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Development of olfactory ensheathing glia from the neural crest

Olfactory ensheathing cells (OECs) are a unique class of glial cells that ensheath bundles of olfactory axons and provide permissive pathways for olfactory axon entry into the adult forebrain. Their ability to intermingle with astrocytes in the central nervous system, myelinate demyelinated axons and promote axon sprouting has led to great interest in their therapeutic potential for spinal cord repair. However, the olfactory mucosa cultures used to produce OECs also contain antigenically-similar Schwann cells, whose migration is inhibited by astrocytes and which induce astrocytes to undergo reactive hypertrophy and produce axon growth-inhibiting chondroitin sulfate proteoglycans. Reliably distinguishing OECs from Schwann cells in culture is a major challenge for OEC-mediated transplantation therapy. For the last 25 years, OECs have been assumed to originate from the olfactory epithelium, but we have recently found that they are derived from neural crest cells (NCCs), like all other peripheral glia including Schwann cells (Barraud et al., 2010, *PNAS* 107, 21040-5). This opens up new possibilities for elucidating the mechanisms underlying OEC development, about which virtually nothing is known.

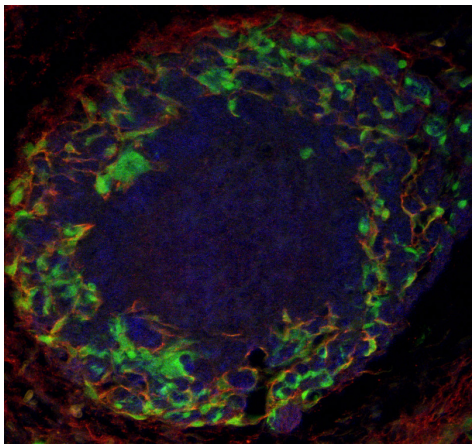

Figure: cross-section through the olfactory bulb of a chicken embryo that had received a graft of GFP-labelled neural crest cells, showing GFP-positive (green) neural crest-derived olfactory ensheathing cells (OECs) in the olfactory nerve layer of the olfactory bulb.

We will investigate the role of candidate signalling pathways in OEC versus Schwann cell development, taking advantage of the precise spatial and temporal control afforded by state-of-the-art *in ovo* electroporation techniques in the chick embryo, in which a cDNA of interest (e.g. one that will cell-autonomously block or activate a specific signalling pathway) plus GFP (to identify targeted cells) can be targeted specifically to NCCs, and its expression activated at any desired stage of development by injecting doxycycline into the egg. Using such techniques, we can investigate the role of multiple signalling pathways in OEC development, and bypass any earlier requirements for these pathways in developing NCCs. This will give us insight into the normal control of NCC differentiation into OECs, rather than Schwann cells.

Overall, the proposed experiments will yield critical information about OEC development *in vivo,* informing future strategies for generating these important cells in culture and advancing our basic understanding of how different glial phenotypes arise during development. This will be an essential baseline for future research on OECs and also potentially for the derivation of OECs from human patient-specific NCC-derived stem cells (which persist in skin and hair follicles) for spinal cord repair in the clinic.