Adult Neurogenesis & Therapeutic Cell Replacement

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Course News

Final Exam Monday (Dec 17) at 1:30pm

The exam will cover lectures 2-41 and labs 1-10.

A –L last names in MoosT 2-650
M – Z in MoosT 2-620

PLEASE BRING #2 PENCILS!!!

Check out last year's exam on the course website!!!

Adult Neurogenesis

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Death of a Dogma

“Once development has ended, the fonts of growth of the cells, axons and dendrites dries up irrevocably. In adult centers, the nerve paths are fixed and immutable: everything may die, nothing may be regenerated.”

Santiago Ramon y Cajal, 1928

Mammals

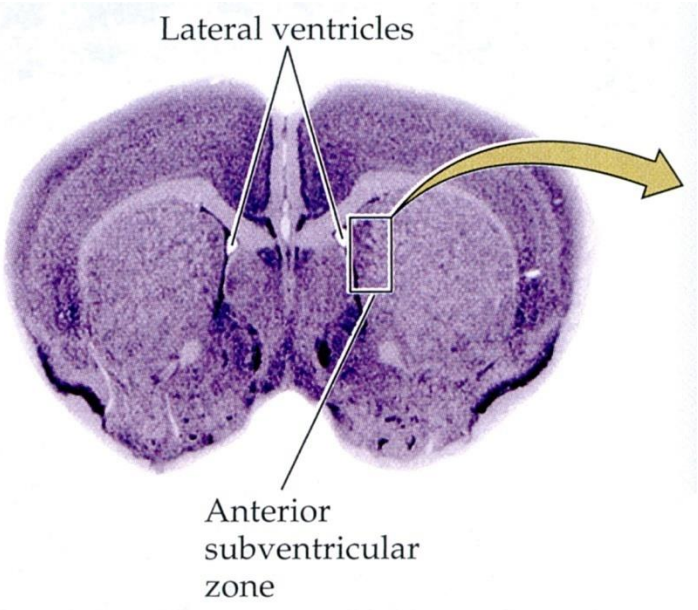
- The dogma for almost 100 years was that no new neurons are generated in the adult mammalian brain.
- In the 1960s & 70s, there were reports of cells that looked like neurons that were generated by cell division in a few locations in the adult rat brain.

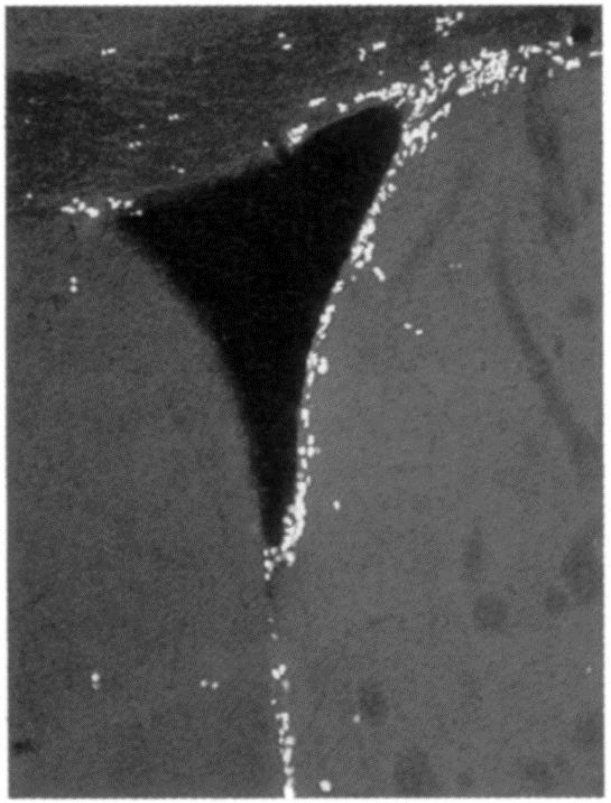
  These reports were mostly discounted.
- Over the past 25 years, neurogenesis has been definitively identified in two locations in the adult mammalian brain (including humans)…SVZ and SGZ.

Subventricular Zone (SVZ)

- New neurons and astrocytes are generated in the subventricular zone (SVZ) adjacent to the lateral ventricle in the forebrain.

  They can be labeled with markers of cell division.

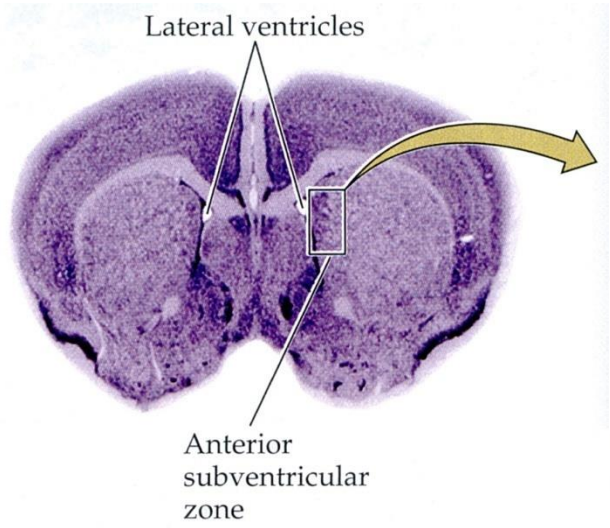


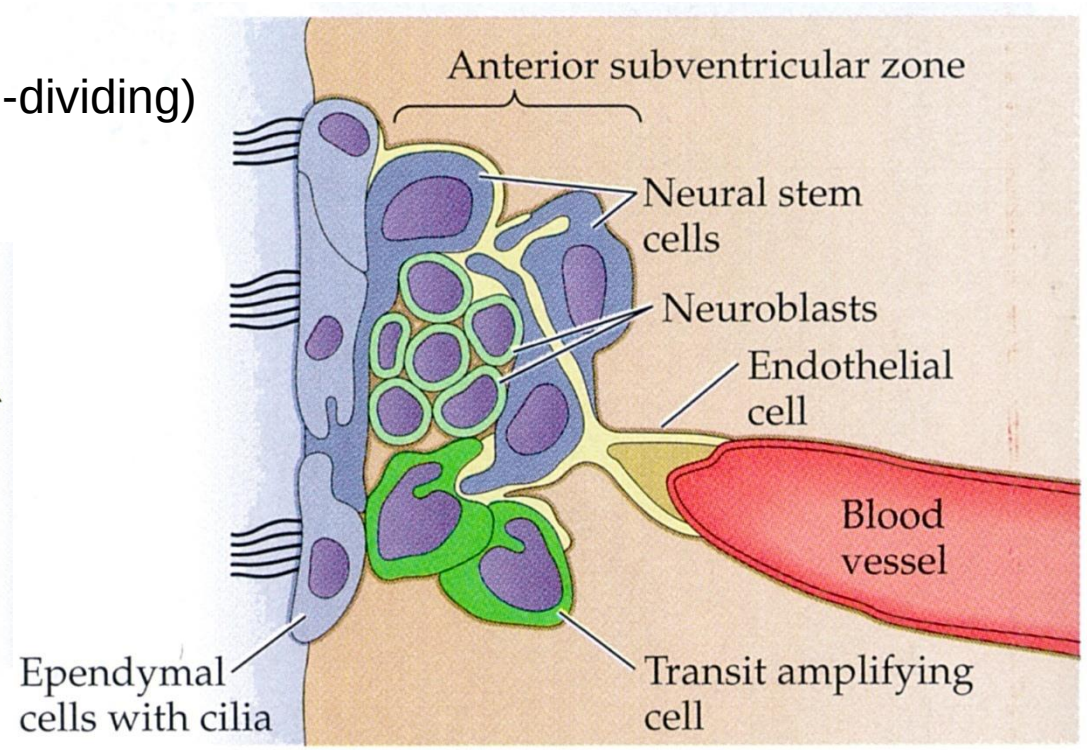


subventricular zone

Subventricular Zone (SVZ)

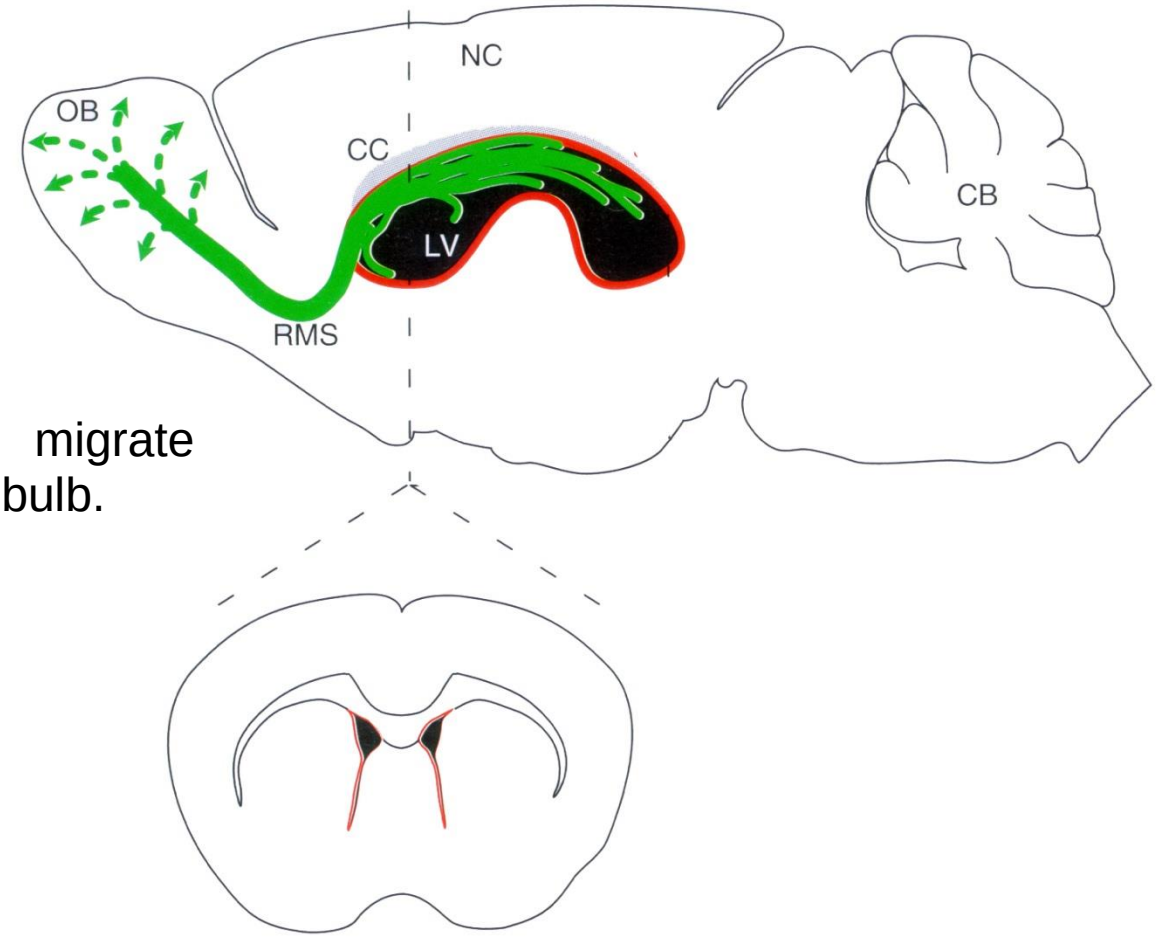
- Types of cells in the SVZ:
- ependymal cells (line the ventricle)
- neural stem cells (slowly dividing; produce transit amplifying cells)
- transit amplifying cells (rapidly dividing; produce neuroblasts & glioblasts)
- neuroblasts & glioblasts (non-dividing)
- blood vessels

