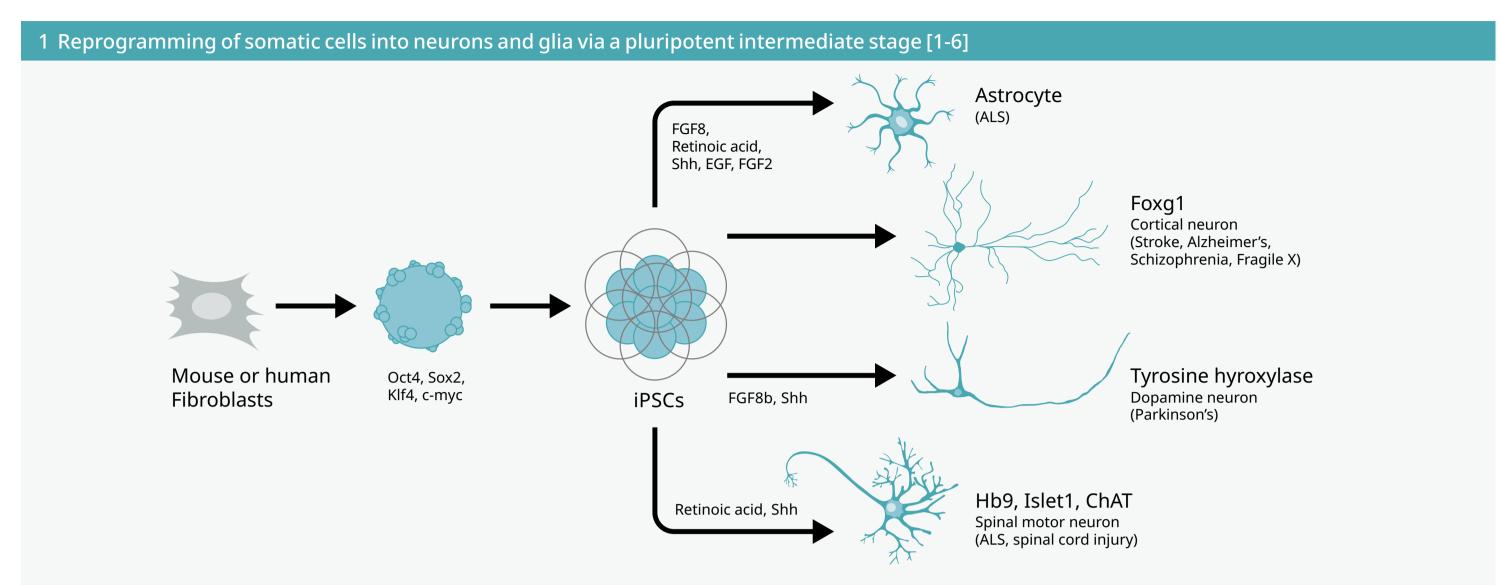
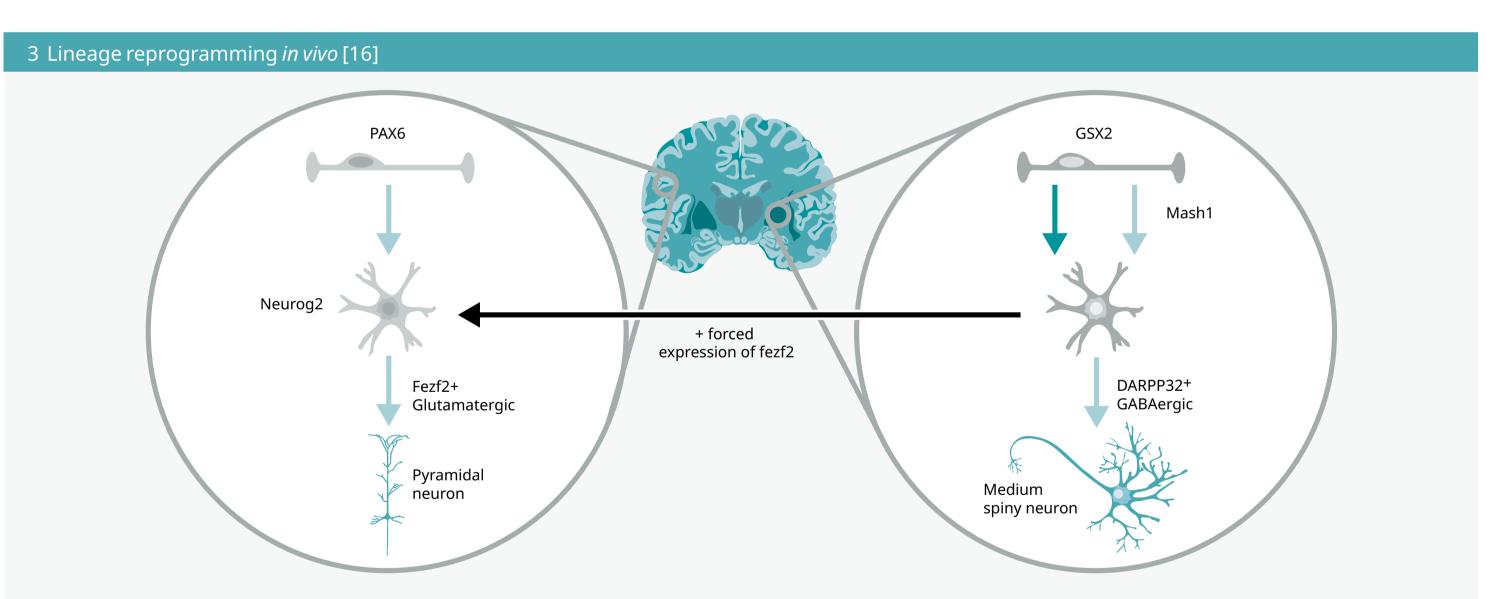
New Avenues for Brain Repair

