg tggacatact  
 1201 cctcaactat gtccgcaga catttgatcg ctccaccaag gtgctggact ttcatcaccc  
 1261 acaccagttg ctggaggca tggaggcgtt 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 tgatggata ttttctcctg ggggcGCCat atccaacatg tacagcatca tggctgctcg  
1621 ctacaAGTAC ttcccggaaag ttaagacaaa gggcatggcg gctgtgccta aactggtctt  
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 ttccagtaaac atgcacatcg gctgcctggg gaggtggcgt gctcatgtcc aggaagcacc  
2101 accataaact caacgcata gaaaggGCCa actcagtca cttggAACCCt cacaagatga  
2161 tgggcgtgct gttcgagtgc tctgcatttcc tcgtcaagga aaagggtata ctccaaggat  
2221 gcaaccagat gtgtgcagga taccttttcc agccagacaa gcagtatgtat gtctcctacg  
2281 acaccgggaa caaggaattt cagtggtggc gcccacgtgg tatcttcaag ttctggctga  
2341 tgtggaaagc aaaggcaca gtgggatttggaaaaccagat caacaaatgc ctggaaactgg  
2401 ctgaataacctt 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 gaacaaacctt ctatgttg ctggaaacaca caggccattt  
2821 cattgaggga aaacataata tcttgaagaa tattgttaaa accttactta aagcttgg  
2881 gttcttagtta gcagggaaaat gttttttttt taaaaagggtt cacattagga acagagtata  
2941 tatgtacagt tatacataacc tctctctata tatacatgtt tagtgagtgt ggcttagtaa  
3001 tagatcacgg cttttccc gctccaaagag aatttactttt accttcagca gttaccgagg  
3061 agctaaacat gctgcAAacc agcttgcata acaactccag gaaaactgtt tttcaaaacg  
3121 ccatgtccta ggggccaagg gaaatgtgt tggtgagaat cgacccact gtcacgttt  
3181 ctccacctga agtgatgatg gatgagaaaa aacaccacca aatgacaagt cacaccctcc  
3241 ccatttagtat cctgttaggg gaaaatagta gcagagtcat tgttacaggt gtactatggc  
3301 tgtatTTTA gagattaattt tgttgtagatt gtgtaaattt ctgttgcctg accttgg  
3361 tgggagggggg agactatgtg tcatgatTC aatgattgtt taattgttagg tcaatgaaat  
3421 atttgcttat ttatattcag agatgtacca tgtaaagag gctgttttta tttttttccc  
3481 atttgtaatg tatttttattt atatatgaaatg taagttctga aactgttta tggtatTTT  
3541 gtgcatttgt gagccaaaga gaaaagatta aaatgtgatg gatttgattt tatttagag  
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 kwgqgvgwlw
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.

```

(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 gtcttctct 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 tcttcctcat
1081 ggtcgttctc ctgggactgg atagccatgtt tgtgtgtgtt gaaaggctgg tgacagcgct
1141 ggtggacatg taccctcactg tgttccgcaa gaagaacccgg aggaaagtcc tcatacctgg
1201 agtatctgtc gtctccttcc ctgtggggct gatcatgtc acagaggccg gaatgtacgt
1261 gttccagctc tttgactact atgeggccag tggcatgtgc ctccctgttcg tggccatctt
1321 cgagtcctc tttgtgttcc gggtttacgg agccaagccg ttctacgaca acatcgaaga
1381 catgatttggg tacaggccat ggcctttat caaatactgt tggctttcc tcacaccagg
1441 tgtgtgcaca gccaccccttcc tcttccttcc gataaaatgtc actccgctga cctacaacaa
1501 gaagttacacg taccctgtgtt gggggatgc cttgggttgc ctccctggctc tgccttcctg
1561 gtctgcattc ctgcctggag cctctacaga ctccggaccc tcaaggcccc ctccagagag
1621 agaatccgctc agctcatgtt cccagccgag gacccggcccc agccggaccc agcaggaccc
1681 tccggctcccg ccaccccccag gacccactgtc ctccggactca cagagctaga gtctcaactgc
1741 tagggggcag gcccttgat ggtgcctgtt tgccctggct tggggatggc tgggggggg
1801 acgtggcaga agcagccccca tttgtttccct gccccccgacc tggagttggat aagacaagag
1861 gggtatttttggat ggtccacccct gctgagctgg aggccctccca ctgcaacttt tcagctcagg
1921 ggttggtaa cagatgtgaa aaggccatgtt ccaagactgtt ccctcggaga cccttgaagg
1981 c

```

**[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 vkvftfeak ihhletrpaq rpraggphle yfvrlervrrg dlaallsgvr
181 qvsedvrsqa gpkvpwfprk vseldkchhl vtkfdpdl dhpqfsdqvy rqrrkliae
241 afqyrgdpri prveytaeei atwkevyt kglyathacg ehleafalle rfsgyredni
301 pqledvrsrl 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 agtgtgtgtt ccagcatgtg tgtgtgtgtg tgcatgtaca cgtgtgcacc
61 tgtatcgctt gtgtgtgtgc atgtgtatgt tacacgtgtc atgcgtgcac gcacatgtgt
121 agtgtgtgtt cgtgtgtgtt gtgtgcctgt gtcatgtatg agcacaacttg tatatgtgt

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2521 cagagagct ggcccaagg aagagtctag taagtttagt tcccatggg ctccatgaa  
2581 agcacaactg gccccggcagg aaaccgaatt aaaaagcaat atttgtatca gtggaagaca  
2641 tttgctgaaa ggttaaatcc acatccggca gtgtgggcca tgagcctccg gcgtgggtt  
2701 catcaggcat gtctcttcctc ctggctggg cacctgagca ctggggccgc cctggcaga  
2761 gctggggcgg ggtgctgggg ggctggagc tgccctcaccc agggatcctc agcagccgac  
2821 cctggggag gcaaatacgaa ctcttctgg ggacatttag gggagctcg gggagccatg  
2881 cagagcttca ccaggcctgg acactgggca tgaggctgg gccacccaag ggccatcacc  
2941 agggactcag gtgggtgggc ctcaagccctg ggtgacagaa gctcacgggc cgcaaggcga  
3001 ggccagaggg tgaggcctca ggctgaggc ttggaggca atccctccaa cgccctctg  
3061 agcaggcacc cagacctact gtgggcagga cccacaggag gtggaggcct ttggggaaaca  
3121 ctgtggaggg gcatagcatc tccgagagag gacagggtct gcaactgggtg ctgagagaca  
3181 gcagggggccg agcggttaggc ttccctgccc ccaggatgt tccagaggag cgcaaggag  
3241 gggcattaat atcggtggcaaa gaaaggccag gcattgcaga gtgagcagcg acggaaactgg  
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3361 accggggatc acggagcccc aaatcccttct gggccaggaa gtggggagg ttggggggtc  
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4201 aagggggccac aggacccca gggaaagccag gagctagcag tggccatag aggggctgag  
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4561 caaatgcct cctgacatct gaggctggag gctggattcc cctgtttggg gttttctggg  
4621 tcggtctgcc acgaggttct ggtgttcatt aaaaagtgtgc ccctggctg ccagaaagcc  
4681 cctccctgtg tgctctttg agggctgtgg ggccaaagggg acctggctg tctcagccccc  
4741 ccgcagagca cgagccctg gtcccgcaaa gcccggggc tgaggatgat tcagacaggg  
4801 ctggggagtg aaggcaatta gattccacgg acgagccctt tctcctgcgc ctccctccctt

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4861 cctcacccac cccgcctcc atcaggcaca gcaggcaggg gtggggatg taaggaggg  
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4981 agggctgtgg agacggagcc cggacctcca cactgagcca tgcccacccc cgacgccacc  
5041 acgccacagg ccaagggtttt cccgaggccc gtgtctgacg tggacgcca gcaggcagag  
5101 gccatcatgg taagaggcga ggttaggtgcc cggcgccgc agtggaccgg agcccaggc  
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7141 tggcccttgc tggcccttgc tggcccttgc tggcccttgc tggcccttgc tggcccttgc

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7201 gtggggctgt gtgggctgag ttcttgatccc ctctatagca gaggtgcagc tgcccgaggcc  
7261 cccgaggccg gcacaggatc cagcaggaaa gtctcaggcc tcagtcagc ccccatggca  
7321 tcttagccaca cccccgtttt tttgaggat cctgagccca ccccttagggc tgaggctacc  
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9541 catcctgtcg ggccatcccc agtgtgctga gggaccgccc ctcatggccc cctatcccc  
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9661 caagaggcct gcgttggtag gggctcaggc aggagagggc acccacagtt caggaggggg  
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12241 tcaccacgac ctggaaagagg cctcagtgtc ccgcctgtga ccagttggct cagaaaagcc  
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12361 ggctgcagac tctggccccc agttgtacgag ggctctgcgc ctctcctccc caggagctat  
12421 gcctcacgca tccacgcgcc ctttccctgt aagttcgacc cgtacacgcgt ggcacatcgac  
12481 gtgctggaca gccccccaggc cgtgcggcgc tccctggagg gtgtccagga tgagctggac  
12541 accctgtccc atgcgtcgag tgccattggc taggtgcacg gcgtccctga gggcccttcc  
12601 caacccccc tggccctgca ctgtcccgga gctcaggccc tggtgagggg ctgggtcccg  
12661 ggtgcggggcc atgcctcccc tgcgtccagg ctccactgc ccctgcaccc ttcttcagc  
12721 gcaacagctg tgcgtgcggc tggtgagggtt gtgcgtccctg tggtgagggtc ctgtccctgg  
12781 tcccaagggtc ctgggggctg ctgcactgccc ctccgcctt ccctgacact gtctgctgccc  
12841 ccaatcaccc tcacaataaa agaaactgtg gtctctacac ctgcctggcc ccacatctgt  
12901 gcccacagaga cagaccctgg gatcctcaga ctcccacacc cccaccccaag cctcaactcag  
12961 aggttcgccc ctggcctctt tcctctctg ggagatggct ggccgcctg gccaggcage  
13021 tggcccttcc gggcctgggtt tccctgcctca ccctgaggcc cggcccaagct ctgagccccca  
13081 agcagctcca gaggctcggg caccctggcc gagtcggcc atctccgtgg ggtgcctcc  
13141 caagggtggg agccacgtga cagtggagg gcctctcta ggctggcag ggagcagggg  
13201 tcacaaactg tgcgtggcgg ggggtggctc agaggtgggc ctgcaggccctt aaccctccct  
13261 gctgacacggg ctcccaagccc ttgagagaaa cagggatggaa ggaacacgtg ccctgatgccc  
13321 ctcacccacc cggagcggc cctgcgaacc aaggggaacc tcagtgtggc cccacacatg  
13381 tgtgctgatg gggagggtct ggctgagctg gtgcggcaggc agatggtctg ggctctgtctc  
13441 cccagcggagg caggatgggg gctggatttc agactctgtta agatggccctt ggcttactcg  
13501 aggggcctgg acattgcctt ccagagagag caccaaacac cctccaggct tgaccggcca  
13561 ggggttcccc ttccctacctt ggagagagca gccccaggcc atctgcagg gggtgtgggg  
13621 acaccacgtg gcttcacagg tctctgcctc cctccagcc ccccaactaca cgctgtgggg  
13681 atcctggatc tcagtccttcc ggcgcacaac actggcaaac tcctactcat ccacgaaggc  
13741 cctccctggcc atgggtggcc ttcccaaggctt ggctgtctgt tcctcacaca ctttgttagt  
13801 gcccagccccc tgaggttgc gctgggggtg tctctgaagg gctgtgagcc cccagggagg  
13861 cctggggaaag tgcctgcctt gctccccc ggcctgcca ggcctggct ctggccctt  
13921 acctgggctc ccccatcca gcctccctcc ctacacactc ctctcaagga ggcacccatg  
13981 tcctctccag ctgcggggcc tcagacact gtggcgtctt 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
14281 tgcccctggt gctaagaggc aggttagggc tgcaggcagc agggctcgga gccccatgccc
14341 cctcaccatg ggtcaggctg gacccctcagg tgccctgttct ggggagctgg gagggccggaa
14401 ggggtgtacc ccaggggctc agcccaagatg acactatggg ggtgtatggtg tcattggacc
14461 tggccaggag aggggagatg ggctcccaga agaggagtgg gggctgagag ggtgcctggg
14521 gggccaggac ggagctggcc cagtcacag ctccccacac ctgccccaccc ccagagtccct
14581 gcccaccc ccagatcaca cggaaagatga ggcccgagtg gcctgctgag gacttgctgc
14641 ttgtccccag gtccccaggt catgcctcc ttctgccacc ctggggagct gaggggctca
14701 gctggggctg ctgtcctaag gcagggtggg aactaggcgcc agccaggaa ggggacccct
14761 ccctcactcc cactctccca ccccccaccac ctggcccat ccatggcggc atcttggcc
14821 atccgggact gggacacggg gtccctgggg a caggggtgtg gggacacgggg tcctggg

