Adult Neurogenesis

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- Where are new neurons generated in adult humans?

  (make a list, then discuss with your tablemates.)

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  (make a list, then discuss with your tablemates.)

  - Subventricular zone
  - Subgranular zone
  - Olfactory epithelium

Neurogenesis in Other Regions of Adult Mammalian Brain

- Although controversial and not broadly accepted, low levels of neurogenesis have been reported in other adult mammalian brain regions:
  - 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)

With tablemates, list differences between the SVZ and SGZ. Think: location, types of cells generated, functional significance, etc.

With tablemates, list differences between the SVZ and SGZ. Think: location, types of cells generated, functional significance, final destination of cells etc.

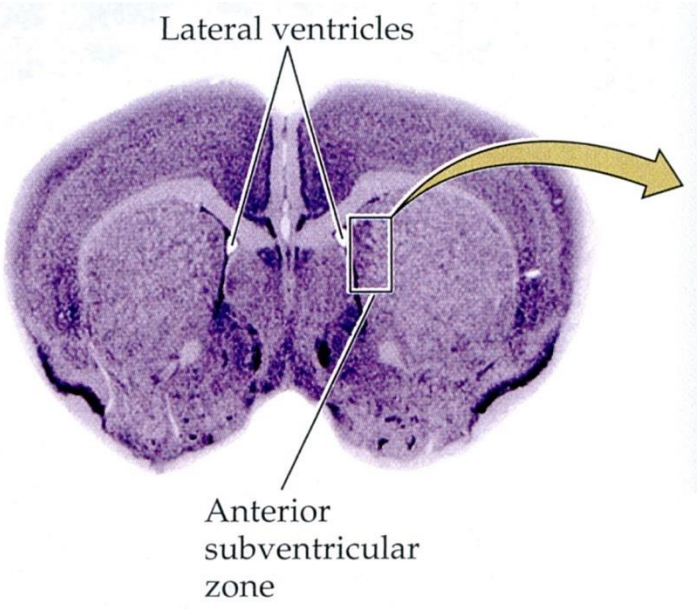
	SVZ	SGZ
Location	Adjacent to lateral ventricles	Below hippocampus
Cell types generated	Olfactory interneurons	Hippocampal granule cells
Functional significance	Olfaction	Learning and memory
Cell types	Neural stem cells, transit amplifying cells, neuroblasts, glioblasts, astrocytes, blood vessels, ependymal cells	Neural stem cells, transit amplifying cells, neuroblasts, glioblasts, astrocytes, blood vessels
Final destination of cells	Olfactory bulb (cells travel far!)	Dentate gyrus of hippocampus (cells don't travel too far)

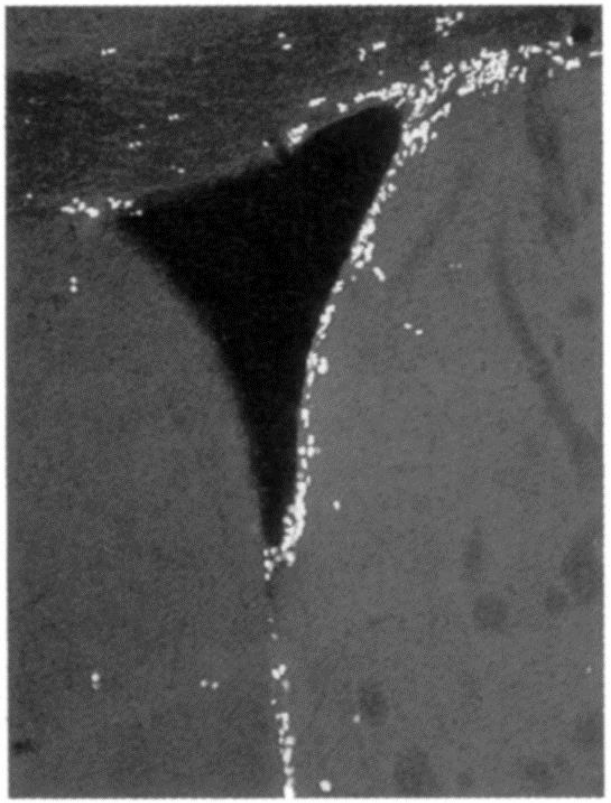
Subventricular zone

Subventricular Zone (SVZ)

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

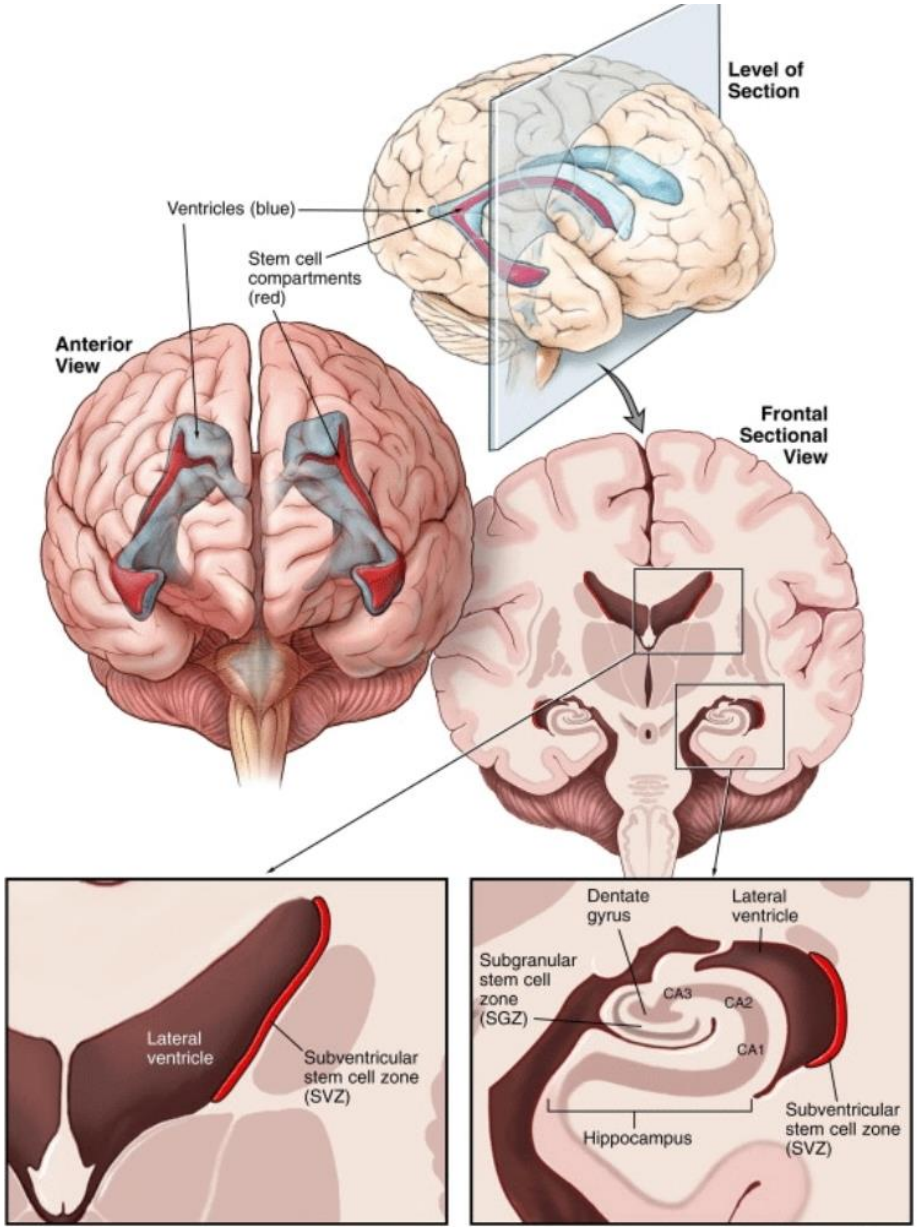
  They can be labeled with markers of cell division.





