



CRUK Cambridge Centre MRes rotation project

Rotation Project Title	RNA helicases as genetic modifiers in ovarian cancer: a new link between the SWI/SNF complex and RNA processing
Head of Laboratory (PI) Name	Professor Eric Miska (Wellcome/CR UK Gurdon Institute)
Second supervisor if applicable	Dr James Brenton (CR UK Cambridge Institute)
Programme	Cellular and Molecular Biology Programme
Supervisor's Email	eam29@cam.ac.uk
Laboratory Location	Tennis Court Rd and Addenbrooke's campus

Project Outline	<p><u>Aims and objectives</u></p> <p>RNA helicases as genetic modifiers in ovarian cancer: a new link between the SWI/SNF complex and RNA processing provides a new therapeutic opportunity. Mammalian SWI/SNF (BAF) chromatin remodelling complexes change local chromatin state and control gene expression. SWI/SNF complex components are mutated in over 20% of cancers, spanning a wide range of tissue types. In a forward genetic screen in <i>C. elegans</i> we identified three independent missense mutations in a conserved nuclear RNA helicase that change viability for animals with mutations in the SWI/SNF complex. We hypothesise that this new genetic interaction between SWI/SNF and RNA processing is a conserved feature that might be exploitable in human cancer for new therapeutic opportunities. This project will focus on clear cell ovarian cancer which responds poorly to conventional treatments and is driven by mutations in the SWI/SNF complex.</p>
Experimental plan	Using the ovarian carcinoma cell line SKOV3, which lacks normal SWI/SNF activity, we will test the interaction between SWI/SNF and nuclear RNA processing using CRISPR/Cas9 genome editing and a small molecule inhibitor approach. We will use RNAseq and ChIPseq as functional readouts of these perturbations. This study will be extended to a panel of clear cell ovarian cancer lines to test therapeutic efficacy and disease modelling.
Main Techniques	<ul style="list-style-type: none"> • CRISPR/Cas9 genome editing • Advanced RNAseq (nascent transcripts, splice, RiboSeq) • ChIPseq • Chemical biology • Cancer cell culture and drug sensitivity assays • Bioinformatic analysis using R
Key References	<p>St Pierre, Roodolph, and Cigall Kadoch. 2017. "Mammalian SWI/SNF Complexes in Cancer: Emerging Therapeutic Opportunities." <i>Current Opinion in Genetics & Development</i> 42 (February): 56–67.</p> <p>Akay, Alper, Tomas Di Domenico, Kin M. Suen, Amena Nabih, Guillermo E. Parada, Mark Larance, Ragini Medhi, et al. 2017. "The Helicase Aquarius/EMB-4 Is Required to Overcome Intronic Barriers to Allow Nuclear RNAi Pathways to Heritably Silence Transcription." <i>Developmental Cell</i> 42 (3): 241–55.e6.</p>