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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 ssaqtnnggg aqmegimnpy talptpqql1
301 aieqsvyssd pfrqgltpqmpgdhmhpq aeplfhdlds 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)

```

1 gtatagggttggccggagtc ggattcgggaa tggaaaacct gggcaaggat atgttaggtgg
61 gggtaggggg ggcaggagaa ggagaaacgc agttgggggg cggaggccata agtacataac
121 gtgttgactt caagtgaaat cagatcagcc agacgagttc 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 ttttcgcg  
781 gcctagaggc aatagcatcc gagaccgag gcctggagcg cccaagttcg aggaggctc  
841 tctccccac caactccagc cccaatttca gccatggca 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  
1141 ggctcaacga cagcttctgg catgagcagt gctgtcgtc aaagagcccc  
1201 tggagaccac ctgcttctac cgggacaaga agctgtacty caagtatgac tacgagaagt  
1261 aagtggccgc acccccgcag cgctccccgc gcaactggcat nnnnnnnnnn nnnnnnnnnn  
1321 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
1381 nnnnnnnnnn nnnnnnnnnn atccagttc ttgaagttcc ttttgtgtt gacttcaggd  
1441 gagaccagg accaagccag atttactca tggtgcatgt acttccttgc tccctgtc  
1501 caggctgtt gctgttaat gtggggctg ctgcaggcc atcgctccca atgagttgt  
1561 tatgcgggcc cagaagagtg tataccacct gagctgttc tgctgtgtg tctgegagcg  
1621 acagcttcag aagggtgtatg agtttgcct gaaggagggg cagctgtct gcaaaggggg  
1681 ctatgagaag gagcggggc tgctcagcc ggtgagccca gcaagctcag 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 taaaagtgt gatgaagaaa gtctctgca gtcagccat gggcaggaa aaggaactgc  
2041 tgaggaaggc aaggaccata agcgcggccaa acgtccgaga accatcttgc caactcaaca  
2101 gaggcagca ttcaaggcct cattgaagt atccctcaag ccctgcagga agtata>tagga  
2161 gggagcaggc agggaaagga gctggggccc acttctctgt gtgcactcag accctctgg  
2221 gatctcagtg ggcattggg gtcacagtgg tgaggaaggc tgcgtcagaca gacccctgcac  
2281 aggccggctca agcctgttgg agactccaga gatcactaag ctgtggccag ggtgtatag  
2341 actctccgtca agcttcatg catgcacacc aactccaaat ggccctgtc acaccttca  
2401 ttccatagag cacaatggg acaagataaa tgataggtt ccattgtggt gtagacccag  
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2581 tataagggtgtt ccatgattgg tttgtccatg cacctgttgatgggtgtttt ggggttgg  
2641 tagttttggc ctgtttcaaa taggactgtatggacattc atgtaaaaaa aaatacagt  
2701 gtttaatgtt acaggagttt attctttctgt gtcacagtcc agaggtgagc aaggcaaggc  
2761 tggtgggtgg ctctgttatac catctctgt gtccaaagcga ctgcgtccagt tgcaccatg  
2821 ttccagtc ccaggttagag aaagaggaaa tggagggca ggcgcctgtt ttttaaggat  
2881 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
2941 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn atgcatatgc atggcttata  
3001 gctaaagcac aacaatagac taaagtctaa accacttga ggcctaattt ccagagcaag

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3061 agaaatccag aaacacctt tgggaatgca catgtaaattt aataattttt attttgttc  
3121 tttacctggt gaaggacttt ctttctacct gaagggaaagc aatgttctcg tgtttggtg  
3181 tatgctcaac attaaaaactt attcaagctcc taaagcagat acagtctttt ggccctcctca  
3241 agtattatat aggagatgtt ctaccctcta ccctgagatg ccagtgtgtc tacatttctc  
3301 gttcaatttt tccaagggtga gagagactct ggctgcagag acagggctga gtgtccgtgt  
3361 cgtccaggtg tggttccaaa accagagago gaaggttaacc tgcttcttac ttttatctgt  
3421 cccccatgtt ctggttccct gaaataatca cagtaggaca nnnnnnnnnnn nnnnnnnnnnn  
3481 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
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3601 tactttgtga acatgctgca ggccacctga cttctaattcc tatggtctc tccttatcg  
3661 atgaagaagc tggccaggcg acagcagcag cagcagcaag atcagcagaa caccagagg  
3721 ctgagctctg gtaagctggt gcctctccc aggcaagtct ggctgaaatc caggctgttc  
3781 ctaccagagg cctccacta cccagcttt tggatgacat atctggactc agtgaagcct  
3841 agaccacacc cactggagaa ataaggcctt caagggaaaga ctgagccacg aggaacttgt  
3901 gagagggttt agggctctg agctgcaggc tttagaactgc tgattggggta tggcactgac  
3961 cttatccaca gctgtccaggc ctggatccca ccacagcgtc agggactgct tgcagagtca  
4021 cagatacgtt cagtttctca tcttgcttag ttctccttcc aggctaattt atttaataga  
4081 agacacctcg gtgacttggc tctttccaaa ataacataaa gtagtaaaaa taatgatagt  
4141 aaaataacaa tgccttcctt tggtaaacac tcttataatgat tgggtttctc atacatgctg  
4201 acttgacttt tacaacaccc attccctggag gcgagtggag aagttgttat tatccctatg  
4261 tcacagatga gcaaacaag gctctgcaag attgaatgtg gcccttagatc ggttaaggca  
4321 gggggctggg actagaactc taactgtgtt ccacaggcca tgggccttct catcttacc  
4381 cagatgtgtc tttgaaaaag nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
4441 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
4501 cacgttgaga atgacctggc ttcttcttgc ttccacagct cagacaaacg gtgggtggag  
4561 tgctggatgc gaaggaatca tgaaccctca cacggctctg cccacccac agcagctcct  
4621 ggccatcgag cagagtgtct acagtcaga tcccttcga cagggctca cccacccca  
4681 gatgccttgg aaccacatgc acccttatgg taagaggac ttaageccct cgggcctct  
4741 cataacttgt gtgggtttct cattccctcc taaacacatc taggcagttc ccagatgctc  
4801 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn  
4861 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn aaatgagtca cttttcaag  
4921 accctcatgc cagtgtttca tctccatttc aggtgccag cccctttcc atgacacttgc  
4981 tagcgacgac acctccctca gtaacctggg tgatgtttc ctagcaacct cagaagctgg  
5041 gcctctgcag tccagagtgg gaaacccat tgaccatctg tactccatgc agaattctta  
5101 cttcacatct tgagtcttcc cctagagttc tgtgactagg ctcccatatg gaacaaccat  
5161 attcttttag gggtcactgg cttaggaca gggaggccag ggaagagggtg gggtggggag  
5221 ggagtttgt 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 npdaaglps  
 61 asaaaavsaadf msnlsllees edfpqapgsv aaavaaaaaa aatggcgdf qgpeagclhp  
 121 appqpppppgp lsqhppvppa aagplaggpr kssssrrnaw gnlsyadlit kaiessaekr  
 181 ltlsqiywem vksvpfyfkdk gdsnssagwk nsirhnlslh skfirvqneg tgksswwmln  
 241 peggksgksp rrraasmmdnn skfaksrsra akkkasrlsqg qegagdsgps qfskwpspg  
 301 shsnddfdnw stfrprtssn astisgrlsp imteqddlge gdvhsmvypw saakmastlp  
 361 slseisnpen menlldnlnl lssptsltvs tqsspgtmmq qtpcysfapp ntslnspspn  
 421 yqkytyggss msplpqmpiq tlqdnkssyg gmsqyncapg llkelltsds pphndimtpv  
 481 dpgvaqpnsr vlgqnvmmgp nsvmstygsq ashnkmmnps shthpghaqq tsavngrplp  
 541 htvstmphts gmnrltqvkt pvqvlphpm qmsalggys vsscngygrm gllhqeklps  
 601 dldgmfierl dcldmesiern dlmdgdtldf nfdnvlpnqg 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 ggccgcaggct  
 121 ctgccccggc cccggcggctc tggccggccg tccagtcgtc gcggcggacc ccgaggagcc  
 181 tcgatgtgga tggcccccgcg aagttaaatgtt ctgggctcgc gtttccactc cgccgcgcct  
 241 tcctcccaagt ttccgtccgc tcgcccacc ggcttcgttc ccccaaatct cggaccgtcc  
 301 cttcgcgcgc cttcccgctc cggcccgatg gctgcgttct cccctcttg gctctctgc  
 361 ggctggggga gggggggggg tcaccatggc cgaggcgcct caggtggtgg agatcgaccc  
 421 ggacttcgag ccgctgcccc ggccgcgcgc gtgcacccgtt ccgctgccc ggccggagtt  
 481 tagccagtc aactcggcca cttccagccc ggccgcgtcg ggccagcgcgg ctgccaacccc  
 541 cgacgcgcgc gggggcctgc ctcggccctc ggctgcgcgt gtcaagcgcgcg acttcatgag  
 601 caacctgagc ttgctggagg agagcgagga cttcccgcaag ggcggccgtt ccgtggccgc  
 661 ggccggccgcg gggccggccgc cccggggggg ctgtgggggg acttccaggg  
 721 cccggaggcg ggctgcgtc acccagcgcgc accgcagccccc cccggccgcgg ggccgcgtgc  
 781 gcagcaccccg ccgggtgcccc ccgcgcgcgc tggccgcgtc gggggccagc cgccgcacag  
 841 cagctcgccc ccgcgcacacg cgtggggca cctgtccctac gcccgcctca tcaccaaggc  
 901 catcgagagc tcggcggaga agcggcgtcac gctgtcgacg atctacgagt ggtatggtaa  
 961 gagcgtgccc tacttcaagg ataagggtga cagcaacacgc tcggcgggctt ggaagaattc  
 1021 aattcgtcat aatctgtccc tacacagcaa gttcattcgt gtgcagaatg aaggaactgg  
 1081 aaaaagtctt tggtggatgc tcaatccaga gggtgtggcaag agcggggaaat ctccttaggag  
 1141 aagagctgca tccatggaca acaacagtaa atttgctaag agccgaagcc gagctgccaa  
 1201 gaagaaaagca tctctccagt ctggccaggaa ggggtgggg gacagccctg gatcacagtt

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1261 ttccaaatgg cctgcaagcc ctggctctca cagcaatgt gactttgata actggagtag  
1321 atttcgcctt cgaactagct caaatgctag tactattagt gggagactct caccattat  
1381 gaccgaacag gatgatctt gagaaggggg tttgcattct atgggttacc cgccatctgc  
1441 cgcaaagatg gcctctactt taaccagtct gtctgagata agcaatcccg aaaacatggaa  
1501 aaatctttt gataatctca accttctc atcacaaca tcattaactg tttcgaccca  
1561 gtcctcacct ggccacatga tgccggcagac gccgtgtac tcgtttgcgc caccaaac  
1621 cagtttgaat tcacccagcc caaactacca aaaatataca tatggccat ccagcatgag  
1681 ccctttgccc cagatgccta tacaaacact tcaggacaat aagtgcgagtt atggaggat  
1741 gagtcagtt aactgtgcgc ctggacttta gaaggagttt ctgacttctg actctccccc  
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1921 tcataacaaa atgatgatc ccagctccca tacccacccct ggacatgctc agcagacatc  
1981 tgcagttAAC gggcgcccc tggccacac ggtaagcacc atgccccaca cctcggttat  
2041 gaaccgcctg acccaagtga agacacctgt acaagtgcct ctgccccacc ccatgcagat  
2101 gagtgccctg gggggctact cctccgttag cagctgcaat ggctatggca gaatgggcct  
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2221 tgacatggaa tccatcatcc ggaatgaccc catggatggaa gatacattgg attttaactt  
2281 tgacaatgtg ttggccaaacc aaagcttccc acacagtgtc aagacaacga cacatgctg  
2341 ggtgtcaggc tgagggttag tgagcagggtt acactaaaaa gtacttcaga ttgtctgaca  
2401 gcaggaactg agagaagcag tccaaagatg tctttccatca actccctttt agttttcttgc  
2461 gttaaaaaaaaaaa aaaaacccctt cttttttcc ttgcgtcaga cttggcagca  
2521 aagacatttt tcctgtacag gatgtttgcc caatgtgtc aggttatgtg ctgctgtaga  
2581 taaggactgt gccattggaa atttcattac aatgaagtgc caaactcaact acaccatata  
2641 attgcagaaa agattttcag atctggtgt gtttcaagt ttgttatata aegcgttagat  
2701 acagattgtt ttttgtgtt ttttgggtt ttctaaatat ccaattggtc caaggaaatg  
2761 ttatactctt ttgttaatac tttgtatggc cttcatgtctt gataagttaa acttttgg  
2821 gtactacctg ttttgcggg aactgacggc tcacaaagaa ctgaatctcc attctgcatt  
2881 tccattgaac agccttggac ctgttcacgt tgccacagaa ttccatgtgaa aaccaagtag  
2941 cctgttatca atctgtaaa ttatggact ttgttaactt ttggaaaaaaa aaagattaa  
3001 tgccagctt gtacaggctt tttctatTTT ttttgggtt ttgttatTTT tgccaaatttgc  
3061 tacaaacatt taaatggttc taatttccag ataaatgatt ttgtatgtt ttgttgggg  
3121 ttaagaacat ttttggata gatattgaac tgtaataatg tttcttaaa actagagtct  
3181 actttgttac atagtcagct tgtaaattttt gtggaaaccac aggtatTTGG ggcagcatt  
3241 ataattttca ttttgttattc taactggatt agtactaatt ttatcatgtc ttaactgg  
3301 tgtacactttt gggatgctac ttgtatgtt ttctgactaa tcttaaatca ttgtatatt  
3361 tacttgcata ttcaacgtttt cagggccctgg ttggggcagga aagtgtatgtt tagttatgg  
3421 cactttgcgt ttcttattta ggataactta atatgtttt atgtatgtat tttaaagaaaa  
3481 ttccatgtc ttctactgaa ctatgcgtac tgcatagcat caagtcttct cttagacacc

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3541 ctgttagtcct gggaggcctc ataatgttg tagatcagaa aaggagatc tgcatctaaa  
3601 gcaatggtcc tttgtcaaac gagggatttt gatccacttc accatttga gttgagcttt  
3661 agcaaaaagtt tccccctata attcttgcctt cttgtttcag tccaggtgga ggttggttt  
3721 gtagttcgc cttgaggaat tatgtcaaca ctcataacttc atctcattct cccttctgcc  
3781 ctgcagatta gattacttag cacactgtgg aagtttaagt ggaaggaggg aatttaaaaa  
3841 tgggacttga gtggtttga gaatttgtt tcataagtgc agatgggttag caaatggaaat  
3901 agaacttact taaaaattgg ggagatttt ttgaaaacca gctgttaagtt gtgcatttag  
3961 attatgttaa aagccttggc ttaagaattt gaaaatttct ttagcctgta gcaacctaaa  
4021 ctgtatattcc tatcattatgt ttttattact ttccaatttac ctgtactgaa cagacacaaat  
4081 taattggctt tggccttat ttgcattttc agtattttca agtcatgtgg aaagccaaaa  
4141 gtcatacaca tgaagagaac aggtgcacag cactgttctt cttgtgttct tgagaaggat  
4201 ctaatttttc tggatatacg ccacatcaca cttgctttgt ctgtatgtt aattgcattt  
4261 tcattggctt ggtatttcctt aatgtttaa caagaacaca agtgttctg ataagatttc  
4321 ctacagtaag ccagcttat tggatgttc ccactgtgtt gatcattttt ttgaaaggattc  
4381 attgaacagc caccactcta tcattttcat tttggggcag tccaaagacat agctggttt  
4441 agaaacccaa gttcctctaa gcacagcctc ccgggtatgtt aactgaactt ggtgccaag  
4501 tacttgttgc ttaatttcta ttactacgtt ctgtactttt cttccgtgc cattactgca  
4561 tcataataca aggaacctca gagccccat ttgttcattt aagaggcaac tacagccaaa  
4621 atcaactgttta aaatcttactt acttcattttttt gtagcttta gggaaatata tcttcctcct  
4681 gagtctgggtt aatttataacctt ctccaaagcc cccattgtgtt gttgaaatcc tggatgtt  
4741 cttggtagc tctctgagaa cagtgaaatgc cagggaaagg catctggctt gttggaaag  
4801 caaacattttt gttggctctg gtagttttt tccgtttaaataa atactgactt tctggagtt  
4861 tgagttatata tcagtttattt tacatgattt ctttgtaaa tggcaatgtt atatcaccta  
4921 tggcagccctt gttgattttt tttctctgggtt ttgtactgtt attaaaagca tattgttattt  
4981 tagagctttt cagatattttt aaatataaaatg atgtattgtt tccgtttaat agacgtatgg  
5041 aatatattttt ggtatagat gtattacttg gaaagttctt ctttgacaaa ctgacaaatgt  
5101 ctaaatgagc acatgtatcc cagtgagcag taaatcaatg gaacatccca agaagaggat  
5161 aaggatgtt aaaaatggaaa tcattctcca acgtatataca aattggactt gttcaactgc  
5221 tggatataatg ctaccaataa ccccaagcccc aactttttt tcttacatttca aagcttctt  
5281 gagttcttaa tttataacta attttttttt agaagttttt tttctgggtt tagttggaa  
5341 ataatcatcc attaaaaaaa atgtttttt gtttgcgttgc acagaccaac ctggcatttt  
5401 agttggcctc tccttgaggt gggcacagcc tggcagtgtt ggcagggtt ggcacatgtt  
5461 tcccatcagg acgttagtcat gcctcctgca tttcgctacc cgagtttagt aacagtgcag  
5521 attccacgtt tttgttccga tactctgaga agtgcctgtt gttgatgttac ttacagacac  
5581 aagaacaatc tttgttataa ttgttataaag ccataatgtt acataaattttt ttttttttt  
5641 gttgggttgc tttttttttt aattatgcag aataagctt ttataggaa tttttttttt  
5701 agcttataaa tacttgatgtt aagtcttgcg aaccacaa

**[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 lalkeaagaa 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 gtcggccggcc gccatggca  
 361 gcccgtctggg caacatgagc gccccgtcca tgaacatgtc gtcgtacgtg ggcgtctggca  
 421 tgagccccgtc cctggggggg atgtcccccgc ggcggggggc catggggggc atggggggc  
 481 cggccggggc ggccggcggt gccccgtgg ggcggcactt gagtcccagc ctgagccgc  
 541 tcggggggca ggcggccggg gcatggggc gcctggggcc ctacgccaac atgaactcca  
 601 tgagccccat gtacgggcag gccccgtga 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 ttccctgaag gtggccgtg cggccgacaa gcccggcaag ggctccctct  
 901 ggaccctgca ccctgactcg ggcaacatgt tcgagaacgg ctgctacctg cccggccaga  
 961 agcgcttcaa gtgcgagaag cagctggcgc tgaaggaggc cgcaggcgcc 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 ctggcccg  
 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 aaaaaaaaaa 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 atgksswwml
181 npeggksgka prrraasmgs sskllrgrsk apkkkpsvlp appegatpts pvghfakwsg
241 spcsrnreea dmwtfrprs ssnassvstr lsplrpesev laeeipasvs syaggvpvtl
301 neglelldgl nltsshslls rsglsgfsdq hpgvtgplht yssslfsepae gplsagegcf
361 ssssqaleall 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 cgttcggtga 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 gagggggaggc atcgtgaggg actgtggcg gcttcactga acgctgagcc  
361 ggggaggctt aactccacgt atggatccgg ggaatgagaa ttcagccaca gaggtgtccg  
421 cgatcataga cctagatccc gacttgcgac cccagagccg tcccgctcc tgcacctggc  
481 ccottccccg accagagatc gctaaccagc cgtccgagcc goccgagggtg gagccagatc  
541 tggggaaaaa ggtacacacg gaggggcgct 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 gccaccggca  
901 aaagcttgcgtg aaccctgagg gaggcaagag cggcaagcc cccggccgccc  
961 gggccgcctc catggatagc agcagcaagc tgctccgggg ccgcagtaaa gcggccaaaga  
1021 agaaaccatc tggctgcca gctccacccg aagggtgccc tccaaacggc cctgtcgccc  
1081 actttgcca gttggctaggc agcccttgcgt ctcgaaaccg tgaagaagcc gatatgtgga  
1141 ccaccttccg tccacgaaatc agttcaaattt ccagcagtgtt cagcaccggc ctgtccccct  
1201 tgaggccaga gtctgaggtg ctggggaggaa aataccagc ttcaagtgcg agttatgcg  
1261 ggggtgtccc tccacccctc aatgaaggcgc tagagctgtt agatgggctc aatctcacct  
1321 cttccattc cctgctatct cggagtggc tctctggcctt ctcttgcag catctgggg  
1381 ttaccggccc cttacacacc tacagcagctt ccctttcag cccagcagag ggcccccgt  
1441 cagcaggaga agggtgcttc tccagctccc aggctctggg ggcctgctc acctctgata  
1501 cggccaccacc ccctgtgac gtcctcatga cccaggtaga tccattctg tccaggcgtc  
1561 cgactttctt gttgtgggg gggcttcctt cttccagtaa gttggccacg ggcgtcgccc  
1621 tgtgtccca gcccctagag gtcaggccg ccagcgtt ggtcccacc cttttatga  
1681 tagcaccacc tccagtcgt gcaagtgcgc ccattccaa ggctctgggg actcttgtgc  
1741 tcacacccct tactgaagct gcaagccaaag acagaatgcc tcaggatcta gatcttgata  
1801 tgttatatggaa gacacctgggatgtgacatgg ataacatcat cagtgacccctc atggatgagg  
1861 ggcggggact ggacttcaac tttgagccag atccctgagt catgcctggg agctttgtcc  
1921 cctgcttcag atgtggagcc aggctgttccatcttacccttgc agccctcccc  
1981 aggaatttgg gaccctgtt tagagctagg gtggggctgt gtcacacaca ggtgttgaag  
2041 aaattataaa gataaaagctg ccccatctgg ggacgatatg gggaggggaga tgggggggg  
2101 aaggggagag gtttttctc actgtgccaat ttagggggta agggcccttc tcaggagcc  
2161 tcatcggtt tcccttattcc tacccactta ggctttgttcaagatgagc aatctgttg  
2221 gaaatgtgaa gtcaccagtg gccttacccc tgccttggg agcaggattt tttttagag  
2281 agtcttatctt gagctgagcc aggctagctg gagctgtgggat tttctatgca gtggccctt  
2341 aggccagtgatgtgatgtggggatctt ggaaggccaa aggtctgagc  
2401 actggagtggtt ctcggccagcc caaatcaccc tttagaaggctt gcaagataaca gaaaggctt  
2461 ttataaaactt taaaagaaat ataaacacaa atatagagat ttttaacca 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 aggatggtaa agttaggtac agagacctcc
2941 ctgttcaagg cccctgacag ctgtccctgc ctttcttccc cttccctgac tgcaaaaaaa
3001 atgtgaaagt gtgtgtggca gcaggcageg gggagggggag gaacaggaa gggggagctg
3061 gggagcttgg ctgagggctt gggaaatgag cagggatggg gggggatgtg gatcaggtt
3121 actagcacct gccaggaggagg ccatactgggg ctcccttcacc ccccaagcccc ccaaaggcagc
3181 cttccccca gtgccttttgcatgtcccc tcccccaccc ctgctgtggg ttcccatcat
3241 ttccctgtgtc agcgccctggc ctaccatgt tgtatcatgt gctagattgg agtggggaaag
3301 tgtgtcaaataatga 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 elqfpf1qde dtvatlleck tlfilrg1pg
61 sgkstlarvi vdkyrdgtkm vsadaykitp garga seey krl dedlaay crrrdirilv
121 lddtnherer leqlfemadq yqyqvvlvep ktawrldcaq lkekknqwqls addlkk1kpg
181 lekdflplyf gwfltkksse tlrkagqvfl eelgnhkafk kelrqfvpgd eprekmdlvt
241 yfgkrppgvl hcttkfcdyg kapgaeeyaq qdvlkksysk aftltisalf vtpkttgarv
301 elseqqqlqlw psdvdkspt dnlprgsrah itlgcaadv avqtgldl ilrqekggsr
361 geevvgelsrg klyslngrw mltlakrnmev rai ftgyygg gkp vptqgsr 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)

```

1 ctccgcgcag ggggggggcc cgggagcgct ggtgcggca gaggcggcga cggcggcgcc
61 cttccctatc atgaggcttc tccggaaaaa gccacacatt cctgcccag atcttctcc
121 gcaagatgtc atcctcagg gccaaggaca agcctgagct gcagttccc ttccctcagg
181 atgaggacac agtggccacg ctgctagat gcaagacgct cttcatcttgc cgccgcctgc
241 caggaagcgg caagtccacg ctggcacggg tcatcgtggca aagtaaccgt gatggcacca
301 agatgggtgc ggctgacgct tacaagatca cccccggcgc tegaggagcc ttctccgagg
361 agtacaagcg gctcgatgag gacctggctg cctactgccc cggccggac atcagaattc
421 ttgtgcttga tgacaccaac cacgaacggg aacggctgg aca gctcttt gaaatggccg

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481 accagtagcca gtaccagggtg gtgctgggtgg agcccaagac ggcgtggcgg ctggactgtg  
541 cccagctcaa ggagaagaac cagtggcagc tgtcggtga tgacctgaag aagctgaagc  
601 ctgggctgga gaaggacttc ctggcgtct acttcggctg gttcctgacc aagaagagct  
661 ctgagaccct ccgcaaagcc 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 cctcggctgt gcagctgacg  
1081 tagaggccgt gcagacgggc cttgacctct tagagattct gggcaggag aagggggggca  
1141 gcccggcga ggaggtgggc gagctaagcc gggcaagct ctattccttgg gcaatgggc  
1201 gctggatgtg gaccctggcc aagaacatgg aggtcaggcc catcttcacg gggtaactacg  
1261 ggaaaggcaa acctgtgccc acgcaaggta gcccggagg gggcgccttg cagtcctgca  
1321 ccatcatatg agtgttctca ccaccactta tgcccctaga agggaaagggg agagggaaac  
1381 gtgcctctg tttgatcctt gttttgtgac attttttttt ttttttttt tactcaaagt  
1441 taacctacatgt gtaactttttt aaaaacttgt aaaataactg accctccctt cctgtccgccc  
1501 ctcttcctt ctaatgtca cgctccaaac acaagggtggg caggaggca ccattcagga  
1561 acctggacca aagctgacga ggctgggcca agccaggat gggccacag ccagaacccc  
1621 gagccctact tccaggttct ggttagctca gccccagccc agcccagctg ctctgcccag  
1681 agctgggtga gtggggagac acctcagac cccgaaaccc ccactgaccg gaggcaaaag  
1741 gcaactggggc tgggggttagt tttccatggt cacagagaac tagtgggtggc tctgagaagg  
1801 ggaggacactc tgggcttga ttccatctcc ttgtctttt tcttttttt tagagacagg  
1861 gtccctgtat ttcccaagct ggagtgcagt ggtgcgtca tggctcaactg cagcctcgaa  
1921 ctcctgggtca agcaatcc tcctgagtga tcccattttt taatcagtgt agccccaaaga  
1981 aggctggggc tatttaccag ggtaaaaaa ggagcttacc tcccacctt ggtcttaagt  
2041 ccctgcccccc tccccttcac accataacta ggtaacagtt tgataacttag ggaagaaagc  
2101 agaacagtttta agcagccgc acatccccgc tggctggggg cctcaactcca ggaaggggct  
2161 ggactggctg tccttccag tggcctggct ccgctgtgtg gatggggaga tcggggccag  
2221 aggcagaacc ctggtgagga agctccagtc ctgcctctca cccagcccat ctgcctcca  
2281 tggtgccctt ggaggcctct ggcctccctt taacaggggc tggtgccac caagagccaa  
2341 tggagtagac ccctggctgg taaggccaa gtcacccggg ttgcttctgg gaaggggttt  
2401 ctaacactag tctgtgtgt gtggttccctg ggggtccctc cactgcctc tggcttgc  
2461 cagggccctt ctaatcggt tgcactcaa caaaagtgtt ttggattttt gttactatcc  
2521 tggctttggc caacctcagc aacctgtaag actgataatg aaataaatca 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 gdrgapkrks gkdshhpart ahygslpqks hgrtqdenpv vhffknivtp rtpppsqgkg  
241 rglslsrfsw gaegqrpgfg yggrasdyks ahkgfkgvda qgtlskifkl ggrdsrsqgsp  
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 gaaaacagtgcagccaccccgagagcctgtatgtatggcgtcacagaa gagaccctcc  
61 cagaggcactgatccaagta cctggccaca gcaagtacca tggaccatgc caggcatggc  
121 ttccctccaa ggcacagaga cacgggcata ctggactcca tcggcgctt cttggcggt  
181 gacaggggtgcgcggctctggcaaggactcac accacccggcaagaactgct  
241 cactatggctccctggccaaaggatcacacggccggaccc aagataaaa cccctgatgc  
301 cacttttca agaacattgt gacgcctcgacaccacccc cgtcgaggg aaaggggaga  
361 ggactgtccc tgagcagatt tagctggggg gccgaaggcc agagaccagg atttggctac  
421 ggaggcagag cgtcggactataaatcggtcacaaggat tcaaggagt cgatgccag  
481 ggcacgcttccaaaatttttaagctgggagaagagata gtcgcgtctgg atcaccatg  
541 gctagacgct gaaaacccac ctgggtccgg aatcctgtcc tcagtttcaaataactg  
601 ccttaaactttaatcccac ttgcctctgt tacctaatta gaggcagatga ccctcccc  
661 aatgcctgcggagttgtgcacgttaggg tcaggccacgcacgcctacc ggcaatttcc  
721 gcccacacgttaaatggaaaacatggaaaaca gaaaacggttaaaactgtcccttctgtgt  
781 gaagatcacttgcctcccgcaatgtgc cccagacgc acgtgggtcttcaggggcc  
841 aggtgcacacgacgtccctccacgttcacccctccacccggacttttttcttcggctgtgg  
901 ctggcacccttgcgtttttgtggactactggatgggggggggggggggggggggggggggg  
961 gggacgtggcggcagaga ggactgttgacatcaagcttcctttttttctgtgtgtgtgt  
1021 tctttcttcaccccttt  
1081 tgggttactacatgtgggagctttttgtatgtgacatgcgggtggcagtttttttttttttt  
1141 gtccaaacgtggcagcaca gagagggggc caccctccca ggccgtggctccacacac  
1201 cccaaatttgc tgaattcgcgtgtggcagaggggggggggggggggggggggggggggg  
1261 aatggcctca catagggaaac agggcttccatggatggatgtatggaga tgcacggc  
1321 tggccctctggacgtccacggttgcctgcatggggcccaagggcgcctctatgaacaa  
1381 cctcggttccaaaccacgcgcacagccggagacttcagg aagacttgcg cactcagagc  
1441 agaagggttag gactctcta gacgcctcg cagccgcgcctgcgtggccat agacactggc  
1501 tgtgaccggg cgtgtggca gggcagtgcaagttggccatggactaaccctccctgagaa  
1561 gataaccgggtcattacttccctccaa gacggcggtgttggcgtggcactaaccctccct