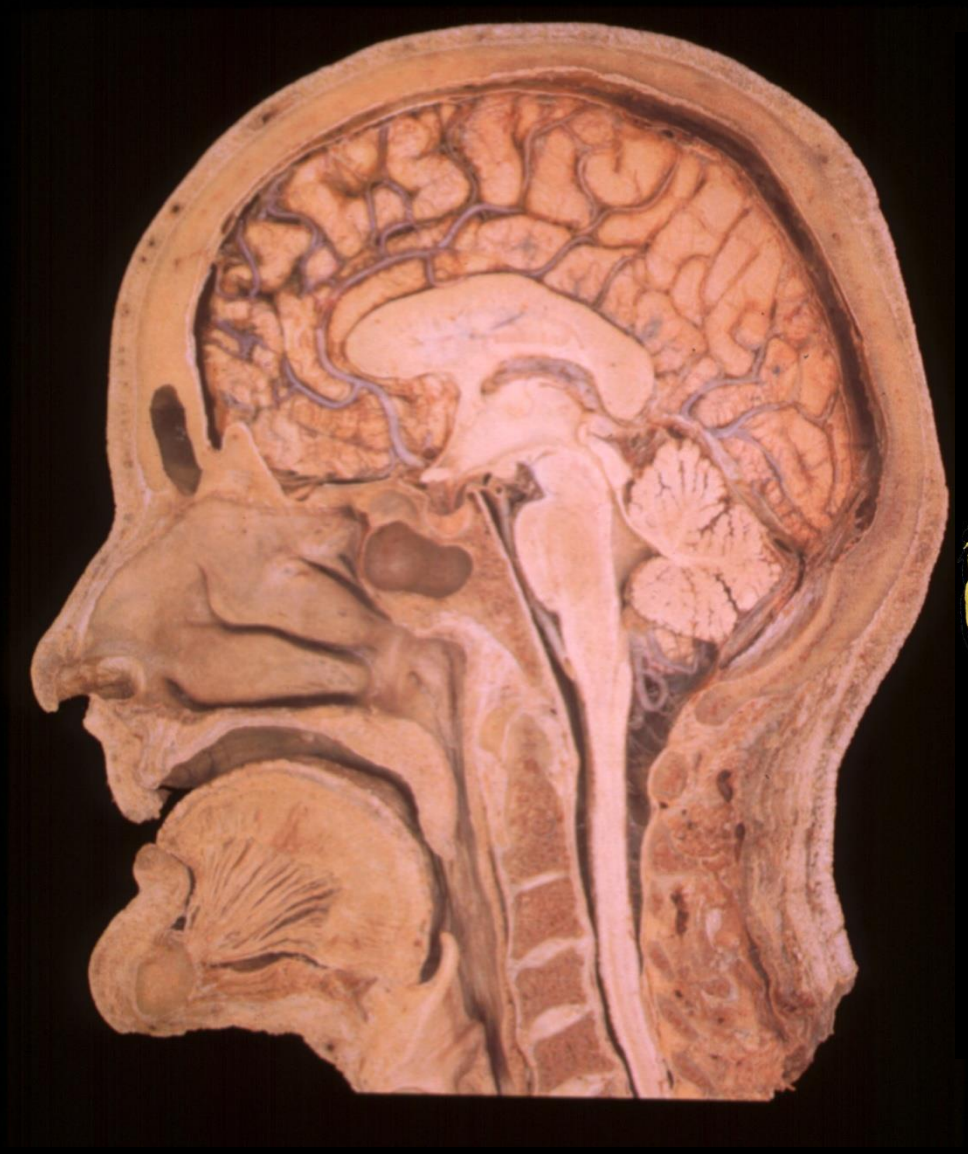


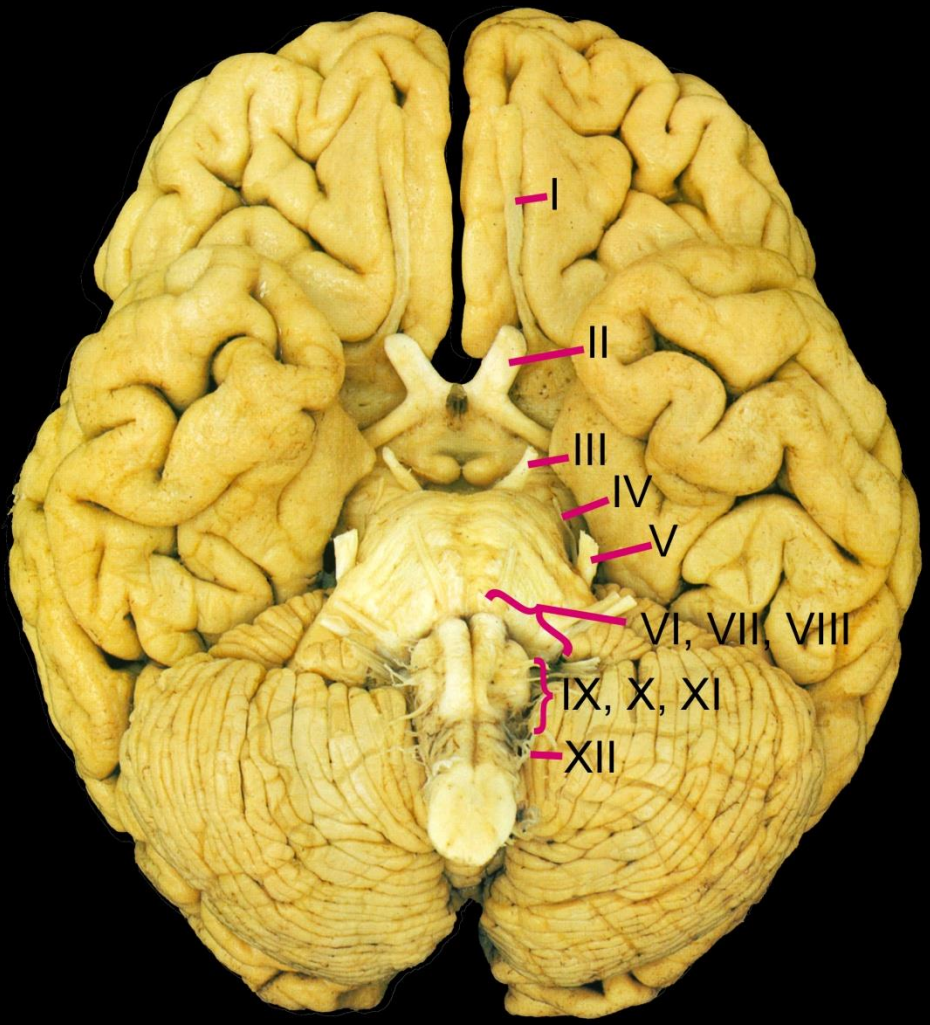


Subventricular Zone (SVZ)

- Neuroblasts and glioblasts migrate from the SVZ to the olfactory bulb.



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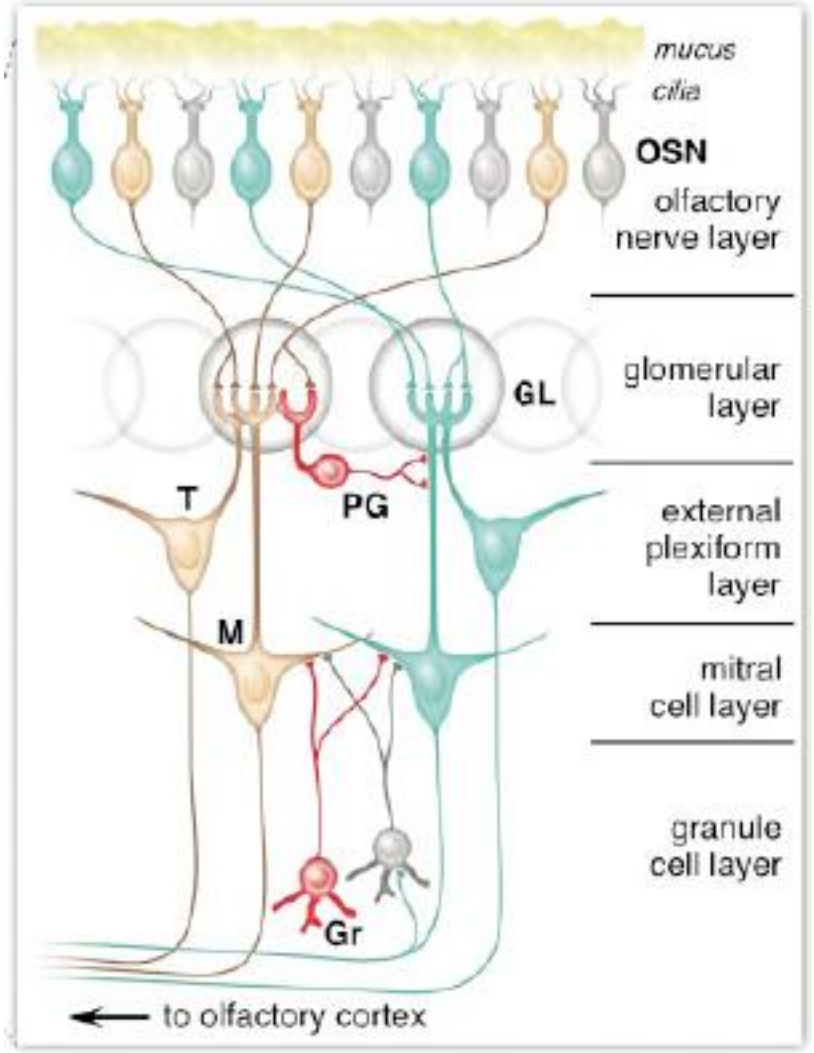
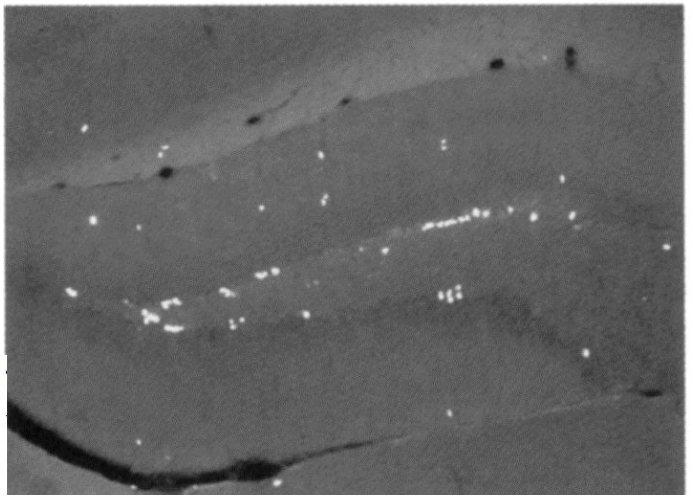
Subventricular Zone (SVZ)