subventricular zone

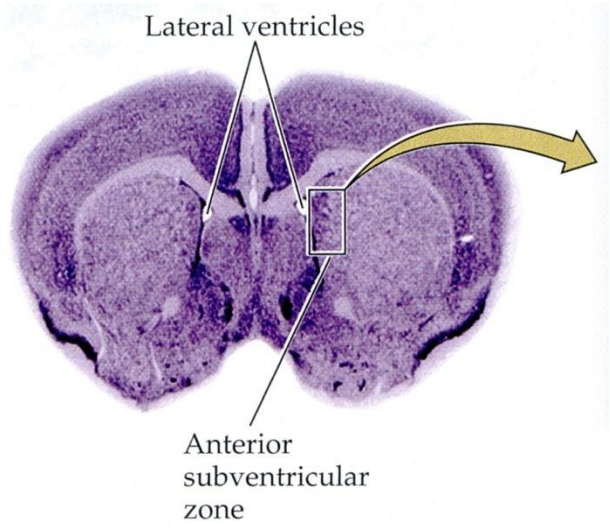
Subventricular and subgranular zones

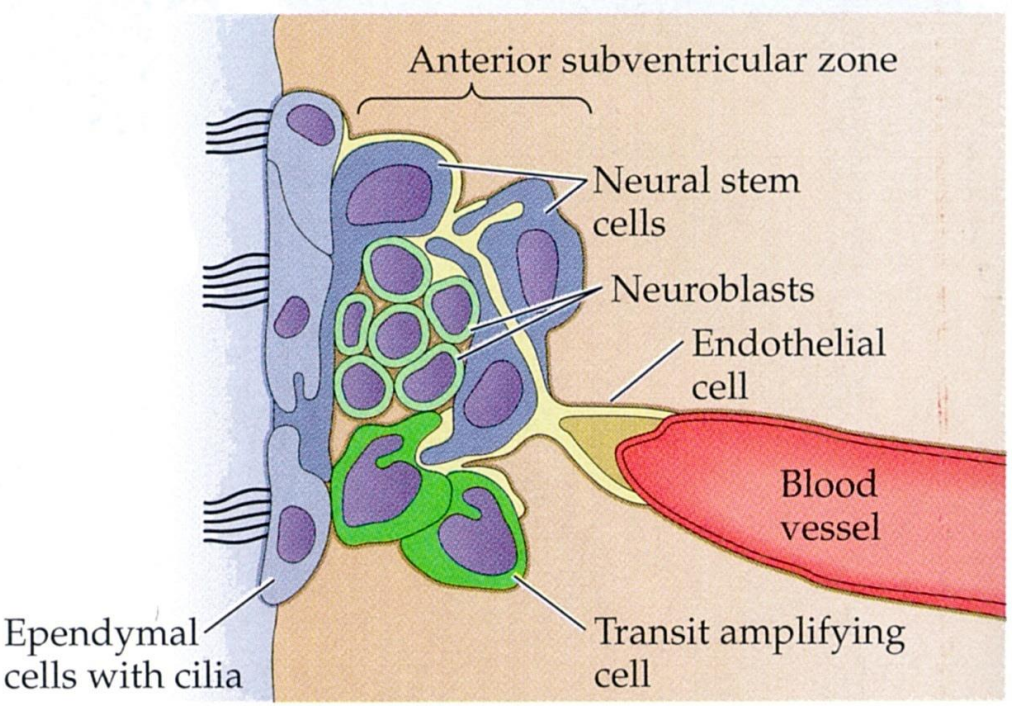


Subventricular Zone (SVZ)

- 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

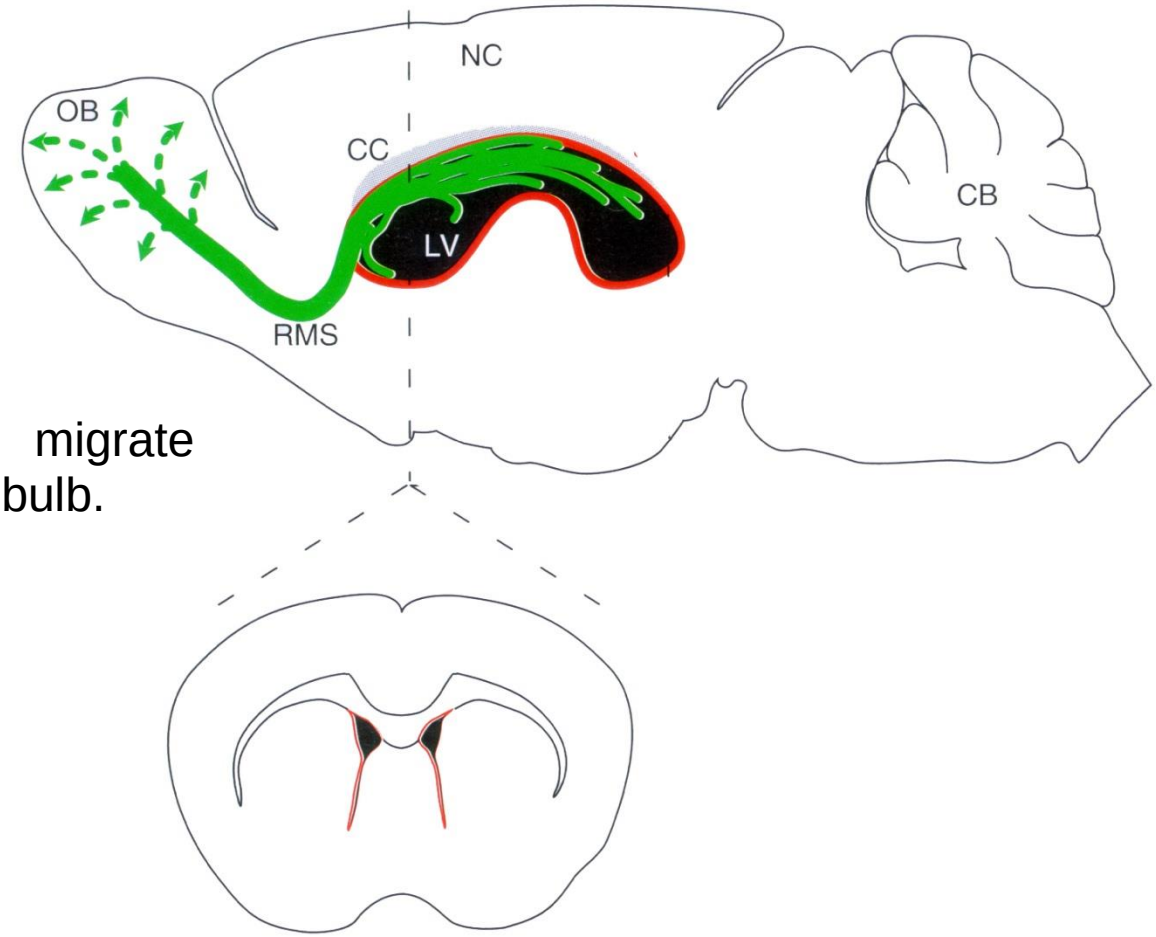
And astrocytes!