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1621 cacctgtcc cgaattactc accgagacac acgggctgag cagacggccc ctgtatgga
1681 gacaaagaga tcttctgacc atatccttct taacacccgc tggcatctcc ttgcgcct
1741 ccctccctaa cctactgacc cacctttga ttttagcgca cctgtgattt ataggccttc
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 tgaatatttga aataaaacaa taaactttt

```

**[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

```

**[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.

```

(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 gaaccatggg cagtgccgc tcaggggcct ttggacatct
301 cttcaggccct gacaatttca tctttggtca gagtgccggc ggcaacaact gggcaaggg
361 tcactacacg gagggggccgg agctgggtgg ttcggccctg gatgtgggtgc ggaaggagtg
421 taaaaactgc gactgcctgc agggcttcca gctgaccac tcgctggggg gccgcacccgg
481 ctccggcatg ggcacgttgc tcatcagcaa ggtgcgtgag gagtatcccg accgcacatcat
541 gaacacccatc agcgtcgatc cctccatccaa ggtgtcagac acgggtgggg agccctacaa
601 cgccacgctg tccatccacc agctgggtgg aacacccggat gagacctact gcatcgacaa
661 cgaggcgctc tacgacatct gcttccgcac cctcaagctg gccacgccc cctacgggg
721 cctcaaccac ctggatcgcc accatcgag cggagtcacc acctccctgc gcttccgggg
781 ccagctcaac gctgacactgc gcaagctggc cgtcaacatg gtgccttcc cgccgtcgca

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841 cttcttcatg cccgggttcg cccccctcac agcccggggc agccagcagt accggggcct
901 gaccgtgccg gagctcaccc agcagatgtt cgatgccaag aacatgtatgg ccgcctgcga
961 cccgcgcac ggccgttacc tgacgtggc caccgtgttc cggggccgca tgcgtccatgaa
1021 ggaggtggac gagcagatgc tggecatecca gagaagaaac agcagctact tcgtggagtg
1081 gatccccaaac aacgtgaagg tgccgtgtg tgacatccc ccccgccggcc tcaagatgtc
1141 ctccacccctc atcgggaaca gcacggccat ccaggagctg ttcaagcgca tctccgagca
1201 gttcacggcc atgttccggc gcaaggcctt cctgcactgg tacacggggcg agggcatgg
1261 cgagatggag ttcacccgagg ccgagagcaa catgaacgcac ctggtgtccg agtaccagca
1321 gtaccaggac gccacggcccg aggaagaggg cgagatgtac gaagacgacg aggaggagtc
1381 ggaggcccaag ggccccaagt gaagctgctc gcagctggag tgagaggcag gtggggccg
1441 gggccgaagg cagcagtgtc taaacccccc gagccatctt gtcggccaca ccctgttttc
1501 ccctcgccct agggctccct tgccgcccctc ctgcagtatt tatggcctcg tcctccccac
1561 ctaggccacg tgtgagctgc tcctgtctct gtcttattgc agctccaggc ctgacgtttt
1621 acggttttgt ttttactgg tttgtgtta tatttcggg gatacttaat aaatctattg
1681 ctgtcagata cccttaaaaa 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 maqpypppaqy ppppqngipa eyapppphpq qdysqqtpvp tehgmtlytp aqthpeqpqgs
61 eastqpiagt qtvpqtddeaa 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

```

**[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 gctctctctc tctgactctc tcctctctct ctgtggcct ggtgaaatgt
121 tcttggctgt aggcacacag agccttggac tcaaggctgt tggagtgcag gacacctgt
181 ctccggctct ggagggtgaa attctgcctc tgagaagcta acagtcttcc tgggttcgccc
241 actccctccc agcagcccccc tccttgcctaa ggacggtccca gaaggagccc cactggggcc
301 tccccgtca gcaaaggcaga cctcacccctc cactaccacg ttgaagtcaac agcagccaga
361 gggaaattctg ccaccatctt cccaggtctg cagccccctcc 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 cccgacttgcg 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 tatggctg agatttatgg aggctacgca  
1321 gcttacagat acgctcagcc cgctgcagcg gggcagcc acagcgacag ttacggcaga  
1381 gtctacgcag ctgcccaccc gtaccatcac accatcgggc cccggccgac ctacagcatt  
1441 ggaaccatgt gaaacccccc accgtttcc ttcggacca tgaaggccaa aaacaaaaaaaa  
1501 aaaaaaaaaa tcacaaaaca aaaaaaaca aaaaagatgt taagatccaa gcaaaaaaaaa  
1561 aaaaaccaac caaaccacaa ggcattcaac caagtccaa tcccgcttcc tgccacacg  
1621 cccgcacccga gggagcacgc cggcaggggc gccgaggacg ggcggccagga caggacggcc  
1681 ccaccgcgtc ctggctggca gcacagtggg aacacgcccc tccgtctcag gcagtggggg  
1741 agttggggg gaagggggcct cccttgggg acccgtgggg ggctctgttt tccatccagt  
1801 cttcccttcc cagccccca ctcccaagac agacagtgtg gagccccagcg gggggggagc  
1861 aggccccggc ctgagccaggc 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 ggaaggccag  
2161 ccagccagga gccactccctc acaectccaa gtgtggccaa gtggggccctg aggccaaggaa  
2221 cttacttgct cttccctggcc atctctccct ttctggagga ggcggggggc ctgtgtacac  
2281 caaggctgac ctcgtgtcgc ctgtggac ccagccctcc ctgcgcgtcc cctgtgagcc  
2341 cagtccaccc tggggcccca gggccaggga cggggccagcg cccggctgca tcgcgagggtt  
2401 gggagtcaca gtggctgtgg gcctggacgg gcacagccag agcaggggcc catgggaagg  
2461 gcaaggatg gggaaagccctg gggggggccc ttcctgtctc ccaaggccagg tgtccaggt  
2521 gcgggagccag caccaaggac agccaggctt acccgggtggg aggagccagg gcagagccagg  
2581 tggcagggag gaacccctgg cgaggcaggc agcactgaag tagggaaagca gcaaaaaata  
2641 caggctccca acgtggctcc actgtctcat gaagtgtcaa aaatttaaaa atacacccatca  
2701 ctttctattc agcatcagct attgaaatgg aattctccctt ttcttattccctt gtgtacata  
2761 gccccacgccc ctgcctccgg ctttgcctcc tgcacagagc 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 caaaccagga 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 veacfqkfkt 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

```

**[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.

```

(SEQ ID NO: 26)
1 ggcatacgcc gtcccggtc cgccgggtg cctccacggt ccggccccg cgccgggtct
61 gcacagtccc tggcggtcc ccggggccccc ggccggggccg ttccggccggc tccggctccct
121 gcatccgggc gcagcgcgcgca ggcegaggg cgccgcaggcc 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 atccctctgc tttagccctt tgtagtagcta ggactacagg cacaggccac cgtgcctggc
481 taatttttaa tttttaaaaa agagacaggg tctggctatg ttgcccaggc tggccatgaa
541 ctccctggct caagcggttc tccagccctc acctcccaaa 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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**[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 vspqaepvwtt ppapapaapp stpaapkrrg
181 ssgsvdetlf alpaasepvi rsssaenmdlk 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 eeseatppspv lpdivmearpl 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 ggccatcac
121 cggcgccggag gcaggaggag cagtcattt gttccgggg 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 tgaggagcc cgaggacgag gaggaagaag aggaggagga
421 agaggaggac gaggacgaaag acctggagga gctggaggtt ctggagagga agccgcgcgc
481 cgggctgtcc cggggcccaag tgcccaccgc ccctggccggc ggcgcgcggcc ttatggactt
541 cggaaatgac ttctgtccgc cggcccccgg gggacccctg ccggccgcctc ccccccgtcgc
601 cccggagccgg cagccgtctt gggaccccgag cccgggtgtcg tccgaccgtgc ccgcgcgcac

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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 ttttcgtgc gcatctgagc ctgtgatacg  
901 ctccctgtca gaaaatatgg acttgaagga gcagccaggt aacactattt cggctggta  
961 agaggatttccatctgtcc tgcttgcac tgctgtttctc tgtctctct  
1021 ctcagccgtcttcaaag aacatgaata ccttggtaat ttgtcaacag tattacccac  
1081 tgaaggaaca cttcaagaaa atgtcagtga agcttctaaa gaggtctcag agaaggcaaa  
1141 aactctactc atagatagag atttacaga gtttcagaa tttagaatact cagaaatggg  
1201 atcatcggttc agtgtctctc caaaagcaga atctgcgttca atagtagcaa 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 ccagtcgc aagatgttca aaggatcgat 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 gtaaggaaag catgtgaaag  
1981 tgaattgtt gaaatgtt gtcataatgat tgcattatgaa aaaaaatgg acttgggtca  
2041 aacatcagaa gttatgcaag agtcaactta tcctgcgtca cagcttgc catcatttga  
2101 agagtcagaa gtcactcctt caccatgtt gcctgacattt gttatggaa caccattgaa  
2161 ttctgcagtt cctagtgctg gtgttccgt gatacagcccg agctcatcac cattagaagc  
2221 ttcttcagtt aattatgaaa gcataaaaca tgagcctgaa aaccccccac catatgaaga  
2281 ggccatgatgtatcactaa aaaaagtatc aggaataaag gaagaaatta aagagcctgaa  
2341 aaatattaaat gcagcttcc aagaaacaga agctccttat atatctattt catgtgattt  
2401 aattaaagaa acaaagcttt ctgctgaacc agctccggat ttctctgatt attcagaaat  
2461 ggccaaatgtt gaacagccag tgcctgatca ttctgagctt gttgaagatt cctcacctgaa  
2521 ttctgaaacca gttgactttaat ttagtgcattt ttcaataatctt gacgttccac aaaaacaaga  
2581 tgaaactgtt gtcgttgc gaaatgtt cactgagact tcattttgatgtt caatgtatgaa  
2641 atatgaaat aaggaaaaac tcagtcattt gccacctgag ggagggaaagc catatggaa  
2701 atcttttaag ctcagtttag ataacacaaa agataccctg ttacctgatg aagtttcaac  
2761 attgagcaaa aaggagaaaaa ttcccttgc gatggaggag ctcagttactg cagtttattt  
2821 aatgtatgac ttatattttt ctaaggaagc acagataaga gaaactgaaa cgtttcaga  
2881 ttccatctcca attgaaatata tagatgatgtt ccctacatttgc atcagttctca aactgattt  
2941 attttctaaa ttagccagg aatataactga cctagaagta tcccacaaaaa gtgaaattgc

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3001 taatgccccg gatggagctg ggtcattgcc ttgcacagaa ttgcggccatg accttttctt  
3061 gaagaacata caacccaaag ttgaagagaa aatcagttc tcagatgact tttctaaaaa  
3121 tgggtctgct acatcaaagg tgctcttatt gcctccagat gtttctgctt tggccactca  
3181 agcagagata gagagcatag ttaaacccaa agttcttgtg aaagaagctg agaaaaaaact  
3241 tccttccat acagaaaaag aggacagatc accatctgct atattttag cagagcttag  
3301 taaaacttca gttgttgacc tcctgtactg gagagacatt aagaagactg gagttggttt  
3361 tgggccagc ctattctgc tgctttcatt gacagtattc agcattgtga gcgttaacagc  
3421 ctacattgcc ttggccctgc tctctgtgac catagcttt aggtatatac agggtgtgtat  
3481 ccaagctatc cagaaatcg atgaaggcca cccattcagg gcataatctgg aatctgaagat  
3541 tgcttatatct gaggagttgg ttcaagaagta cagtaattct gctttggtc atgtgaactg  
3601 cacgataaaag gaactcaggc gccttctt agttgtatgt ttagttgatt ctctgaagtt  
3661 tgcagtggtt atgtgggtat ttacctatgt tggtgcctt ttaatggtc tgacactact  
3721 gatttggct ctcatattc tcttcagtgt tcctgttatt tatgaacggc atcaggcaca  
3781 gatagatcat tatctaggac ttgcaaataa gaatgttaaa gatgctatgg ctaaaatccaa  
3841 agaaaaatc cctggattga agcgaaagc tgaataaaa cgccaaaaat aatttagtagg  
3901 agttcatctt taaaggggat attcatttga ttatacgggg gagggtcagg gaagaacgaa  
3961 ctttgacgtt gcagtgcagt ttcacagatc gtgttagat ctttattttt agccatgcac  
4021 tgtttgagg aaaaattacc tgcattttactt gcatgtgtt catcatctt agtattgtaa  
4081 gctgctatgt atggatttaa accgtaatca tatcttttc ctatctatct gggcactgg  
4141 tggataaaaa aacctgtata ttttactttt tgccagatag tcttgccgca tcttggcaag  
4201 ttgcagagat ggtggagcta gaaaaaaaaa aaaaaaaagcc ctttcagtt tggtcactgt  
4261 gtaggtccg ttagattga tgcagatttt ctgaaatgaa atgtttgtt agacgagatc  
4321 ataccggtaa agcaggaatg acaaagctt ctttctggt atgttctagg tggatgtgaa  
4381 ctttactgt tatattaatt gccaatataa gtaaatatag attatatatgt tatagtgtt  
4441 cacaagctt agacctttac cttccagcccccacagtg cttgatattt cagagtcagt  
4501 cattggttat acatgtgttag ttccaaagca cataagctg aagaagaaa atttcttagga  
4561 gcactaccat ctgtttcaa catgaaatgc cacacacata gaaactccaaatcataatttca  
4621 ttgcacagac tgactgttagt taatttgtc acagaatcta tggactgaat ctaatgttcc  
4681 caaaaatgtt gtttgggttgc aaatataaaa cattgtttagt caagaaatta ttaattacaa  
4741 aatgaagatt tataccattt ggggttaagc tgcactgaac taaatctgtg gaatgcattt  
4801 tgaactgtaa aagccaaagta tcaataaaagc ttatagactt aaaaaaaaaa aaaaaaaaaa  
4861 aaaaaaaaaa a

[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 navpgttmlrp qrpgdlqlga slyelvgyrq ppsssssts stsstsssst  
61 tapllpkaar ekpeapaapepp gpqpgsqahp 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 cccccaggcg 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 cacccttc  
 1081 cccggcccca cccctggac gttaaagtga ccagagccgaa tgttcgatgg cgcctcgcc  
 1141 cagttttgggg ttctgggtcg gttccagccg ctttaggcag aaagtgcctcg ctctcacca  
 1201 gcaatatctt ctccctgtcc ctggagttgc ggcgttcggc gggccgatgt agaactttag  
 1261 ggccttcgcg gtcggggccgc cggccggggc gcagccgcagg gccatccccg agcgctaccc  
 1321 cccggagcg ggcacgcgcg gtcggccatc ctggggctgc cgctcgagca gtggccgggg  
 1381 cgggggggtg gttttttcc ttcttcctccg ccagaggccg cggccgcgcctc tgttccggcc  
 1441 ggccagggtcc tatcaaagga ggctgcgcgc actcaagagg cagaaaaaga ccagtttag  
 1501 ggtgcagacg gtcggggacg tggcagacgg acggaccctc ggcggccagg tggtccggcg  
 1561 cgggggtgcgg tggtagggg 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 ggcgtctgtt 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

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**[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.

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(SEQ ID NO: 32)
1 gggtgcttat tataatcgaa cgccgacacca gcccgggtt ccaggcttc ccctgaggct
61 ttccggagcg agtcctcaa atcgcatcca gagtaagtgt ccccgccccca cagcagccgc
121 agecttagatc ccaggacacg acttcctca actccgtgt gaccggaaat gctccgatac
181 agggggtctg gatccctact ctgcgggcca tttctccaga ggcactttgc tcttctgtcc
241 tccccacact caccgtgca tctccctcaaa caaaaggcgg aagtccggac gacaacagct
301 ctttctgccc aagccccagt cagctggta gctccccgtt gttccagat gcaacacatg
361 gactctgggc cccgcggccgg ctctgggtgc atgtcggtgt gctgtgttt gctgtgtgtt
421 gtccatggag ataagggtgga tccgttttaga gaaccaaatac attagttctc tatttagatc
481 tccattctcc ccaaagaaag gcccactt cccactcggtt tattccagcc cgggggctca
541 gttttccac acctaactga aagccccggaa cctctagaat gcccacccgca ccccgagggt
601 caccaacgcg ccctgaaata acctgttgc tgagagcaga ggggagatag agagagctta
661 attataggta cccgcgtgca gctaaaaggaa gggccagaga tagtagcgag ggggacgagg
721 agccacgggc cacctgtgca gggaccccgca gctgtggatc tgccgtgcag gccccggcc
781 cttttctgtc tctcaactgac tcactcttc tctctctccc tctctcttc tctcatttc
841 tctctttctt cctccctctcc tggaaagttt cgggtccggag ggaaggagga ccctgcgaaa
901 gctgcgacga ctatctccc ctggggccat ggactcggac gccagcctgg tgcgtccggcc
961 cccgtcgctcg ccagagcccg atgacctttt tctgcggcc cggagtaagg gcagcagccg

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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 gcaagcgcatt gcacgcaccc aacatgcaca tggatggcct  
1321 ccgcgaggtc atgcgcgtacg cacacggccc ttccggtgccg aagcttcca agatgcgcac  
1381 gctgctgtc ggcgcgaaact acatccat gtcaccaacat tcgtggagg agatgaagcg  
1441 actggtgagc gagatctacg ggggcacca cgcgtggcttc cacccgtcg cctgcggccgg  
1501 cctggcgacac tccgcgcaccc tgccgcgcgc caccgcgcac ccggcagcagc cagcgcacgc  
1561 cgcacatcac cccgcgggtgc accacccat cctgcgcgc ggcgcgcag cggctgtgc  
1621 cggcgctgc ggcgcggctg tgccgcgcgc ctctctgcgc ggatccgggc tgccgtcggt  
1681 cggctccatc cgtccaccgc acggctact caagtctccg tctgtgcgc cggccggcccc  
1741 gctggggggc gggggggcg gcaagtggggc gagcggggggc ttccagact gggggggcat  
1801 gcccgtcccc tgcagcatgt gccaggtgcc gcccgcgcac caccacgtgt cggctatggg  
1861 cgcggcagc ctgcgcgcgc tcacccatc cgcacactgta ggcgtactggc gcccgcgcgt  
1921 tctggcgaca ggggagccag gggccgcggg gaagcgagga ctggcctgcg ctggcctcg  
1981 gagctctgtc gcgaggaggg ggcaggacc atggactggg ggtggggcat ggtggggatt  
2041 tcagcatctg cgaacccaag caatggggc gcccacagag cagtgggag tgaggggatg  
2101 ttctctccgg gacctgatcg agcgctgtct ggcgtttacc tgagctggc cagtagacat  
2161 cgttttatgaa aaggtaacc ctgtgtgcatt tcctcacttag aactcatccg acccccgacc  
2221 cccacccctcg ggaaaagatt ctaaaaactt cttccctga gagcgtggcc tgactgcag  
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 tgtagtttattt attttaaaat agaaactacc ccacccactc atctttccctt  
2761 ctctaagcac aaagtattttt ggttattttt gtacactgaga acgttaacaga attaaaaggc  
2821 agttgtgtg gaaacagttt gggttattttt ggggttctgt tggctttta aaattttttt  
2881 ttgtgtgtt gtaaaattttt caatgtatgatgatgatgatgatgatgatgatgatgat  
2941 cgtgactgcc agcccatcg gagtcataac cggcttcctt ctatgggtt ttatgggtt  
3001 cacgttaac acaaatggta aactccctcca cgtgtttccctt ggttccgtg caagccgcct  
3061 cggcgctgc tgcgttgc aactgggtttt gtacccgttgc ccgtgtaaaca cccttcctt  
3121 gatcgacccg cccctcgac agatgtatc atctgttttta tttttgtaaa aacaaagtgc  
3181 taaaataat ttattactt tttgggttgc aaaaacggaaat aaatgtactga gtgtttagat  
3241 tttaaataaa atttaagca aaaaaaaaaaaaaaaa aaaaa

