CRUK Cambridge Centre MRes rotation project

Rotation Project Title	Network modelling in Acute Leukaemias to determine critical nodes for maintenance of disease and as targets for therapy
Head of Laboratory (PI) Name	Brian Huntly (Cambridge Stem Cell Institute)
Second supervisor if applicable	Florian Markowetz (CRUK Cancer Institute)
Programme	Quantitative MRes/PhD
Supervisor's Email	bjph2@cam.ac.uk
Laboratory Location	CSCI

Project Outline	**Aims and objectives** All cancers are characterised by aberrant transcriptional states, and this is perhaps best exemplified in haematological malignancies, such as acute myeloid leukaemia (AML) and malignant lymphomas. These aberrant transcriptional states generate tumour specific transcriptional networks that maintain the malignant stem cells and allow the tumour to proliferate and spread. However, **how these networks are generated and their relationship to driver mutations within individual cancers remains unknown**. In addition, **network nodes are likely to be therapeutic vulnerabilities within these cancers and their identification will facilitate better treatment in these aggressive malignancies**. This project will focus on annotating these networks and then validating critical network nodes using functional perturbation experiments.
Experimental plan	This project will utilise a wealth of available genomic data[1, 2, 3] that annotates the transcriptional, epigenetic and 3-dimensional DNA topology across the evolution of leukaemias and lymphomas generated in sophisticated mouse models based on known and common tumour-specific mutations. We will build association-networks for the transcriptional and epigenetic data sets based on well-established approaches like Gaussian graphical models and Bayesian approaches. These nodes will be validated in human Leukaemia and Lymphoma gene expression and genomic datasets. Functional validation of candidate critical network regulators through perturbation experiments will be performed in relevant animal, and where possible, human systems to elucidate disease biology and to identify putative therapeutic targets for this aggressive blood malignancy. Additionally, we will use Nested Effects Models to infer cellular networks from downstream effects of perturbations and will evaluate how these networks change following perturbation. This project would be suitable for a candidate with both quantitative and bench skills or a quantitative biologist who wishes to learn molecular techniques and to perform functional experiments
Main Techniques	• Gaussian graphical models • Bayesian approaches to machine learning • Nested effects models • Functional experiments of network perturbation: • including genetic – knockout, sh-RNA mediated knockdown, CRISPR/Cas9 mediated genome editing (of both coding and non-coding regulatory elements) • and pharmacological inhibition of candidate regulators (epigenetic regulators and where possible transcription factors)

Key References	

1. Horton S, Giotopoulos G, Yun H, Vohra S, Sheppard O, Bashford-Rogers R, Rashid M, WI Chan, Sasca D, Yiangou L, Osaki H, Bsheer F, Gallipoli, Burrows N, Erdem A, Anastasiya S, Foerster S, Zhao W, Sustic T, Okusun J, Hodson D, Wright P, Smith K, Maxwell P, Fitzgibbon J, Du MQ, Adams D, **Huntly BJP**. Early loss of *Crebbp* confers malignant stem cell properties on lymphoid progenitors. ***Nat Cell Biol.*** 2017 Sep;19(9):1093-1104. doi: 10.1038/ncb3597. Epub 2017 Aug 21

2. Gozdecka M, Meduri E, Mazan M, Tzelepis K, Dudek M, Knights AJ, Pardo M, Yu L, Choudhary JS, Metzakopian E, Iyer V, Yun H, Park N, Varela I, Bautista R, Collord G, Dovey O, Garyfallos DA, De Braekeleer E, Kondo S, Cooper J, Göttgens B, Bullinger L, Northcott PA, Adams D, Vassiliou GS*, **Huntly BJP***. UTX-mediated enhancer and chromatin remodelling suppresses myeloid leukaemogenesis through non-catalytic inverse regulation of ETS and GATA expression programmes (***Nature Genetics***). Nat Genet. 2018 May 7. doi: 10.1038/s41588-018-0114-z. [Epub ahead of print] *co-senior author

3. Unpublished

4. **Markowetz, F**. & Spang, R. Inferring cellular networks--a review. ***BMC Bioinformatics*** 8 Suppl 6, S5, doi:10.1186/1471-2105-8-S6-S5 (2007).

5. Wang, X., Castro, M. A., Mulder, K. W. & **Markowetz, F**. Posterior association networks and functional modules inferred from rich phenotypes of gene perturbations. ***PLoS Comput Biol*** 8, e1002566, doi:10.1371/journal.pcbi.1002566 (2012).

6. **Markowetz, F**., Bloch, J. & Spang, R. Non-transcriptional pathway features reconstructed from secondary effects of RNA interference. ***Bioinformatics*** 21, 4026-4032, doi:10.1093/bioinformatics/bti662 (2005).

7. Wang, X., Yuan, C., Hellmayr, W., Lui, F. & **Markowetz, F**. Reconstructing evolving signalling networks by Hidden Markov Nested Effects Models ***Annals of applied statistics*** 8, 1-647 (2014).