Subventricular Zone (SVZ)

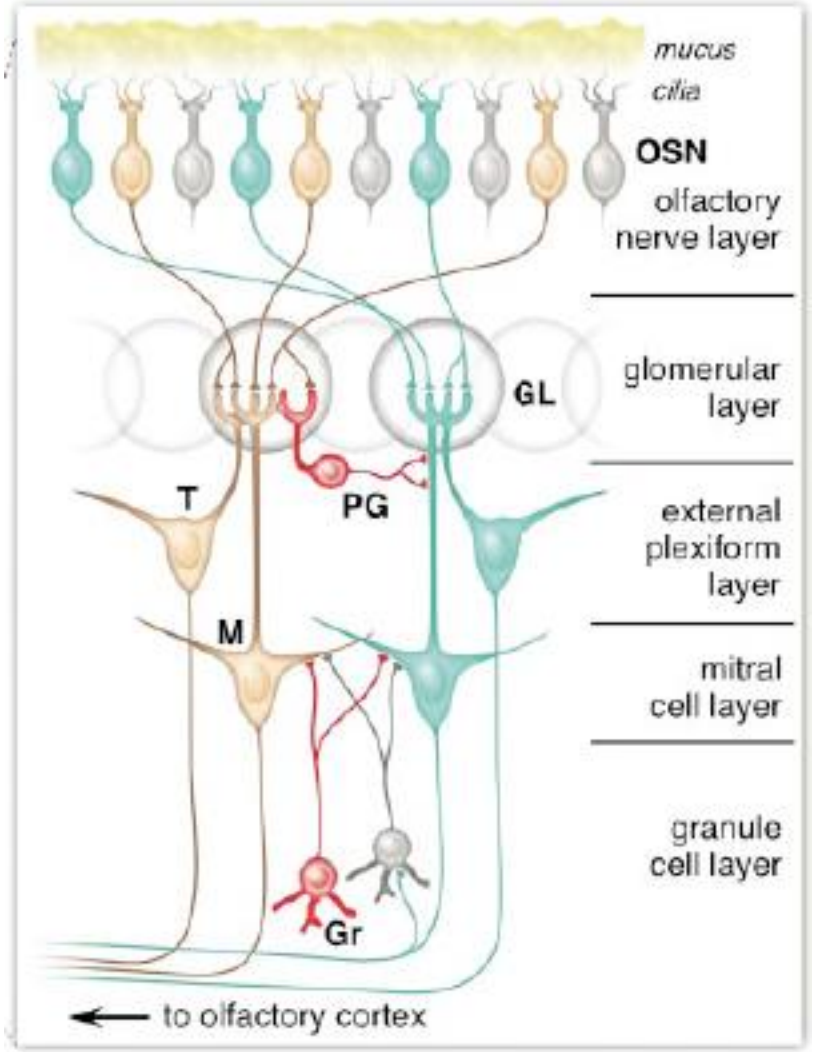
- Neuroblasts and glioblasts migrate from the SVZ to the olfactory bulb.



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.

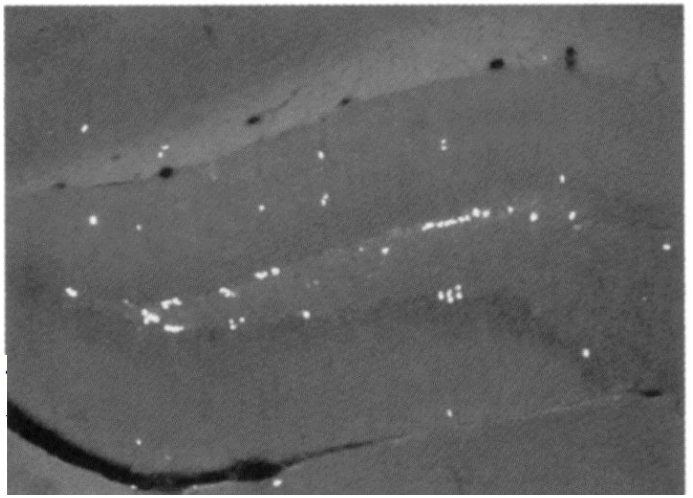
These interneurons are GABAergic/inhibitory.