**[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
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**[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 ggctgcc

**[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 gtgttaagctg actggcccca gggactctt ttaacagtaa cttaggagtc aggtctcagt  
 661 gataaagcgt gcacccgtgca gcccggcatg gccgtgtaga ccctaaccgg gagggaaccc  
 721 tgactacaga aattaccccg gggcacccctt aaaacttcca ctacctttaa aaaacaaagc  
 781 cttatccagc attatttggaa aacactgtcg ttctttaaat gcttccatca tccatgcaga  
 841 taacagctgg ttggccggtg tgccctgtca agggcgtgtt ggcttccggcc 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 cggagggtggaa gctgagccccc gtgggctcg aggagccccc ctgcctgtcc ccggggagcg  
 361 cgcctcgct agggcccgac ggccggccggc gccgatcggt cctgcgagcc agcccgggc  
 421 caggcgagct gggcaaggc aagaaggc acgaggaccc cgaggccggac gatgacaagt  
 481 tccccgtgtg catccgcgag gccgtcagecc aggtgctcag cggctacgac tggacgctgg  
 541 tgcccatgcc cgtgcgcgctc aacggcgcca gcaaaagcaa gccgcacgctc aagcggccca  
 601 tgaacgcctt catgggtgtgg gctcaggcag cgccgcaggaa gctcgcggac cagtaaccgc  
 661 acctgcacaaa cgctgagctc agcaagacgc tggcaagct ctggaggctg ctgaacgaaa  
 721 gtgacaagcg ccccttcatac gaggaggctg agcggctccg tatgcagcac aagaaagacc  
 781 acccggaacta caagtaccag cccaggccgc ggaagaacgg gaaggccgcc 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 gacccgaagg gggacggccg ctccatgggg gagggcggg  
 1081 agccctcacat cgacttcggc aacgtggaca ttggtgagat cagccacgag gtaatgtcca  
 1141 acatggagac ctttgatgtg gctgagttgg accagtcaccc gccgcctaat gggcaccagg  
 1201 gccatgttag cagtcactca gcagccggct atgggctggg cagtgccctg gccgtggcca  
 1261 gtggacactc cgcttggatc tccaagccac caggcgtggc tctgcccacg gtctcaccac  
 1321 ctgggtgtggaa tgccaaagcc caggtgaaga cagagaccgc ggggccccag gggccccac  
 1381 actacaccga ccagccatcc acctcacaga tcgcctacac ctccctcagc ctgccccact  
 1441 atggctcagc cttccctcc atctccgc cccagtttgta ctactctgac catcagccct  
 1501 caggacccta ttatggccac tggggccagg cctctggctt ctactcggcc ttctctata  
 1561 tggggccctc cagccggccc ctctcacccgg ccacatctgtc cccacccccc tcaggcccc  
 1621 agtcccacag ccccacacac tgggagcagc cagttatatac gacactgtcc cggccctaaa  
 1681 gggggccctg tggccaccac ccccccggcc gcccctgcgg ccagccctgtg tgccctgttc  
 1741 cttggccacc tcagggctgg tgggtggcagt ggaggaggct gaggaggctg aagaggctg  
 1801 caggtcgcccc ggctttctgt ctggctcaact gccctgtatgc cccacccggcc ccacccaggc  
 1861 tccagcagca aagccccagg agaacaggct ggacagaggaa gaaggagggtt gactgttgc  
 1921 cccacactga aagatgaggg gctgcaccc ttccctgtt cccaggaa tgaccctcta tccaggacc

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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 ggcttccctag agagtgcacag ctgctcaggc cctaaaccctt ggctccagga
2581 gacacaggcc ccagcaccca gggtgctgc ggccggctga agacactaga atccgtaccc
2641 gtacattctg cccttgcctc ttacccttg cctcccaagt gtatttgaat aaagtatgtt
2701 gctatatctg cccctatccc cctgttctgc ageccccccaa atccacatgt aactcattac
2761 tgtctcctgt tatttatctc agtagtcccc tctccctagcc actctagccc ctattaactc
2821 tgcattaaagc attccacata ataaaattaa aggtcccggt taaaaaaaaaaaaaaaa
2881 aa

```

**[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.

```

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

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DRYKLWVDTCSIEFGGLDICAVEALHGKDGRDHIEEVVGSSMPLIGDHQD
EDKQLIVEVVNKMAQALPRQRQRDASPGRGSHGQTPSPGALPLGRQTSQ
QPAQPPAQQRPPPQGGPPQPGPQRPQGPQPLQQRPPQGQQHLSGLGPPA
GSPLPQRLPSPTSAPQQPASQAAPPTQGQGRQSRPVAGGPQGAPPARPPA
SPSPQRQAGPPQATRQTSVSGPAPPKASGAPPGGQQRQGPQKPPGPAGP
TRQASQAGPVPRTPPPTTQQPRPSGPGPAGAPKPKQLAQKPSQDVPPPATA
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 gttgccccct tccctaccct ctccttagag 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 aattaactgg agttttgtt
541 ttccctcatac tgtaaaatag acattatatt atccacccca ctggattgtt gtgagggtgg

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601 gatggaaatga tgcgtgaaa cagcgttagc ttaagagttt ggtacaatac gtgacaataa  
661 gattatgaat tagtgcttt atttgtgtca gaatcataaa gatttgacag gttcccatat  
721 cccacctctg ctggactac ctcatggct catatgaaa gattatgg tacactatgt  
781 gtgtgcacca tggatgggc ctgcctctgt ggaaagtctt tgggtgcagg gggagacagg  
841 catggcact gatgacatca ggtagtttc gtgagtttg gcgggtgtcca gagcaaagg  
901 atgtggcgat atataccaag tggatgggtt tggatgggtt gacacgcacc agggcttaggg  
961 ctgcagagaa tgtctgtgtt gcagatctag gtttccat gatcatcggt gggatgtgt  
1021 ttgtctgca agtgtatgtt catatgagtt tccctgggtc tctgtgtgtc agtgtgttac  
1081 ctgtgtgtgtt ggggttatgg gtgtatgtt gcatgtatgtt aacatgccc tttgtgttac  
1141 tctggacttg tatgtctgtt tttatgtt gattggcggtt tttttttt gtacatgccc  
1201 tcgtatgtttt ctttactttt gtgtgtgtttt atatgtgtgtt cttttttt gtggcccttcca  
1261 ggccccccctt gccacccctgg gcaagggtgtt gtacaccacc caagtgttcca cttccgccttgg  
1321 tctgtatgttgc tctgtgttgc ccccgcttc tgcctagctg agcctgtgtg gatgtgggg  
1381 actaatctcc ccggggggcac tgcgtgttgc ctcacccccc tctgtgagggg gtttattttt  
1441 ctactttcgt gtctctgttgc tgcctccat tttttttt cccccaaaaaa atgccttctg  
1501 agttgaatat caacactaca aaccggatgtt ctgcgactgtt cagaggggccc tgcgtatgt  
1561 tgcaagtggg ttttaggacc aggttggggc ggggtggggg tgcctaccc tgcgttgc  
1621 ccgacccact ggacaaggac ccaaccccaat tttttttt tgcgtatccc ctatcgagaa  
1681 gggggggggg aaacaggatg cggcgaggcg cgtcgactt gcaaggcttca gcaaccgg  
1741 cagtgccttc gccccccctt ggcggcgccg cccacccggc cctcagactt gaaggcg  
1801 tgacgttactt cggccgtttcc cccggaaactt ccctttttttt ccacccgggtt cgcgttgc  
1861 ccggccggccgg cccaggccggc cccggaccacg cggaggccggc gataggggggg cccggccgg  
1921 accatctgttgc ctgcggcgcc ggcgacttgc cgttgccttca gtctgtgttgc ggcagccgg  
1981 gagtcgtgttgc gtgccttggaa ggcgactgtt gtccttgggc accggccggt cccggccgg  
2041 ggctcttggc cagaccaccc ctagggaccc cttttttttt tgcgttgc gaaatccat  
2101 cggccggccggc tgcggaccc caactttatg gcaatcttc cttttttttt catgacagac  
2161 ctgcgttgc cggccggccggc cccacccggc cccgggttgc gcaaggccggc agccacccgg  
2221 ggccggccggc cccggccggc cggagggttgc tccgggggttgc cccacccggc cttccggcc  
2281 gccccccatggc cccgggttgc gggggggggg ggtttttttt cttttttttt cttccggcc  
2341 aagcagacca cggccggccggc agctgcacc ttcagccggc aggtgggggggggggg  
2401 ggcgcaggcc gggggggggc cccctccagg gtcgtgttgc tcatcgacga gccggccaccc  
2461 gactggtaag

[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)  
MLLLADMDVVNQLVAGGQFRVVKEPLGFVVKVLQWVFIAIFAFATCGSYSGE  
LQLSVDCANKTESDLISIEVEFEPFRLHQVYFDAPTCRGGTTKVFLVGDY

SSSAEFFVTAVFAFLYSMGALATYIFLQNKYRENNKGPMDFLATAVFA  
FMWLWSSSAWAKGLSDVKMATDPENI I KEMPVCROTGNCTKELRDPVTSG  
LNTSVVFGFLNLVLWVGNLWFVFKETGWAAPFLRAPPGAPEKQPAPGDAY  
GDAGYGQGPGGYGPQDSYGPQGGYQPDYQGPAGSGGSGYGPQGDYQQQGY  
GPOQAPTSFSNQM

[0114] By "SYP nucleic acid molecule" (or synaptophysin gene) is meant a polynucleotide encoding an SYN1 polypeptide. An exemplary SYP nucleic acid molecule (e.g., mRNA) is provided at NCBI Reference Sequence: NM 003179.2.

(SEQ ID NO: 42)  
1 gccccctgca ttgctgtatgc tgctgtggc ggacatggac gtggtaatc agctggggc  
61 tgggggtcag ttccgggtgg tcaaggagcc cctcggttt gtgaagggtgc tgcaatgggt  
121 ctccgccatc ttccgccttg ccacatgcgg cagctacagt gggggactcc agctgagcgt  
181 ggatttgtcc aacaagaccc agagtgacct cagcatcgag gtcgagttcg agtaccctt  
241 caggctgcac caagtgtact ttgtatgcacc cacctgcggg gggggccacca ccaaggctt  
301 ctttagttggg gactactcct cgtcagccga attctttgtc accgtggccg tgggtgcctt  
361 cctctactcc atgggggctc tggccaccta catcttcctg cagaacaagt accgagagaa  
421 taacaaagggg cccatgtgg actttctggc cacggctgtg ttcgccttca tgggtgtact  
481 tagctcatcg gcatgggcca aggggctgtc agatgtgaag atggccacag acccagagaa  
541 cattatcaag gagatgcctg tctgcccggc acaggaaac acatgcagg agctgagaga  
601 ccctgtgacc tcgggactca acacccctggg ggtgttggc ttccctgaacc tgggtgtctg  
661 ggtcgccaaac ctgtgggttcg tggtaagga gacaggctgg gccggccctgt tcctgcccgc  
721 gcctccggc gccccggaga aacaacccggc accccggggac gcctacggc atgcaggcata  
781 cgggcaggggc cccggggggt acggggccca ggattccctac gggcctcagg gcccgttacca  
841 gcctgactat ggtcaaccag cccgcagcgg tggcagtggc tacggggctc agggcgacta  
901 tgggcagcaa ggctacggcc cgcagggtgc acccacctcc ttctccaatc agatgttagtc  
961 tggtcagtga agcccaggag gacctggggg gggcaagagc tcaggagaag gcctggccccc  
1021 ctccccaccc ctataccctt ggttccacc cctcaagccca ggagaccctg tctttgtgt  
1081 ttatatatat atatattata tataaatatc tatttatotg tctgagccct gccctcaact  
1141 caactccctc atccactagg tgcccaatc tgatggggcc ccctcttta cccctccct  
1201 ttccctgtat cccttgcccc ctctctgtt acctccctg tcccttgagg ttaaggggat  
1261 ctaaaaggag gacagggagg gaacagaccc cggctgtgt gggaggggtgg ggcgtacttc  
1321 agactctctc ctctctctcc ctccactctt cccaaactctg gccttgggtc ctccagcaat  
1381 gcctgcttgc acaaaggccg ttagggaaat ccaactccag ggttaaagaa aggcagagat  
1441 tgggggggt tgggttagag aggacagttt aggacccaag gtgggtttgg agaggagggtg  
1501 tggagttggag gggtcagcgg ggggggtggg ttccagacag agtggatctg ggtctgt  
1561 gagaggagtg cgcttagagca ttctgggggt gggcttggaa gggcgttgc ggcagggttc  
1621 tagaaggggc gaggctttaa gcgaggcaga atgggtggct ccagagtagg tgggtcttgg  
1681 attggtagcca gagccatgg aaagggtgtg gcttggaaaca ttggggagac tgagttgtat  
1741 tctaaagggg acagatcttgc agcaaggccaa gaagtggat tcaggaatgg gccaaggccag  
1801 ggttccagac agggtggggc tttagaatggg gttccatgg tggtttcaga aaggccagcc  
1861 cctccccatg gtgcagtgaa gaaaatgttt tacaatggct ggggttggc agtggagagg  
1921 ggacttggat aggagttcc agatgggttt tggtaggggt gggggagaat ggctctggct  
1981 acgacttggg acgaaagtgg cctgagaaga gtcgagtgat atggcttgc ggggtggggc  
2041 tqggatccaaq aqaaqaqcac cccaccacac acacccttcc ccactccctgt qatqaaacaa

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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 cggattgttt caaagaaccc ccctcccca ggaagaacaa atatgattct
2401 cctctccaa ataaactcct 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 ysnalsalghvn ctikelrrlf lvddlvdslk favlmwvfty vgalfngl1
1141 lilalislfv 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 cacgccaaac tggggcgagaa gtccgcgtggc
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 tgcaccccgcc ccctgcggcc ggccgcgcgc tgatggactt  
541 cggaaatgac ttctgtccgc cggegcggcc gggacccctg cggccgcgtc ccccggtcg  
601 cccggagcgg cagccgtctt gggaccccgag cccgggtgtcg tgcacccgtgc ccgcgcacat  
661 cccgctgtct gtcgcgcag tctcgccctc caagctccct gaggacgacg agccctccgc  
721 cggccctccc cctccctccc cgccgcgcgt gagcccccag gcagagcccg tggatggacccc  
781 gecagccccg gtcggcccg cgccccccctc cacccggcc gggcccaagc gcaggggctc  
841 ctccggctca gtggatgaga cccttttgc tcttcctgtc gatctgtgc ctgtgatacg  
901 ctccctcgca gaaaatatgg acttgaagga gcagccaggt aacactattt cggctggtca  
961 agaggatttc ccatctgtcc tgcttggaaac tgctgcttct ctcccttctc tggatccctct  
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 atccctaggga  
1261 agaaataatc gtgaaaaata aagatgaaga agagaagttt gtttagtaata acatccttca  
1321 taatcaacaa gagttaccta cagctttac taaattggtt aaagaggatg aagttgtgtc  
1381 ttcagaaaaaa gcaaaagaca gttttatga aaagagatgt gcagtgaaag ctccatgag  
1441 ggaggaatat gcagacttca aaccatttga gcgagatgg gaagtgaaag atgtaagga  
1501 agatagtatgat atgttggctg ctggaggtaa aatcgagacg aacttggaaa gtaaagtgg  
1561 taaaaaatgt tttgcagata gccttggca aactaatcac gaaaagata gtgagatgt  
1621 taatgtatgat acttcttcc ccagtacgcc agaaggtata aaggatcggt caggagcata  
1681 tatcacatgt gtcctttta acccagcagc aactgagacg attgcaacaa acatcccc  
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 gtacagggaaatgatgt  
1981 tgaattgaat gaagttactg gtacaaagat tgcttatgaa aaaaaatgg acttgggtca  
2041 aacatcgaaat gttatgcaag agtcaactcta tcctgcagca cagcttgc catcatgt  
2101 agagtcagaa gctactcctt caccaggatggtgcgtacatt gttatggaaag caccattgaa  
2161 ttctgcgtt ccttagtgcgt gtgcgtccgt gatacagcc agtcatcac cattagaagc  
2221 ttcttcgtt aattatgaaa gcataaaaca tgacgtgaa aaccccccac catatgaa  
2281 ggccatgatgt gtatcactaa aaaaagtatc aggaataaaag gaagaaatta aagagcctga  
2341 aaatattaaat gcagcttcc aagaaacaga agtcccttat atatctattt catgtgat  
2401 aattaaagaa acaaagcttt ctgtgtacc agtccggat ttctctgatt attcagaaat  
2461 ggccaaagtt 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 ctatTTTTT agccatgcac  
4021 tgggttggg aaaaatttacc tgcattgtact gccatgtgtt catcatctt agtattgtaa  
4081 gctgctatgt atggatttaa accgtaatca tatcttttc ctatctatct gaggcactgg  
4141 tggaaataaa aacctgtata ttttactttt 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 gccaataataa gtaaatatag attatataatg tatagtgttt  
4441 cacaaagctt agacctttac ctccagcca ccccacatgt ctgtatattt cagagtcgt  
4501 cattgggtat acatgtgttag ttccaaagca cataagctag aagaagaaat atttcttagga  
4561 gcactaccat ctgttttcaa catgaaatgc cacacacata gaactccaac atcaatttca  
4621 ttgcacagac tgactgtatg taatTTTgc acagaatctt tggactgaat ctaatcttc  
4681 caaaaatgtt gtttgggttgc aaatataaa cattgtttagt caagaaatta ttaattacaa  
4741 aatgaagatt tataccattt tgggttaagc tgcactgtac taaatctgtg gaatgcattt

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4801 tgaactgtaa aagcaaagta tcaataaagc ttatagactt aaaaaaaaaaaa aaaaaaaaaaaa

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 ggcccgacag  
 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 attcccgtgc agacccctc caacctgcag attcgagaaa ccagcccttga caccactgt  
1261 gtgtcagaag gccaccta gaggAACatc gtggtaaga ccgtggagat gcgggatggaa  
1321 gaggtcatta aggAGTccaa gcaggAGCAC aaggATgtGA tGTGAGGCAG gaccCACCTG  
1381 gtggccctcg ccccgctca tgaggggccc gacGAGAAGC aggatAGTTG ctccgcctct  
1441 gctggcacat ttccccagac ctgagctccc caccacccc gctgtcccc tccctctct  
1501 gtcccttaggt cagcttgctg ccctaggctc cgTCAGTATC aggccTGCCA gacGGCACCC  
1561 acccAGCACC CAGCAACTCC aactAACAAg aaACTCACCC CCAAGGGGCA gtCTGGAGGG  
1621 gcatggccAG cagcttgctg tagaatgagg aggaaggaga gaaggggagg agggcgggggg  
1681 gcacctaCTA catcgccctc cacatccctg attccTGTG ttatggaaac tgTTGCGGAGA  
1741 gatggaggTT ctctcgaggT atctggAAC tGtGcCTTG agtttcctca ggctgctggAA  
1801 ggAAAActGA gactcAgaca gggAAAGGAA ggccccAcAG acaaggTAGC CCTGGCCAGA  
1861 ggcttGTTT gtctttggT ttttatgagg tggatATCC ctatGCTGCC taggCTGACC  
1921 ttGAACtCTT gggCTCAAGC agtctACCCa cctcAGCCTC ctgtgtAGCT gggattataG  
1981 attggagCCA ccatGCCAG CTCAGAGGt tgTTCTCTA gactGACCCt gatcAGTCTA  
2041 agatgggtgg ggacgtccTg ccacTgggg cagTCACCTG cccAGAtCC AgaaggACCT  
2101 cctgAGGAT gactcaAGTg tctcAGTCCa cctgAGTGC catCCAGGGa tgccatCTG  
2161 gggcAcGCTg tggcAGGTg ggAGCTTgat tctcAGCact tggggatCT gttgtgtacG  
2221 tggagaggGA tgaggTgCTg ggAGGGATAG agggggggCTg cctggCCCCC agctgtgggg  
2281 acagAGAGGT caAGGCCAGG aggACTGCC CGTGCAGACT ggAGGGGACG CTGGTAGAGA  
2341 tggagggAGGA ggcaATTGGG atggcGCTAG GcatacAAGT agggggTTGTg ggtGaccAGT  
2401 tgcacttggC ctctggattG tgGGAATTAA ggaAGTgACT catcctCTTG aAGATGCTGA  
2461 aacaggAGAG aaAGGGGATG tatccatGGG ggcAGGGCAT gacttGtCC catttCtaAA  
2521 ggccttCC ttgctgtgtc ataccaggCC gccccAGCT ctgagCCCT gggactgCTG  
2581 ctctttaACC ccAGTAAGCC actGCCACAC gtctGACCCt ctccacCCC tagtgaccGG  
2641 ctgctttCC ctaAGCCAAg ggCCtTtGc ggtccCTtCT tactcacACA caAAATGtAC  
2701 ccAGTATTCT aggtAGTgCC ctatTTACA attgtAAAC tgaggCACGA gcaaAGTgAA  
2761 gacACTggCT catattCCTG cageCTggAG gcccGGTGTc cAGGGCTGAC acgtCCACCC  
2821 cagtGcAccC actCTGCTT gactGAGCAG actGGTgAGC AGACTGGTGG gatctGtGCG  
2881 cAGAGATGGG ACTGGGAGGG CCCACTTCAG ggttCTCTC tccCTCTAA ggcogaAGAA  
2941 gggccttCC ctctccccAA gacttggTGT ctttCCCTC CACTCTTCC tgecAccCTG  
3001 tgctgctgCT gctGCTAAATC ttCAggGCAC tgctgCTGCC tttAGTcGCT gaggAAAAT  
3061 aaAGACAAAT gctGCGCCt tccccAAAAA AAAAAAA