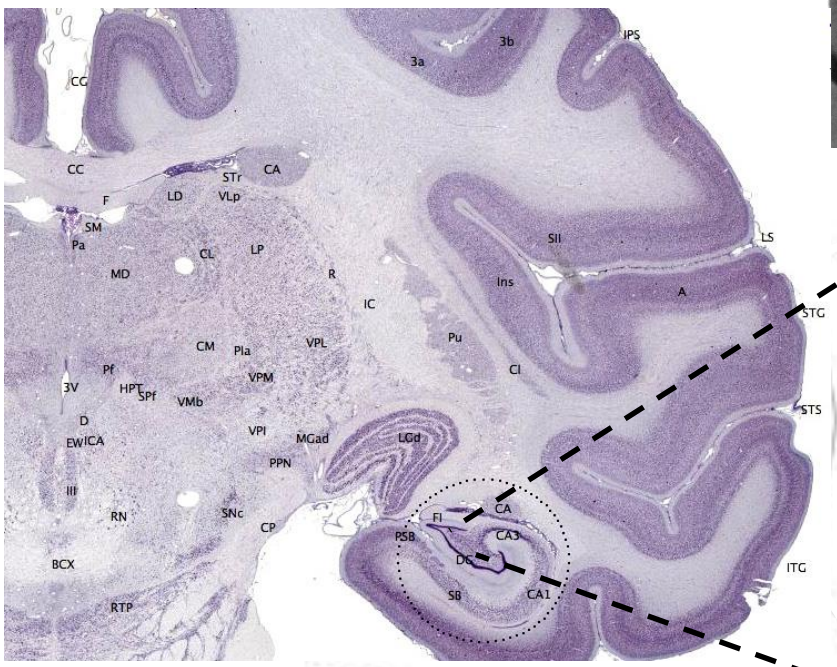
- Neuroblasts differentiate into multiple types of interneurons in the olfactory bulb.
- There is no net growth of the olfactory bulb. (i.e. Neurons must continually die.)
- Blocking SVZ cell genesis resulted in impairment in odor discrimination in mice.

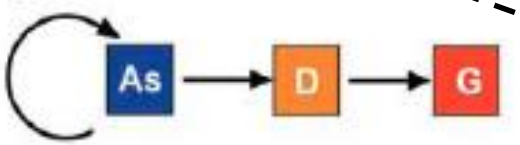


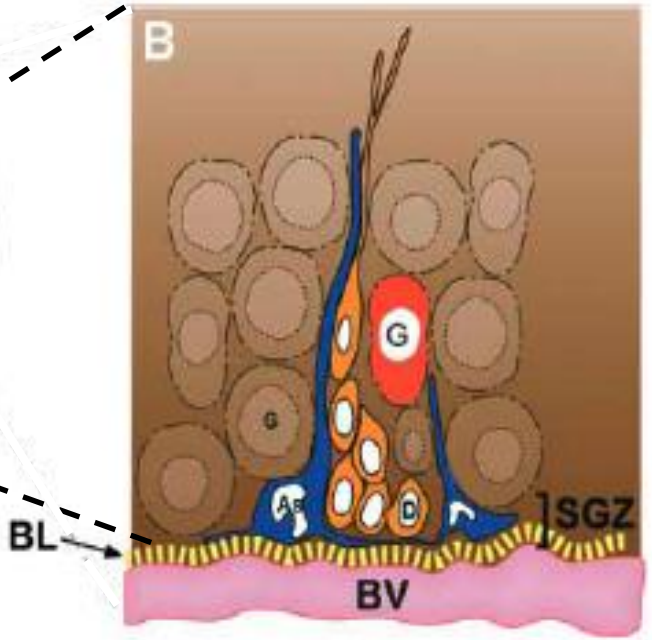
Subgranule Zone (SGZ)

- Neurons and glia are generated just below the granule cell layer in the dentate gyrus of the hippocampus.



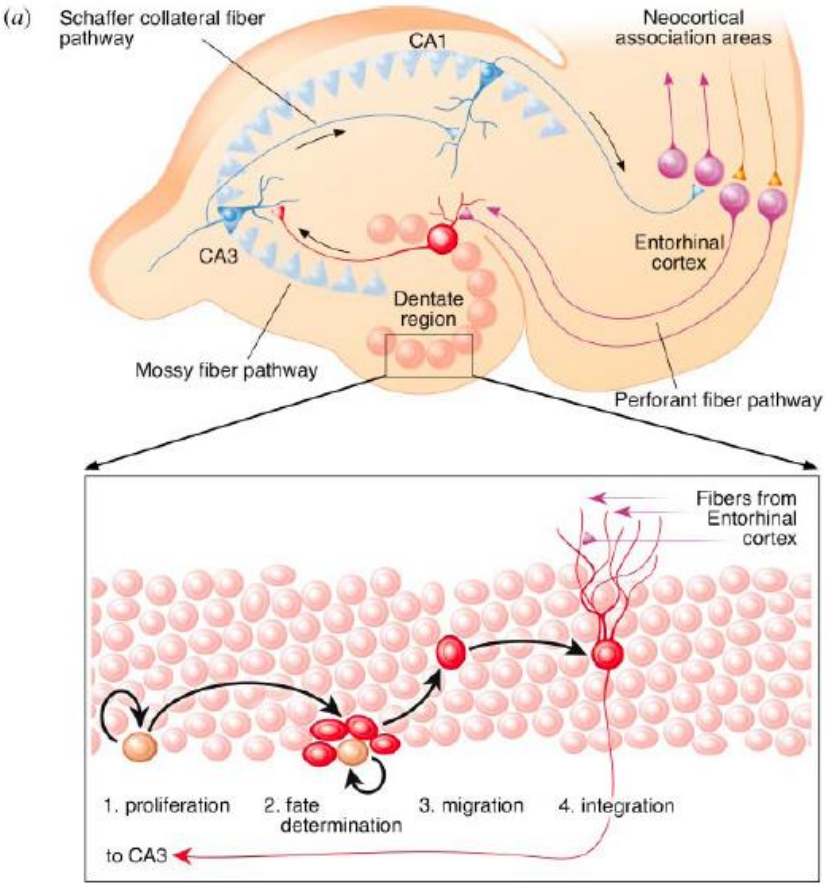






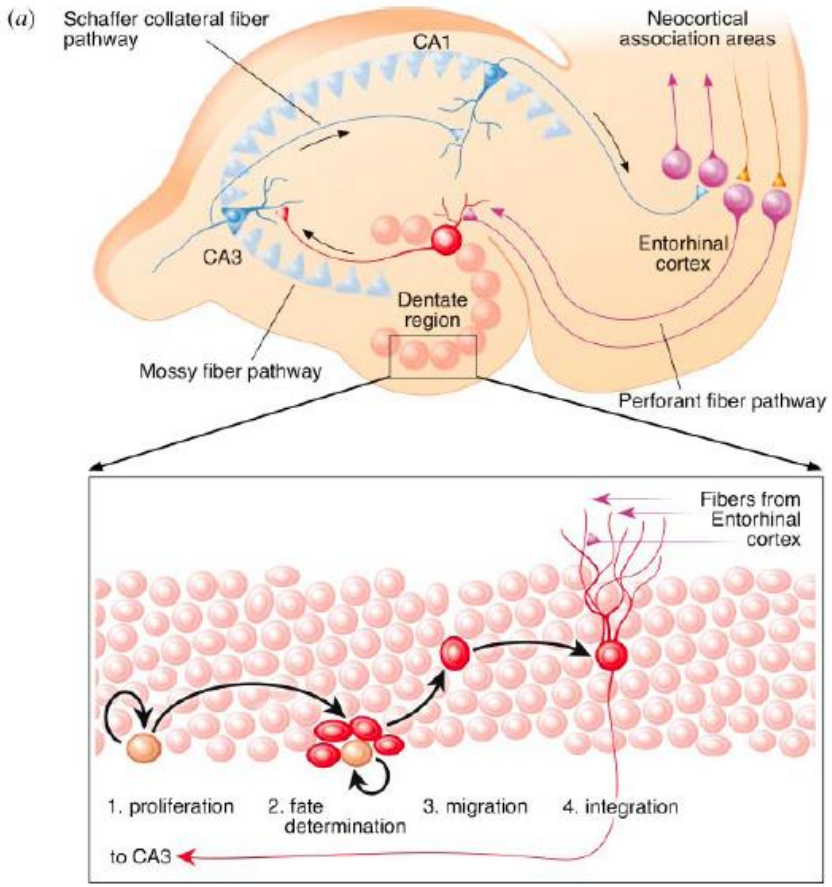
Subgranule Zone (SGZ)

- Cells migrate the short distance from the SGZ into the granule layer of the dentate gyrus.
- Most new neurons die.
- Some new neurons integrate and have adult granule cell properties 4-8 weeks after division.
- ~700 cells are generated per day.
- ~2% per year of the granule cells are replaced.



Subgranule Zone (SGZ)

- New neurons receive synapses from axons in adjacent regions.
- They send axons to other regions of the hippocampus.



Subgranule Zone (SGZ)

- New neurons have a role in learning and memory:

  Reduced neurogenesis with an antimitotic agent or with irradiation reduced learning in several paradigms.

  Spatial and episodic memories were enhanced with treatments that increased neurogenesis.

Subgranule Zone (SGZ)

Fluoxetine, a commonly used antidepressant, increased SGZ neurogenesis in rats and humans. (It is a selective serotonin reuptake inhibitor sold by the trade names Prozac and Sarafem.)

