In adult rodent brains, neural stem cells are found in the subventricular zone (SVZ), and subgranular zone of the dentate gyrus (SGZ)

Neural stem cells in adult have similar morphology as in embryo: elongated radial processes, present Glial markers.
Radial glia / neuron stem cells produce rapidly dividing intermediate precursor cells (IPCs) and immature ganglion cells (IGCs) which will later differentiate

Adult neural stem cells can become quiescent:

- Slower cell cycle
- Lower metabolism
- Lower transcription
- More dependent on glycolysis and lipid metabolism
- Less dependent on oxidative phosphorylation and lipid synthesis

Neurogenesis can be regulated by signals released by cells in the NSC niche.
Cells include:

- Endothelial cells from blood vessels
- Other neurons
- Glial cells: astrocytes, oligodendrocytes, microglia.

Neurons generated from NSC populations integrate into pre-existing neuronal circuits:

- Neurons generated from the subvenricular zone (SVZ) becomes the olfactory sensory neurons
- Neurons generated from the subgranular zone (SGZ) in the hippocampus becomes hippocampal neurons involved in neural plasticity.
    - Though there are debates on the neurogenesis activity in the hippocampal SGZ, as there are lack of proliferation marker Ki67 and young neuron marker DCX. Consensus is reached in neurogenesis activity in SVZ.

Single cell RNA sequencing is used to map the developmental stages of the NSC

In hippocampus it has been shown the rate of neurogenesis peaks during juvenile stage and decreases as the organism reaches sexual maturity.

- Three models predicting the neural stem cell dynamics in the hippocampus:
    - Division-depletion model: division of active stem cell lead to decrease in total number of stem cells, proposed to occur during early stages of neural development
    - Stem cell heterogeneity model: Active stem cells can become resting state stem cells, as an intermediate. Proposed to occur during juvenile stages.
    - Stem cell self renewal model: Active stem cells can convert back to quiescent stem cells. Proposed to occur at late stages, e.g. middle age.

Labelling Ki67(active proliferation marker) and EdU (Proliferation history marker) shows as age progress, more proliferated neurons return back to quiescent stages compared to earlier stages where proliferated neurons become differentiated.

Ki67-CreER; tdTomato used to identify proliferating cells, which will show red fluorescence signal upon tamoxifen

administration. Cell cycle gene is also labelled. Resting cells produced from previously active NSC will show red signal but no cell cycle markers.

The transcriptome of these cells are then characterised with single cell RNA sequencing
By ordering cell types along a pseudotime axis, the changes in transcriptome can be visualised, hence predicting mechanism.

Two genes found to be differentially expressed in quiescent and actively proliferating cells: Apoe and Ccnd2

- Apoe is expressed in quiescent cells while Ccnd2 is expressed in proliferating cells
- Pseudotime analysis: In older mice, NSCs fall into deeper quiescent (near dorment) stage, expressing very low Ccnd2.
- As the mice grow older, its quiescent population increase with a deeper quiescent stage, mechanism underlying this transition:
    - Ascl1 gene is highly expressed in differentiating neurons. **Ascl1 conditional KO lead to permanently dorment cells.** Hypothesis: Ascl1 regulates chromatin accessibility epigenetically. At low level prevent packing too densely.
    - Huwe1 ubiquintin ligase regulates Ascl1 by targeting for degradation, **Huwe1 cKO lead to rapid proliferation**.
    - As age increases, level of Ascl1 decreases, cells become more quiescent.
    - A low level of Ascl1 is required to maintain the quiescent stage. **Ascl1 cKO different from old age control**