[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 fqefmafva 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 aagggttcgc agcctagtag gagctgagct
481 ttccagccgt gtttagctta attaggaagc ttgatttgc ttgtgattga aaaattgaaa
541 accttttcc aaaggctgtt ttaacggccct 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 gcgaggccct 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
TSSYSCMLPTSPSVNGRSYDTYTPPHMQTHMNSQPMGTSGETSTGLISPQ
VSVPVQVPGSEPDMSSQYWPRQLQ

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**[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 gggcaggat tacgagactg gtcccatcg acccaggcgca atcggtggta gtaaaaccgag  
361 agtagcgact ccagaagttg taagcaaata agccccagtat aagcggggagt gcccgtccat  
421 ctttgcttgg gaaatcccgag acagattact gtccgagggg gtctgtacca acgataaacat  
481 accaagcggtg tcatcaataa acagagttct tcgcaacctg gctagcgaaa agcaacagat  
541 gggcgccagac ggcgttatg ataaactaag gatgttgaaac gggcagaccg gaagctgggg  
601 cacccgcctt ggtttgtatc cggggacttc ggtgccaggg caacctacgc aagatggctg  
661 ccagaaacag gaaggagggg gagagaataac caactccatc agttccaacg gagaagattc  
721 agatgaggct caaatgcgac ttcaagctgaa gcggaagctg caaagaaataa gaacatcctt  
781 tacccaaagag caaatttgagg ccctggagaa agagtttgag agaaccattt atccagatgt  
841 gtttgcggca gaaagactag cagccaaat agatctacctt gaagcaagaa tacaggtatg  
901 gttttctaat cgaaggggcca aatggagaag agaagaaaaaa ctggagaatc agagaagaca  
961 ggccagcaac acacctagtc atattcctat cagcagtagt ttccagcacca gtgtctaccat  
1021 accaaattcca caacccacca caccggtttc ctccctcaca tctggctcca tggtggccg  
1081 aacagacaca gcccaccaa acacctacag cgctctgcgg cctatgccc gcttcaccat  
1141 ggcaaaaac ctgcctatgc aaccccccagt ccccagcccg acctctctat actcctgcata  
1201 gctgccacc acccccttcgg tgaatggcg gagttatgtat acctacaccc ccccacatata  
1261 gcagacacac atgaacagtc agccaatggg cacctcgccg accacttcaa caggactcat  
1321 ttccccctggt gtgtcagttc cagttcaagt tcccgaaagt gaaacctgata tgtctcaata  
1381 ctggccaaga ttacagttaa

[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)  
MEGCMGEESFQMWEILNRRLEAYLARVKALEEONELLSAELGGLRAQSADT  
SWRAHADDELAALRALVDQRWREKHAAEVARDNLAELEGVAGRCQQQLRL  
ARERTTVEAVNRRAVEAEKCARAWLSQQVAELERELEALRVAHEEERVG  
LNAQAAACAPRPCAPPGRPPAPAPEVEELARRLGEAWRGAVRGYQERVAHM  
ETSLGQARERLGRAVQGAREGRLELQQLQAERGGLERRAALEQRLEG RW  
QERLRATEKFQOLAVEALEQEKOGLQSQIAQVLEGRQQLAHLKMSLSLEVA  
TYRTLLEAENSRLQTPGGGSKTSLSFDQPKLELQFPRTPEGRLGGSLLPV  
LSPTSLSPSPATLETVPVAFLKNOEFLQARTPTLASTPPIPPTQOAPSPA  
VDAEIRAQDAPLSLLQTQGGRKQCAPEPLRAEARVAPIASVLPGPEEPGGQ  
RQEASTGOSPEDHASLAPPSPDHSSLEAKDGESEGGSRVFSICRGEEGGQ  
IWGLVEKETAIEGKVVSSLQQEIWEEDDLNRKEIQDSQVPLEKETLKSLG  
EEIQESLKTLENQSHTLERENQECPRSLEEDLETLSLEKENKELLKD V  
EVVRPLEKEAVGQLKPTGKEDTQTLQSLQKENQELMKSLEGNLETFLFP G  
TENQELVSSLQENLESLTALEKENQEPLRSPEVGDEEALRPLTKENQEPL  
RSLEDENKEAFRSLEKENQEPLKLEEDQSI VRPLETENHKSLRSLEEQ  
DQETLRTLEKETQQRRLS LGEQDQMTL RPPEKVDL EPLKSLDQE IARPL E

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NENQEFLKSLKEESVEAVKSLETEILESLKSAGQENLETLKSPETQAPLW  
TPEEINQGAMNPLEKEIQEPLESVEVNQETFRLLLEENQESLRSLGAWNL  
ENLRSPEEVDKESQRNLEEEENLGKGEYQESLRSLEEGQELPQSADVQR  
WEDTVEKDQELAQESPQGMAGVENEAEALNLRQDGFTGKEVVVEQGEL  
NATEEWWIPGEHPSPEPKERQRLVegasVKGGAEGLQDPEGSQVQGA  
PGLQAPQGLPEAI EPLVEDDVAPGGDQASPEVMLGSEPAMGESAAAGAEPG  
PGQGVGGLGPQHLTREEVMPEPLEEESLEAKRVQGLEGRPKDLEEAGGL  
GTEFSELPGKSRDPWEPPREGREENSEAEPGRGAAEAPPAETLGHGTGSDAP  
SPWPGLSEEAEEDVPPVLVSPSPTYTPILEDAPGPQPAEGSQEASWVGQ  
GRAEALGKVSEQEELGSGEIPEGPQEEGEESREESEEDELGETLPDSTP  
LGFYLRSPTS PRWDPTGEQRPPPQGETKGKGEWDPAVLASEGLEAPPSEKE  
EGEEGEEECCRDSLSEEFEDLGTEAPFLPGVPGEVAEPLGQVPQLLLDP  
AAWDRDGESEDGFADEEESGEEGEEDQEEGREPGAGRWGPGSSVGSQLQALS  
SSQRGEFLESDSVSVPWDDSLRGAVAGAPKTALETESQDSAEPGSEE  
ESDPVSLEREDKVPGPLI PSGMEDAGPGADIIIGVNGQGPNLEGKSQHVN  
GGVMNGLEQSEEVGQGMPLVSEGDRGSPFQEEEGSALKTSWAGAPVHLGQ  
GQFLKFTQREGDRESWSSGED

**[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 ctggcccgaa agcggacgac ggaggaggta gcccgcacacc ggcgcgcccgt  
481 cgaggcagag aaatgcgcacc gggcctggct gaggtagccag gtggcagcgc tggagcgcga  
541 gctagaggct ctacgcgtgg cgacacgagga ggagcgcgtc ggctgaacg cgcaggctgc  
601 ctgtgcccccc cgctgcccccc cgccgcccccc cggccctcccc ggcgcggcccc cggaggtaga  
661 ggagctggca aggcaactgg gcgaggcggt ggcggggca gtgcgcggct accaggagcg  
721 cgtggcacac atggagacgt cgctggggca ggcggcgag cggctggggcc gggcggtgca  
781 ggggtccccgc gagggccgccc tggagctgca gcagctccag gctgagcgcg gaggcctcc  
841 ggagcgcagg gcagcggtgg aacagaggaa ggaggggccgc tggcaggagc ggctgcgggg  
901 tactgaaaag ttccagctgg ctgtggaggc cctggagcag gagaacacagg gcctacagag  
961 ccagatcgct caggtccctgg aaggctggca gcagctggcg cacctaaga tgccctcag  
1021 cctggagggtg gccacgtaca ggaccctctt 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 atccctccag gcccgtaccc ctaccttggc cagaacccca atccccccca cacctcaggc  
1321 accctctctt getgttagatc cagagatcag agccaggat gctcctctt ctctgtccca  
1381 gacacagggt gggagggaaac aggtccaga gcccctgcgg gctgaagcca gggtggccat  
1441 tcctggcagc gtctgtgtcg gaccagagga gcctggggcc cagcggcaag aggccagtag  
1501 aggccagtc ccagaggacc atgcctcctt ggaccacccc ctcagccctg accactccag  
1561 tttagagggt aaggatgggg aatccgggtgg gtcttagatgt ttctgtat 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 gaaatcttttta gaaggtatac tagagacatt ttatccca ggaacggaaa atcaagaatt  
2101 agtaagttct ctgcaagaga acttagagtc attgacatgt ctggaaaagg agaatcaaga  
2161 gccactgaga tctccagaag tagggatgt gggaggactg agacactctga caaaggagaa  
2221 tcaggaaccc ctgaggtctc ttgaagatgt gaaacaaagag gccttagat ctctagaaaa  
2281 agagaaccag gagccactga agactctaga agaagaggac cagagtattg tgagacctct

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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 cacccgtgt  
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 ggactacttc agccgattcg ggaccaagtg tgccgggtc  
421 ggccgcacaga tctacgcccag cgactgggtg cggagagctc gggcaacgc ctaccaccc  
481 gcctgcttcg cctgcttcgc tgcaagcgc cagctgtcca ctgggtggaa gttccggctg  
541 gtgcaggaga aggtgtctg ccgcattccac tacgacacca tgattgagaa cctcaagagg  
601 gcccggaga acgggaacgg ccteacgttg gagggggcag tgccctcgga acaggacagt  
661 caacccaaagc cggccaagcg cgccggacgc tccttcaccgc cggaaacagct gcaggttatg

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**[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 GCGGGGCGGG TGGCGAAGGC AGGGTCTGCC CGCCAGTGGA TTCCCGGGTG  
 421 tcccgCGTGG agcaggcttG CCCAGCTGGG aAGCCCATCA AACCTCAGTC ttggcccaca  
 481 gtggggAGAGA gaccAGTGGG TCCCAGACGG AGGCCATCGC CCgttttGG cgacccTCCAC  
 541 tggcgtGAAT AAAAGCACCC CTCTTtAcc CTCAGAAACT gtgggtAGCA aggtataaaaa  
 601 cggagtctGG gaccggtaAG tcccAGGTG AGCCCGTATA cagctctGCC atctctGAGG  
 661 ggttatGCG ATTCTGAGCA ggtgtcAGGG GCTCATGTC gaggAGTGCG ggcggactAC  
 721 agccctggcg GCGGGGAGGA CTCGCAAAGG CGCCGGGAA gagggactGG tgagccccGA  
 781 gggagcGGGG gacgaggACT cgtgtcCTC CTCGGCCCCG CTGTCCCCGT CGTCCTCGCC  
 841 ccggTCCATG GCTCGGGCT CGGCGTCCC TCCTGGCAAG TGTGTGTGCA acagttGCGG  
 901 CCTGGAGATC GTGGACAAAT ACCTTCTAA GGTGAATGAC CTATGTGGC ATGTCGGTG  
 961 tctctcCTG 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 ATTAAAAAG  
 1261 agaaAGTAGAA AATGGGAATG GGATTAGTGT GGAAGGTGCG CTCCCTCACAG AGCAAGATGT  
 1321 taaccatCCA AAACCAAGCAA AAAGAGCTCG GACCAGCTT ACAGCAGATC AGCTTCAGGT  
 1381 tatGCAAGCA CAATTGCTC AGGACAACAA CCCAGATGCA CAGACACTCC AGAAATTGGC  
 1441 agaaAGGACA GGCTTGAGCA GACGTGTGAT ACAGGTGTGG TTTAGAGCAG  
 1501 ccacaAGAAA CACGTCACTC CTAATCACTC ATCCTCCACC CGAGTCACAG CAGCCCCACC  
 1561 CTCCAGGCTG TCTCCACCA TGTAGAAGA AATGGCTTAT TCTGCCTACG TGCCCCAAGA  
 1621 tggAACGATG TTAACTGCGC TGCGATAGTTA TATGGATGCT CATTCAACCA AAACCTCTGG  
 1681 ACTCCAGCCC TTGTTACCCC ATTCAATGAC ACAACTGCCA ATAAGTCATA CCTAATTCTT  
 1741 TTTTCAGGGA TAGACTTGAT TAAGGATATA AATTGTCTAT TTATTATGTA 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 ttatatttgc caatgtttc
2221 tgaatgaact gaataaagct tctgttgtag catgocatgc aaacacattt 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)

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MQLEHCLSPSIMLSKKFLNVSSSYPHSGGSSELVLDHPIISTTDNLERSS
PLKKITRGMTNQSDTDNFPSDKSPGDVQRSKLSPVLDGVSELRLHSFDGS
AADRYLLSQSSQPQSAATAPSAMFPYPGQHGPAPAFSIGSPSRYMAHH
VITNGAYNSLLSNSSPQGYPTAGYPYPQQYGHYSQGAPFYQFSSSTQPGLV
PGKAQVYLCNRPLWLKPHRHQTEMIITKQGRRMFPLSFNISGLDPTAHY
NIFVDVILADPNHWRFQGGKWVPCGKADTNVQGNRVMHPDPNTGAHW
RQEISFGKLKLTNNKGASNNNQMVVLQSLHKYQPRLHVVEVNEDGTEDT

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SQPGRVQTFTFPETQFIAVTAYQNTDITQLKIDHNPFAGFRDNYDTIYT
GCDMDRLTPSPNDSPRSQIVPGARYAMAGSFLQDQFVSNYAKARPHPGAG
AGPGPGTDRSVPHTNGLLSPQQAEDPGAPSPQRWFVTPANNRLDFAASAY
DTATDFAGNAATLLSYAAAGVKALPLQAAAGCTGRPLGYYADPSGWGARSP
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 gagggcgagt
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 caggggacgt ccagagaagt aaactctctc ctgtcttggc cggggctctc gagcttcgtc
601 acagtttgcg tggctctgcgct gcagatcgct acctcctctc tcagtcgcagc cagccacagt
661 ctgcggccac tgctcccagt gccatgttcc cgtaccccg ccagcacgg ccggcgccacc
721 ccgccttctc catcgccagc cctagccgt acatggccca ccacccggc atcacaacgc
781 gagcctacaa cagcctcctg tccaaactcct cggccgcaggg atacccacgc gccggctacc
841 cctacccaca gcagtagccgc 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 cggggccgCgg ggccccggcc  
1681 cgggtacggA cccgcagcgtg ccccacacca acgggctgct gtc当地ccgag caggccgagg  
1741 acccggggcgc gccc当地cgcc caacgcgtgt ttgtgacgCc ggccaacaac cggctggact  
1801 tc当地ggcctc ggc当地tatgac acggccacgg acTTcgccggg caacgcggcc acgctgtct  
1861 cttacgcggc ggc当地ggcgtg aaggcgcgtc cgc当地cgaggc tgcaaggctgc actggccgccc  
1921 cgctcggcta ctacgc当地ac ccgtcgggct gggggccccc cagtc当地ccg cagtaCTgc  
1981 gc当地caaggc gggc当地cggtg ctgc当地ctgct gggccaaacag cccgc当地ggcc gccgc当地gc  
2041 tggccggcgc caatccctac ctggggcagg aggccgaggg cctggccgCc gagcgc当地tc  
2101 cgctgc当地cc gggc当地ccggc gaggacgCc agggcaaggA cctgtccgat tccagctggA  
2161 tc当地gacgc当地 ctc当地cgatc aagtccatcg actccagega ctc当地gggatt tacgagcagg  
2221 ccaagcggag gggatcgtc cccgc当地gaca cgc当地ctgtc cggagatTC tcccccgetca  
2281 agagc当地gggt gtc当地ggccag cgggactgCg agaagaactg ccccaaggac attagcggct  
2341 actatggcTT ctactcgac acgttagggc cccctgccc cccggccccc cccggccccc  
2401 gaccccccagc cagccctca cagcttcc cccgc当地ccgc ctc当地ccacac tcccttgc  
2461 gc当地ccactc attttatttgc accctcgatg gccgtctgca gcaataagt gcaaggctcc  
2521 gagcgtgatt ttaacccttt ttgc当地cagca gtc当地tgc当地 ttagctcacc gaccttcaac  
2581 tttgc当地ttaa acctttggt ttccctactt actcttctc tggaggtaa tcccttaca  
2641 atcccccctcc cccctcgatc tcccttaccc cctacttctc tttttgttaa tggaaactt  
2701 cacctttagg agacctggc agtc当地tgc当地 ggc当地cageg attc当地ggcc gcaaggctc  
2761 ggc当地ccaca ttaaccatag gatgttgact ctagAACCTG gacccaccca ggc当地tcc  
2821 tccctatcccc gagttggg atggatggat ggtggtagg gatgttaata attttagtgg  
2881 aacaaggct gtgaaatgtat tgc当地atgtt gtaatttAT tgc当地acgaaat ggctatTTT  
2941 tattctcgatc aaggc当地aaa accaggatc gcttaaccTT ttttccccc ccccccTT  
3001 cttttcttcc tccctctca tacttctct tccctctt ttaatttct tgc当地gataaa  
3061 tattcttaaga ggctctagaa acatgaaata ctc当地atgtg atgggTTTCC cacttctt  
3121 caatccgttgc catgaaataa ttactatgtg cc当地atgtc cacaatagc taaggagaat  
3181 ccacccaaac acctttaaag gatagggtgc tggatc当地agg caagtc当地gatt aagtggcatg

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3241 atgcctgcaa agcaaagtca actggagttg tatgttcccc ccacccatca aatagaatag
3301 ctcgacatca gcaatattat tttgccttat ttgttttcc ccaaagtgcc aaatccatta
3361 ctggctctgtc caggtgccaa atatgtgac aaactgttcc tgaatatctt tcagtaaaaa
3421 ttcacccatata tatgtctgtaa atctttgtaa tgaataactctt attaatgata tagatgactg
3481 aattgttggt aactatagtg tagtctagtg aagatgaatt gtgtgagttg tatattttac
3541 tgcatttttag ttttggaaaat gacttccccca ccacccatgaa acagctgaaa tttgacttcc
3601 ttgggagaac actagcatta atgcaagtaa gactgatccc cccctaagtc ttgttatatt
3661 tgataaggag catataatccc cctggaaataa gattagtagg atttctaatacg ttgtgttagca
3721 aacctataact ttttgttatt taaaaattaa tggaaatataat gcatcataca caatattcaa
3781 tctagattcc agtccatggg gggattttc ctaataggaa ttcaagggttcaaaacgtgtgt
3841 atattttggc tcttctgtaa atctaatacggtt gtgattttta tatttggatc gttttgtctg
3901 tgaactgaat aatttataaca agaacacact ccattggaa acgttttgcgtt ttttgcgt
3961 ttgtatcgcc 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  
ISSLVTGMAALDSKASGKMGRAVYYMMTTTIIAVVIGIIIVIIIHPGKG  
TKENMHREGKIVRVTAADAFLDLIRNMFPPLNVEACFKQFKTNYEKRSFK  
VPIQANETLVGAVINNVSEAMETLTRITEELVPVPGSVNGVNALGLVVFS

