ImmunoTools *special* Award 2019
or
ImmunoTools *ACADEMY* Award 2019

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Enhancing anti-tumour immunity in Oesophageal Adenocarcinoma through the modulation of immunometabolism with the novel small molecule inhibitor Quininib and its' analogues.

Background

Oesophageal Adenocarcinoma (OAC) is the main histological subtype of oesophageal cancer in the western hemisphere and is the 8th most common cancer in the world. Its incidence is predicted to rise by 150% by 2040 in line with the rising obesity epidemic. The overall survival of these patients is dismal, with a 5 year rate of 37% globally this cancer represents one of the most lethal malignancies worldwide. Treatment options include surgery and neo-adjuvant chemo-radiotherapy with early stage patients often going straight to surgery, however due to a delay to diagnosis the majority of patients will receive neo-adjuvant therapy.

Only 30% of patients respond to neoadjuvant chemo-radiation therapy leaving others with little option of hope. Immunotherapy has recently offered new hope in many cancer types including gastro-oesophageal cancer, where it has been demonstrated to be safe and well tolerated with some effect on overall survival. However at best only 40% of patients respond to the most successful class of immunotherapeutics, the checkpoint inhibitors, therefore resistance to therapy is common. As such there is a strong impetus on elucidating the mechanisms of resistance to checkpoint blockade therapy and developing new therapies to help boost the efficacy of immunotherapy.

Immunometabolism, has recently emerged as a major barrier to anti-tumour immunity, primarily due to secreted compounds and nutrient competition within the tumour microenvironment. Dysregulated immunometabolism is intrinsically linked to T-cell dysfunction seen within the microenvironment of many solid malignancies, including oesophageal adenocarcinoma.

Our department has developed the novel small molecule inhibitor *Quininib* and a family of functional analogues that are metabolically active showing effects in inhibiting tumour cell metabolism as well as having additive radio sensitising and anti-angiogenic effects.

Hypothesis

We hypothesise that by targeting both tumour and immune cell metabolism in Oesophageal Adenocarcinoma we can shift the balance of anti-tumour immunity against the tumour and improve responses not only to immunotherapy but also to classical neo-adjuvant chemo-radiotherapy.

My project is a 4 year PhD project funded by the Irish Research Council's government of Ireland Postgraduate Scholarship scheme.

General objective

We aim to characterise the effects the analogues of *Quininib* have on T-cell biology and function and test a lead compound in human *ex vivo* tissue samples from adenocarcinoma patients.

Specific objectives

- To describe the metabolic effects of the tumour microenvironment in OAC on T-cell biology, function and phenotype.
- To test a panel of *Quininib* analogues' ability to modulate T-cell metabolism, function and phenotype and to select a lead compound to take into *ex vivo* experiments.
- To test a lead compound in human *ex vivo* OAC patient biopsies, and to assess the impact on tumour infiltrating lymphocytes.

This project demands a large quantity of immunological work, including but not limited to T-cell activation, differentiation an immunophenotyping via FACS analysis. As such, this project and by extension OAC patients will highly benefit from support from the **ImmunoTools** Award 2019. Given the proximity of the novel drugs to the clinic, this project has a high translational potential and has already begun testing in the *in vivo* settings in mice models, showing some promise. This project is the first characterisation of the immunological effects of these drugs and has substantial potential for collaboration and dissemination of work carried out.

These products would greatly assist me in my project and enable me to more robustly test the effects of various factors of the microenvironment on T-cell biology. They would help me in the activation and differentiation of my T-cell subtypes and also allow me to probe novel areas of immunometabolism.

Aside from my duties in the lab, I am passionate about SciComm and am active on social media, particularly Twitter, where I regularly discuss with the public and other scientists about life as a researcher.

ImmunoTools *special* AWARD for **Andrew Sheppard** includes 13 reagents

FITC - conjugated anti- human	Annexin V-FITC
PE - conjugated anti- human	CD71, IL-6
PerCP - conjugated anti- human	CD4
APC- conjugated anti- human	CD3
recombinant human cytokines	rh IFNgamma, rh IL-2, rh IL-10, rh TGF-beta3, rh IL-12, rh VEGF-A/VEGF-165, rh IL-13, rh Leptin
ELISA	Human IFN gamma, Human TNF-alpha

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