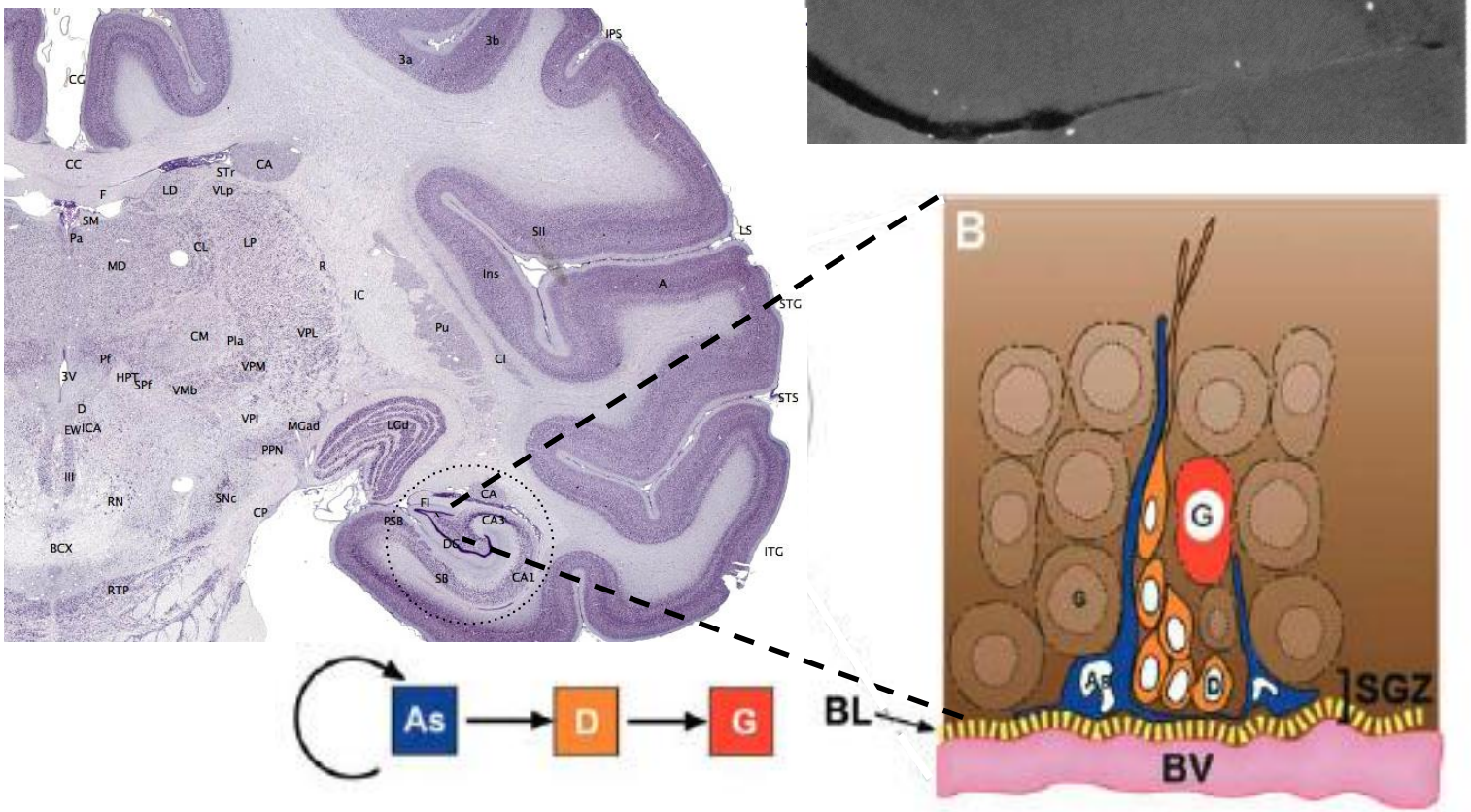


Subgranular zone

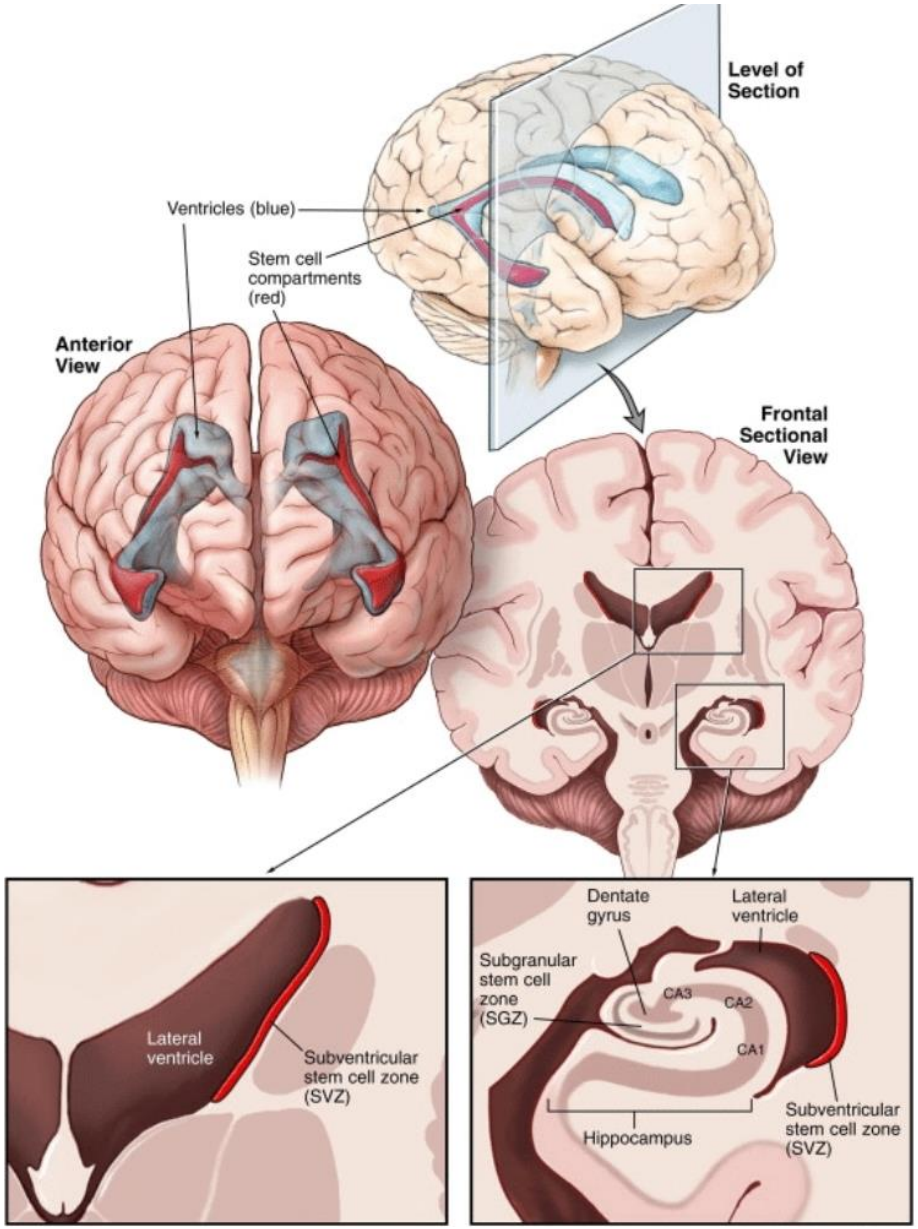
Subgranule Zone (SGZ)

- Neurons and glia are generated just below the granule cell layer in the dentate gyrus of the hippocampus, the subgranule zone (SGZ).





Subventricular and subgranular zones

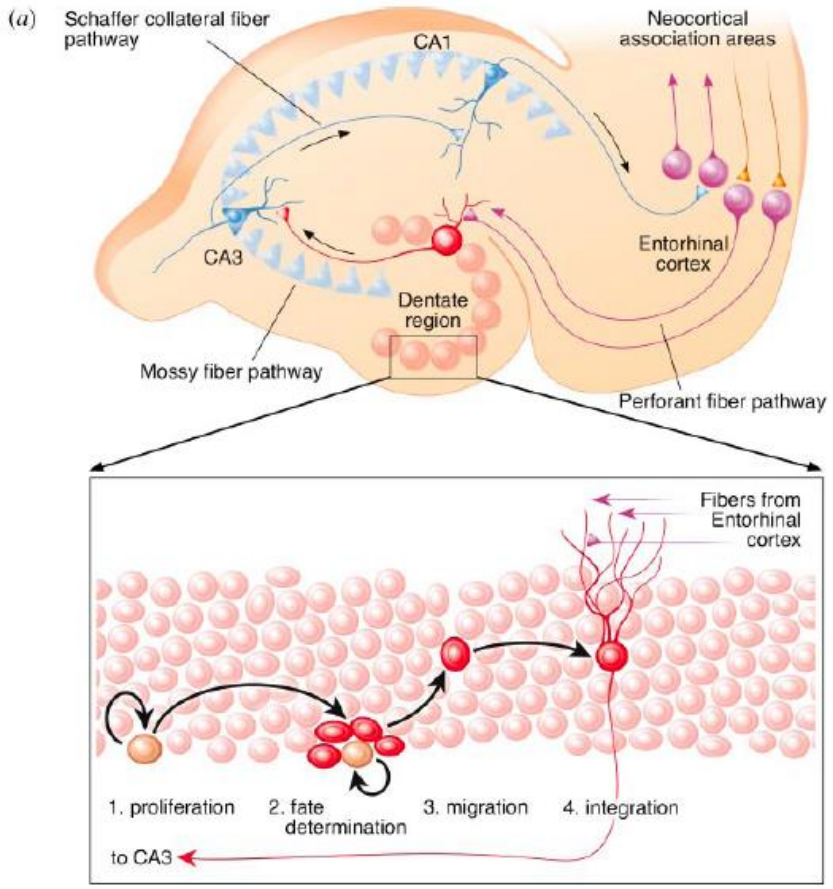


The subgranular zone share many of the same cell types as the subventricular zone

- neural stem cells (slowly dividing; produce transit amplifying cells)
- transit amplifying cells (rapidly dividing; produce neuroblasts & glioblasts)
- neuroblasts & glioblasts (non-dividing)
- blood vessels

And astrocytes!

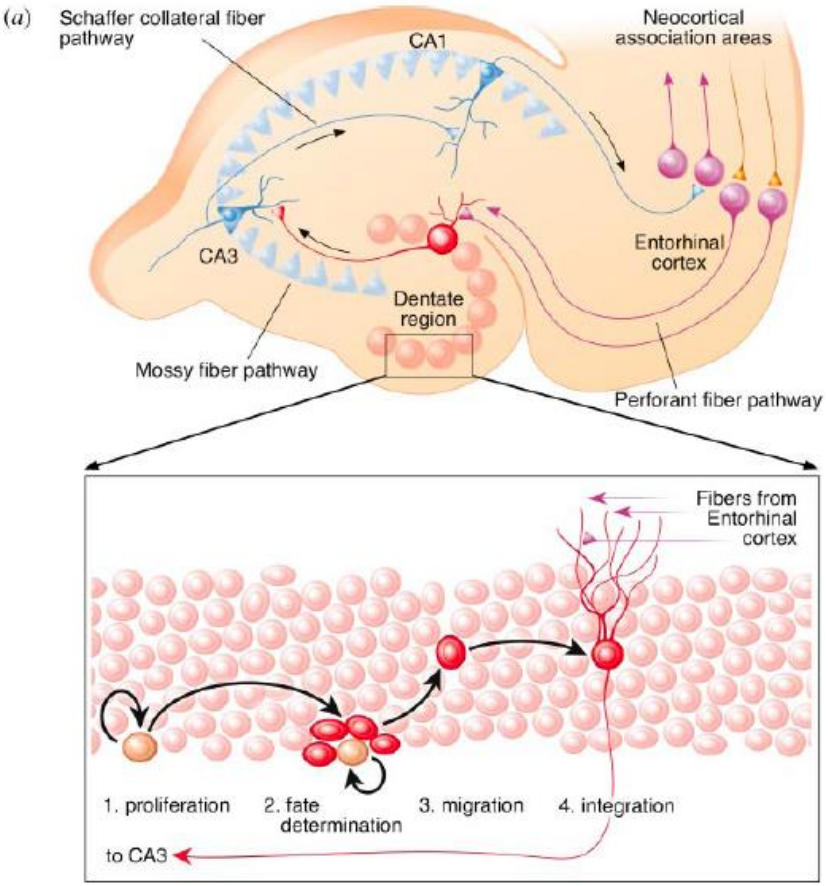
- (no ependymal cells- SGZ isn't situated by a ventricle
- Caveat: the cell types in the SGZ versus the SVZ have different names and morphologies, but ultimately serve analagous purposes.