-continued  
MCFGFVIGNMKEQQQALREFFDSLNEAIMRLVAVIMWYAPVGILFLIAKG  
IVEMEDMGVIGGQLAMYTVTIVGLLIHAVIVLPPLLFLVTRKNPWWFIG  
GLLQALITALGTSSSSATLPIFKCLEENGVDKRVTFRVLPVGATINMD  
GTALYEALAAIFIAQVNNEFNLFGQIITISITATAASIGAAGIPQAGLVT  
MVIVLTSVGLPTDDITLIIAVDWFLDRLRTTNVLGDSLGGAGIVEHLSRH  
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 gggcacatgc acactgtcgg ggctagccctt cctgtttacg  
61 cgccgtcgcc attgttgcgtc cgtgttaccc gctggggat tcacccgtt actgtttgtat  
121 atcttccacc ccttacaaaa tcagaaaatgt tttgttttcc aataccaaag aggagggttg  
181 gctttctgtg ggtgattccc agacactgaa gtgcaagaa gagaccctcc tagaaaatgt  
241 aaatatgact aaaagcaatg gagaagagcc caagatgggg ggcaggatgg agagattcca  
301 gcaggaggatc cgtaaacgc cactttggc caagaagaaa gtgcagaaca ttacaaagga  
361 ggtatgttataa agtttacccgtt ttcggatgc tttttgtctt ctcacatgc ccgtgtcat  
421 ttttttttcc tttccctgggg aacttctgtat gggatgttca cagatgtgg ttttttcc  
481 gtacttctcc tttccctgggg aacttctgtat gggatgttca cagatgtgg ttttttcc  
541 tatcatctcc agtcttgcgtca caggaatggc ggcgttcatat ggttggat cagggaaatgt  
601 gggatgtcgtat ggttggat ctttttttcc aacttctgtat gggatgttca cagatgtgg ttttttcc  
661 aatcattgtc atcatcatcc atcctggaa gggcacaatgc acagagaagg  
721 caaaaattgttca ctttttttcc aacttctgtat gggatgttca cagatgtgg ttttttcc

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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 gcccctggc 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 tgccattttc 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

-continued  
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 ctgctggcc agggctgtgg  
61 agacggagcc cggacctcca cactgagcca tgcccacccc cgacgccacc acgccacagg  
121 ccaagggtt cccgaggccc gtgtctgacg tggacgcca gcagggcagag gccatcatgt  
181 ccccgccgtt cattgggcgc aggccagacc tcacgcgatcca cgcggcaag gageggagg  
241 cggcggtggc agcagccggcc gctgcagtc cctccggagcc cggggacccc ctggaggctg  
301 tggcccttga ggagaaggag gggaaaggccg tgctaaacct gctcttccccc ccgaggggcca  
361 ccaagccctc ggcgcgtgtcc cgagctgtga aggtgtttga gacgtttggaa gccaaaatcc  
421 accatctaga gaccggccc gcccagggcc cgccgagctgg gggcccccac ctggagact  
481 tcgtgcgcct cgaggtgcgc cgaggggacc tggccgcctc gtcagtggt gtgcgcagg

-continued

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541 tgcagagga cgtgcgcgac cccgcggggc ccaaggccc ctggttcca agaaaagtgt
601 cagagctgga caagtgtcat cacctggtca ccaagttcgac ccgtgacctg gacttggacc
661 acccggtt ctggaccag gtgtaccgcc agcgcaggaa gctgattgtc gagatcgct
721 tccagtagac gcacggcgc cccatcccc gtgtggagta caccgcggag gagattgcca
781 cctggagga ggtctacacc acgtgaagg gcctctacgc caccgcgc tgccggggac
841 acctggggc ctttgcttg ctggagcgct tcagggcta cccggaaagac aatatcccc
901 agctggagga cgttcggcgc ttctgtggagg agcgcacggg ctccagctg cggcctgtgg
961 cccgcctgtc gtccggccgg gacttctgg ccagctggc ctccggctg ttccagtgc
1021 cccagttat cccgcacgcg tcctgcggca tgcaactcccc tgagccggac tgctgcacg
1081 agctgtggg geacgtgccc atgtggccg accgcaccc cgcgcgttc tgcaggaca
1141 ttggcctggc gtccctgggg gcctcgatg agaaattga gaagctgtcc acgctgtact
1201 ggttcacggt ggagttgggg ctgtgtaaagc agaacggggg ggtgaaggcc tatggtgccg
1261 ggctgtgtc ctcttacggg gagcttctgc actgcctgtc tgaggaggct gagattgggg
1321 ctttcgaccc tgaggctgcg gccgtgcgc cctaccaaga ccagacgtac cagtcgtct
1381 acttcgtgtc tgagagttc agtgcgcgc aggacaagct caggagctat gcctcacgca
1441 tccagcgccc ctttcgggt aagtgcgacc cgtacacgcg ggcacatgcg tgctggaca
1501 gccccaggc cgtggggcgc tccctggagg gtgtccggga tgagctggac acccttgc
1561 atgcgttag tgccattggc tagtgtgcacg 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  
REMRGAVLRLGAARGQLRLEQEHLLEIAHVQRLLDLEARQREEAEEAAR  
ALARFAQEAEARVDLQKKAQALQEECGYLRRHHQEEVGELLGQIQGSGA  
AQAOQMQAETRDALKCDVTSALREIRAQLEGHAVQSTLQSEEWFRVRLDRL  
SEAAKVNTDAMRSAQEEITEYRQLQARTTELEALKSTKDSLRLQRSELE  
DRHQADIASYQEAQQLDAELRNTKWEAAQLREYQDLLNVKMAVDIEIA  
AYRKLLGEEECRIGFGPIPFSLPEGLPKIPSVSTHKVKSEEKIKVVEKS  
EKETVIVEEQTEETQVTEEVTEEEEKEAKEEEKGEEEGGEEEEAEGGEEE

-continued  
TKSPPAEEAASPEKEAKSPVKEEAKSPAEAKSPEKEAKSPAEVKSPEKA  
KSPAKEAKSPPEAKSPEKEAKSPAEVKSPEAKSPAKEEAKSPAAEAKS  
PEAKSPVKEEAKSPAEAKSPVKEEAKSPAEVKSPEAKSPTKEEAKSPE  
KAKSPEKEEAKSPEAKSPVKAEEAKSPEAKSPVKAEEAKSPEAKSPVKE  
EAKSPEAKSPVKEEAKSPEAKSPVKEEAKTPEAKSPVKEEAKSPEKA  
KSPEAKTLDVKSPEAKTPAKEARSPADKFPEAKSPVKEEVKSPEAK  
SPLKEDAKAPEKEIPKKEEVKSPVKEEKPQEVKVKEPPKKAEEEKAPAT  
PKTEEKDKSKKEEAKPKVKEAPKPKVKEEKKEPAVEKPKESKVEAKKEAEDK  
KKVPTPEKEAPAKVEVKEAKPKEKTEVAKKEPDDAKAKEPSKPAEKKEA  
APEKKDTKEEKAKKPEEKPKTEAKAKEDDKTLSKEPSKPKAEEAKSSST  
DQKDSKPPEKATEDKAAGK

**[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 cgctgcattgg cggcgccgc ctccactacg cgctagcccg aaagggtggc gcaggcgaa

-continued

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 aggtggcga gtgcggcgc 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 cagcaaggaa agaggcaag tcacccggctg  
1861 aggccaaagtcc tccagagaag gccaagtccc cagtgaaaggc agaagcaag tcacccggctg  
1921 aggccaaagtcc cccagtgaag gaagaagcaa aatctccagc tgaggtcaag tccccggaaa  
1981 aggccaaagtcc tccaaacgaa gaggaaaggaa agtccccgtga gaaggcaag tccccagaga  
2041 aggaagaggc caagtccccctt gagaaggccaa agtccccagt gaaaggccaa gcaaagtcccc  
2101 ctgagaaggc caagtccccca gtgaaggcag aagcaaggc ccctgagaag gccaagtccc  
2161 cagtgaaaggc agaagcaag tccccgtgaga aggcaaggc cccagtgaag gaagaagcaa  
2221 agtccccctgaa gaaggccaa tccccgtga aggaagaagc aaagaccccc gagaaggccaa  
2281 agtccccagt gaaaggccaa gctaaagtccc cagagaaggc caagtccccca gagaaggccaa  
2341 agacttgcgttgaa gtcaggatc ccagaagcca agactccagc gaaggaggaa gcaagggtccc  
2401 ctgcagacaa attccctgaa aaggccaaa gccctgtcaa ggaggaggc aagtccccag  
2461 agaaggccaa 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 tggacaattaa  
 3361 tgatagctt ttagtgcata tggatacat gccaatgcc acacgtaaac acttgactat  
 3421 aaaaactgcc cccctcctt ccaaataagt gcatttattt cctctatgtt caactgacag  
 3481 atgaccgca taatgaatga gcaatggaa atacattatg cttgagatgt cttaacctat  
 3541 tccaaatgc cttctgttt ccaaaggagt ggtcaagccc ttgcccagag ctctctattt  
 3601 tggaaagacg gtccagggtgg ggccgggac tggccactga attatgccag ggccacttt  
 3661 ccactggagt tcacttcaa ttgctctgt gcaataaaac caagtgcctt taaaatgaaa  
 3721 a

**[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  
 EAVALKGEQEKEAQHKDQTAALPLAAEETANLPPSPPPSPASEQTVTVE  
 EAAGGESALAPSVFQAKDKVSNSTLSKIPALQGSTKSPRYSSACPSTTK  
 RATFSDSLLIQPTSAGSTDRLPYSKSGNKDGVTKSPEKRSSLPRPSSILP  
 PRRGVSGDRDENFSLNSSISSSARRTRSEPIRRAGKSGTSTPTTPGST

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AITPGTPPSYSSRTPGTPGTPSYPRTPHTPGTPKSAILVPSEKKVAIIRT  
 PPKSPATPKQLRLINQPLPDLKNVKSIGSTDNIKYQPKGGQVRILNKKI  
 DFSKVQSRCGSKDNIKHSAGGGNVQIVTKKIDLSHVTSKCGSLKNIRHRP  
 GGRVKIESVKLDFKEKAQAKVGSLDNAHHVPGGGNVKIDSQKLNPREHA  
 KARVDHGAEIITQSPGRSSVASPRLSNVSSSGSINLLESPQLATLAEDV  
 TAALAKQGL

**[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 tctctttttt ctccggaggg cgctaagtcc gtgagcggtg  
 181 gcagtcgoga ccgcgggtgc atccagtttc tggccccaga ttttattgtt ctaatccaaa  
 241 gtatcttata acttctggct ggaattaaga ttcttcagct tgcgtctaaac cgaggaagca  
 301 ttgattggga gctactcatt cagaaaaatta aaagaaagaa gccagaaaaat attatcaacc

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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 attcccaatac 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 cccagtgat 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 tctctctca cagttctatc tcttcttcag
1261 cacggcggac caccaggctc gagccaattc gcagagcagg gaagagtggt acctcaacac
1321 ccactacccc tgggtctact gccatcaactc ctggcaccccc accaagttat tcttcacgca
1381 caccaggcac tccttggaaacc cctagctatc ccaggacccc tcacacacca ggaacccca
1441 agtctgccat ctgggtggcc 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 aaagttgggt
1861 ctcttgataa tgctcatcat gtacctggag gtggtaatgt caagattgac agccaaaagt
1921 tgaacttcag agagcatgt aaagcccggt tgaccatgg ggctgagatc attacacagt
1981 ccccaaggcag atccagcggtg gcatcccccc gacgactcag caatgtctcc tctgtggaa
2041 gcatcaacccct gctcgatct cctcagcttgc ccactttggc tgaggatgtc actgctgcac
2101 tcgcttaagca gggcttgtga atatttctca tttagcatttggaaatataat atttaggcatt
2161 gagcttggc caggagtggg ctctgagcag ttgttatatt cattttttat aaaccataaa
2221 ataataataatc tcatccccaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2281 aaaaaaa

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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

VRYIYTIDGSRKIGSMDELEEGESYVCSSDNFFKKVEYTKNVNPNSVN  
KT SANMKAPQSLASSNSAQARENKDFVRPKLVTIIIRSGVKPRKAVRVLLN  
KKTAHSPEQVLTDITEAIKLETGVVKLYTLDGKQVTCLHDFFGDDDVFI  
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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**[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  
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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)  
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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  $\mu$ 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  $\mu$ m and inter-electrode space is 350  $\mu$ 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 (OxiSelect<sup>TM</sup> 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 (OxiSelect<sup>TM</sup> 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  $\mu$ 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  $\mu$ 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 STEMdiff<sup>TM</sup> 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.  $\alpha$ -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  $\mu$ 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  $\mu$ M MPP+. Recently, some studies have identified human enzyme caspase-1 as the protease that cleaves  $\alpha$ -synuclein *in vivo* [74]. This cleavage generates  $\alpha$ -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 $\beta$ ). 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  $\mu\text{m}$  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  $\mu\text{m}$ ) 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  $\mu\text{m}$  in diameter; the size increased to 300 $\pm$ 40  $\mu\text{m}$  during the first 17 days in differentiation medium. From day 17 onwards size remained constant around 310  $\mu\text{m}$ . 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  $\mu$ V and maximum of 40  $\mu$ 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<sup>+</sup> and the broadly used pesticide rotenone, were selected. Both MPP<sup>+</sup> 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  $\mu$ M rotenone and 100  $\mu$ M MPP<sup>+</sup> for 24 h (FIGS. 4E and 4F). This effect was likely selective even at cytotoxic concentrations of 10  $\mu$ M rotenone and 1000  $\mu$ M MPP<sup>+</sup> 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  $\mu$ M and 5000  $\mu$ M, respectively) led to general cytotoxicity and affected also other neuronal types stained positive for neurofilament 200 (FIGS. 4E and F). 5  $\mu$ M of rotenone and 1000  $\mu$ 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 OxiSelect<sup>TM</sup> In Vitro ROS/RNS Assay Kit (Cellbiolabs, San Diego, CA) as an indication of oxidative stress. Exposure to rotenone at 5  $\mu$ M and MPP+ at 1000  $\mu$ 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  $\mu$ M rotenone and 70% $\pm$ 9 after exposure to 1000  $\mu$ 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  $2\times 10^6$  NPCs mixed with  $2\times 10^4$  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<sup>®</sup>) electro Medium (Gibco) supplemented with 5% B-27<sup>®</sup> Electrophysiology (Gibco), 1% glutamax (Gibco), 10  $\mu$ g human recombinant GDNF (Gemini), 10  $\mu$ 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  $\beta$ -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  $\mu$ l Eppendorf tubes.  $2\times 10^4$  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]. iPSCs 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% CO<sub>2</sub>. 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% CO<sub>2</sub>.

#### BMPS Differentiation

[0245] At 100% confluence NPCs were detached mechanically and counted. 2×10<sup>6</sup> 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% CO<sub>2</sub> 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 CaCl<sub>2</sub>. 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% CO<sub>2</sub>. 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). 1×10<sup>6</sup> 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 10<sup>4</sup> 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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accactggc	ccctccccc	cg	cc	at	cccttcc	9360
attggccac	gttggac	ccgtgc	atgggctgg	gaggagcc	ggggatgc	9420
cctggaa	tccgtgt	ggggccctc	caggac	ggcaca	gagagacta	9480
ggccgggaa	aa	tgca	agaatgtt	gttgggg	agaggctacc	9540
catccctgt	ggccat	actgtgt	gggacc	ctcatggcc	cctatccct	9600
gggattcc	aa	ccca	cc	ctcc	gggg	9660
caagaggc	gtgttgt	gggtc	aggcag	accac	caggagggg	9720
gttccggc	ctggg	gcattag	ggcctg	tgg	gtcc	9780
gtctacac	ccgt	acgcac	ccgc	gggg	ggcc	9840
tttgc	tttgc	cggcgtt	ccgg	gggg	gggg	9900
gttcc	ttct	ttgtt	ccgg	gggg	gggg	9960
atgg	tcac	ccat	atgt	gggg	gggg	10020
cgcgtggcc	cttgc	gcac	ccag	gggg	gggg	10080
cgcggggac	ttc	ccgtt	ccat	gggg	gggg	10140
ccacgcgt	cc	ccgtt	ccat	gggg	gggg	10200
gagggtgg	gg	ccgtt	ccat	gggg	gggg	10260
tgtgc	ccac	ccat	atgt	gggg	gggg	10320
tcgc	ccat	ccat	ccat	gggg	gggg	10380
gggg	ccat	ccat	ccat	gggg	gggg	10440
caaggagg	cc	ccat	ccat	gggg	gggg	10500
cacggcc	cc	ccat	ccat	gggg	gggg	10560
gg	cc	ccat	ccat	gggg	gggg	10620
gg	cc	ccat	ccat	gggg	gggg	10680
cggt	cccc	ccat	ccat	gggg	gggg	10740
ccacagg	at	ccat	ccat	gggg	gggg	10800
cacgg	at	ccat	ccat	gggg	gggg	10860
ccat	ccat	ccat	ccat	gggg	gggg	10920
accctgg	cc	ccat	ccat	gggg	gggg	10980
accagg	cc	ccat	ccat	gggg	gggg	11040
agctt	cc	ccat	ccat	gggg	gggg	11100
atgg	cc	ccat	ccat	gggg	gggg	11160
gccccca	cc	ccat	ccat	gggg	gggg	11220
agaaaact	cc	ccat	ccat	gggg	gggg	11280
cccagtc	cc	ccat	ccat	gggg	gggg	11340
actcttca	cc	ccat	ccat	gggg	gggg	11400
gggtgc	cc	ccat	ccat	gggg	gggg	11460
tgagat	cc	ccat	ccat	gggg	gggg	11520
ccagt	cc	ccat	ccat	gggg	gggg	11580
taggtct	cc	ccat	ccat	gggg	gggg	11640
ttgc	cc	ccat	ccat	gggg	gggg	11700
ttgc	cc	ccat	ccat	gggg	gggg	11760
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SEQ ID NO: 9 moltype = AA length = 382  
FEATURE Location/Qualifiers  
source 1..382  
mol\_type = protein  
organism = Homo sapiens

SEQUENCE :	9	Organism : Homo sapiens				
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QCASCKEPE	TTCFYRDKKL	YCKYDYEKLF	AVKCGGCFFEA	IAPNEFVMRRA	QKSVYHLSCF	120
CCVCERQLQ	KGDFEPVLKEG	KGKCGDYEKQ	ERELLESLVSP	AASDGSKSDD	EESLCKSAHG	180
AGKGTAEEGK	DHKRPKRPRRT	ILTTQQRRAF	KASFEVSSKP	CRKVRETLAA	ETGLSRVQQ	240
VWFQNQRKAM	KKLARRQQQQ	QQDQONTQRL	SSAQTNNGGS	AGMEGIMNPY	TALPTPQQQLL	300
AIEQSVYSSD	PFRQGLTPPPQ	MPGDHMHPYG	AEPLFHDLDS	DDTLSLSNLGD	CFLATSEAGP	360
LSQRSGNPID	HLYSMONSYF	TS				382

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SEQ ID NO: 10          moltype = DNA length = 5310
FEATURE
misc_difference        Location/Qualifiers
901..1000
note = a, c, t, g, unknown or other
misc_difference        1301..1400
note = a, c, t, g, unknown or other
misc_difference        1821..1920
note = a, c, t, g, unknown or other
misc_difference        2881..2980
note = a, c, t, g, unknown or other
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agacacac	cg	tgacttgc	tctttccaaa	ataacataaa	gtatgtaaaa	4140
aaataaca	tc	tc	tgttgcac	tcttata	atgttctc	4200
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catatgtgt	tttgc	aaaa	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	4440
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gcctctcg	cg	tcc	ttcc	ttcc	ttcc	5100
cttcacatct	tgatgttcc	ccttagt	ttgtact	ttccat	ttccat	5160
attctttgc	gggtcact	ttttag	ttcc	ttcc	ttcc	5220
ggagtttgt	ttgggat	tttgc	tttgc	tttgc	tttgc	5280
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SEQ ID NO: 11            moltype = AA   length = 655  
 FEATURE                Location/Qualifiers  
 source                1..655  
 mol\_type = protein  
 organism = Homo sapiens

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 ASAIAVSADF MSNLSSLLEES EDFPQAPGSV AAAVAAAAAA ATGGILCGDF QGPEAGCLHP 120  
 APPQPPPPGP LSQHPPVPPA AAGPLAGQPR KSSSSRRNAW GNLSYADLIT KAISSAEKR 180  
 LTLSQIYEWM VKSPVYFKDK GDSNSSAGWK NSIRHNLSLH SKFIRVQNEG TGKSSWWMLN 240  
 PEGGKSGKSP RRRASMDNN SKFAGRSRRA AKKKASLQSG QEGAGDSPGS QFSKWPASPG 300  
 SHSNDDFDNW SFRPRTSSN ASTISGRSLP IMTEQDDLGE GDVHSMVYPP SAAKMASTLP 360  
 SLSEISNPEN MENLLDNLNL LSSPTSLTVS TQSSPGTMQQ QTPCYSFAPP NTSLNSPSPN 420  
 YQKYTYQGSS MSPLPQMPIQ TLQDNKSSYQ GMSQYNCAPG LLKELLTSDS PPHNDIMTPV 480  
 DPGVQAQPNR VLGVQNVMMGP NSVMSTYGSQ ASHNKMMNPS SHTHPGHAAQ TSAVNGRPLP 540  
 HTVSTMMPHTS GMNRLTQVKT PVQVPLPHQM QMSALGGYSS VSSCNGYGRM GLLLHQEKLPS 600  
 DLDGMFIERL DCDMIESIRN DLMDGDTLDF NFDFNVLPMQS FFPHSVKTTTH SWVSG 655

