CRUK Cambridge Centre MRes rotation project

Rotation Project Title	Deciphering Leukaemogenic Mechanisms by Integrated Systems-Scale Analysis
Head of Laboratory (PI) Name	Berthold Göttgens
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Programme	Quantitative MRes/PhD
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Laboratory Location	Cambridge Stem Cell Institute (CSCI)

Project Outline	**Aims and objectives** Survival rates in acute myeloid leukaemia (AML) remain disappointingly low. Major obstacles precluding progress in developing new therapies include (1) difficulties in studying the critical preleukaemic phase of the disease, and (2) major shortcomings in our current ability to translate molecular observations into a holistic understanding of tissue function. The proposed studentship will integrate experimental and computational approaches designed to directly tackle these two major issues.
Experimental plan	From large-scale single cell RNA-Seq analysis, we will identify the molecular changes that give rise to altered leukaemogenic differentiation landscapes in preleukaemic mouse models. In parallel, we will develop a next generation computational platform for leukaemia modelling by connecting single cell molecular profiles with whole tissue dynamics. This proposal will exploit state-of-the-art single cell approaches to identify new molecular targets for future leukaemia therapies. Preleukaemic cells are widely recognised as an important contributor to patient relapse, thus emphasizing the need for new therapies specifically targeted at the root cause of the disease during its preleukaemic phase. Importantly, the proposed integrated experimental and computational framework will not only accelerate our mechanistic understanding of leukaemia, but also provide unprecedented power to simulate new therapies in silico, and thus benefit a wide range of cancer patients.
Main Techniques	• Single cell RNA-Seq data generation and analysis • Inference of transcriptional programmes • Simulations of cellular flux through the blood differentiation hierarchy and its perturbation in leukaemia • Integrating abstract tissue models with molecular regulatory network models
Key References	Dahlin J.S., Hamey F.K., Pijuan-Sala B., Shepherd M., Lau W.W.Y., Nestorowa S., Weinreb C., Wolock S., Hannah R., Diamanti E., Kent D.G., **Göttgens B.***, Wilson N.K.* (2018). "A single cell hematopoietic landscape resolves eight lineage trajectories and defects in Kit mutant mice" ***BLOOD*** 131: e1-e11 *joint senior authors Ibarra-Soria X., Jawaid W., Pijuan-Sala B., Ladopoulos V., Scialdone A., Jörg D.J., Tyser R., Calero-Nieto F.J., Mulas C., Nichols J., Vallier L., Srinivas S., Simons B.D., **Göttgens B.***, John C Marioni J.C.* (2018). "Defining murine organogenesis at single cell resolution reveals a role for the leukotriene pathway in regulating blood progenitor formation". ***Nature Cell Biology*** 20: 127-134 *joint senior authors

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