TITLE

METHODS FOR TREATING AND/OR REVERSING NEURODEGENERATIVE DISEASES AND/OR DISORDERS

BACKGROUND

[0001] A stroke is the sudden death of brain cells in a localized area due to inadequate blood flow. A stroke occurs when blood flow is interrupted to part of the brain. Without blood to supply oxygen and nutrients and to remove waste products, brain cells quickly begin to die. Depending on the region of the brain affected, a stroke may cause paralysis, speech impairment, loss of memory and reasoning ability, coma, or death.

SUMMARY

[0002] The present disclosure relates to methods for treating and/or reversing neurological diseases or disorders associated with neuronal cell loss (*e.g.*, cell death caused by cerebral ischemic stroke, hemorrhagic stroke, cerebral palsy, or traumatic brain injury) in a brain. Such methods may be useful for treating symptoms resulting from stroke or other brain injuries.

[0003] The present disclosure also provides methods for treating a disease or disorder associated with neuronal cell loss in a brain including, for example, for treating the symptoms resulting from stroke or other brain injuries, by obtaining an expanded neural stem cell population and introducing a therapeutically effective amount of the expanded neural stem cell population to at least one area of the brain of a subject, wherein the neural stem cell population differentiates into neurons that integrate *in vivo* into the brain of the subject. Without wishing to be bound by a theory of the ~~invention~~disclosure, it is believed that the integrated neurons then promote repair of the injured tissue by replacing the dead neurons, regenerating the host neurons, and/or inducing plasticity of the host circuitry to re-establish the damaged neuronal connections that include the donor neurons.

[0004] In one aspect, the present invention refers to the use of an expanded stem cell population in the manufacture of a medicament for treating a disease or disorder associated with neuronal cell loss in a brain, wherein the use comprises expanding at least one neural stem cell isolated from spinal cord tissue of a human to form the expanded stem cell population and wherein, a therapeutically effective amount of the expanded stem cell population is to be introduced to at least one area of the brain of a subject. In some ~~embodiments~~examples, introducing the therapeutically effective amount of the expanded population includes injecting at least a portion of the therapeutically effective amount into one to a plurality of areas of the brain of the subject.

[0005] In some ~~embodiments~~examples, expanding the at least one neural stem cell includes culturing the neural stem cell in the absence of serum.

[0006] In some ~~embodiments~~examples, expanding the at least one neural stem cell includes exposing the at least one neural stem cells to at least one growth factor. In some ~~embodiments~~examples, the growth factor is selected from the group consisting of bFGF, EGF, TGF-alpha, aFGF and combinations thereof.

[0007] In some ~~embodiments~~examples, at least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the expanded stem cell population is capable of generating neurons in brain tissue of the subject.

[0008] In some ~~embodiments~~examples, introducing the therapeutically effective amount of the expanded stem cell population includes injecting at least a portion of the therapeutically effective amount into a plurality of areas of brain tissue of the subject.

[0009] In some ~~embodiments~~examples, the areas of the brain involve the motor pathway—the neuronal fibers that conduct electrical signals to and from the brain, brainstem, and spinal cord that govern muscle contraction. Such areas include the motor cortex, striatum, internal capsule, thalamus, midbrain, brainstem, and cerebellum. Due to stroke or trauma, a discrete area –or areas within this pathway may be damaged, resulting in symptoms of paralysis, spasticity, rigidity, and other motor dysfuctions.

[0010] In another ~~embodiment~~example, a suspension of the spinal cord-derived human neural stem cells are injected into, near, or around the affected area(s). The injected cells differentiate into neurons and glia which integrate into the affected area to promote repair of motor pathway that results in motor recovery and/or amelioration of the motor dysfunction.

[0011] In some ~~embodiments~~examples, the subject had an event that caused cerebral ischemia such as a heart attack or stroke.

[0012] In another aspect, the present invention refers to the use of a therapeutically effective amount of an expanded population in the manufacture of a medicament for treating stroke in a subject in need thereof, wherein the use comprises: expanding *in vitro* at least one said neural stem cell isolated from spinal cord tissue of a human to form an expanded population; concentrating the expanded population; and wherein the therapeutically effective amount of said expanded population is to be introduced to at least one area of the subject brain. The present disclosure also provides methods for treating stroke in a subject in need thereof comprising isolating at least one neural stem cell from spinal cord tissue of a human; expanding *in vitro* said neural stem cell to form an expanded population; concentrating the expanded population; and introducing a therapeutically effective amount of said expanded population to at least one area of the subject brain.

[0013] In other ~~embodiments~~examples, the expanded neural stem cell population is derived from a spinal cord tissue including, for example, a post-mortem fetal spinal cord tissue of a human.

[0014] In some ~~embodiments~~examples, the gestational age of the post-~~mortum~~ mortem fetus is between about 5 and about 20 weeks.

[0015] In some ~~embodiments~~examples, expanding the at least one neural stem cell includes culturing the neural stem cell in the absence of serum.

[0016] In some ~~embodiments~~examples, expanding the at least one neural stem cell includes exposing the at least one neural stem cells to at least one growth factor. In some ~~embodiments~~examples, the growth factor is selected from the group consisting of bFGF, EGF, TGF-alpha, aFGF and combinations thereof.

[0017] In some ~~embodiments~~examples, at least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the expanded stem cell population is capable of generating neurons in brain tissue of the subject.

[0018] In some ~~embodiments~~examples, introducing the therapeutically effective amount of the expanded stem cell population includes injecting at least a portion of the therapeutically effective amount into a plurality of areas of brain tissue of the subject.

[0019] These and other ~~embodiments~~examples of the ~~invention~~disclosure are described in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The foregoing summary, as well as the following detailed description of the disclosure, will be better understood when read in conjunction with the appended figures.

[0021] Figure 1 shows that transplantation of human spinal-cord derived neural stem cells (HSSC) improved neurological behavior after cerebral ischemia. Neurological behavior measurement protocols were used to assess neurological function before and after MCA ligation in HSSC-implanted rats (n = 10) and buffer-injected control rats (n = 10). HSSC rats exhibited significantly reduced body asymmetry in comparison with control rats in a body swing test (Panel A). Locomotor activity was examined before and after cerebral ischemia in all animals. Vertical activity, vertical movement time, and the number of vertical movements showed a significant increase after cerebral ischemia in rats receiving HSSC transplantation in comparison with control rats (Panels B-D). Furthermore, measurement of grip strength was performed to examine the forelimb strength of all experimental rats after each of the two treatments (Panel E). The results revealed a higher ratio of grip strength in the HSSC group than in the control groups.

[0022] Figures 2A-B shows images obtained from an immunohistochemical (IHC) analysis of exogenously transplanted HSSC engrafted in the ischemic rat brain. The penumbra of HSSC-treated ischemic rat brains were immunostained with antibodies for