SEQ ID NO: 12            moltype = DNA   length = 5738  
 FEATURE                Location/Qualifiers  
 source                1..5738  
 mol\_type = unassigned DNA  
 organism = Homo sapiens

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 ctggcccccgc cccggcgcgc tggccggcgc tcacatgttgc gggccggacc ccggaggagcc 180  
 tcgatgttgc tggcccccgc aagttaaatgttgc gtcggcgcgc gtcggcgcct ccggccgcct 240  
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 caaacatgttgc ttgttgcgggg agaggcggagg cttccgcgc ggcgcgcgc ccgtggccgc 660  
 ggcgggttgcg cggccggccgc ccgcgcgcgc caccgggggg ctgttgcgggg acttcacagg 720  
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 cagctgttgc cgcgcgcacgc cgtggggcaa cctgttgcacgc ggcgcacccca tcaccaaggc 900  
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 aagagctgttgc tttccatgttgc acaacatgttgc aatgttgcacgc agccgcacccgc gagctgttgc 1200  
 gaagaaaacgc tttccatgttgc ggggttgcacgc gacggccctg gatcacatgttgc 1260  
 ttcccaatgttgc cttccatgttgc gtcgttgcacgc cagcaacacgc tcggccgggttgc ggttgcgttgc 1320  
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tcataacaa	atgtatgat	ccagtc	tacccaccc	ggacatgtc	agcagacatc	1980	
tgc	ca gtc	gggcgtcccc	tgc	ggtaa	ggcacc	2040	
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ataat	tttca	ttt	ttt	tttca	at	3300	
tgttac	ttt	ttt	ttt	tttca	at	3360	
tacttgc	ata	ttt	ttt	tttca	at	3420	
ca	ttt	ttt	ttt	tttca	at	3480	
tttcat	tc	ttt	ttt	tttca	at	3540	
ctgt	atgtt	ttt	ttt	tttca	at	3600	
gcaat	gttcc	ttt	ttt	tttca	at	3660	
agcaaa	aggat	ttt	ttt	tttca	at	3720	
gtat	ctgc	ttt	ttt	tttca	at	3780	
ctgc	atgtt	ttt	ttt	tttca	at	3840	
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agaactt	act	ttt	ttt	tttca	at	3960	
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ctac	at	ttt	ttt	tttca	at	4380	
attg	aa	ttt	ttt	tttca	at	4440	
aga	acc	ttt	ttt	tttca	at	4500	
tactt	gtt	ttt	ttt	tttca	at	4560	
tca	ata	ttt	ttt	tttca	at	4620	
atc	actt	ttt	ttt	tttca	at	4680	
gag	tgtt	ttt	ttt	tttca	at	4740	
cctt	gtt	ttt	ttt	tttca	at	4800	
caaa	cattt	ttt	ttt	tttca	at	4860	
tgag	tata	ttt	ttt	tttca	at	4920	
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ctaa	atgt	ttt	ttt	tttca	at	5160	
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gagtt	ttt	ttt	ttt	tttca	at	5340	
ataat	atgt	ttt	ttt	tttca	at	5400	
agtt	ggc	ttt	ttt	tttca	at	5460	
tcctt	ttt	ttt	ttt	tttca	at	5520	
atccc	atgt	ttt	ttt	tttca	at	5580	
aaga	acaa	ttt	ttt	tttca	at	5640	
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SEQ ID NO: 13                  moltype = AA    length = 457  
 FEATURE  
 source                  Location/Qualifiers  
 1..457  
 mol\_type = protein  
 organism = Homo sapiens

SEQUENCE: 13

MLGAVKMEGH EPSDWSSYYA EPEGYSSVSN MNAGLGMNGM NTYMSMSAAA MGSGSGNM

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GSMNNMSYYVG	AGMSPSLAGM	SPGAGAMAGM	GGSAGAAGVA	GMGPHLSPSL	SPLGGQAAGA	120
MGGGLAPYAN	NNSMSPMGQG	GLSRDARDPKT	YRTSYSTHAKP	PYSYSLISITM	AIIQSPKNM	180
TLSIEIYQWIM	DLFPPFYRQNQ	NNSQNSNRSIRS	LSFNDNCFKLVR	PSPPDKPGKG	SFTWLTHPDSD	240
NMFENGCYLR	RQKRKFCKEIQ	LALKEAAGAA	GSGKKAAGA	QASQAQQLGEA	AGPASETPAG	300
TESPHSSASP	CQEHHKRGGLG	ELKGTPTAA	SPPEPAPSPG	QQQQAAAHLL	GPPHHPGPLP	360
EAHLKPEHHT	AFNHPFSIGLN	MNSSEQQHHH	SHHHHQPKHM	DLKAYBQVMH	YPGYGSPPMPG	420
SLAMGPVNTK	TGLDASPLAA	DTSYQGVGS	RPMINSS			457

SEQ ID NO: 14 moltype = DNA length = 2428  
FEATURE Location/Qualifiers  
source 1..2428  
mol\_type = unassigned DNA  
organism = Homo sapiens

SEQ ID NO: 15 moltype = AA length = 505  
FEATURE Location/Qualifiers  
source 1..505  
mol\_type = protein  
organism = Homo sapiens

SEQ ID NO: 16 moltype = DNA length = 3365  
FEATURE Location/Qualifiers  
source 1..3365  
mol\_type = unassigned DNA

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SEQ ID NO: 17          moltype = AA  length = 421
FEATURE                Location/Qualifiers
source                 1..421
                      mol_type = protein
                      organism = Homo sapiens
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LDLDTNHRERL LEQLFEMADQ YQYQVVLVEP KTAWRLDCAQ LKEKNQWQLS ADDLKKLKPQ 180
LEKDFLPLYF GWFLTJKKSSE TLRKAGQVFL EELGNHKAKF KELRQFVPGD EPREKMDLV 240
YFGKRPPGV1 HCTTKFCDYG KAPGAEEYAQ QDVLKKYSYK AFTLTISALF VTPKTTGARV 300
ELSEQQQLQW1 PSDVDKLSPT DNLLPRGSRAH ITLGCADAVE AVQTGLDLLE ILRQEKGGSR 360
GEEVGELSLRG KLYSLGNGRW MLTLAKNMEV RAIIFTGYYGK GKPVPTQGSR KGGALQSCTI 420
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SEQ ID NO: 18 moltype = DNA length = 2598

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aatgcctgcg aggttgtgca cgtagtaggg tcagggcacg gcagctacc ggcaatttc	720
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SEQ ID NO: 21            moltype = AA   length = 378  
 FEATURE                Location/Qualifiers  
 source                1..378  
 mol\_type = protein  
 organism = Homo sapiens

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 FQLTHSLGGG TGSGMGTLLI SKVREEYEPDR IMNTFSVVPD PKVSDTVVEP YNATLSIHQL 120  
 VENTDETYCI DNEALYDICF RTLKLATPTY GDLNHLVLSAT MSGVTTSLRF PGQLNADLRK 180  
 LAVNMVPPR LHFFMPGFAP LTARGSQYR ALTVPLELTQ MFDAKNMMAA CDPRHGRYLT 240  
 VATVFRGRMS MKEVDEQMLA IQSKNNSYYF EWIPNNVKVA VCDIPRGLK MSSTFIGNST 300  
 AIQELFKRIS EQFTAMFRRK AFLHWYTGEGL MDEMEFTEAE SNMNDLVSEY QQYQDATAEE 360  
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SEQ ID NO: 22            moltype = DNA   length = 1720  
 FEATURE                Location/Qualifiers  
 source                1..1720  
 mol\_type = unassigned DNA  
 organism = Homo sapiens

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mol_type = protein
organism = Homo sapiens

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cgtttggggg ttctgggtcg gttccagccgg ctttggccgtt aagatgttgcgttgc cttccacca	1200
gcacatctcttcc tccctgttgc cttccggccgc gggccggatgttgc gggccggatgttgc	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
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aacgaaaaaa	aaccgttgc	catccagttt	tcccgattta	ctaaaatagg	taaccaggcg	1860
tctcacagtc	ccggctcttg	caagagcgt	aatgaacgtt	ctcataaca	cgcaggagta	1920
cggggagccc	tgaacccccc	gctgtcg	ggatccccc	tgcgggtggg	acggcgggaa	1980
ggcgctttcc	gctgttcctc	agcggggccgg	gcccttgacc	agcgcggccc	gcaggcttcc	2040
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gttacaaaat	tcttttaccc	aagggtatgc	tatgacattt	ccgcgttta	ctttgatttt	2160
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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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agccttagatc	ccagggacag	actctccctca	actcggctgt	gaccacaaat	gctccgatac	180
aggggggtctg	gatccctact	ctggggccca	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	gccttcactt	cccaactcggt	tattccagcc	cgggggctca	540
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cttttctgtc	tctactgtc	tcacttc	tctcttc	tcttcatttc	tcttcatttc	840
tctcttttct	ctccctctcc	tggaaatttt	cggttccgg	ggaaggagga	cccttcgcaaa	900
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cccgctcg	ccagagcccg	atgacattt	tctgcggccc	cgaggttaagg	gcagcagccgg	1020
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cgcggccagc	ctggccgc	tcacccctca	cgcccaagtga	gcctactggc	gcggcgcgt	1920
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gagctctgtc	gogaggaggg	gcccgggg	atggactggg	ggtggggcat	ggtggggatt	2040
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ttctctccgg	gacctgtatcg	agcgctgt	ggctttaaacc	tgagctggc	cagttagacat	2160
cgttttatga	aaaggatccg	ctgtgtc	tccacttag	aactcatcg	accccccgg	2220
ccacacccctccg	ggaaaaagatt	ctaaaaactt	ctttccctga	gagcgtggcc	tgacttgcag	2280

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agcaacacgc	cgaccggccc	ctccagggtc	gtccccggcc	caaggccgg	ggccacaagt	2460
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agaatatggt	tttctaataa	atctgtggat	gttccttctt	caacagtatg	agcaagttta	2640
tagacattca	gagtagaaacc	atcttgtggat	tggaaataacc	caaactgcg	gattttcaggg	2700
ccgggttgcgc	tgtatgttatt	atttttaaaat	aaaaactacc	ccaccggactc	atctttcttt	2760
ctttaagcac	aaagtgtttt	ggtttatttt	gtacctggaa	acgtcaacaga	attaaaaggc	2820
agttgctgtg	gaaacaggtt	gggttatttt	gggggttctgt	tgggtttta	aaattttctt	2880
ttttggatgt	gttaattttat	caatgtatgg	gtaaatggcg	aatgtactgg	tgtttgttca	2940
cgtgactgc	agccccatcg	gagtctaaagc	ccggcttctt	atattttgtt	ttatttttgc	3000
cacgttttac	acaatgtttaa	aactctttcca	cgtgttctt	gcgttccgtg	caacgcgcgt	3060
ccggcgctgc	tcgttgc当地	actgggtttt	gtagcgctcg	ccgtgttaca	cccttctct	3120
gatcgaccc	cccttcggcag	agatgtatc	atctgtttt	ttttttgtaaa	aacaatgtgc	3180
taataaatat	ttatctactt	ttttttgttca	aaaacggaaat	aaatgtactga	gtgttggat	3240
tttaaaataaa	attnaaacgc	aaaaaaaaaa	aaaaaa			3275

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

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SEQ ID NO: 34          moltype = DNA  length = 1488
FEATURE                Location/Qualifiers
source                 1..1488
                      mol_type = unassigned DNA
                      organism = Homo sapiens
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SEQUENCE: 34
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ttgttcgaat gccccctcca ctcggaccc gagtggattt ctccctgggt ggggactca 180
atgtctggctt caaggagacc cggggcagt gaggggcaga gatgtatggg ctcaatgacc 240
gttgcggcag ctacatcgag aagggttcgtt tcctgaaaca gcaaaaacaagg ggcgtggctg 300
ctgagctgca ccagtcggcc gggaaaggac ccaccaagct ggcagacgtc taccaggctg 360
agtcggcaga gtgcggctgc cggctcgat aacttacccgc caacacgcgc cggctggagg 420
tttagaggggaa caatctggca caggacctgg ccactgttag gcagaagctc caggatggaa 480
ccaaacctggag gctggaaagcc gagaacaacc tggctgccta tagacaggaa gcagatggaa 540
ccaaacctggc cggcttcgtt ctggaggggaa agatgtatgg gtcggaggagg gatgtccgg 600
ttcttgaggaaa gatccacggag gaggagggtt gggaaactcca ggagacgtc gcccggacago 660
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ccaaatgttgc agacctggaca gacgtctgtt cccgcacacg gggatgttc cgcacaggcc 840
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tgtcagaagg ccacccatcaag aggaacatcg ttggtaagac cgtggagatg cgggatgggg 1260
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ctggccacatt tccccagacc tgatgtccccc accaccacccag ctgtcccccc ecctccctgt 1440
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SEQ ID NO: 35          moltype = AA  length = 92
FEATURE                Location/Qualifiers
source                  1..92
                        mol_type = protein
                        organism = Homo sapiens
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SEQ ID NO: 36 moltype = DNA length = 1135  
FEATURE Location/Qualifiers

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tgagaaggcc	ctgctcaccc	tcctcgggga	ggggaaagcac	cagggttgtt	ggcatcgagg	2040
gccttaccac	tcctatgact	cctgtttct	ctctcacaga	tagtgagggt	ctgacatgcc	2100
catgccacct	atgcccacagt	gcctaagggc	taggccacc	agagactgtg	cccgagctg	2160
gcgggtttc	ccactcaggg	gctgagacta	gctttgagga	gcctcatgg	ggagtggggg	2220
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gacacaggcc	ccagcaccca	gggtgctgc	ggcaggctga	agacactaga	atcctgaccc	2640
gtacattctcg	cccttgctc	ttaccctctg	cctcccaagtg	gtatattgt	aaagtatgt	2700
gtatatatctg	ccctatctt	cctgttctgc	agecccccaa	atccacatgt	aactatattac	2760
tgtctctctgt	tatttatctc	agtgttccc	tctctctac	actctagccc	ctattaactc	2820
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aa						2882

SEQ ID NO: 39                    moltype = AA length = 705

FEATURE                         Location/Qualifiers  
source                         1..705  
mol\_type = protein  
organism = Homo sapiens

SEQUENCE: 39

NYLRRRLSD SNFMANLPNG	YMTDLQRQP PPPPPGAHSP GATPGPGTAT	AERSSGVAPA	60
ASPAAPSPGS SGGGGFFSSL	SNAVKQTTAA AAATFSEQVG	GGSGGAGRRG AASRVLLVID	120
EPHTDWAKYF KGKKIHINGID	IKVEQAESD LNVLVAHANG	FSVDMEVLRN	180
DFVLIQRQHAF SMARNGDYRS	LVIGLQYAGI PSVNSLHSVY	NFCDPWVFA	240
TEEFPLIDQT FYPNHKEMLS	STTYPPVVVM GHASHGMGKV	KVDNQHDFQD	300
YATAEFPIDA KYDVRVKQIG	QNYKAYMRTS VSGNWKTNTAC	SAMLEQIAMS	360
SEIFGGLDIC AVEALHGKD	RDHIIIEVVG SMLPIGDHQD	DRYKLWWDTC	420
QRQRDASPGR GSHGQTPSPG	ALPLIGRQTSQ QPAGPPAQOR	EDKQLIVEVL VNKMAQALPR	480
LQRQRPPOGQ QHLGLGPPA	GPSPLQRLPS PTSAPQQPS	PPPQGGPPQP GPGPQRQGPP	540
GAPPAAARPRA SPSPQRQAGP	PQATRQTSVS GPAPPKASGA	QAAPPTQGQG RQSRPVAGGP	600
TROASQAGPV PRTGPPTQQ	PRPSGPGPAG APKPELAQKP	PPGGQQRQGP PQKPPGPAGP	660
NKSQSLTNAF NLPEPEAPP	SLSQDEVKA	SDVPPPATA AAGGPPHPQL	705

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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gagggaaacca aatctccagaa	agatagaatgc	actttccca	gtgtatgtt	gaggccccac	180
ttgaacccag	gcactgttc	tccagacccc	acacttac	tgcctgttt	240
actgatttaa tgaataaagg	tgaacaat	gaaataagtgg	atgagtccac	tgaaaattct	300
gcaggcaag agactccata	tctacttact	tcttgcctat	cttctgcac	ctctcctagt	360
ccaccatcac tgctcaact	ggtaaagggt	ctacccaaatc	tggccctcgc	taccacaacc	420
cccttcagct ttgtccagcc	acattggcgc	tggatgttcc	cttctctgg	catatctta	480
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tgacgtcaact cgccggctcc	ccgcaaaactc	cccttccgg	ccaccttgg	cgcgtccgcg	1860
ccgcccgcggc cccaggccg	ccgcaccac	cgaggcgca	gataggggg	cacgggcgcg	1920

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gacttggtaag						2470

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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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TESDLSEIEVE FEYFPFLRHQV YFDAPTCRGG TTKVFLVGDY SSSAEFFVTV AVFAPLYSMG 120
ALATYIFLQN KYRENNKGPM LDFFLATAVFA FMWLVSAA AKGLSDVKMA TDPENIIKEM 180
PVCRQTGNTC KELRDPVTSG LNNTSVFGL NLVLWVGNLW FVFKETGWAA PFLRAPPGAP 240
EKQAPGDAY GDAGYGQQPG GYGPQDSYGP QGGYQPDYQG PQAGSGGSGYQ PGQDYGQQGY 300
PQGQAPTSEs NOM 313

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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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attttctaaa	ttagccaggg	aataatactga	cctagaaga	tcccaaaaaa	gtgaaattgc	3000
taatggcccc	gatgggactg	ggtcattgccc	ttgcacagaa	ttgccccatg	accccttctt	3060
gaagaacata	caacccaaag	ttgaagagaa	aatcaggattc	tcagatgact	ttttttaaaaaa	3120
tgggtctgc	acatcaaagg	tgcttattt	gcctccagat	gttttgcctt	ttggcactca	3180
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ccaagctatc	cagaatatcg	atgaaggcca	cccatttcagg	gcatactctgg	aactctgaat	3540
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cacgataaaag	gaactcagcgc	gcctcttttt	agtgtatgt	tttagtgatt	ctctgaaatgt	3660
tgcaatgttt	atgtgggtat	ttacccatgt	ttgggccttgc	ttaatggtc	tgacactact	3720
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tgttgcgtt	aaaaattatcc	tgcgttgc	gcccattgtt	catcatctta	agtgttgc	4080
gtgtctatgt	atggattttt	accgttaatca	tatcttttc	ctatctatctt	gaggccactgg	4140
tggaaataaaa	aacctgtata	tttttacttt	ttgcagatag	tcttgcgc	tctttgcag	4200
ttgcagagat	ggtggggctt	aaaaaaaat	aaaaaaagcc	cttttcagg	tgtgcactgt	4260
gtatggcttc	tgtatgttt	ttgcagattt	ctgaaatgt	atgtttttt	agagagatct	4320
ataccggat	agcggaaat	acaaaggctt	ttttttttgtt	atgttttgc	ttttgttgc	4380
tttttactgt	tatataattt	gccaatataa	gttataatag	attatataat	tatagtgtt	4440
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cattttttat	acatgttgc	ttccaaagca	cataaactgt	aagaagaaaat	attttcttgc	4560
gcactaccat	cttggtttca	catggaaatgc	cacacacata	gaactccaa	atcaatgttca	4620
ttgcacacat	tgactgtatg	taatttttgc	acaaatctt	ttqactgtat	ctaatgtttc	4680
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aatggatgtt	tataccatgt	ttggtttgc	tgtactgt	taaaatctgt	gaatgttttt	4800
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aaaaaaaaaa	a					4871

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

SEQ ID NO: 46 moltype = DNA length = 3097  
FEATURE Location/Qualifiers  
source 1..3097  
mol\_type = unassigned DNA  
organism = Homo sapiens