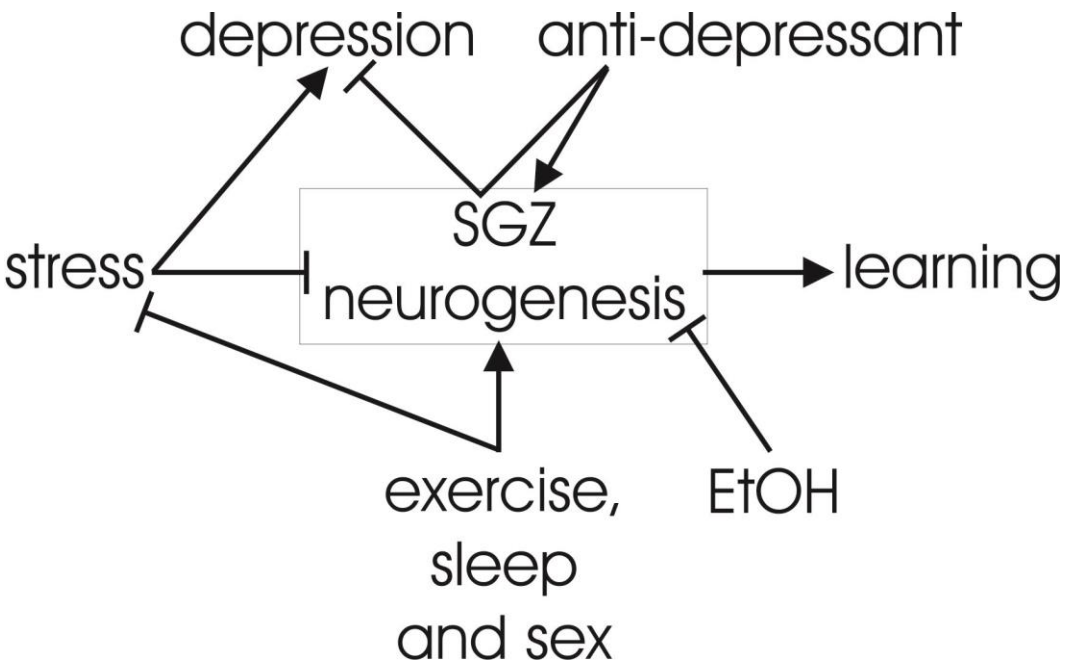
Fluoxetine ameliorated anxiety-related feeding suppression in rats.

Fluoxetine had no effect on anxiety or depression if neurogenesis was blocked.

Subgranule Zone (SGZ)

- Factors that regulate SGZ neurogenesis:
- Stress reduces neurogenesis, as do glucocorticoids; stress increases glucocorticoids, which are produced by the adrenal cortex.
- Sleep deprivation reduces neurogenesis.
- An enriched environment increases neurogenesis.
- Exercise increases neurogenesis.
- Sex increases neurogenesis.
- Antidepressants increase neurogenesis.
- Ethanol reduces neurogenesis.

What does this tell us?



Neurogenesis in the Aged Brain

- Neurogenesis is significantly reduced in aged humans and rats compared to young adults:

  SVZ ↓ 70%

  SGZ ↓ 80-90%

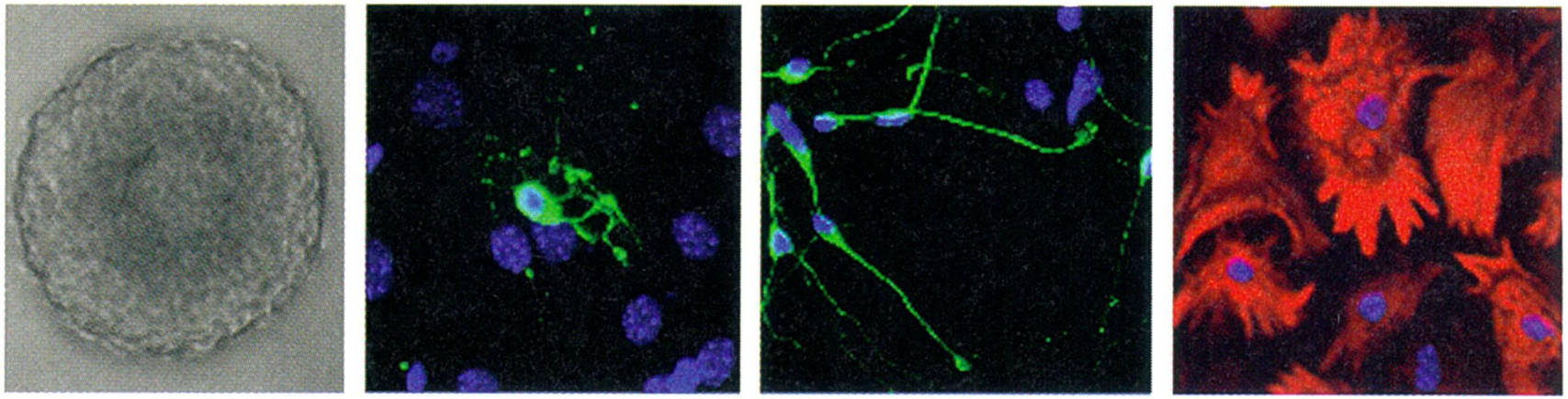
- Exercise improved neurogenesis and learning in aged rats.

Neurogenesis in Other Regions of Adult Mammalian Brain

- Although controversial and not broadly accepted, low levels of neurogenesis have been reported in other areas of the adult mammalian brain:
  - substantia nigra (Zhao M et al., 2003)
  - amygdala & piriform cortex (Bernier PJ et al., 2002)
  - striatum & cortical interneurons (Dayer AG et al., 2005)
  - hypothalamus (Xu Y et al., 2005)

Neural Stem Cells (NSCs)

- Neural stem cells (NSCs) have been harvested from adult SVZ and SGZ.
- NSCs divide in tissue culture as long as certain growth factors are in the medium.
- NSCs in culture form neurospheres.
- Neurospheres can generate neurons, astrocytes and oligodendrocytes.

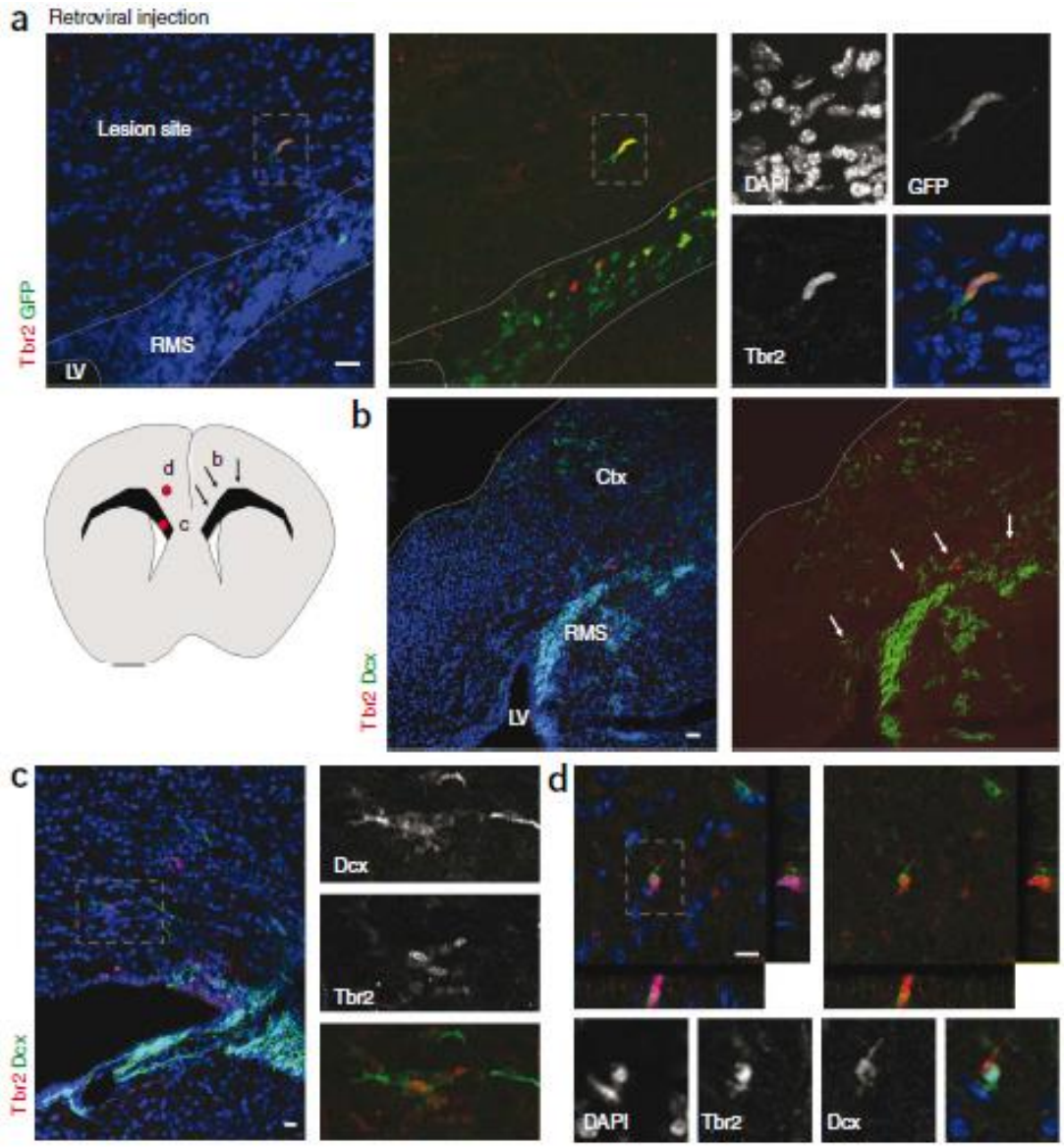


Neurogenic Niche

- NSCs also have been harvested and cultured from many other adult brain regions including cerebellum, midbrain and spinal cord. These cells do not generate neurons in vivo.
- NSCs from adult spinal cord divide and generate neurons when transplanted to SGZ but not when transplanted back to the spinal cord.
- SVZ and SGV are special environments that promote neurogenesis. They have high levels of factors that promote cell division.

