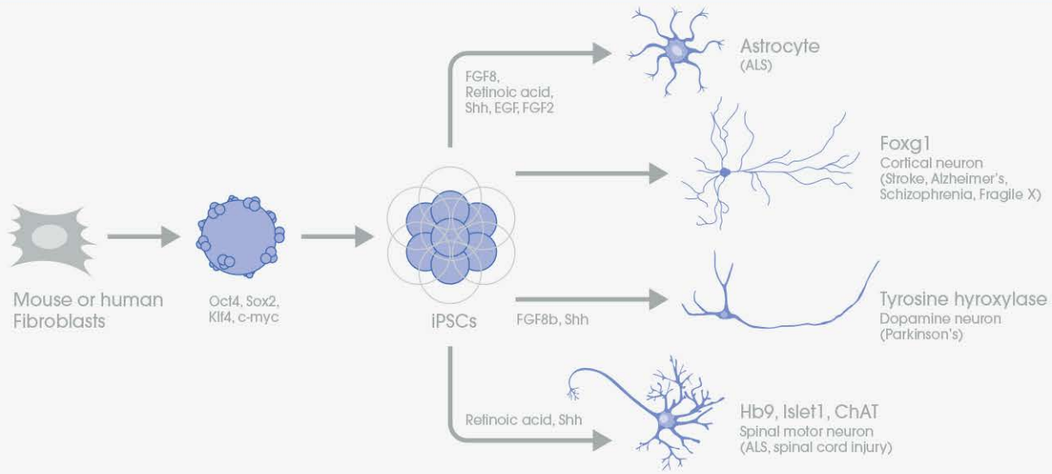
New Avenues for Brain Repair

By Paola Arlotta, Benedikt Berninger, Alejandro Schinder and Abcam

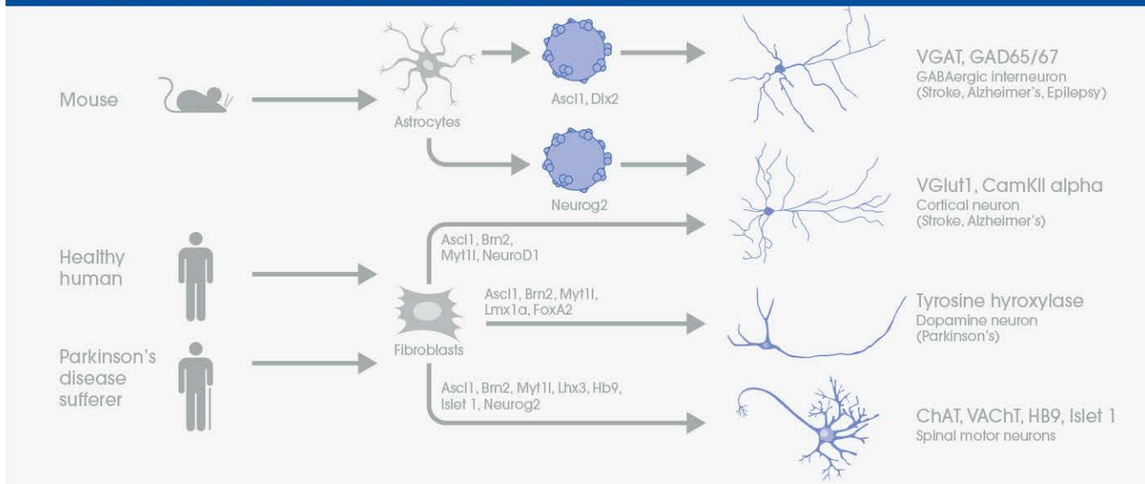
abcam

1 Reprogramming of somatic cells into neurons and glia via a pluripotent intermediate stage (1-6)



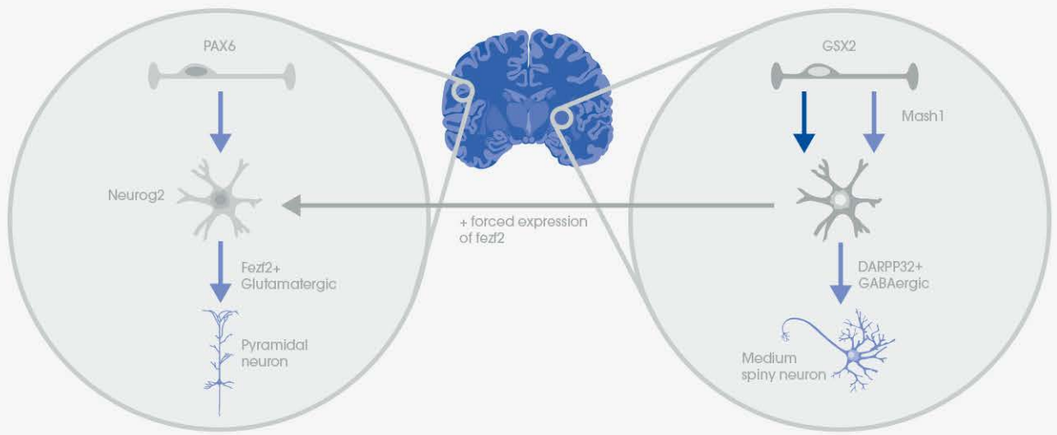
Fibroblasts or other somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs) by a defined cocktail of transcription factors. These iPSCs are very similar to embryonic stem cells and can be selectively driven towards the genesis of neurons and glia, either by signaling molecules 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.