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% of the granule cells are replaced per year.
- New neurons receive synapses from axons in adjacent regions.
- They send axons to other regions of the hippocampus.

These granule cells are glutamatergic/excitatory.



- Make a list of factors that increased or decreased neurogenesis in the adult SGZ.

  (discuss with your tablemates.)

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.

Subgranule Zone (SGZ)

College as a place for learning:

- 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.

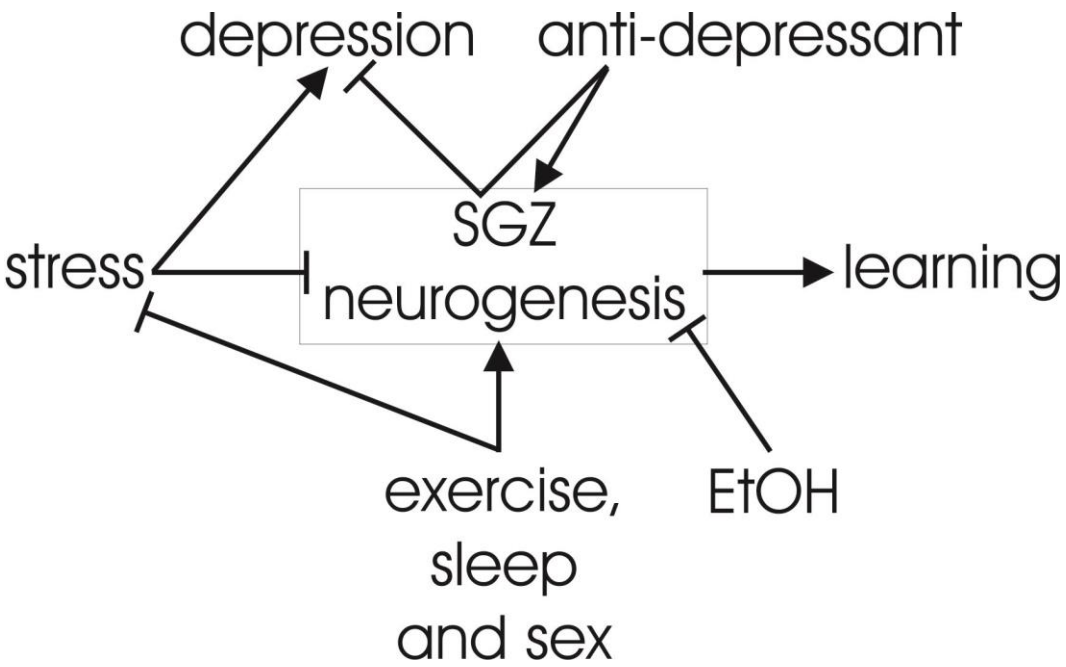
- · Exercise increases neurogenesis.

- / + · Sex increases neurogenesis.

? · Antidepressants increase neurogenesis.

- · Ethanol reduces neurogenesis.

What does this tell us?



Subgranule Zone (SGZ)

- New neurons have a role in learning and memory:

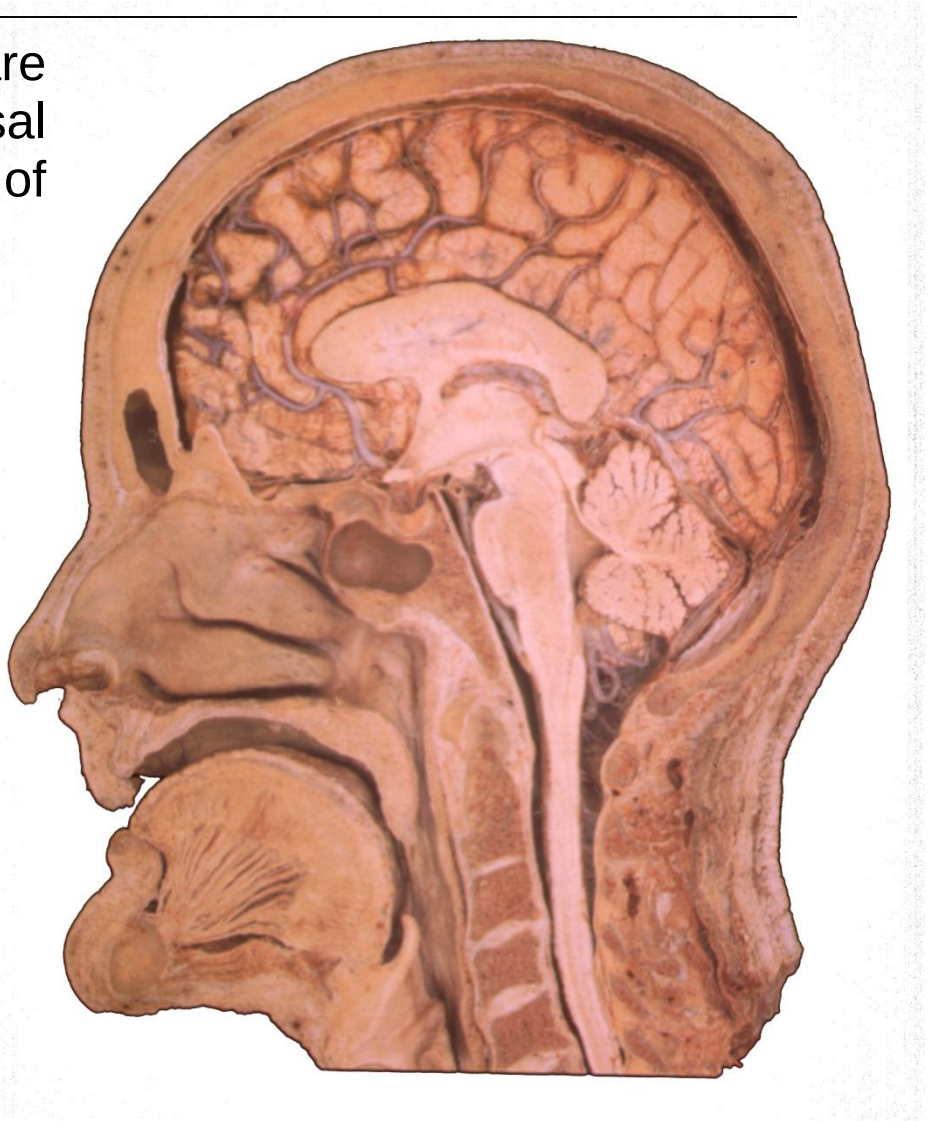
  Reduced neurogenesis reduced several types of learning.

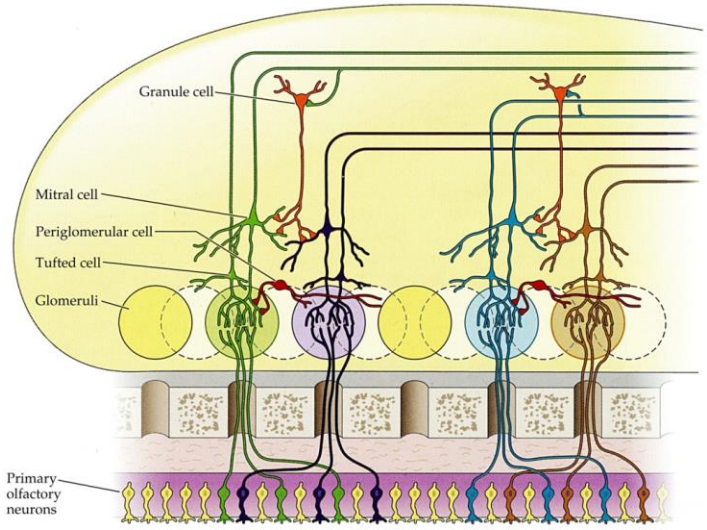
  Spatial and episodic memory were enhanced with treatments that increased neurogenesis.