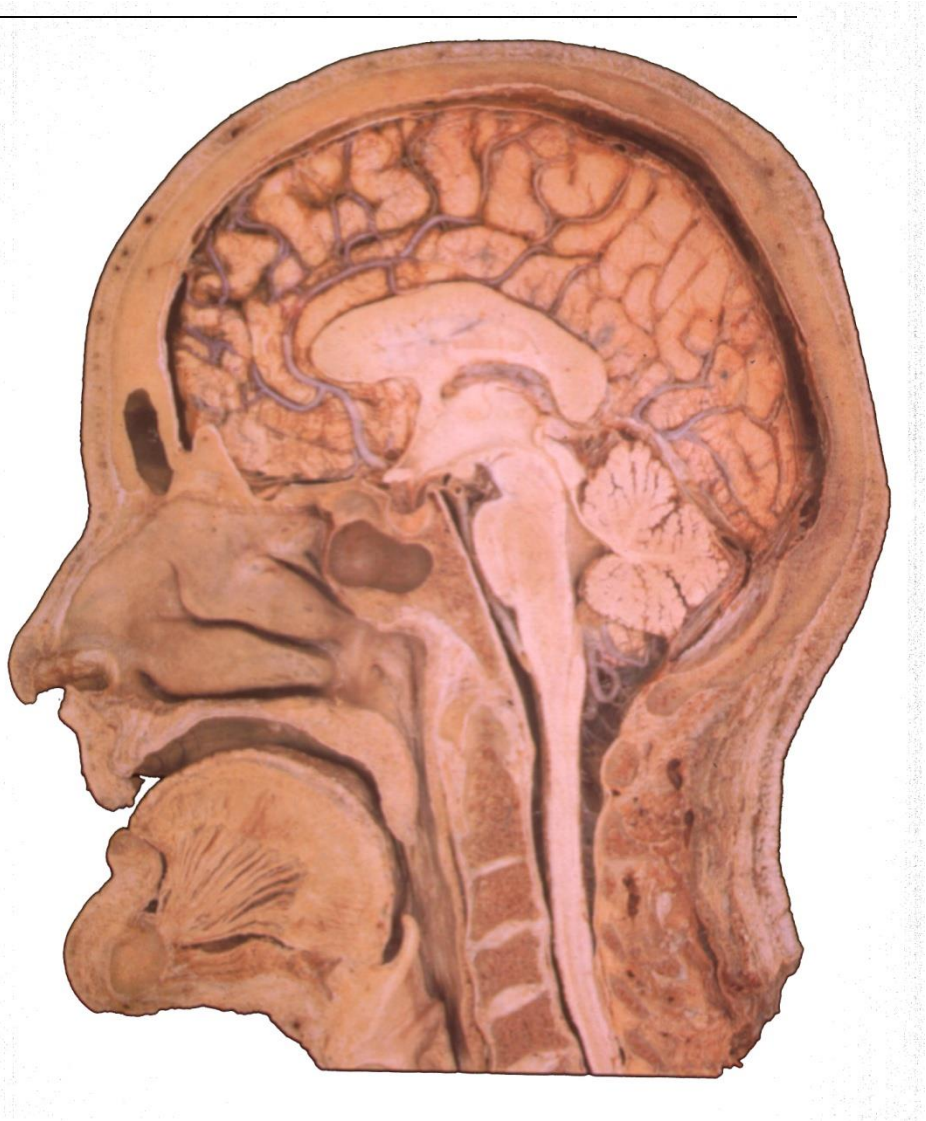
Injury Induced Neurogenesis

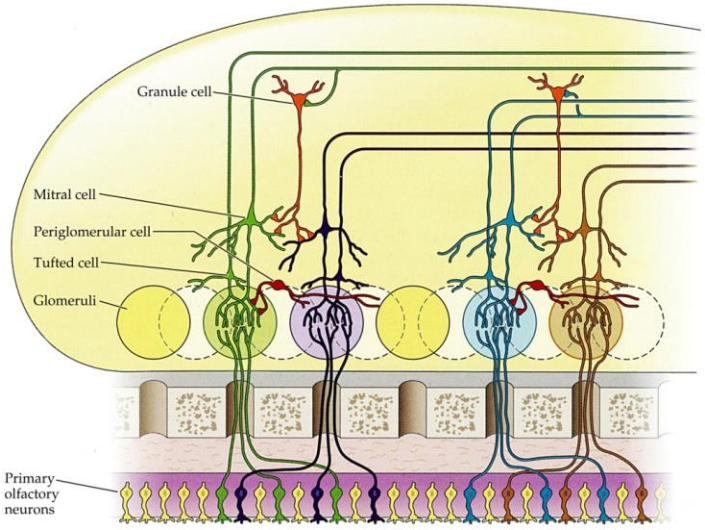
- Following stroke, some new neurons generated in the SVZ migrate into the cerebral cortex.



Neurogenesis in the Olfactory Epithelium

- New olfactory receptor neurons are continually generated in the nasal epithelium from a population of resident progenitor cells.
- The new neurons grow axons from the nose into the olfactory bulb in the brain.
- The new neurons function.
- There does not appear to be an increase in the number of receptor neurons, so neurons must continually die.



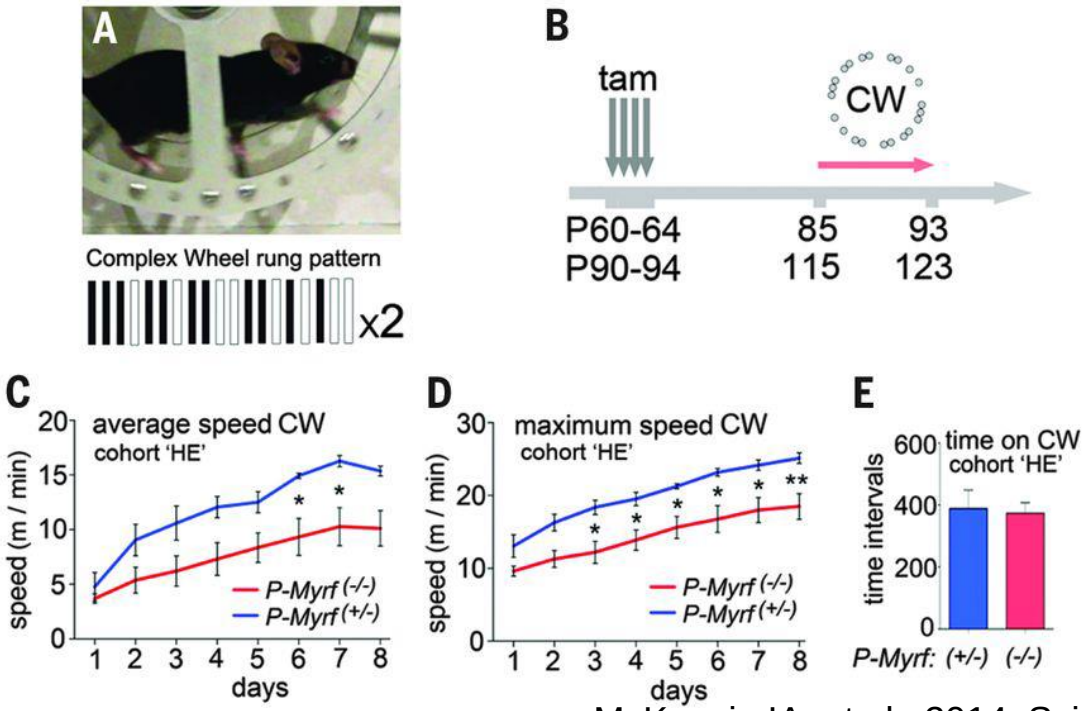


Gliogenesis in the Adult Nervous System

- Astrocytes and oligodendrocytes are produced at low levels throughout the nervous system in the adult.
- Oligodendrocytes are generated in the adult brain from oligodendrocyte precursor cells (OPCs) leading to new myelin formation.

Gliogenesis in the Adult Nervous System

- Genesis of oligodendrocytes was prevented in adult mice with an inducible gene knockout.
- Mice not producing new oligodendrocytes were unable to learn to run on a wheel with irregularly spaced rungs.
- New oligodendrocytes are not required to recall a prelearned skill.

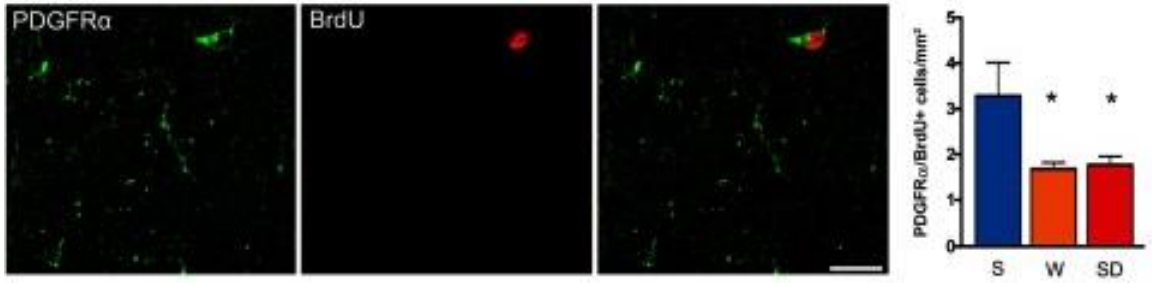


McKenzie IA, et al., 2014, Science 346:318

Gliogenesis in the Adult Nervous System

- Oligodendrocytes and new myelin are generated preferentially during sleep.
- Increasing or decreasing sleep resulted in a proportional change in genesis of new oligodendrocytes and myelin.

(Bellesi M, et al., 2013)



Therapeutic Cell Replacement (Stem Cells)

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Neuronal Death

- Neurons are lost due to four main causes:
  - Trauma
  - Toxin
  - Hypoxia
  - Neurodegenerative disease

Neuronal Death

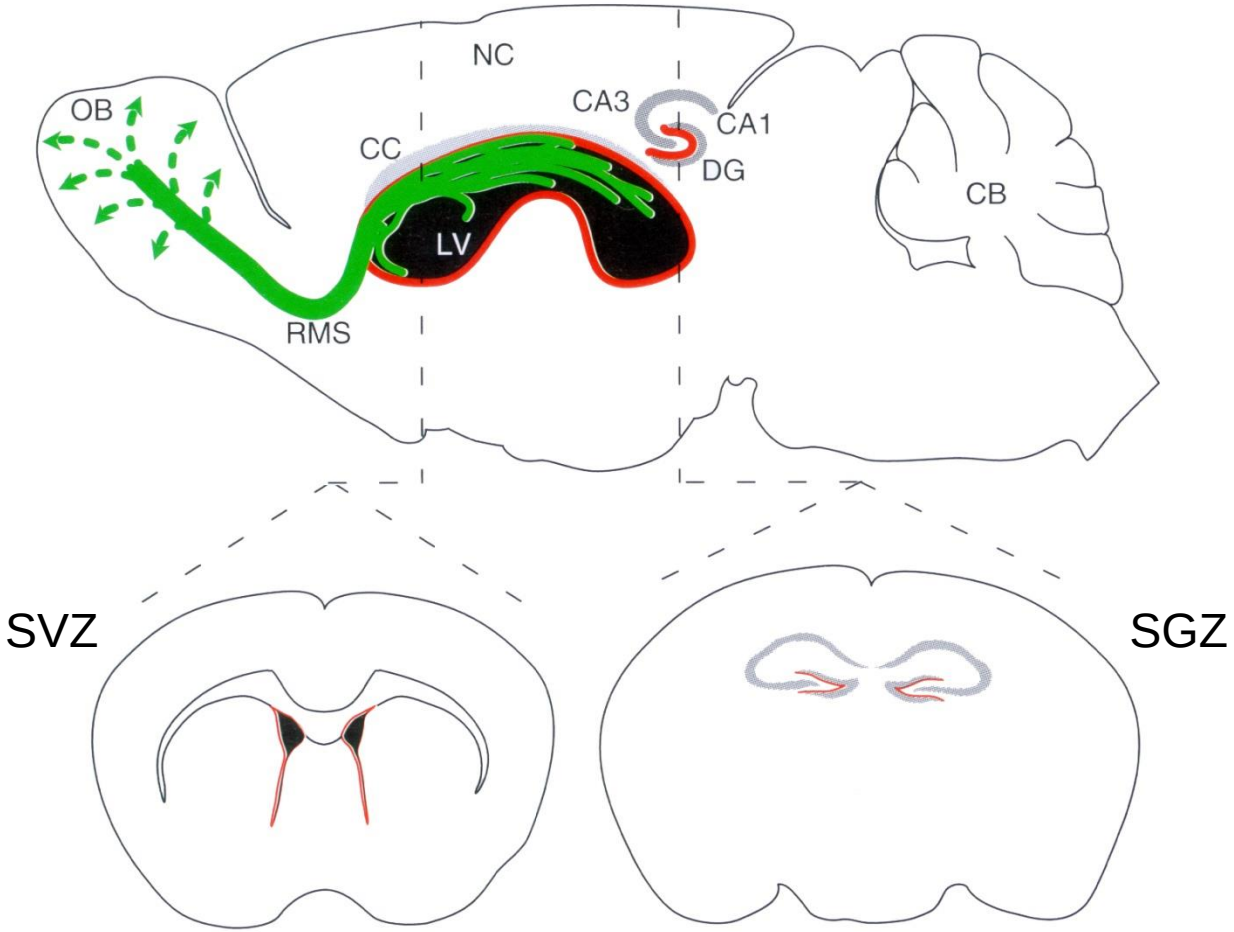
- Most common cause of trauma:
  - Auto accidents!
- Common toxins:
  - Alcohol!
  - Pesticides
- Common causes of hypoxia / loss of blood supply:
  - Heart attack
  - Local vascular obstruction (e.g. clot, arterial sclerosis)
  - Burst aneurism
  - Drowning