2 Direct lineage reprogramming of somatic cells into neurons (8-15)



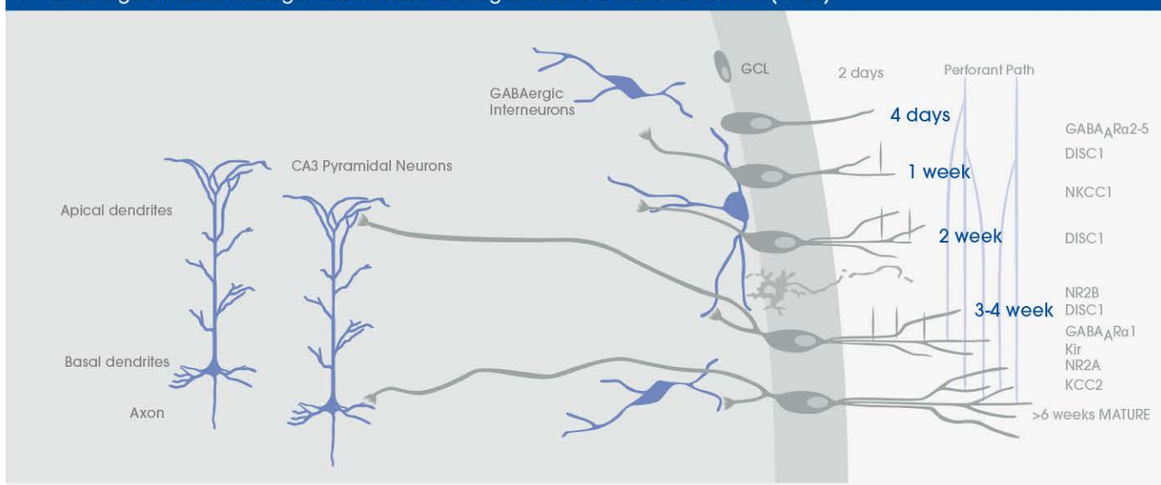
Instead of reprogramming via a pluripotent intermediate, somatic cells can also be reprogrammed directly. Mouse astroglia can be reprogrammed into glutamatergic and GABAergic neurons by forced expression of Neurog2 or Ascl1, respectively. Alternatively, fibroblasts can be directly converted into various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

3 Lineage reprogramming in vivo (16)



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.

4 Learning from adult neurogenesis the rules for integration into a neuronal network (17-21)



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:

1. Krencik R, Weick JP, Liu Y, Zhang ZJ, Zhang SC (2011) Specification of transplantable astroglial subtypes from human pluripotent stem cells. Nat Biotechnol 29: 528-534. **2.** Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, et al. (2011) Modelling schizophrenia using human induced pluripotent stem cells. Nature 473: 221-225. **3.** Kim JE, O'Sullivan ML, Sanchez CA, Hwang M, Israel MA, et al. (2011) Investigating synapse formation and function using human pluripotent stem cell-derived neurons. Proc Natl Acad Sci U S A 108: 3005-3010. **4.** Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, et al. (2008) Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. Proc Natl Acad Sci U S A 105: 5856-5861. **5.** Nguyen HN, Byers B, Cord B, Shcheglovitov A, Byrne J, et al. (2011) LRRK2 mutant iPSC-derived DA neurons demonstrate increased susceptibility to oxidative stress. Cell Stem Cell 8: 267-280. **6.** Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, et al. (2008) Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science 321: 1218-1221. **7.** Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676. **8.** Heinrich C, Blum R, Gascon S, Masserdotti G, Tripathi P, et al. (2010) Directing astroglia from the cerebral cortex into subtype specific functional neurons. PLoS Biol 8: e1000373. **9.** Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Sudhof TC, et al. (2010) Direct conversion of fibroblasts to functional neurons by defined factors. Nature 463: 1035-1041. **10.** Pang ZP, Yang N, Vierbuchen T, Ostermeier A, Fuentes DR, et al. (2011) Induction of human neuronal cells by defined transcription factors. Nature 476: 220-223. **11.** Caiazzo M, Dell'Anno MT, Dvoretskova E, Lazarevic D, Taverna S, et al. (2011) Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature 476: 224-227. **12.** Qiang L, Fujita R, Yamashita T, Angulo S, Rhinn H, et al. (2011) Directed conversion of Alzheimer's disease patient skin fibroblasts into functional neurons. Cell 146: 359-371. **13.** Son EY, Ichida JK, Wainger BJ, Toma JS, Rafuse VF, et al. (2011) Conversion of mouse and human fibroblasts into functional spinal motor neurons. Cell Stem Cell 9: 205-218. **14.** Yoo AS, Sun AX, Li L, Shcheglovitov A, Portmann T, et al. (2011) MicroRNA-mediated conversion of human fibroblasts to neurons. Nature 476: 228-231. **15.** Pfisterer U, Kirkeby A, Torper O, Wood J, Nelander J, et al. (2011) Direct conversion of human fibroblasts to dopaminergic neurons. Proc Natl Acad Sci U S A 108: 10343-10348. **16.** Rouaux C, Arlotta P (2010) Fezf2 directs the differentiation of corticofugal neurons from striatal progenitors in vivo. Nat Neurosci 13: 1345-1347. **17.** Laplagne DA, Esposito MS, Piatti VC, Morgenstern NA, Zhao C, et al. (2006) Functional convergence of neurons generated in the developing and adult hippocampus. PLoS Biol 4: e409. **18.** Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, et al. (2008) Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 11: 901-907. **19.** Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, et al. (2007) Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 130: 1146-1158. **20.** Bergami M, Rimondini R, Santi S, Blum R, Gotz M, et al. (2008) Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. Proc Natl Acad Sci U S A 105: 15570-15575. **21.** Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, et al. (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439: 589-593.

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