CDB SEMINAR

# Francois Guillemot

The Francis Crick Institute

Monday, May 28, 2018

16:00-17:00 A7F Seminar Room

## Stem cell heterogeneity in the adult brain

**Summary**

· Stem cells in the hippocampus of the adult brain produce neurones that have important functions in memory and mood control. Most adult hippocampal stem cells are quiescent while a small fraction proliferate and produce neurones in response to various physiological stimuli or to injury. How stem cells compute the diverse stimuli and downstream niche signals they receive to produce appropriate numbers of adult neurones remains an open question.

· We found that the transcription factor Ascl1 is essential for activation of hippocampal stem cell. We also obtained evidence that Ascl1 expression is controlled by different post-translational mechanisms at different stages in the hippocampal stem cell lineage. Ascl1 is transcribed in most quiescent stem cells but Ascl1 protein accumulation in these cells is suppressed by the transcriptional repressor Id4, via sequestration of Ascl1 dimerisation partner and degradation of monomeric Ascl1. Ascl1 protein is also actively degraded in proliferating hippocampal stem cells, by a different mechanisms involving the E3 ubiquitin ligase Huwe1. We are characterising the niche signals that controlling Ascl1 protein levels via regulation of Id4 and Huwe1.

· Further investigation of Huwe1 function in proliferating hippocampal stem cells has shown that active elimination of the pro-activation factor Ascl1 is essential for a fraction of these cells to return to quiescence. Moreover, examination of Huwe1 function in mice of different ages has revealed that stem cells that have previously proliferated and have returned to quiescence (which we call 'resting stem cells') have a unique role in maintaining homeostatic hippocampal neurogenesis. In contrast, stem cells that have not previously proliferated ('dormant stem cells') have a limited role in homeostatic neurogenesis, suggesting they may serve as a reserve stem cell population.

We are currently investigating whether resting and dormant stem cell populations are differentially activated by niche signals and by physiological neurogenic and injury stimuli.

**Host:**

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