**Neural stem cells**

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Neural stem cells are capable of self-renewal and can generate neurons, astrocyes and oligodendrocytes. During nervous system development, NSCs within the primitive neural ectoderm give rise to neural progenitors, which rapidly become regionally and temporally specified, first generating large projection neurons and later small interneurons and glia. Small numbers of NSCs persist in the adult brain. They proliferate slowly and produce new neurons throughout life to replenish cells in the hippocampus and olfactory bulb. NSCs and progenitor cells can be isolated from embryonic stem cells, induced pluripotent stem cells, and fetal and adult brain samples. They can be induced to differentiate into neurons and glia in vitro and in vivo. NSCs grown in culture allow in vitro modeling of nervous system development and diseases. NSCs are also under investigation as potential therapeutic agents for neurodegenerative diseases and nervous system injury.

### Fetal neural stem cells

The CNS begins as a tube of neuroepithelial cells, the most primitive form of neural stem cells that give rise to the cortex, neuroepithelial cells transition into radial glial cells, which then give rise to neural progenitors, neurons, astrocytes and oligodendrocytes. In other regions of the developing brain, NSCs in the subventricular zone of the lateral ventricles have been thought to be important for migration and axon outgrowth. These NSCs can be isolated and expanded from rodent brains; however, they are more difficult to isolate from human brains due to blood brain barrier and sensitivity to mechanical trauma. NSCs derived from fetal brains are more difficult to derive from human brains due to the more compact parenchyma and lack of external cues.

### Adult NSCs

NSCs are located within two regions of the adult human and rodent brain: the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampus. Adult NSCs generate new neurons throughout the lifetime of the organism. The neural stem cells from the hippocampus and subventricular zone are thought to be important for memory and olfaction. These NSCs can be isolated and expanded from rodent brains; however, they are more difficult to isolate from human brains due to blood brain barrier issues. Another type of NSC outside of these two regions expresses the marker NG2 and can also proliferate in vitro and in vivo. However, this cell type is not normally give rise to new neurons in vivo. NG2 cells can be isolated after injury and can generate new oligodendrocytes.

### Generation of pluripotent ES cells

Pluripotent ES and iPS cells can be expanded indefinitely in culture because they express telomerase, which prevents chromosome aging. Both types of cell types can be made in mouse or human tissues, including NSCs. NSCs can be grown in culture under specific conditions to maintain their stem cell identity. To generate ES cells, mouse or human pluripotent ES and iPS cells can be expanded in culture to determine their characteristics of the region from which they were isolated.

### Differentiation of neural stem/progenitor cells

NSCs and progenitor cells can be differentiated in vitro by exposure to specific morphogens or growth factors that promote early maturation into either neurons or glia. The differentiation process is highly dependent on the specific region and cell type. In some cases, NSCs can be exposed to specific transcription factors that promote differentiation into specific cell types. For example, exposure to growth factors such as BMP or FGF can promote differentiation into neurons or glia. NSCs can also be differentiated into specific neuron and glial types by exposure to specific morphogens or growth factors. Optimization of differentiation protocols to specific NSC types is necessary to ensure that the differentiated cells maintain their functional characteristics.

### Transplantation

Exploited cases in partially differentiated populations of NSCs can be transplanted into the CNS of experimental animals to test their potential to differentiate into functional neurons or glial cells in vivo. Such animal studies are the first steps towards developing cell therapies for neurological disorders. At present, two clinical trials are underway in the USA involving transplantation of NSCs derived from human ES cells. In one trial, NSCs derived from human ES cells were transplanted into the brains of children with Batten’s disease, a neurodegenerative disorder characterized by progressive loss of vision, hearing, and motor function. The second trial involves the transplantation of NSCs derived from human ES cells into the brains of patients with spinal cord injury. These trials are ongoing and will provide important insights into the potential of NSCs for treating neurological disorders.

### References


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**Huntington’s disease**

Loss of inhibitory GABAAergic neurons in the striatum leads to neuronal death in Huntington’s disease patients. As the disease progresses other brain areas deteriorate, and patients suffer severe cognitive decline. Replacement or protection of striatal GABAAergic neurons using NSCs derived from ES cells may slow the disease, but the progressive spread of degeneration is difficult to address. Culturing of NSCs into multiple sites in both the striatum and cortex might be a feasible avenue.

**Parkinson’s disease**

Parkinson’s disease is caused by loss of dopaminergic production in the brains of treated individuals. Dopaminergic-producing neurons can be derived from ES cells and could be used eventually to replace those that are lost to disease. Although the clinical trials of human ES cell derived dopamine neurons using primary fetal neural tissue revealed that dopamine neurons could cause side effects. More work is in progress to develop strategies to overcome mechanisms that may enable the functional integration of transplanted dopaminergic neurons.

**Amyotrophic lateral sclerosis**

In ALS, progressive cell death is caused by loss of cortical and spinal motor neurons. Efforts to replenish motor neurons from NSC transplants are challenging, as the new neurons would need to grow long axonal projections to connect to the denervated muscles. An alternative approach to cell therapy is the development of small molecules that could promote trophic survival in the CNS of experimental animals to test their potential to differentiate into functional neurons or glial cells in vivo. Such animal studies are the first steps towards developing cell therapies for neurological disorders.