Olfactory epithelium

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.





Therapeutic Cell Replacement (Stem Cells)

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Neuronal Death

- Trauma:
  - Auto accidents!
- Toxins:
  - Alcohol!
  - Pesticides
- Hypoxia / loss of blood supply:
  - Heart attack
  - Local vascular obstruction (e.g. clot, arterial sclerosis)
  - Burst aneurism
  - Drowning

Neuronal Death

- Neurodegenerative diseases:
  - Alzheimer's disease – cortical neuron loss
  - 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

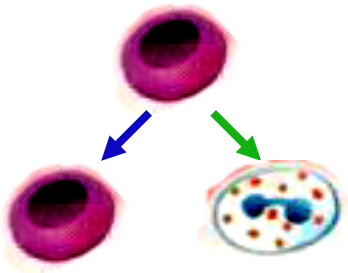
- Define ‘stem cell’.

  (discuss with your tablemates.)

Therapeutic Neuron Replacement

- Definition of a stem cell:

  1. Capable of self-renewal [by cell division].
  2. Capable of generating multiple differentiated cell types



Therapeutic Neuron Replacement

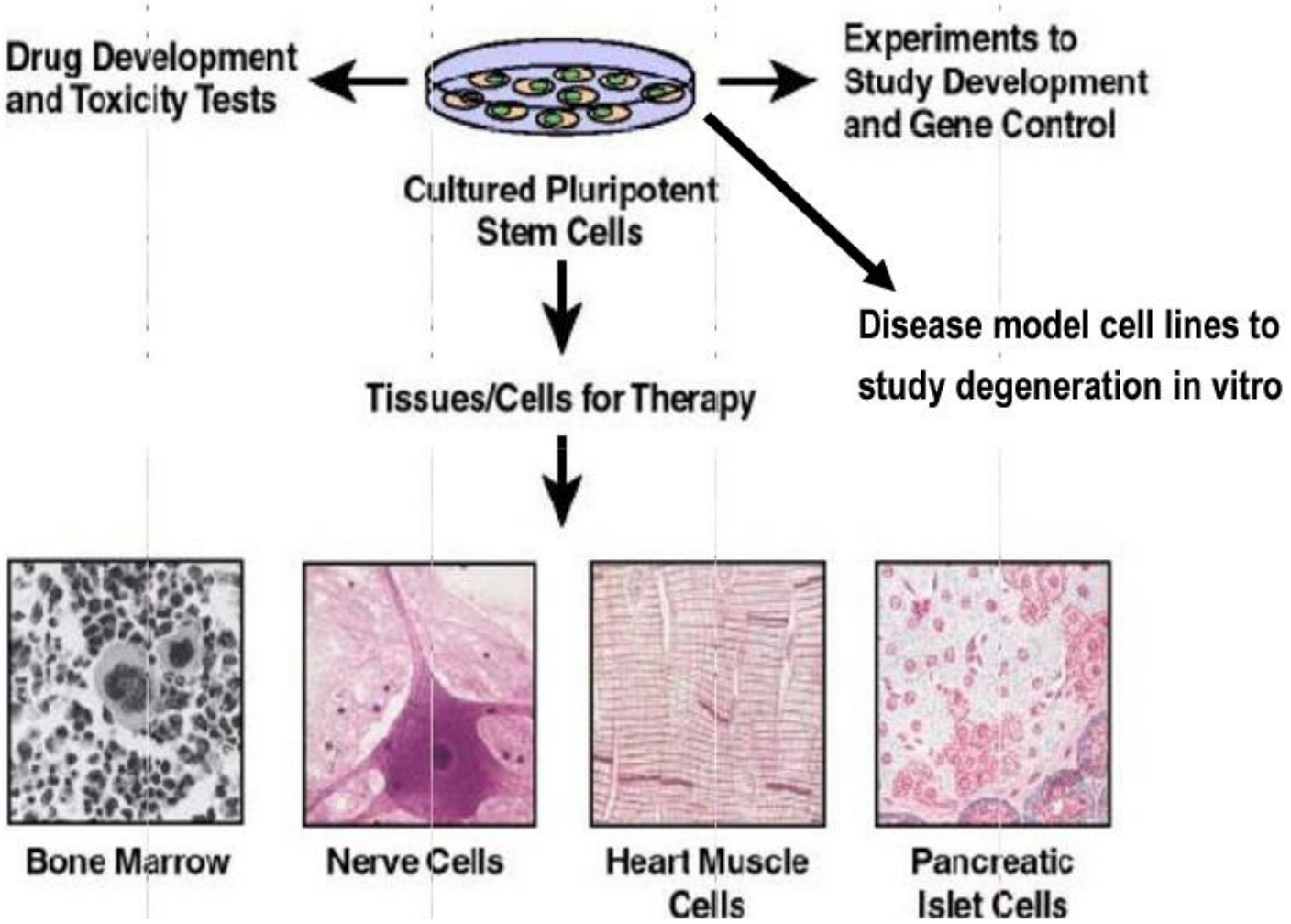
- Types of stem cells:
  - Embryonic stem cell (ESC)
  - Umbilical cord stem cell
  - Neural stem cell (NSC)
  - Other adult tissue derived stem cells
  - Induced pluripotent stem cell (IPSC)

The self renewal capability of neural stem cells depends on location in the brain.

- The SVZ and SGZ occupy areas known as **neurogenic niches** – these niches, or environments, are rich in blood supply and have high levels of factors that promote cell division
- Neural stem cells in other areas of the brain (cerebellum, spinal cord, midbrain) have been found to divide in cell culture but not in vivo.
- Adult spinal cord NSCs, when transplanted to the SGZ, divide, supporting the theory that a neurogenic environment is integral to the self renewal capabilities of stem cells.

With tablemates, list uses for stem cell (besides cell replacement):

Multiple Uses for Stem Cells

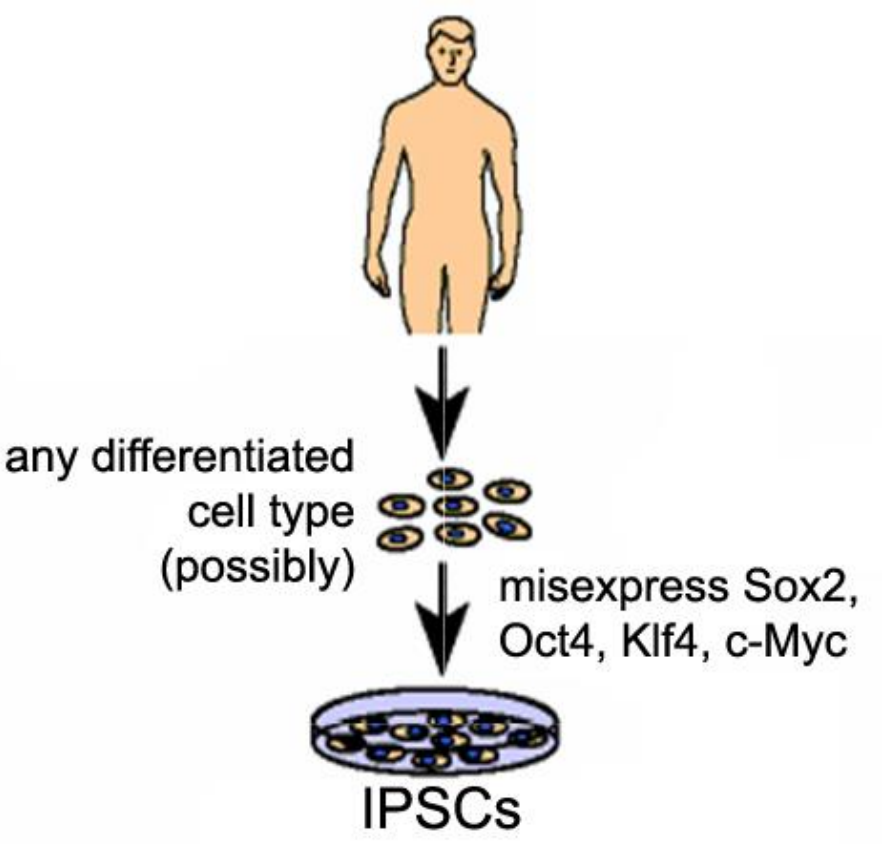


- What are IPS cells? Why are they appealing for therapeutic cell replacement?