by Paola Arlotta, Benedikt Berninger, Alejandro Schinder and Abcam

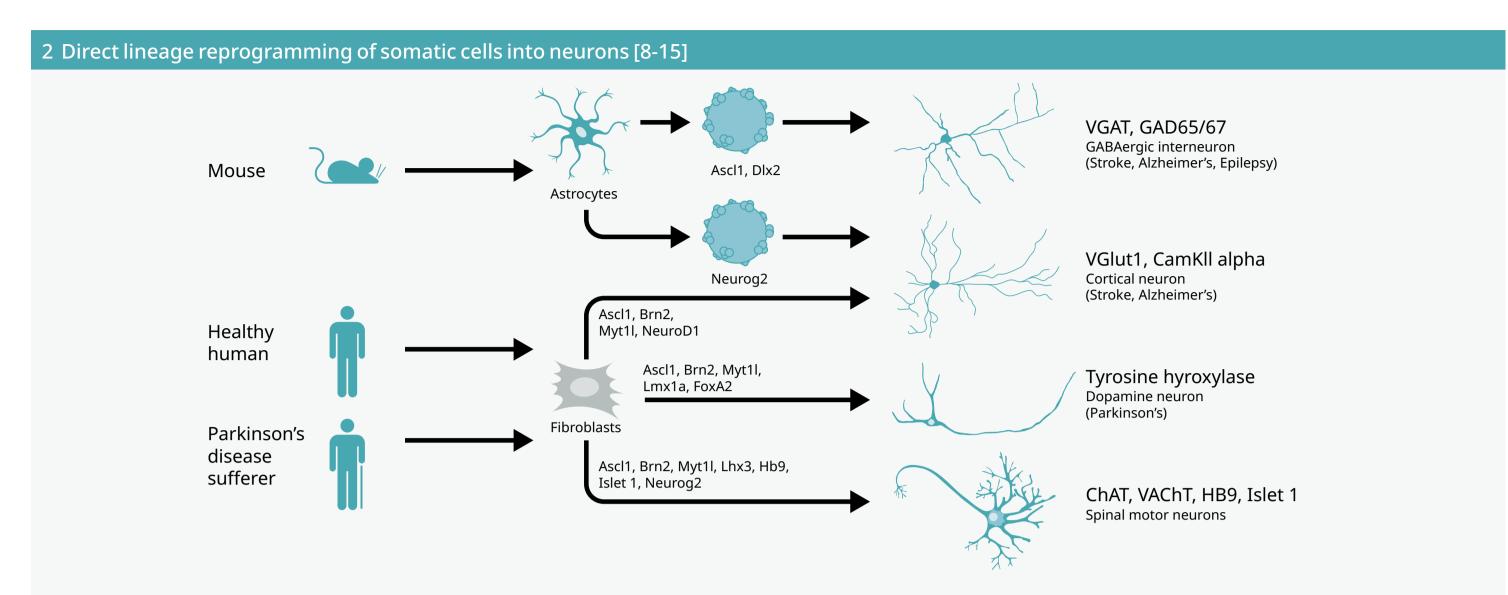




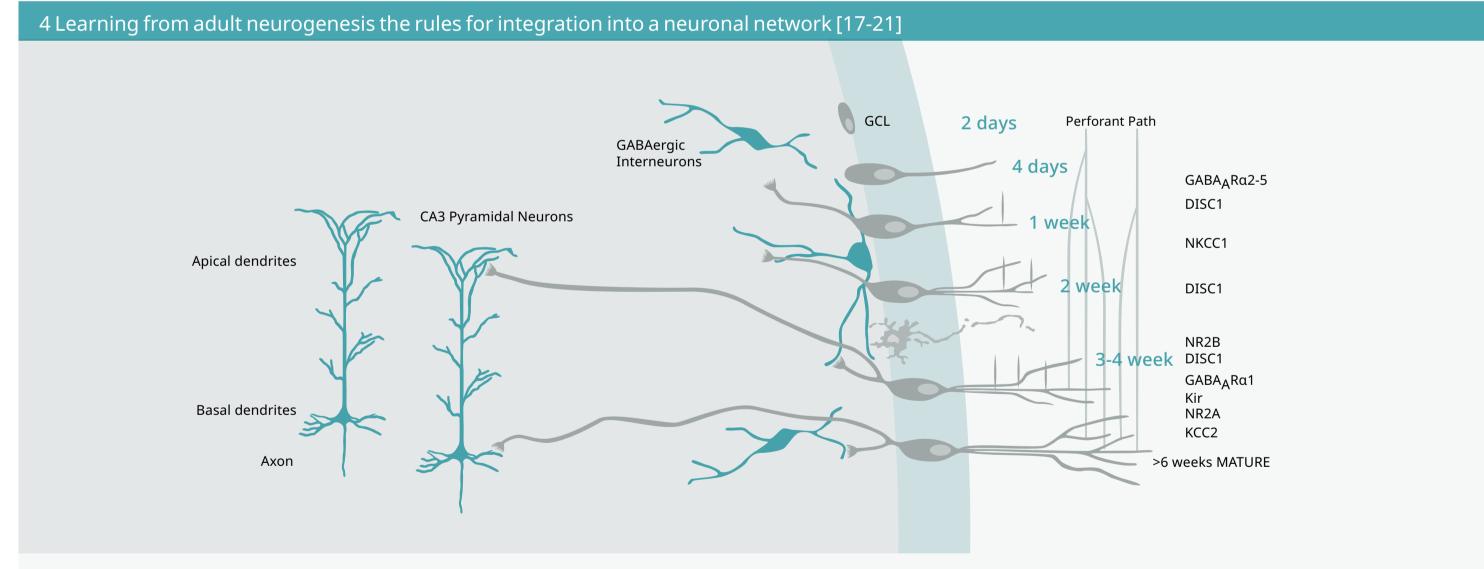
Fibroblasts or other somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs) by a defined cocktail of transcription factors. These iPSCs are very similar to embryonic stem cells and can be selectively driven towards the genesis of neurons and glia, either by signaling molecules or by specific transcription factors. Many clinically important types of neurons have been generated in vitro using this strategy, also from patients suffering from neurodegenerative diseases like Parkinson's disease. Patient iPSC-derived neurons can be used to study the mechanisms underlying the disease's pathology.



GABAergic medium spiny neuron progenitors can be lineage reprogrammed into corticofugal neurons, solely by forced expression of the transcription factor Fezf2. Amazingly, some axons of these corticofugal neurons direct themselves to the spinal cord, very similar to those of corticospinal motor neurons. Corticospinal motor neurons are a neuron population that dies in amyotrophic lateral sclerosis (ALS) but also become severed in spinal cord injury. A future challenge is to examine the possibility of such lineage reprogramming in the adult CNS in order to replace neurons degenerated due to disease or injury.



Instead of reprogramming via a pluripotent intermediate, somatic cells can also be reprogrammed directly. Mouse astroglia can be reprogrammed into glutamatergic and GABAergic neurons by forced expression of Neurog2 or Ascl1, respectively. Alternatively, fibroblasts can be directly converted into various types of neurons, including glutamatergic, dopaminergic and spinal motor neurons, by different cocktails of transcription factors and neuron-specific microRNAs. Neurons derived from fibroblasts of a patient with Alzheimer's disease have revealed defects in the processing and localization of amyloid precursor protein.



A key challenge of all approaches to cell-based therapy concerns the integration of new neurons into a pre-existing neuronal network. The adult neurogenesis process taking place in the dentate gyrus of the hippocampus (depicted) and the adult olfactorybulb provides examples of how this can occur. The survival and maturation of newly generated neurons depends on receiving signals from the surrounding network, e.g. GABA and neurotrophins. Additionally, maturation of new neurons is a protracted process, normally slowed down by DISC1, a gene implicated in schizophrenia.

References:

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 $N.B.\ The\ above\ reading\ list\ is\ not\ exhaustive\ and\ is\ only\ intended\ to\ provide\ a\ quick\ overview\ of\ the\ topic.$