CRUK Cambridge Centre MRes rotation project

Rotation Project Title	**Predicting treatment responses using in silico mechanistic models of cancer**
Head of Laboratory (PI) Name	Jasmin Fisher
Second supervisor if applicable	
Programme	Quantitative studentship
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Laboratory Location	Department of Biochemistry, Hopkins Building, Tennis Court Road

Project Outline

Aims and objectives

Our lab is focused on studying the mechanisms by which oncogenic signalling pathways regulate the onset, progression, maintenance and (when blocked) regression of cancers. We do this by computationally representing oncogenic pathways as executable models. In this way, we can understand how biological decisions are made and how faulty decisions drive the pathology of cancer. The overall approach, called *Executable Biology*, involves the design of executable computer algorithms that mimic biological phenomena to identify discrepancies between hypothesized mechanistic models and experimental observations. Over the years these kinds of executable models have been shown to be highly effective both in developing deeper insights into biological phenomena and in the development of novel therapies.

The aim of this rotation project is to get a taste of the what it means to develop in silico mechanistic models of cancer and how these models can be used to predict the response of different therapeutic regimes.

The student can choose between the following two existing models:

1. A signalling network model of triple negative breast cancer (TNBC) using the BioModelAnalyzer (BMA) tool.
2. A spatial model of glioblastoma (GBM) tumour growth using the F# programming platform.

The objective is to simulate different drug combinations (TNBC) or radiation therapy regimes (GBM) on the computational models, compare the results in silico to the in vitro data from our collaborators in the Caldas lab at the CRUK Cambridge Institute and the Chalmers lab at the Cancer Research Centre in University of Glasgow, and iteratively calibrate the computational models until they reproduce all the experimental data.

The overall goal is to correlate treatment responses with molecular mechanistic explanations and thereby improve personalised therapies for cancer patients.

Experimental plan	The TNBC model will apply the BMA tool, which provides a user-friendly graphical interface to streamline the encoding and analysis of complex signalling networks. The work will involve an iterative cycle of simulation, analysis and refinement of a discrete network model. The GBM model will be based on the F# programming and will involve the same iterative cycle in a continuous spatial model.
Main Techniques	• BMA http://biomodelanalyzer.org/ • F# https://fsharp.org/
Key References	• M.K. Yu, J. Ma, J. Fisher, J.F. Kreisberg, B. J. Raphael, T. Ideker. Visible Machine Learning for Biomedicine. *Cell* 173: 1562-1565, June 2018. • Silverbush D., Grosskurth S., Wang D., Powell F., Gottgens B., Dry J.R. and Fisher J. Cell-Specific Computational Modeling of the PIM pathway in Acute Myeloid Leukemia. *Cancer Research,* 77(4), February 2017. • Hall B., Piterman N., Hajnal A., and Fisher J., Emergent Stem Cell Homeostasis in The *C. elegans* Germline Revealed by Hybrid Modelling, in *Biophysical Journal,* 109:428-438, July 2015. • Chuang R., Benque D., Cook B., Hall B.A., Ishtiaq S., Piterman N., Taylor A., Vardi M., Koschmieder S., Gottgens B. and Fisher J. Drug Target Optimization in Chronic Myeloid Leukemia Using an Innovative Computational Platform. *Scientific Reports*, 5:8190, 2015. • Moignard V., Woodhouse S., Haghverdi L., Lilly J, Tanaka Y, Wilkinson A.C, Buettner F., Nishikawa S.I., Piterman N., Kouskoff V., Theis F.J., Fisher J., Göttgens B. Decoding the Transcriptional Program for Blood Development from Whole Tissue Single Cell Gene Expression Measurements. *Nature Biotechnology*, 33:269–276, 2015. • Fisher J. and Henzinger T.A., Executable Cell Biology, in *Nature Biotechnology*, vol. 25, no. 11, pp. 1239-1249, 2007.