SEQUENCE: 46

	Organism = Homo sapiens					
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agccaggatgg	agaggagacg	catcacccc	gctgtcgcc	gctctactcg	ctcttcaggg	120
gagatgtatgg	tggggggcct	ggcttcggc	ccgcgttgg	ttccctggcc	ccgccttc	180
ctggctcgaa	tgcccccttc	actcccgaa	ccgggtggatt	tctccctggc	tggggcactc	240
aatgtctggc	tcaaggagac	ccggggccagt	gagcgggcag	agatgtatgg	gctcaatgac	300
cgttttgcga	gctacatcg	gaagggttcg	ttcttgcgaac	acggaaaacaa	ggcgctgggt	360
gctgagctgc	accagctgcg	ggccaaaggag	cccaccaaagc	tggcagacgt	cttacagggt	420
gagctgcgag	agctgcgcgt	ggggcttcgt	caactccacc	ccaaacgcgc	ccggctggag	480
gttgagaggg	acaatctggc	acaggacctg	gccactgtga	ggcagaagct	ccaggtgaa	540
accaacctga	ggcttggaaac	cgagaacaaac	ctggctgcct	atagacacgga	agcagatgaa	600
gccccccctgg	cccgctctgg	tctggggagg	aaggatgtgt	cgtgtggagg	ggagatccgg	660
tttgttggag	agatccacca	ggaggagggtt	cgggaactcc	aggagcaget	ggeccgcacag	720
caggcttcatg	tggagcttga	cgtggccca	cacagactca	ccgcacccct	aaaaagatgc	780
cgcacgcagt	atgaggcaat	ggcgttcacgc	aacatcgatg	aaggccaaga	gtgttacccg	840
tccaaagtgg	cagacctgac	agacgctgt	gccccaaacg	cggagctgt	ccgcaggccc	900
aaggcacaag	ccaaacgacta	ccggccgcag	ttgcactct	tgacttcgca	cctggaggat	960
ctggccggca	cgaaacgatc	cctggggagg	cagatgcgcg	agcaggagga	ggccgcacgt	1020
ccggggccgg	ccatgtatcc	ggaggccgtc	ggccgcgttgg	aggaaagggg	ccagacgttc	1080
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ctggacatcg agatgccac	ctacaggaag ctgctagagg	gcgaggagaa ccggatcacc	1200
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gtgtcagaag gccaccaa	gaggaacatc tggtgaga	ccgtggatg gccccatgg	1320
gaggcattta aggatccaa	gcaggagac aaggatgt	tgtgaggcag gaccacactg	1380
gtggcctcg cccgtctca	tgagggccc gaggcaga	aggatagtgc ctccgcct	1440
gtggcacat ttccccagac	ctgagctccc caccacccca	gtgtgcctcc tccctccct	1500
gtcccttaggt cagctgtcg	ccctaggctc cgtagtata	aggectgcg aacggcaccc	1560
acccagacc cagcaactcc	aactaacaag aaactcacc	ccaaggggca gtctggagg	1620
gcatggccg cagttgtgt	tagatgagg aggaaggaga	gaagggggagg aggggggggg	1680
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gatgggggtt ctctggagt	atctggggat tggtgcctt	agtttctca gggtgttgg	1800
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cctgagcgat gactcaagt	tctcagtcg cctgagctgc	catccaggga tgccatctgt	2160
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tggagggatgg tggggatgt	ggggggatgt cttggccccc	agctgtgggt	2280
acagagagggt caagcccg	aggactgccc cgtgcagact	ggagggggacg ctggtagaga	2340
tggaggaggaa ggcaattggg	atggcgtagt gcataca	agggggttgg ggtgaccagt	2400
tgcacttggc ctctggattt	tggaaattaa ggaagtgtact	catccttctg aagatgtca	2460
aacaggagag aaaggggatg	tatccatggg ggcaggggat	gactttgtcc catttctaaa	2520
ggccttccc ttgtgtgtc	ataccaggcc gccccagcc	ctgagccctt gggactgtc	2580
cttcttaacc ccagtaagcc	actgcacac gtctgaccc	ctccacccca tagtgcacgg	2640
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ccagtttctt aggtatgtcc	ctattttca atttgtaaa	atgggcacga gcaaagtgtaa	2760
gacactggct ctatccctc	cagcttggg gccgggtgc	cagggtgc acgtccaccc	2820
cagtgcaccc actctgttt	gactgagcag actgggtgac	agactgggtt gatctgtcc	2880
cagagatggg actggggagg	cccacttcg gtttctctc	tccctttaaa ggccgaagaa	2940
gggtccttcc ctctcccaat	gactgggtc ctttccctc	cacttccccc tgccaccc	3000
tgtgtgtct gctgtcaat	ttcaggcgc tgcgtgc	tttagtgcgt gagggaaaat	3060
aaagacaaat gtcgcgcct	tccccaaaaaaa	aaaaaaaaaaaaaaaaaaaa	3097

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

SEQUENCE: 47
MSELEKAMVA LIDVFHQYSG REGDKHKLKK SELKELINNE LSHFLEEIKE QEVDVKVMET 60
LDNDGDGECD PQEFLMAFVAM VTTACHEFFE HE                         92

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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

SEQUENCE: 48
ggcaggggg aataagaggc tgcctctgc caccagtctt gcccggcagg acccgacgca 60
gagacgacgc ctgcagcaag gagcaggcagg aggggtgaga caaggaagg gatgtctgag 120
ctggagaagg ccatgttgcg cctcatgcg gttttccacc aatattctgg aaggggggaa 180
gacaaggcaca agcttaagaa atccgaactg aaggagctca tcaacaatg gctttccat 240
ttcttagagg aaatcaaaatg gcaaggaggat gtggacaaatg tcatggaaatc actggacaa 300
gatggagacg cggaaatgtc ctccaggaa ttcatggctt ttggtgcatt gtttactact 360
gcetggccacg atgttttgcg acatggatgtg gattagaaatc cagccaaacc ttctgttaa 420
cagagacggt catcaagaa acggacacgc aagggttgcg acgcctagtg gagctgagct 480
ttccagecggt gtttagtgcg attaggaatc ttgatgttgc ttgtgtatgaaaatgaaa 540
actctttccca aagggttgcg ttaacggctt gcatcatttc ttctgtata ttggccctgt 600
gtgtaaatgtc actggggccca gggacttgcg ttaacaggatc ctttagggatc aggttctcagt 660
gataaaatgtc gacccgtca gccccatcg gccgtgtaga cccttaccccg gagggaaacc 720
tgactacaga aatttcccg gggccaccctt aaaacttccca ctacctttaaa aaaacaaagc 780
cttatccacg atttttgcg aacactgtcg ttctttaaat gctttccca tccatgcaga 840
taacagcttgg tggccctgcg agggttgcgtt ggcttccggc tgctttcccg 900
gatgcgcctg ataccaggat gaaacgtcg cgctggcgcg gtcctggaa aaagcaactc 960
catcagaact cgcaatccga gccagctcg ggggtcccg cgtggccccc gtgacccatg 1020
cgattcaagt cgccggatcg ggtatctgc ctccaaatcg ttccttgcac atgcggctc 1080
cgagggcact accgggggctt ctgagccacc gcgagggcctt gcttcaataaaaag 1135

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SEQ ID NO: 49      moltype = AA  length = 422
FEATURE          Location/Qualifiers
source           1..422
mol_type = protein
organism = Homo sapiens

SEQUENCE: 49
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YETGSIRPRA	IGGSKPRVAT	PEVVSKIAQY	KRECPSIFAW	EIRDRLLSEG	VCTNDNIPSV	120
SSINRVLRLN	ASEKQOMGAD	GMYDLKRLMLN	GQTGSWGTRP	GWYPGTSVPG	QPTQDGCGQQ	180
EGGGENTNSI	SSNGEDSDEA	QMRLQLKRKL	QRNRTSFTQE	QIEALEKEFE	RTHYPDVFAR	240
ERLAAKIDL	EARIQWFSN	RRAKWRREEK	LRNQRRQASN	TPSHIPISSS	FSTSVYQPIP	300
QPTTPVSSFT	SGSMLGRTDT	ALTNTYSALP	PMPMSFTMANN	LPMQPPVPSQ	TSSYSCMLPT	360
SPSVNGRSYD	TYTPPHMQTH	MNSQPMGTSG	TTSTGLISPQ	VSVPVQVPGS	EPDMSQYWPR	420
LQ						422

SEQ ID NO: 50	moltype = DNA length = 1399	
FEATURE	Location/Qualifiers	
source	1..1399	
	mol_type = unassigned DNA	
	organism = Homo sapiens	
SEQUENCE: 50		
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caacatcccg agatttcaga	gccccatatt cgaccccggt ggaatccgc ggcggccac	120
cagagccagc atgcagaaca	gtcacagcgg agtgaatca gtcgggtgg tctttgtcaa	180
cgccgcggcca ctgcggcact	ccacccggca gaagatggta gagctagctc acagcggggc	240
ccggccgtgc gacatttccc	gaattctca ggtgtccaaac ggatgtgtga gtaaaatct	300
gggcaggat tatcagactg	gctccatcg acccaggcga atccgtgtta gtaaaccggag	360
agtagcgact ccagaagttg	taagoaaaat agccaggat aagcgggagt gccgcgtccat	420
cttgcttgg gaaatcccgag	acagattact gtcggagggg gtctgtacca acgataacat	480
accaaagegtg tcatcaataa	acagaggttc tcgcaacctg gtagcgaaaa agcaacagat	540
gggcgcagac ggcgttatc	ataaaatcaag gatgttgaac gggcagaccc gaagctgggg	600
cacccgcctt ggttgttac	cgggacttc ggtgcagggg caacctacgc aagatggctg	660
ccagcaacac gaaggagggg	gagagaatac caactccatc agtccaaacg gagaagattc	720
agatgaggct caaatcgccg	ttcagctgaa gccgaagctg caaagaataa gaacatctt	780
tacccaagag caaatttgggg	ccctggagaa agatgtttag agaaaccatt atccagatgt	840
gtttgcggca gaaagactag	cagccaaat agatctacctt gaagcaagaa tacagtgatg	900
gttttctaatt cgaaggccca	aatggagaag agaagaaaaa ctgaggaaatc agagaagaca	960
ggccageacac acacctagtc	atattccatc ctagcgttagt ttccagccca gtgtctacca	1020
accatttcca caacccacca	cacccgttcc tctccatcata tctggctcca tggtggccg	1080
aacagacaca gccctcacaa	acacccatcg cgctctccg cctatgocca gcttcacccat	1140
ggcaataaac ctgcctatgc	aaccccccagt ccccaagccg acctccatcat actccatgc	1200
gctgcccacc acccccttgg	tgaatggggcgg agttatgtatg acctacaccc ccccacat	1260
gcagacacac atgaacatgg	agccaatggg cacccctggcc accatctcaa caggactat	1320
ttccctgtgt gtgtcgttc	cagtccaaatg tcccccggat gaaacctgtata tgcttcaata	1380
ctggccaaga ttacagtaa		1399

SEQ ID NO: 51	moltype = AA length = 1621
FEATURE	Location/Qualifiers
source	1..1621
	mol_type = protein
	organism = Homo sapiens

SEQUENCE: 51		
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AZRALVDR WREKHAEEVA	RDNLAEEVLRG VAGRCQQLRL ARERITTEVA RNRRAVEAEK	120
CARAWLSSQV AELERELEAL	RVAHEEERVG LNAQAAACAPR CPAPPGRGPA PAPEVEELAR	180
RIGEAWRGAV RGYQERVAHN	ETSLQARER LGRAVQGARE GRLELQQLQA ERGGLLERRA	240
ALEQRLEGRW QERLRLATEKF	QLAVEALEQE KQGLQSQIAQ VLEGRQQLAH LKMSLSLEVA	300
TYRTLLEAEN SRLQTPGGGS	KTSLSFQDPK LELQFPRTPE GRRLGSSLVP LSPTLSPLPSPL	360
PATLETPVPA	RTPTLASTPI PPTPQAPSPA VDAEIRAQDA PLSLLQTQGG	420
RKQAPEPLRA EARVAIPASV	LPGPEEPGQO RQEASTGQSP EDHASLAPPL SPDHSLEAK	480
DGESGGSRVF SICRGEGEQ	IWGLVEKETA IEGKVVSLLQ QEIWEEEEDLN RKEIQDSQVP	540
LEKETLKSLL EIIQESLKL	ENQSHETLER ENQECPRSLE EDLETLKSLE KENKELLKD	600
EVVRPLEKEA VGQLKPTGKE	DTQTLQSLQK ENQELMKSL GNLETFLFPG TENQELVSSL	660
QENLESLTAL EKENQEPPLRS	PEVGDEEALR PLTKENQPL RSLDENKEA FRSLEKENQE	720
PLKTLLEEQD SIVRPLETEN	HKSLSLSEEQ DQETLRTLEK ETQQRRLSLG EQDQMTRLPP	780
EKVDLEPLKS LDQETAPRL	NENQEFKL KEESEVEAVKS LETEILESLK SAGQENLTEL	840
KSPETQAPLW TPEEINQGM	NPLEKEIQLPQ LESVEVNQET FRLLEENQE SLRSLGAWNL	900
ENLRSPPEEVN KESQRNLEER	ENLKGKGEYQE SLRSLEEEQG ELPQSAADVQR WEDTVEKDQE	960
LAQESPPGMA GVENEDEAEL	NLREQDGFTG KEEVVEQGEL NATEEWIPIG EGHPEPPEPK	1020
EQRGLVVEGAS VKGGAEGLQD	PEGSQSQVGA PGLQAPQCLP EAIEPLVEDD VAPGGDQASP	1080
EVMLGSEPM GESAAGAEPG	PGQGVGGLGD PGHLTRREEV EPPLEEEESLE AKRVQGLEGP	1140
RKDLEEAGGL TEFSELPGK	SRDPWEPPRE GREESEABAP RGAEAAFPAA TLGHGTSDAP	1200
SPWPLGSEEEA EEDVPPVLVS	PSPTYTPILE DAPGPQPOAE GSQEASWVGQ GRAEALGKVE	1260
SEQEELGSGE IPEGPQEEGE	ESREEESEDE LGETLPDSTP LGFYLRSPS PRWDPTGEQR	1320
PPPQGETGKE GWDPAVLASE	GLEAPPSEKE EGEEGEEECG RDSDLSEEFE DLGTEAPFLP	1380
GVPGEVAEPL QQPQQLLD	AAWDRDGESD GFADEEESGE EGEEDQEEGR EPGAGRWGP	1440
SSVGLQALS SSQRGEFLES	DSVSVSVPWD DSLRGAVAGA PKTALETESQ DSAEPGSEE	1500
ESDPVSLERE DKVPGPLEIP	SGMEDAGPGA DIIGVNGGQP NLEGKSQHVNV GGVVMGLEQS	1560
EEVGQGMPLV SEGDRGSPFQ	EEEGLALKTS WAGAPVHLGQ QGFLKFTORE GDRESWSSGE	1620
D		1621

SEQ ID NO: 52	moltype = DNA length = 5591
FEATURE	Location/Qualifiers

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gtggggggcca	gggtttctgt	ttggcagcct	ccaggccctg	agtatctcc	agagagggga	4500
attccctggag	tctgatctg	tgatgttag	tgtccccctgg	gatgacagct	tgagggttgc	4560
agtggcttgt	gcccccaaga	ctgccttgg	aacggagtcc	caggacagtg	ctgagccccc	4620
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gctggagcag	tctgaggaag	tggggcaagg	aatgcccta	gtctctgagg	gagaccgagg	4860
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gtgacggcgc	tccatgtgc	tgacttcccc	catccctgc	acgctgtggc	cctgcctggc	5520
tagtccctgc	ctgaataaaag	taatgcctcc	gcttcaaaaa	aaaaaaaaaa	aaaaaaaaaa	5580
aaaaaaaaaa	a					5591

SEQ ID NO: 53                    moltype = AA   length = 348  
 FEATURE                        Location/Qualifiers  
 source                        1..348  
 mol\_type = protein  
 organism = Homo sapiens

SEQUENCE: 53  
 MAQPGSGCKA TTRCLEGTAP PAMAQSDEAA LAGALDKDEQ QASPCTPSTP SVCSPSSAAS 60  
 SVPSAGKNIC SSCGLEILDR YLLKVNLIW HVRCLECVSP RTSLRQQNSC YIKNKEIFCK 120  
 MDYFSRFGTK CARCGRQIYA SDWVRARGN AYHLACFACF SCKRQLSTGE EFGLVEEKVL 180  
 CRIHYDTMIE NLKRAAENGN GLTLEGAVPS EQDSQPKPAAK RARTSFTAEQ LQVMQAQFAQ 240  
 DNNPDAQTLQ KLADMTGLSR RVIQWFQNC RARHKHPTQ HPVPPSGAPP SRLPSALSDD 300  
 IHYTPFSSPE RARMVTLHGY IESHFPSVLT LPALPHLPVG APQLPLSR 348

SEQ ID NO: 54                    moltype = DNA   length = 2835  
 FEATURE                        Location/Qualifiers  
 source                        1..2835  
 mol\_type = unassigned DNA  
 organism = Homo sapiens

SEQUENCE: 54  
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 ctggacaatgg accagggtca ggccctccca ttagcgccta gcacgccttc tgctctgtca 180  
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 ctggaggtct cccgtgtcg cactgtcg cggcaggcaga acagctgtca catcaagaac 360  
 aaggagatct tctcaagat ggactactc agccgattc ggaccaatgt tgccgggtgc 420  
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 caacccaaggc cggccaaaggc cgcggggacg tccttcaccc cggaaacagct gcagggtatg 720  
 caggcgcagt tccgcaggaa caaacacccc gacgcgtcaga cgcgtcggaaa gctggccgac 780  
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SEQ ID NO: 55 moltype = AA length = 356  
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mol\_type = protein  
organism = Homo sapiens

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EKEVLKRVHY DCMLDNLKRE VENGNGISI GALLTEQDVN HPVKPARKART STFAQDQLQM 240
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SAMFPYPGQH GPAHPAFSIG SPSRYMAHHP VITNGAYNSL LSNSSPQGYP TAGYPYPOQY	180
GHSYQGAPFY QFSSTQPGVL PGKAQVYLN RPLWLKFHRH QTENIITKQG RRMFFFLSFN	240
ISGLDPTAHY NIFVDVILAD PNHWRFQGGK WVPCKGADTN VQGNRVMH DSPNTGAHNW	300
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FPETQFIAVT AYQNTDITQL KIDHNPFAGK FRDNYDTIYT GCDMDRLTPS PNDSPRSQIV	420
PGARYAMAGS FLQDQFVSN AKARHPGAG AGPGPGTDRS VPHTNGLLSP QQAEDPGAPS	480
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DPSGWGARSP PQYCGTKSGS VLPCWPNSAA AAARMAGANP YLGEEAEGLA AERSPLPPGA	600
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	organism = Homo sapiens
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SEQ ID NO: 59 moltype = AA length = 542  
FEATURE Location/Qualifiers  
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mol\_type = protein  
organism = Homo sapiens

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NLVEACFKQF KTNYEKRSKF VPIQANETLV GAVINNVEA METLTRLTEEV LPVPGESVNG 240
VNALGLVVFS MCFGVIGNM KEQGQALREF FDSSLNEAIMR LVAVIMWYAP VGILFLIAKG 300
IVEMEDMGVI GGQLAMYTWT VIVGLLIHAV IVLPLLYFLV TRKNPWFVFIG GLLQALITAL 360
GTSSSSATLP ITFKCLEEEN GVDKRVTRFV LPVGATINMD GTALYEAALAA IFIAQVNNFE 420
LNFGQIIIT ISATAASIGA AGIPQAGLVT MVIVLTSVGL PTDDITLIIA VDWFLDRLR 480
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source                 1..1873
                      mol_type = unassigned DNA
                      organism = Homo sapiens
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SEQ ID NO: 61 moltype = AA length = 497  
FEATURE Location/Qualifiers  
SOURCE 1 497

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mol_type = protein
organism = Homo sapiens

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PRAGGPHELEY FVRLEVRRGD LAALLSGVRQ VSEDVRS PAG PKVPWFPFRKV SELDKCHHLV 180
TKFDPDLDD HPGFSDQVYR QRRKLIAEIA FQYRHGDPIP RVEYTAEEIA TWKEVYTTLK 240
GLYATHACGE HLEAFALLER FSGYREDNIP QLEDVSRLPK ERTGFQLRPV AGLLSARDFL 300
ASLAFRVRFQC TQYIRHASSP MHSPEPDCC H ELLGHVPMILA DRTFAQFSQD IGLASLGASD 360
EEIEKLSTLY WFTVEFGLCK QNGEVKAYGA GLLSSYGBEL HCLSEEPEIR AFDPEAAVQ 420
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SEQ ID NO: 62      moltype = DNA length = 1629
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source           1..1629
mol_type = unassigned DNA
organism = Homo sapiens

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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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PAEVKSPPEKA KSPAKKEEAKS PPEAKSPEKA EAKSPAEVKS PEAKSPA EAKSPAEAKS 600
PEKAKSPVKE EAKSPAEAKS PVKEEAKSPA EVKSPEAKS PTKEEAKSPE KAKSPKEEEA 660
KSPPEAKSPV KAEAKSPPEKA KSPVKA EAKSPPEAKS PEAKSPVKE EAKSPPEAKS PVKEEAKSP 720
KAKSPVKEEA KTPEAKSPV KEEAKSPPEKA KSPEAKTLD VKSPEAKTPA KEEARSPADK 780
FPEKAKSPVKE EEVKSPPEAK SPLKEDAKAP EKETPKKEEV KSPVKEEEKP QEVKVKEPPK 840
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SEQ ID NO: 64      moltype = DNA length = 3721
FEATURE          Location/Qualifiers
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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  $\mu\text{m}$  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  $\mu\text{m}$  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  $\mu\text{m}$ , less than about 400  $\mu\text{m}$ , less than about 350  $\mu\text{m}$ , or less than about 300  $\mu\text{m}$ .

**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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