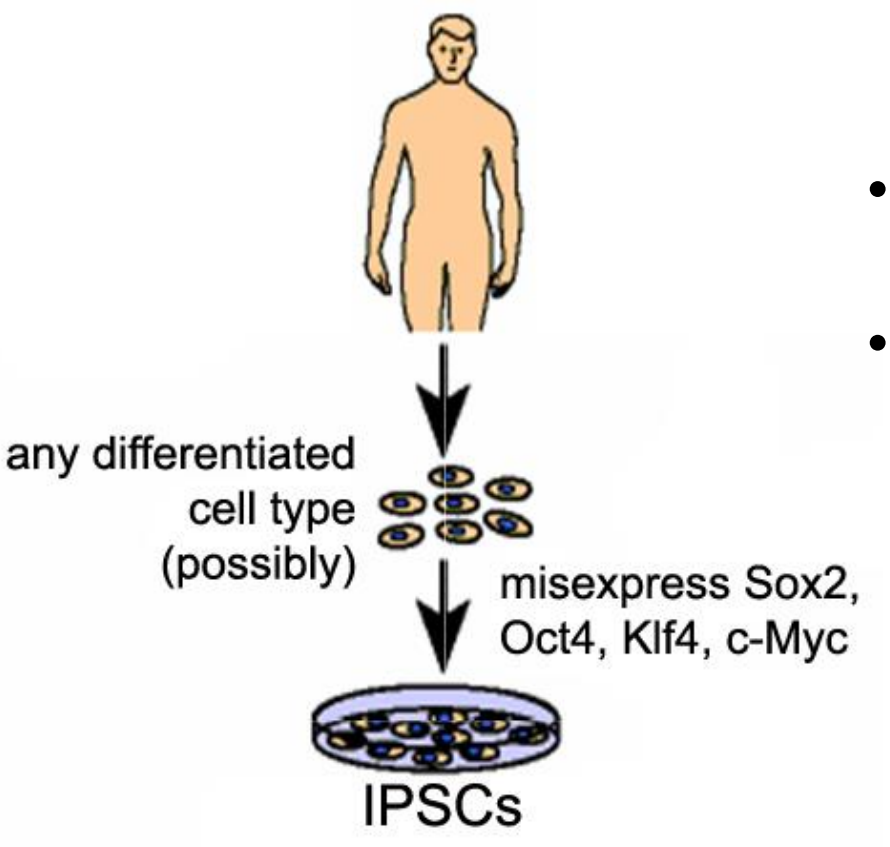
  (discuss with your tablemates.)

Therapeutic Neuron Replacement

- Induce(d)= bring about, give rise to. Pluripotent= capable of giving rise to several types. Stem Cells= capable of self-renewal.
- IPSCs can be generated (possibly) from any differentiated cell type, but usually is done with skin cells

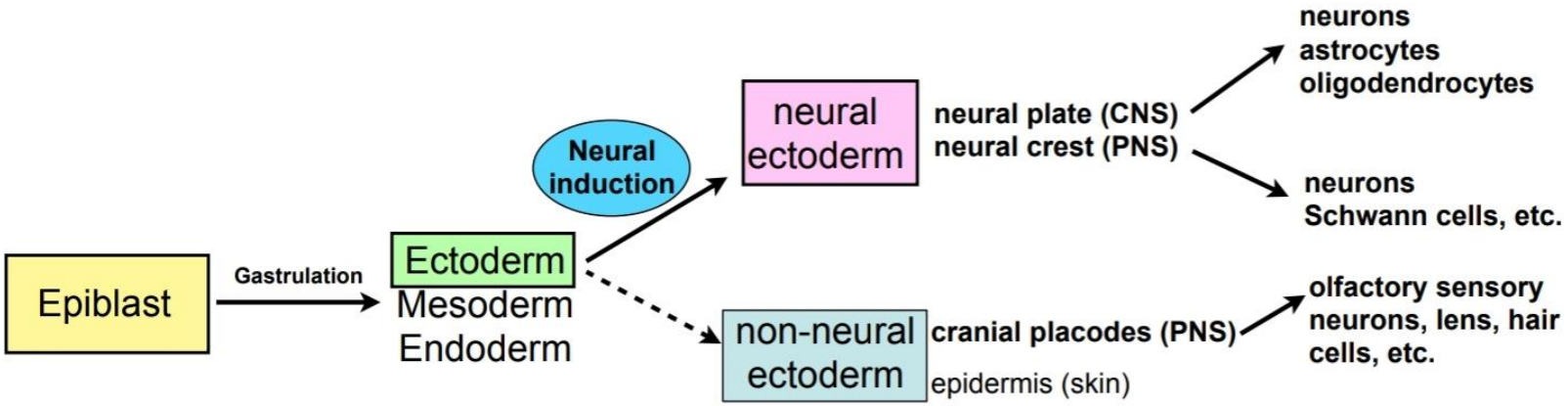


Therapeutic Neuron Replacement



- Wait, what??? How is this possible???
- Scientists arrived at this strategy of generating IPSCs through their understanding of development. Let's take a brief sidebar into that background.

A Brief and Incomplete Generalization of Development

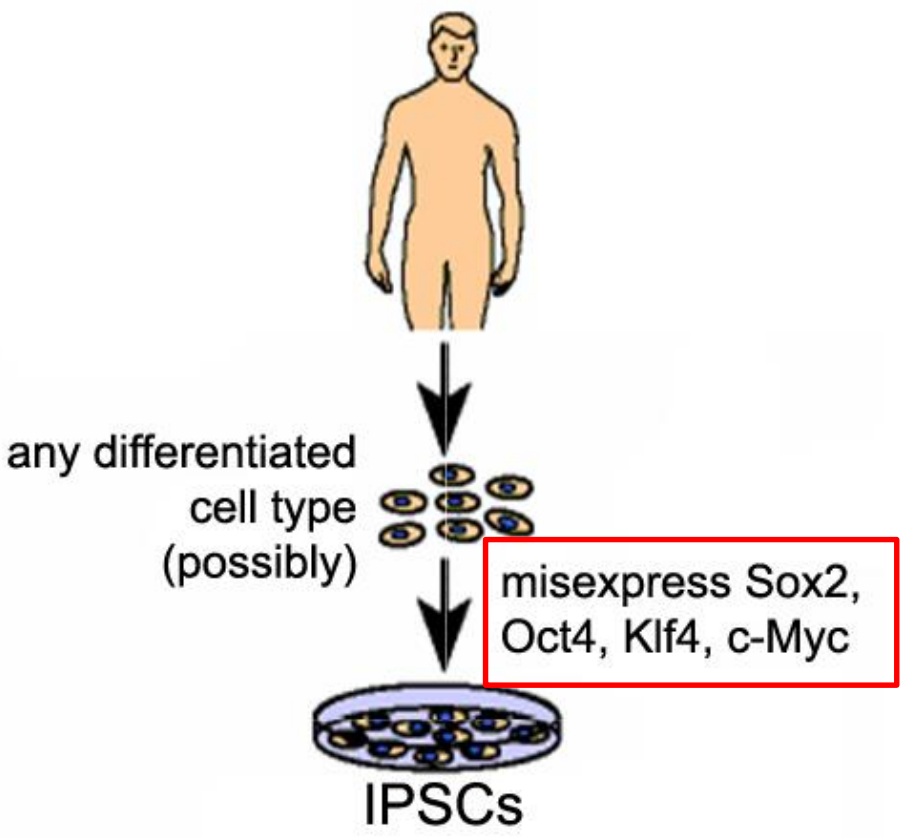


- We have learned in the past that the epiblast leads to formation of ectoderm, which leads to formation of cells of the nervous system as well as skin.
- Cells of the early nervous system differentiate, or become other cells, through a number of factors:
  - Changes in gene expression and production of different proteins
  - Timing
  - Cell position