Neuronal Death

- Common neurodegenerative diseases:
  - Parkinson's disease – dopaminergic cell loss in pars compacta of the substantia nigra
  - Amyotrophic lateral sclerosis (ALS) – motor neuron loss
  - Spinocerebellar ataxia (SCA) – cerebellar neuron loss
  - Huntingtion's disease (chorea) – spiny neuron loss in the striatum (caudate & putamen) of the basal ganglia
  - Retinitis pigmentosa (RP) – retinal rod cell loss
  - Age-related macular degeneration (AMD) – retinal cone cell loss
  - Alzeheimer's disease – cortical neuron loss

Innate Recovery Mechanisms Following Neuron Loss

- Functional plasticity of surviving neurons.
- New neurons generated from endogenous sources. [minimally important if it happens at all]



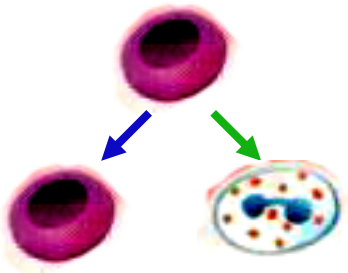
Therapeutic Neuron Replacement

- There is tremendous need for therapeutic replacement of lost neurons.
- Transplantation offers a potential method to replace lost neurons.
- Greatest success in the laboratory and in early clinical trials has been achieved by transplanting developing neurons harvested from fetuses.
- Stem cells potentially offer an alternative source of neurons for transplantation.

Therapeutic Neuron Replacement

- Definition of a stem cell:

  1. Capable of self renewal [indefinitely].
  2. Capable of generating multiple differentiated cell types

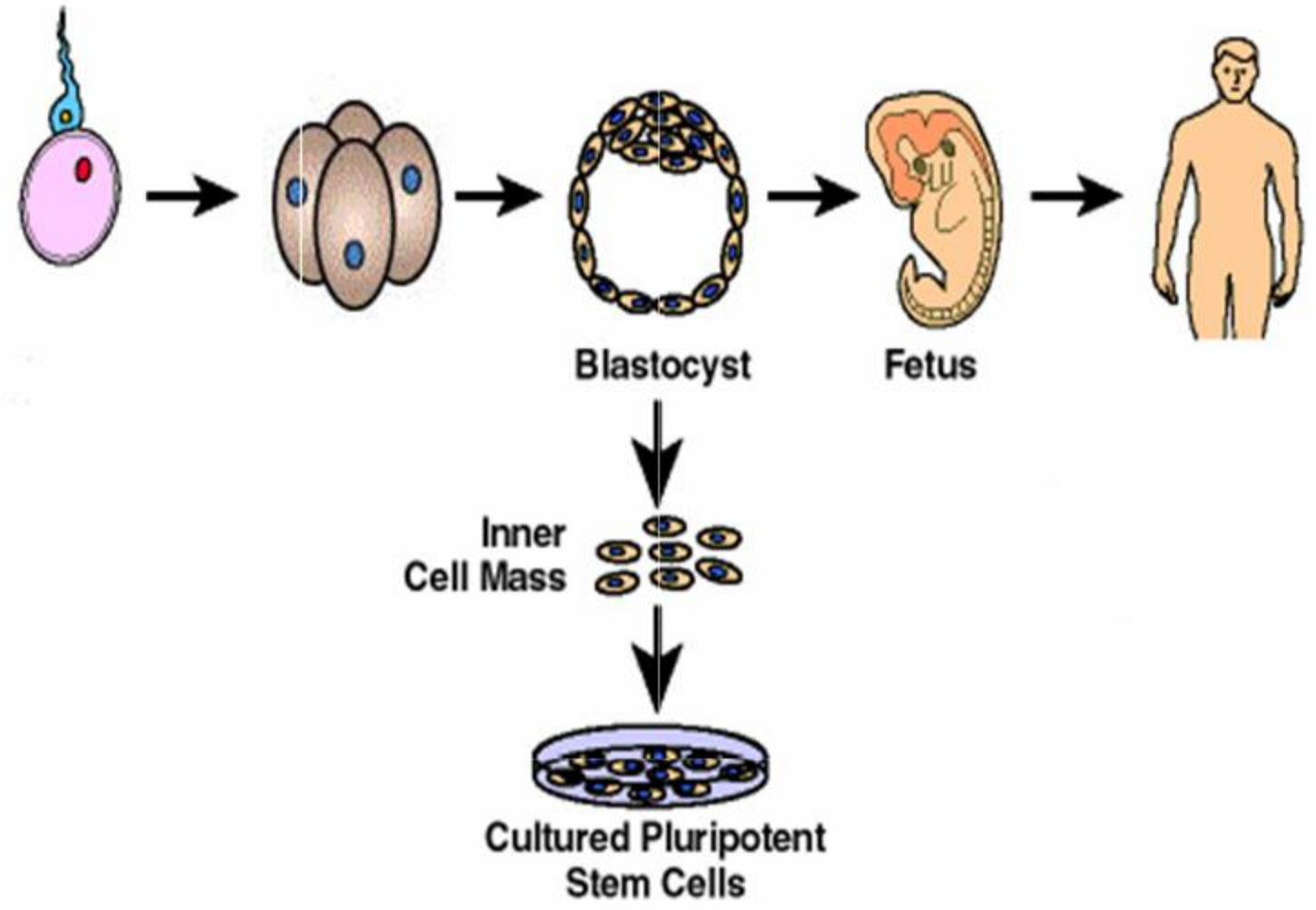


Therapeutic Neuron Replacement

- Types of stem cells:
  - Embryonic stem cell (ESC)
  - Umbilical cord stem cell
  - Neural stem cell (NSC)
  - Other adult tissue derived stem cells
  - Induced pluripotent stem cell (IPSC)

Therapeutic Neuron Replacement - ESCs

- ESCs are generated from the inner cell mass of the blastula stage embryo produced by in vitro fertilization.

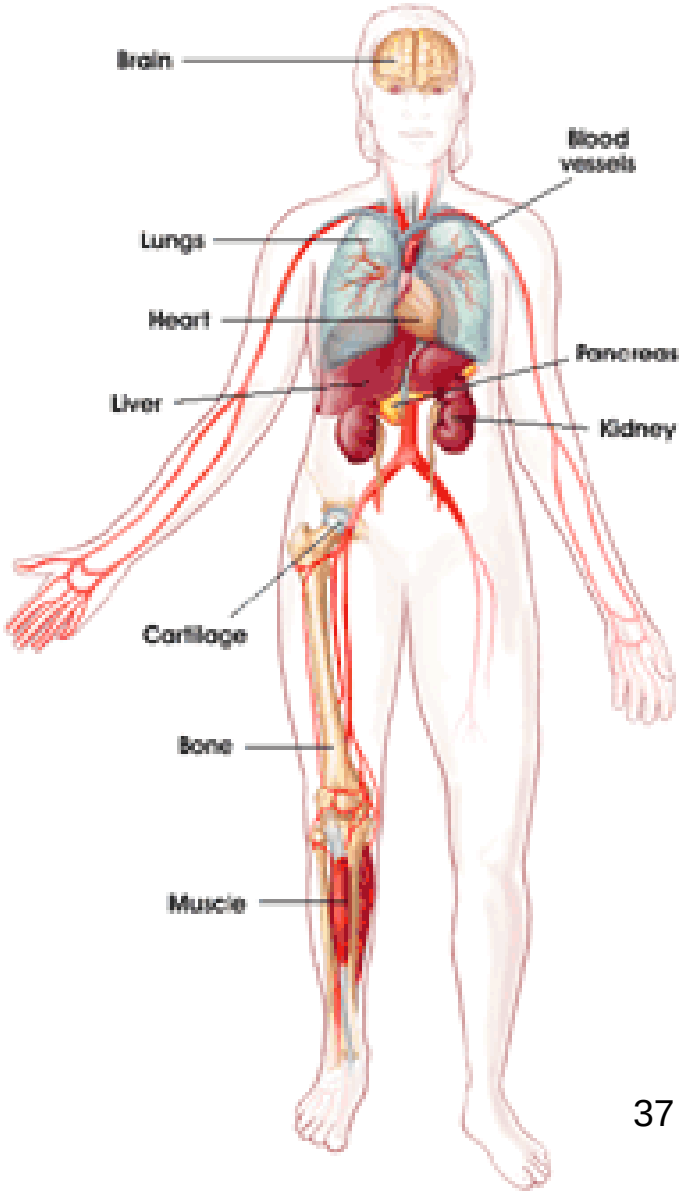


Therapeutic Neuron Replacement

- Neuralized ESCs are typically heterogeneous and often form teratomas in vivo.

