Clinical PhD Project 2024

Spatially-resolved multi-omics to decipher the mediators of therapy resistance and disease progression in oesophageal adenocarcinoma

Principal supervisor's name: Prof **Rebecca Fitzgerald**
Principal supervisor's email address: rcf29@cam.ac.uk

Principal supervisor's CRUK CC theme: Early Cancer Institute

Department for student registration: Department of Oncology
Department or institute where research will take place: Early Cancer Institute

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

PhD project outline:

Oesophageal adenocarcinoma is a major cause of cancer-related morbidity and mortality. Surgical resection is the current curative standard of care but outcomes are improved using either neoadjuvant chemoradiotherapy (naCRT) or perioperative chemotherapy. Neither approach results in adequate tumour regression in most patients, though there is evidence that this may be at least partly mitigated using immunotherapy. A small number of studies have attempted to identify the factors underlying therapy resistance in OAC but most are limited by the use of bulk tumour sampling, which does not adequately discriminate tumour, immune and other stromal populations, nor their in situ relationship. As such, this is an imperfect tool for identifying potentially targetable mediators of treatment resistance and immune response. In contrast, we hypothesise that spatially-resolved analysis of tumour and stromal characteristics will allow for the identification of key mediators of treatment response and immune sensitivity. This will be explored in this PhD, in which the candidate will build on initial spatially-resolved analyses of OAC post-neoadjuvant therapy resection specimens in order to identify and then validate targetable markers of immune response and therapy resistance.

PhD experimental plan:

The candidate will use samples collected as part of the Oesophageal Cancer Clinical & Molecular Stratification (OCCAMS) study to build a cohort of post-neoadjuvant therapy resection specimens. Tumour specimens will be spatially profiled, including using spatial transcriptomics and multiplex immunohistochemistry, and where possible compared to the profile of baseline pre-treatment samples. A model will be generated to integrate these data, the clinical tumour characteristics and its known response to neoadjuvant therapy. From this, the candidate will derive candidate tumour immune, genomic or transcriptomic features that associate with treatment resistance. These will be validated within in vitro models, including using patient-derived organoids as well a novel epithelioid model that allows for the long-term co-culture of tumour and stroma, as well as the analysis of immune infiltration. Finally, the candidate will use existing bulk RNA sequencing from well characterised patient cohorts, including from patients enrolled in OCCAMS, to determine the prognostic and predictive potential of these features.

Main techniques:

Spatial transcriptomics; multiplex immunohistochemistry; RNA-sequencing; bioinformatic analyses; cell culture including use of patient-derived organoids, epithelioids and co-culture.

Key references:

1. Izadi F...Fitzgerald C, Rose-Zerilli MJJ, Underwood TJ. Genomic analysis of response to neoadjuvant chemotherapy in esophageal adenocarcinoma. Cancers (Basel) 2021;13(14):3394.
2. Naeini MM...Waddell N. Multi-omic features of oesophageal adenocarcinoma in patients treated with preoperative neoadjuvant therapy. Nat Comms 2023;14(3155).
3. Croft W... Moss P. The single cell transcriptional landscape of esophageal adenocarcinoma and its modulation by neoadjuvant chemotherapy. Mol Cancer 2022;21(1):200.