Clinical PhD Project 2024

Dissecting glioblastoma infiltration using integrated single cell and spatial genomics

Principal supervisor's name: Dr **Omer Bayraktar**
Principal supervisor's email address: ob5@sanger.ac.uk

Principal supervisor's CRUK CC theme: Brain Cancer Virtual Institute

Department for student registration: Wellcome Sanger Institute TBC
Department or institute where research will take place: Wellcome Sanger Institute

Postgraduate scheme: **Clinical Research Training Fellow (3-year PhD)**

PhD project outline:

The malignant brain tumour glioblastoma multiforme (GBM) displays significant levels of cellular heterogeneity and plasticity that correlate with patient outcomes. It has been suggested that GBM cell states are influenced by the tumour microenvironment (TME). Yet, we lack fundamental knowledge about the spatial organisation of malignant and TME cells in GBM tumours and the TME-derived signals driving malignant cell state transitions. In this project, the PhD student will dissect TME cues that direct GBM infiltration. Recently, our lab initiated GBM-space, a new collaborative effort to map the tissue architecture of GBM and TME-GBM interactions using multi-modal genomics. Deeply profiling 12 tumours across multiple sites, we created the most comprehensive single cell and spatial genomic map of inter- and intratumour heterogeneity to date. Surveying joint RNA and ATAC profiles of over 1 million cells, we expanded the description of recurrent malignant and TME cell states and resolved their gene regulatory networks. Using spatial transcriptomics, we discovered that malignant cell states regionally segregate in GBM and associate with distinct TMEs. We identified zonation of astrocyte (AST)- and mesenchymal (MES)-like malignant cell states, where hypoxic MES-like cell states associated with a unique immune TME. We observed extensive heterogeneity of neural precursor (NPC)- and oligodendrocyte precursor (OPC)-like states and identified specific molecular subtypes enriched at the tumour margins and infiltrated areas. This PhD project will functionally follow up interactions between TME cell states and infiltrative malignant cell types to design interventions against GBM infiltration.

PhD experimental plan:

Aim 1. Computational identification of malignant and TME interactions relevant to infiltration. In this aim, the student will apply state of the art computational approaches to identify receptor-ligand interactions between TME and infiltrating malignant cell states to identify putative regulators of GBM invasion.

Aim 2. Functional analysis of infiltration in xenografts and organoids models. In this aim, the candidates identified in Aim 1 will be functionally tested in mouse xenografts and organoid models where they will be perturbed in high throughput.

Main techniques:

- single cell transcriptomics
- spatial transcriptomics
- computational analysis of cell-cell interactions
- mouse xenografts
- human cortical organoids

Key references:

Bayraktar, O.A. et al. (2020) ‘Astrocyte layers in the mammalian cerebral cortex revealed by a single-cell in situ transcriptomic map’, Nature neuroscience, 23(4), pp. 500–509.

Kleshchevnikov, V. et al. (2022) ‘Cell2location maps fine-grained cell types in spatial transcriptomics’, Nature biotechnology, 40(5), pp. 661–671.

Neftel, C. et al. (2019) ‘An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma’, Cell, 178(4), pp. 835–849.e21.