RESEARCH HIGHLIGHTS

NEURAL DEVELOPMENT

From floorplate to function

Although directed differentiation of embryonic stem cells into dopaminergic neurons has been demonstrated *in vitro*, their ability to promote functional recovery in models of Parkinson's disease has been limited. A new study now demonstrates a method of obtaining floorplatederived engraftable dopaminergic neurons from human pluripotent stem cells (PSCs). These neurons, when transplanted into animal models of Parkinson's disease, produce marked functional recovery with minimal graft cell overgrowth.

Differentiation of PSCs towards a midbrain floorplate fate is thought to require the canonical WNT and sonic hedgehog (SHH) signalling pathways, which induce co-expression of the transcription factors forkhead box A2 (FOXA2; also known as HNF3β) and LIM homeobox 1a (LMX1A) and commitment to a dopaminergic neuron fate. Kriks et al. found that midbrain dopaminergic precursorlike cells could be obtained most effectively by exposure of PSCs to the combined influence of CHIR99021, two SHH agonists, fibroblast growth factor 8 and two inhibitors of SMAD signalling. This method differs from the most widely used strategy for obtaining transplantable dopaminergic neurons from stem cells the generation of neural rosettes (which aim to mimic neural tube development). The resulting cells co-expressed

LMX1A and FOXA2 in a similar way to the native midbrain floorplate dopaminergic precursor cells that later populate the substantia nigra pars compacta (SNpc). These cultured precursors matured into neurons that were tyrosine hydroxylase-positive, and gene expression analyses confirmed the presence of post-mitotic midbrain dopaminergic neuron markers, suggesting that these cells had committed to a midbrain dopaminergic neuron fate. Furthermore, the cultured cells exhibited an electrophysiological phenotype that is characteristic of native mature SNpc neurons.

The authors tested the ability of these cultured neurons to induce functional recovery in mouse and rat models of Parkinson's disease compared with grafts prepared using the rosette method. Four to five months after transplantation, a well-defined graft with minimal overgrowth was observed. Notably, the mice and rats exhibited complete recovery from amphetamine-induced turning. Importantly, in each experiment, floorplate-derived dopaminergic neuron grafts performed significantly better than rosette-derived dopaminergic grafts.

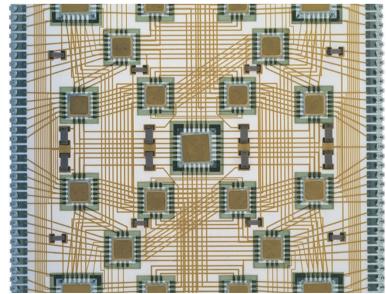
Far greater numbers of neurons would be required to induce functional

recovery in humans. Therefore to test the scalability of this approach, the authors transplanted green fluorescent protein-expressing dopaminergic neuron precursors derived from PSCs into a primate model of Parkinson's disease. The transplanted cells showed good survival rates and generated tyrosine hydroxylase-positive fibres that extended into the surrounding host tissue.

Overall, this study demonstrates an effective way of acquiring human dopaminergic neurons that are transplantable *in vivo* and suggests a novel strategy for the efficient regulation of human PSC specification following transplantation, offering renewed hope for use of these cells in regenerative medicine.

Sian Lewis

ORIGINAL RESEARCH PAPER Kriks, S. et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. Nature 6 Nov 2011 (doi:10.1038/ nature10648)



"

These neurons, when transplanted into animal models of Parkinson's disease, produce marked functional recovery with minimal graft cell overgrowth.