

# Understanding Brain Development and Disease

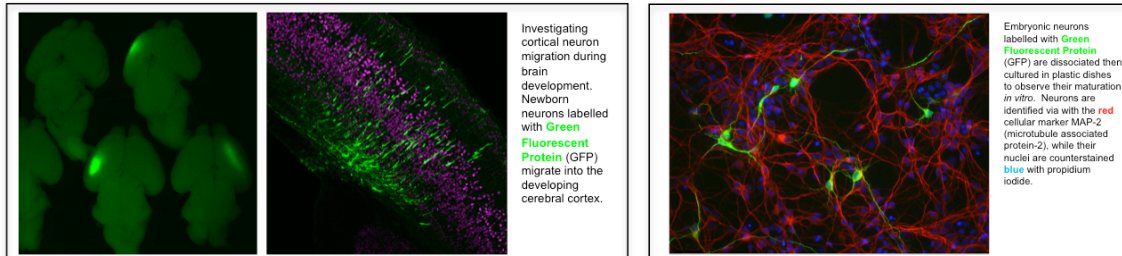
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- The role of transcription factors during nerve cell maturation
- Identification/characterisation of genes important to brain development
- The development and specification of different types of nerve cells
- Characterisation of mouse models of human neurological disorders

How are nerve cells of the fetal brain produced? How do they know to assemble into the final remarkable structure that is the cerebral cortex? Our lab focuses on the molecular and cellular mechanisms that control nerve cell production and maturation. By understanding these processes during foetal development, it may be possible to gain further insight into the pathogenesis of brain disorders (such as epilepsy and mental retardation) which arise as a consequence of abnormal neural development. These studies could, in turn, lead to the development of novel drug treatments or gene therapies for these disorders. In addition, knowledge of key signalling pathways that control nerve cell production will inform on future therapies which exploit the limited endogenous capacity for self-repair within adult brain.

The Heng Group uses cutting edge molecular techniques to study the birth and development of cerebral cortical neurons within fetal mouse brain *in vivo* as well as *in vitro*. These studies are combined with Bioinformatics approaches to identify then characterise genes responsible for aspects of the maturation of newborn nerve cells.



## Lab Research Themes

### Control of nerve cell production by transcription factors

The development of the cerebral cortex involves many steps, including nerve cell production, cell migration and final maturation of correctly-positioned neurons within fetal brain. We have discovered that Neurogenin2, a master regulator for neuron production in the cerebral cortex, initiates a proneural transcription factor cascade which is necessary for the generation of excitatory projection neurons of the developing cerebral cortex. This project will explore the functional interaction(s) between transcription factors which are downstream of Neurogenin2, and how they impart the necessary information for proper cortical neuron differentiation. In addition, we are interested in identifying downstream target genes for proneural transcription factors such as Neurogenin2 and to understand how these are important for controlling aspects of nerve cell maturation, including their proper migration and final connectivity. It is anticipated that we may be able to use this knowledge to eventually direct the migration of newborn nerve cells to sites of injury within damaged brain.

### Do complex brain disorders arise from abnormal brain development?

Neurological disorders such as autism and schizophrenia are prevalent in our community, and yet we know little of how genes (as well as the environment) may be important for the pathogenesis of these conditions. By focusing on clinically-relevant gene(s) that are known to be important for diseases such as autism, we aim to better understand their impact on the early steps brain development. This project will characterise a novel mouse model of autism, with investigations on how the candidate gene controls nerve cell maturation, connectivity and brain behaviour.

### The molecular basis of nerve cell migration during their maturation – novel genes and signalling pathways

During fetal brain development, neurons must undergo active cell migration to reach their proper position within developing brain. Failure to carry out this critical function within immature neurons can lead to aberrant brain development, mental retardation and epilepsy. Recent reports have underscored the importance of a highly regulated gene expression program for the correct production of migration-promoting factors to control this important developmental process in newborn neurons. Recently, we discovered such a gene, known as *Rnd2*, which was found to be important for regulating the migration and maturation of neurons within developing brain (Heng et al, *Nature* 2008). Current projects will address the signalling pathways for *Rnd2* which influence the movement and connectivity of these neurons *in vivo*.

**Project I:** At the peak of brain development, newborn neurons have been shown, rather enigmatically, to move in one of two ways: as a slow moving multipolar-shaped neuron; or a fast-moving bipolar-shaped neuron. We have shown that *Rnd2* is important for neurons to move in both ways, and this project will address the molecular mechanisms that underlie this cellular behaviour. The student will use cutting edge techniques to investigate the molecular function for *Rnd2* in neurons within fetal brain, with emphasis on how *Rnd2* regulates the actin cytoskeleton to control cortical neuron morphology and migration.

**Project II:** *Rnd2* belongs to a family of 3 atypical Rho-like GTP binding proteins with divergent expression patterns during brain development, which could suggest that (i) the different *Rnd* proteins perform common cellular roles, but the timing of their expression dictates their activity; or (ii) the *Rnd* proteins perform unique roles during specific phases of cell maturation. To address these issues, the student will search for downstream interacting partners to all 3 *Rnd* proteins to isolate common/divergent signalling proteins. Suitable candidates from this screen will then be analysed for their function within migrating cortical neurons.

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