Extensive research has mapped out these factors and how they cause specific cells, such as skin, to form from what was once epiblast. The idea of creating induced pluripotent stem cells (IPSCs) is to **reverse engineer** these cells by retracing the steps of development.

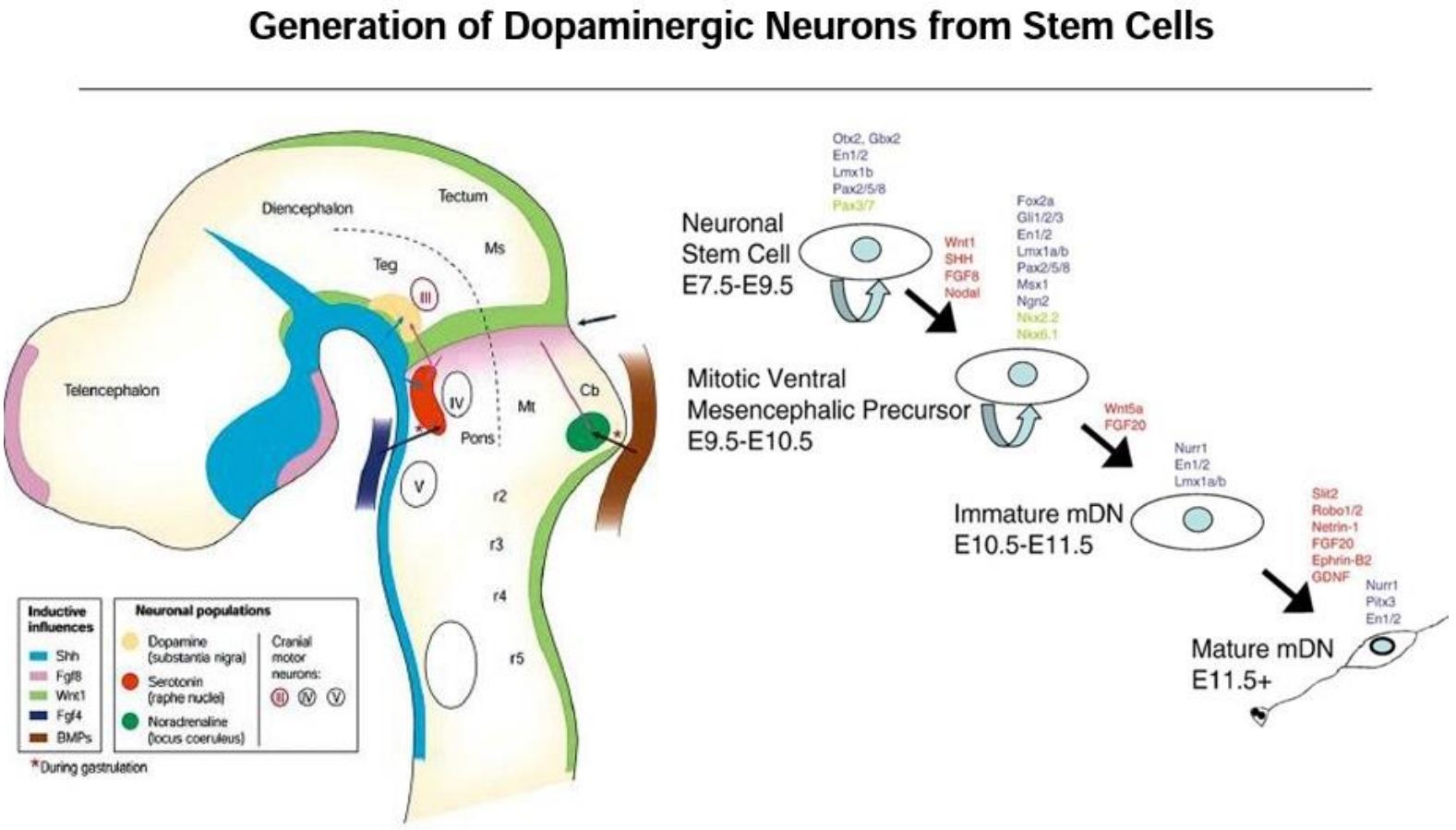
Therapeutic Neuron Replacement

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



- Sox2, Oct4, Klf4, c-Myc are transcription factors known to shape the differentiation of IPSCs into other cell types.
- Misexpressing, or changing/deleting those factors in a cell lead to the reverse engineering of that cell back into a stem cell capable of differentiation into other cell types.

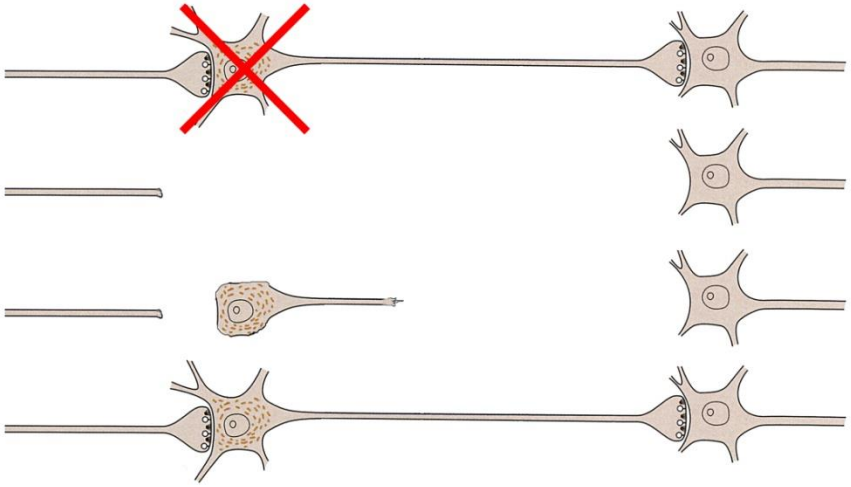
Our knowledge of the development of specific cell types in vivo can be applied to stem cells in culture so that they may differentiate into a cell type of our choice.



- So if we can generate whatever cell types we want, why can't we use stem cell therapies to virtually replace any cell or organ that malfunctions? i.e. what are some of the problems that need to be solved in order to use stem cells to replace neurons?

  (discuss with your tablemates.)

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

Hematopoietic Stem Cell Transplantation (HSCT)

- Stem cell therapies are typically experimental, but HSCT is more common.
- A dangerous procedure only used to treat life-threatening diseases of the blood and autoimmune diseases.
  - Cancer of blood, bone marrow.
- Grafts are taken from bone marrow, peripheral blood, or umbilical cord. Graft types:
  - Autologous= from the patient
  - Allogeneic= from a donor
  - Syngeneic= from a twin. Even if you don't have a twin, it's recommended to have a sibling be a donor- which is a good reason to be nice to them just in case ☺
- It's common for a patient to receive chemotherapy to eliminate the disease and immune system prior to transplantation. This helps with preventing rejection of the graft by the immune system.
- **High treatment-related mortality rate**