Therapeutic Neuron Replacement

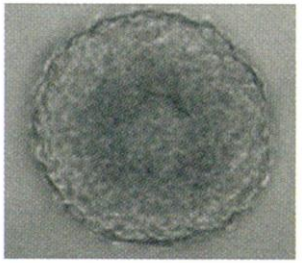
- Organs from which adult stem cells have been isolated:
  - Brain
  - Bone marrow
  - Intestine
  - Liver
  - Skin
  - Muscle
  - Testes

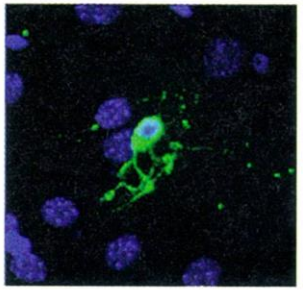


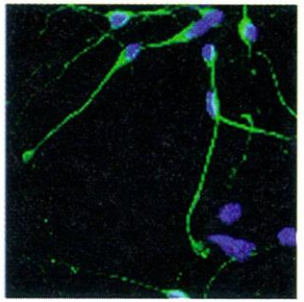
Therapeutic Neuron Replacement

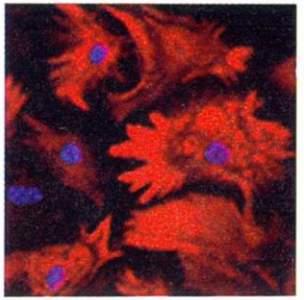
- Parts of the adult nervous system from which neural stem cells have been isolated:
  - SVZ
  - SGZ
  - Cerebellum
  - Midbrain
  - Retina
  - Spinal cord

- Neural stem cells form neurosphere in culture, and can give rise to neurons, astrocytes and oligodendrocytes.



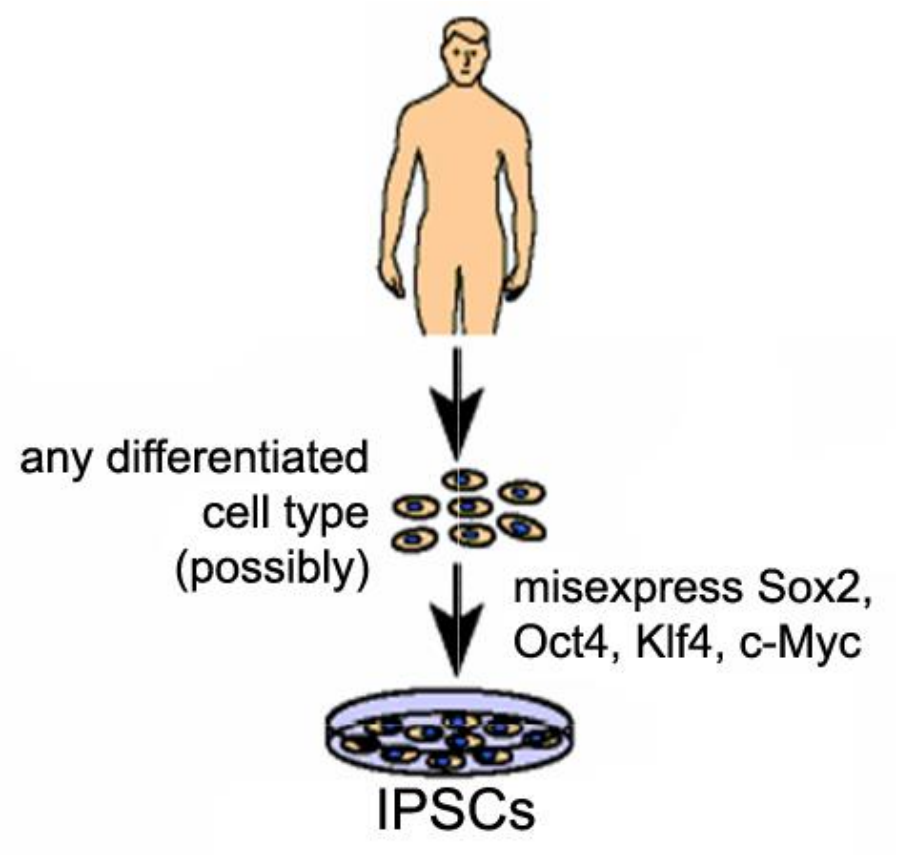






Therapeutic Neuron Replacement

- IPSCs can be generated (possibly) from any differentiated cell type, but usually is done with skin cells



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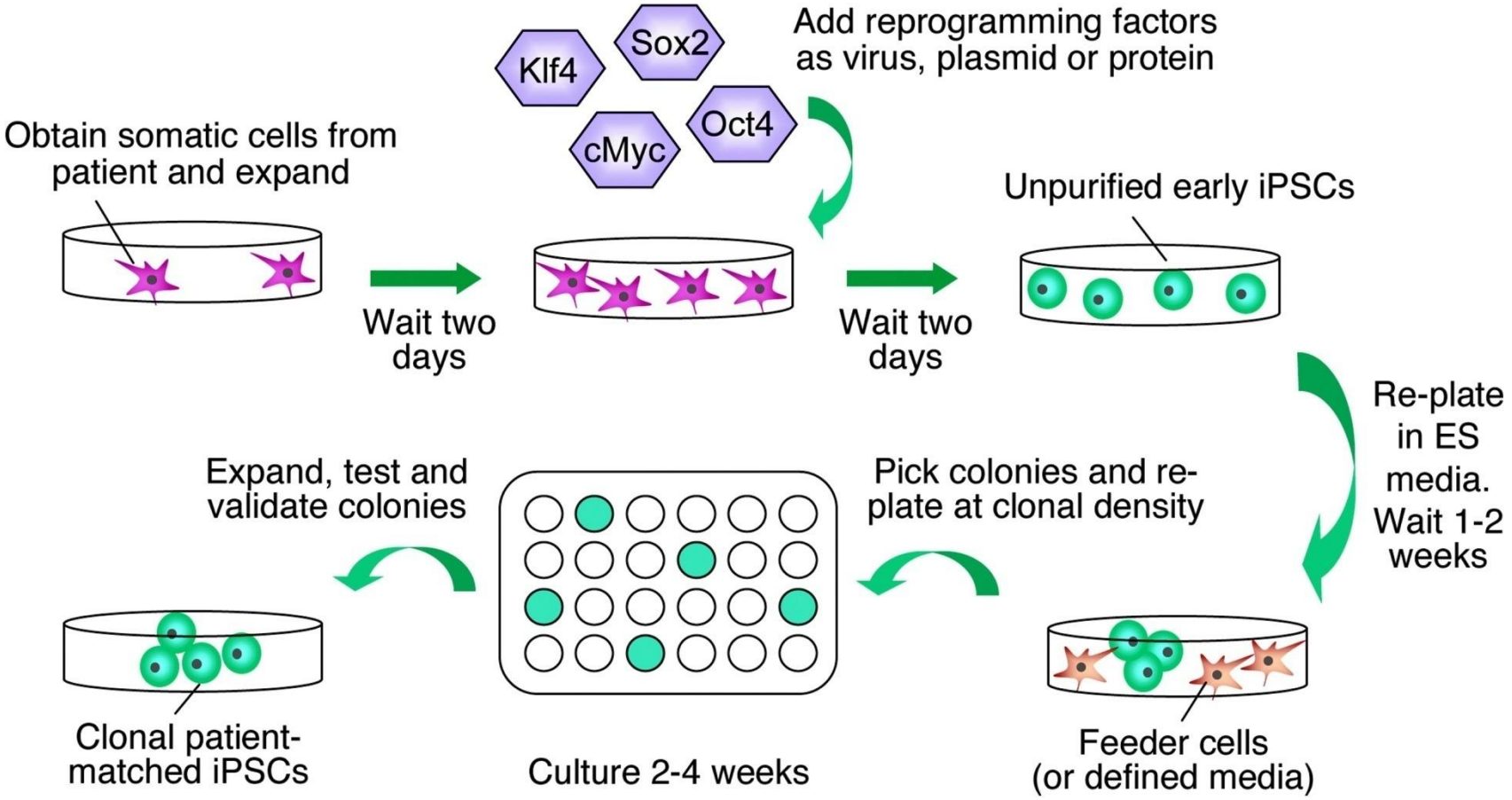
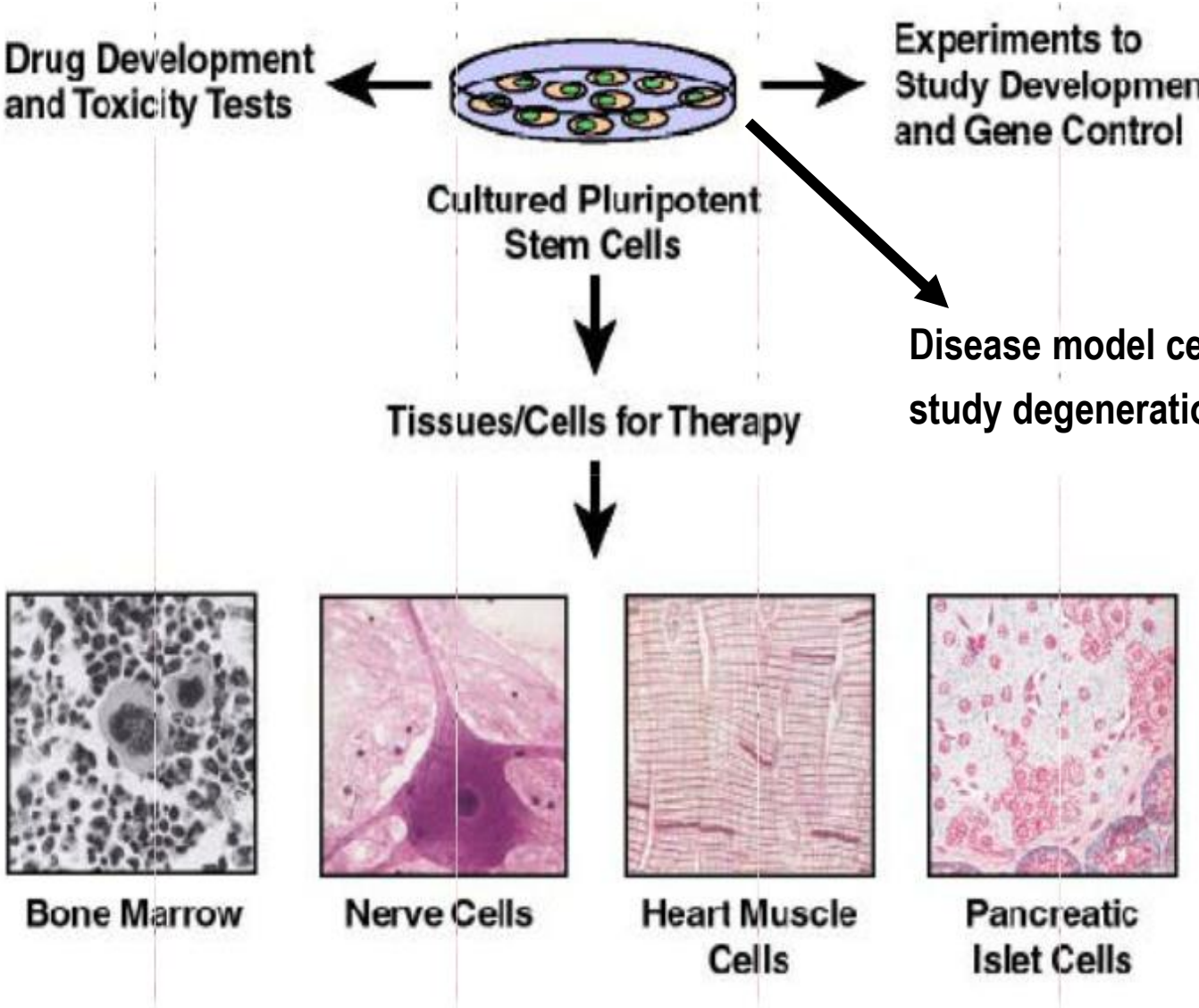
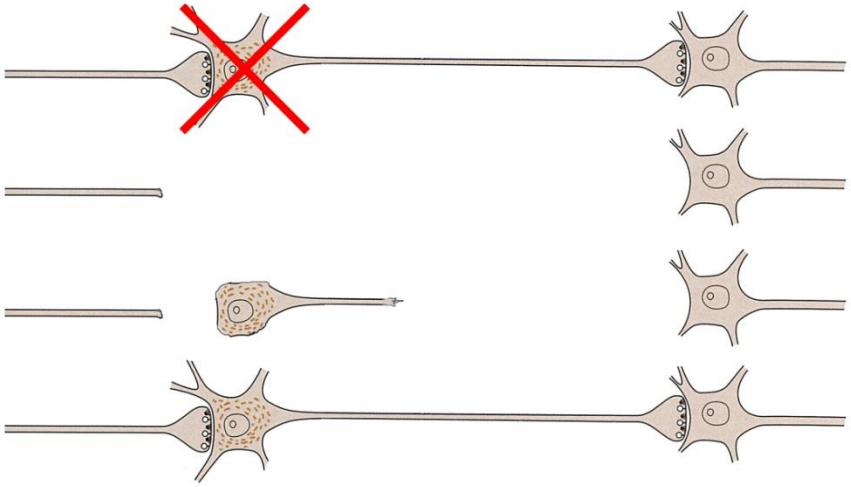


