CRUK Cambridge Centre MRes rotation project

Rotation Project Title	Tracking immune cell dynamics over 20-years for the early detection of ovarian cancer
Head of Laboratory (PI) Name	Jamie Blundell (Early Detection Programme, Hutchison MRC Research Centre)
Second supervisor if applicable	Martin Miller (CRUK-CI) Doug Easton (Director, Centre for Genetic Epidemiology, Strangeways Research lab, Cambridge)
Programme	Early Detection
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Laboratory Location	Hutchison/MRC Research Institute

Project Outline	**<u>Aims and objectives</u>** Immune cells (including T- and B-cells) do not share the same DNA sequence as the rest of our cells. They shuffle a specific part of their genome around to generate a diverse set of sequences that are used for recognizing foreign "antigens". An individual's T-cell receptor (TCR) repertoire (i.e. the set of all their T-cell sequences) therefore records information about what antigens that person has been exposed to throughout their life – including infectious diseases and cancers. As tumours develop, neoantigens on the surface of the tumour cells are recognised by T-cells, causing changes in the TCR repertoire [1,2]. This cancer-specific signal may be detectable years before traditional diagnosis, making TCR repertoire profiling (via next generation sequencing approaches) a promising, yet under-explored, blood-based biomarker for early detection of cancer [3]. The aims of this project are to: (i) Characterize the dynamics of TCR repertoires in ~200 cancer-free controls using ultra deep sequencing of the CDR3 region. (ii) Measure the dynamics of TCR repertoires in ~80 ovarian cancer-cases (iii) Determine whether statistical differences exist that can distinguish between cases and controls and how early these differences arise.
Experimental plan	In this project the student will perform statistical and computational analysis of a unique quantitative lineage tracking data set encompassing millions of T-cell clones in the peripheral blood of hundreds of people with and without cancer that have been tracked over a period of 20-years from an existing "fossil record" of frozen blood samples. The central goal of the project is to determine whether certain T-cell receptor sequences (those that recognise the tumour) produce a measurable signal as cancer develops, and thus whether immune-repertoire tracking could be used as a sensitive detector of early cancer. This project offers a unique opportunity to analyse an incredibly rich, dynamic data set with possible broad applicability to cancer detection / treatment. It offers the student a chance to work as part of an outstanding team of collaborators including members of the Blundell, Miller and Easton labs (all part of the Cambridge Cancer Centre) and the group of Harlan Robins (Fred Hutch Cancer Research Center, Seattle and Adaptive Biotechnologies) who are world-leaders in TCR sequencing. The student will also develop expertise in analysing next generation sequencing data, building quantitative models and machine learning approaches. Key challenges will include:

	(i) Characterizing the background dynamics of T-cell clones in healthy individuals. How large are "normal" fluctuations in abundance? (ii) Establish whether sequences that are common across individuals are likely enriched due to a common antigen exposure or simply commonly generated sequences during somatic recombination (iii) Spotting potentially weak signals against a likely noisy background.
Main Techniques	• Statistical and computational analysis of longitudinal blood samples • Machine learning • TCR-sequencing analysis • Integration with clinical/demographic data Ideal candidate will have a background in Physics, Maths, Quantitative Biology or Computer Science and a passion for performing quantitative analyses of data.
Key References	1. Kirsch, Ilan, Marissa Vignali, and Harlan Robins. "**T-Cell Receptor Profiling in Cancer**." *Molecular Oncology*, Cancer Immunotherapy, 9, no. 10 (December 1, 2015): 2063–70. https://doi.org/10.1016/j.molonc.2015.09.003. 2. Robins, Harlan S., Nolan G. Ericson, Jamie Guenthoer, Kathy C. O'Briant, Muneesh Tewari, Charles W. Drescher, and Jason H. Bielas. "**Digital Genomic Quantification of Tumor-Infiltrating Lymphocytes.**" *Science Translational Medicine* 5, no. 214 (December 4, 2013): 214ra169-214ra169. https://doi.org/10.1126/scitranslmed.3007247. 3. Beausang, John F., Amanda J. Wheeler, Natalie H. Chan, Violet R. Hanft, Frederick M. Dirbas, Stefanie S. Jeffrey, and Stephen R. Quake. "**T Cell Receptor Sequencing of Early-Stage Breast Cancer Tumors Identifies Altered Clonal Structure of the T Cell Repertoire.**" *Proceedings of the National Academy of Sciences* 114, no. 48 (November 28, 2017): E10409–17. https://doi.org/10.1073/pnas.1713863114.