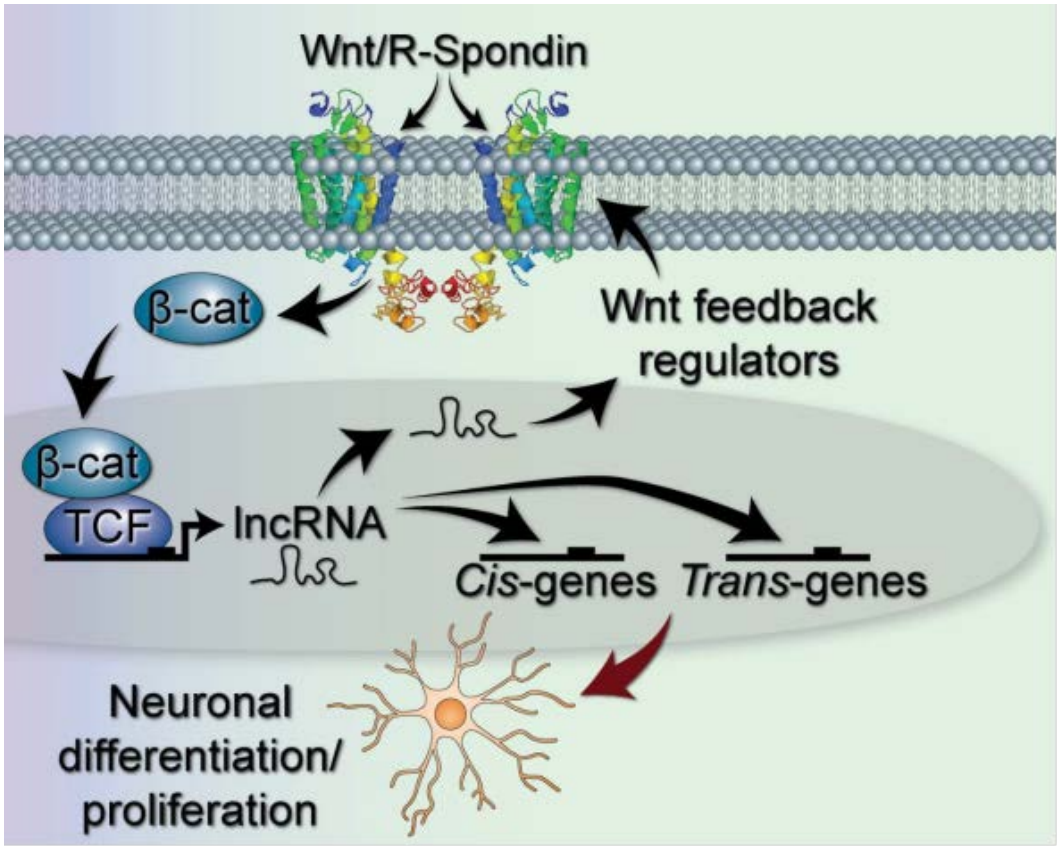
Investigating how novel long non-coding RNAs modulate signalling pathways and neuronal cell fate

Supervisory team:
Main supervisor: Dr Karim Malik (University of Bristol)
Second supervisor: Dr Keith Vance (University of Bath)
Prof James Uney (University of Bristol)

Host institution: University of Bristol

Project description:
Wnt signalling is crucial for intercellular communication and co-ordination of developmental processes. It is a key regulator of cell fate, capable of regulating stemness, differentiation and proliferation. Briefly, signalling is mediated by secreted Wnt ligands that are bound by membrane receptor complexes including Frizzled proteins and LRP5/6. This then triggers inactivation of a cytoplasmic "destruction complex" that is continually turning over cytoplasmic β-catenin, permitting its stabilization and nuclear translocation. The TCF/Lef family of transcription factors are then able to utilise β-catenin as a transcriptional co-activator, and instigate pro-proliferation gene expression programmes (Clevers and Nusse, 2012). Amplification of canonical Wnt signalling can be achieved through the participation of another set of receptors, the leucine-rich repeat-containing G-protein coupled receptors (LGR4, 5, 6) and their ligands, the R-Spondins (Rspos) (de Lau et al., 2011). LGR-Rspo complexes at the cell membrane decrease the endocytic turnover of Frizzled-LRP5/6 by neutralising the ubiquitin ligases RNF43 and ZNRF3 (Hao et al., 2012). LGRs can in turn be inhibited by TNFRSF19, or TROY, which interacts with LGR5 to inhibit Wnt signalling (Fafilek et al, 2013). In addition to the above, many positive and negative regulatory proteins also plug in to the Wnt pathway, reflecting the importance of finely tuned Wnt signalling for cellular and tissue homeostasis. Another emerging class of Wnt regulator is long non-coding RNAs (lncRNAs) (Klingenberg et al, 2017), although very little is known about how lncRNAs might influence Wnt output. In our recent work on neuronal cells, we characterised the Wnt driven transcriptome using RNA sequencing. We identified a novel lncRNA that was robustly induced by Wnt and R-Spondin 2, and propose that this lncRNA is likely involved in regulating Wnt (eg. feedback inhibition) and Wnt-induced neuronal differentiation/proliferation (Szemes at al 2018, 2019). This project will evaluate the role of the new lncRNA in regulating these processes. The project will use state of the art methods, including RNAseq, CRISPR and live-cell neuronal imaging.

REFERENCES Clevers, H. & Nusse, R. 2012. Wnt/beta-catenin signaling and disease. Cell, 149, 1192-205. de Lau, et al 2011. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. Nature, 476, 293-7. Fafilek B, et al. Gastroenterology. 2013 Feb;144(2):381-91 Hao, H. X. et al, 2012. ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. Nature, 485, 195-200. Klingenberg M, et al J Hepatol. 2017 Sep;67(3):603-618. doi: 10.1016/j.jhep.2017.04.009. Epub 2017 Apr 22. Szemes M, Greenhough A, Melegh Z, Malik S, Yuksel A, Catchpoole D, Gallacher K, Kollareddy M, Park, JH and Malik K. (2018). Wnt signalling drives context-dependent differentiation or proliferation in neuroblastoma. Neoplasia, 20, 335–350. Szemes M, Greenhough A, and Malik K. (2019). Wnt signalling is a major determinant of neuroblastoma cell lineages. Frontiers in Molecular Neurosciences, https://doi.org/10.3389/fnmol.2019.00090.


Wnt/R-Spondin
β-cat
Wnt feedback
regulators
β-cat
TCF
lncRNA
Cis-genes
Trans-genes
Neuronal
differentiation/
proliferation