Multiple Uses for Stem Cells



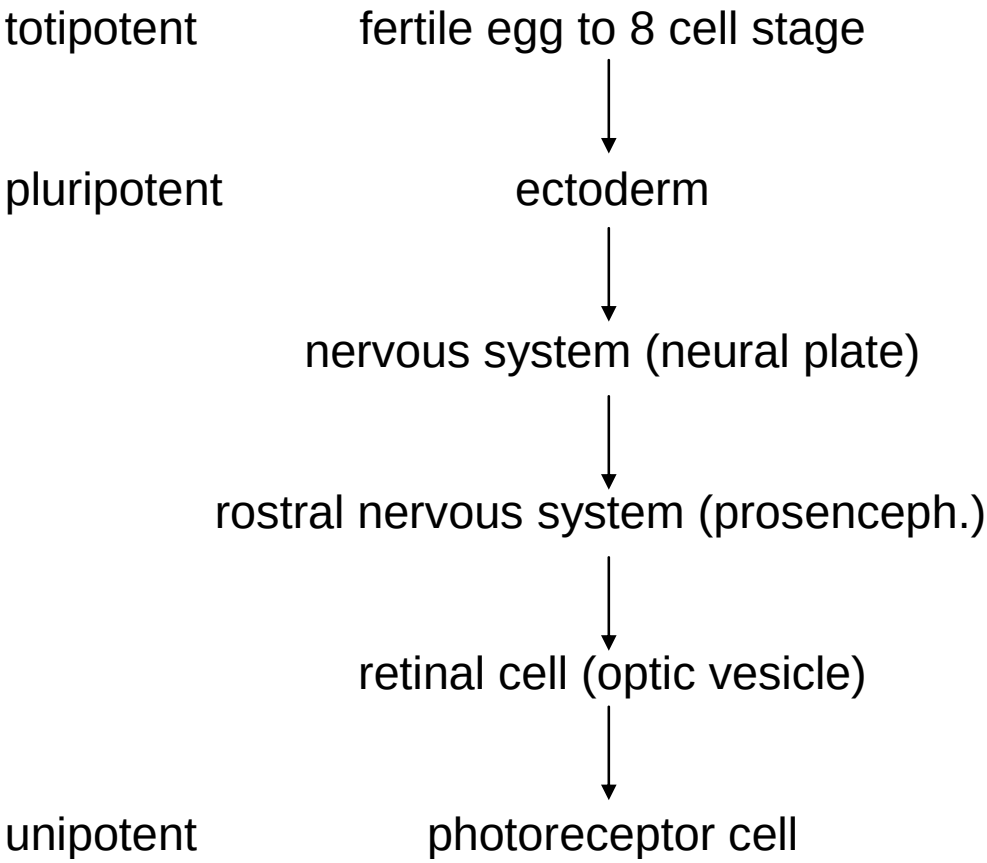
Therapeutic Neuron Replacement



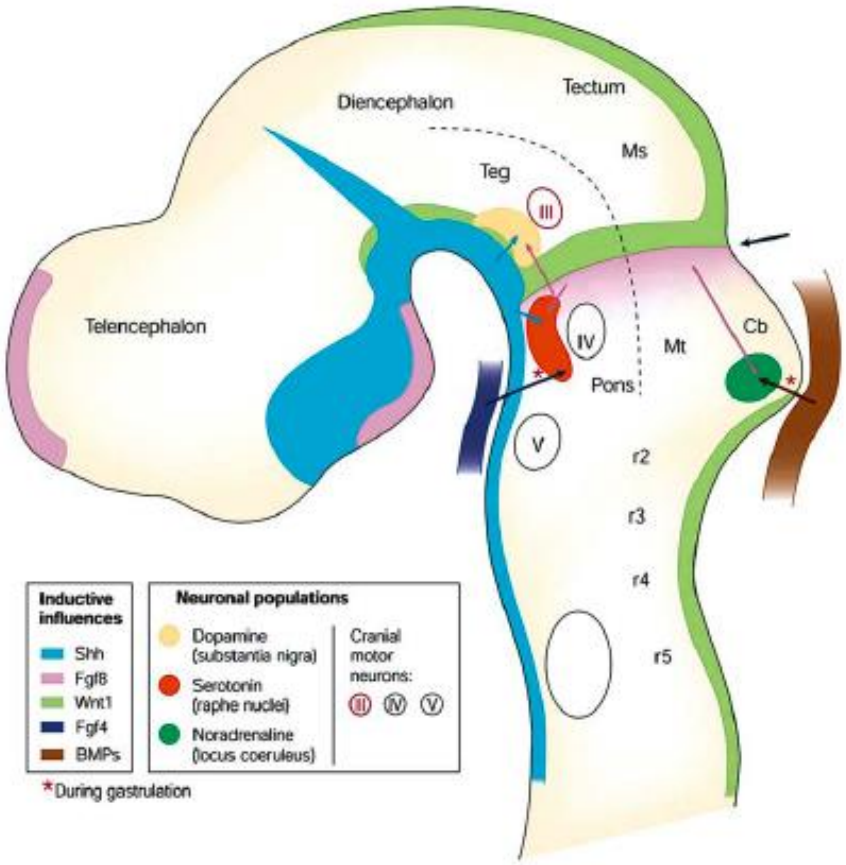
- Successful neuron replacement will require:
  - appropriate donor cell type
  - purified donor cell population at the proper stage of development
  - delivery of new cells to the proper location
  - survival of afferent & target cell populations
  - growth of axons from new cells to appropriate targets
  - formation of new synapses between new axons & target cells
  - connection of original afferents to new cells
  - myelination of the new axons

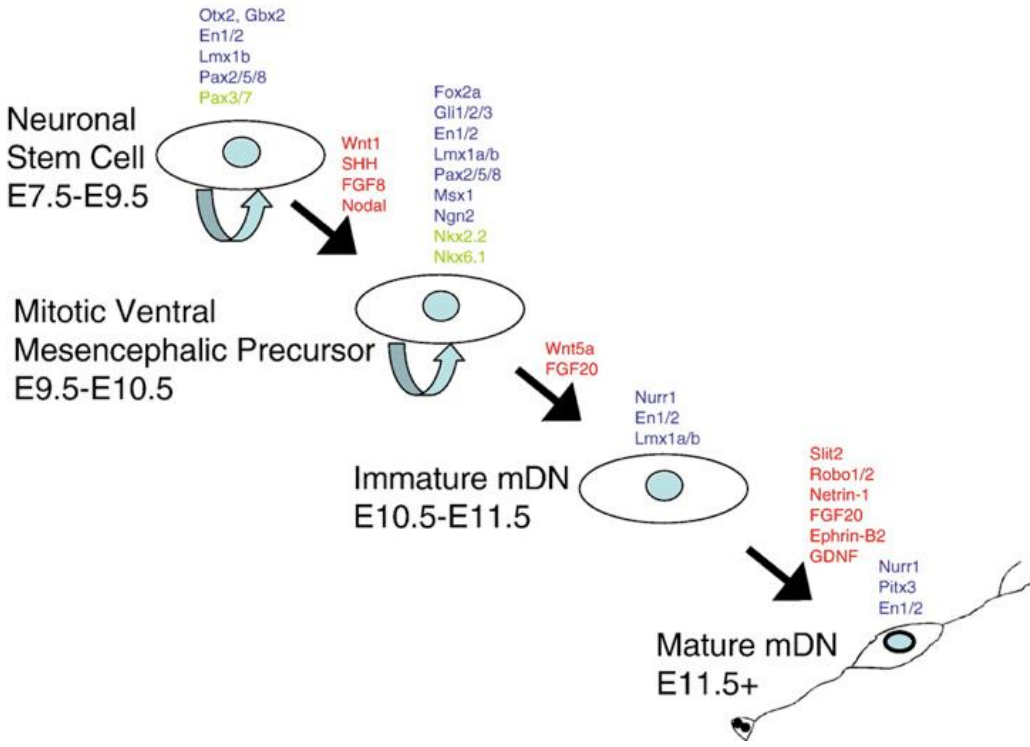
Therapeutic Neuron Replacement

- Methods of inducing desired phenotype:
  - Stepwise recapitulation of development by culturing stem cells in different cytokines.
  - Transfect cells with the fate determining transcription factor genes.



Generation of Dopaminergic Neurons from Stem Cells





Generation of Dopaminergic Neurons from Stem Cells

Dopaminergic neurons produced from iPS cells were implanted into a person with Parkinson's disease. At Kyoto University, 2.4 million cells were injected into 12 sites in the striatum.

Press conference (as reported by Japan Times)
9 Nov 2018