Clinical PhD Project 2024

Evaluation of dynamic metabolism in renal cancer patients treated with systemic therapy using intraoperative labelled nutrient delivery

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Principal supervisor's CRUK CC theme: Urological Malignancies Programme

Department for student registration: Surgery
Department or institute where research will take place: Surgery.

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

PhD project outline:

Kidney cancer is the 7th commonest UK cancer and the most lethal of urological malignancies. Growing evidence suggests that kidney cancers manipulate metabolism to survive and evolve, with key roles in aggressive disease behaviour and poor patient outcomes. This PhD aims to improve the understanding of this complex metabolic reprogramming through the use of 13C-labelled isotopic tracers to evaluate dynamic metabolism. Isotopomer analysis of the 13C label enables the identification of cancer-specific shunts and pathway fluxes. This advanced technique will be performed in vivo in patients with kidney cancer undergoing a renal biopsy and nephrectomy surgery, in which they will receive an infusion of 13C-labelled nutrients with tissue biopsies and biofluids analysed by both conventional liquid chromatography-mass spectroscopy and spatial approaches for assessing tissue metabolites (ethics in place). Patients will also undergo metabolic imaging at the same timepoints using hyperpolarised 13C-pyruvate MRI as an non-invasive correlate. In parallel, complementary experimental in vivo platforms of RCC metabolism will be studied by establishing patient-derived xenografts (PDX) and organoids, that allow further deep phenotyping of metabolism, and a platform for testing experimental therapies that are not amenable to patient studies.

The identification of metabolic phenotypes and vulnerabilities in human RCC using these in vivo modelling platforms are highly translatable to the clinical setting. The design of this experimental pipeline lends itself to the many RCC clinical trials at Cambridge University Hospitals. In this PhD we will utilise isotopic tracer studies before and after ‘window-of-opportunity’ neoadjuvant drug trials (WIRE trial, undertaken in conjunction with AZ) to lead to the discovery and validation of metabolic biomarkers of treatment efficacy, urgently required in RCC as a significant proportion of patients are known to develop therapeutic resistance. The non-invasive methods for probing metabolism in parallel, also have high translational potential. Furthermore, the candidate will use this dual platform studying the same human tumours in different models provides the necessary validation of the PDX model and permits the level of understanding of RCC metabolism which could provide insight into individualised treatment strategies, a favourable approach given the current paradigm shift to precision medicine. By establishing patient avatars alongside the patient clinical pathway, this platform can be utilised to test therapies that could be predictive of patient therapeutic response and impact on their treatment pathway.

The aim of this PhD is to develop an improved understanding of this critical aspect of cancer behaviour will help us identify metabolic vulnerabilities specific to kidney cancer that could be

used in the development of targeted therapies and used to develop biomarkers of treatment efficacy.

PhD experimental plan:

• Analyse existing mass spectrometry data to determine best labelled nutrients to use for human in vivo isotopic tracer work e.g. glucose, pyruvate, lactate, glutamine, branched chain amino acids
• Establish in vivo isotope infusion at time of renal tumour biopsy (already established at CUH/UoC for intra-operative use)
• Recruit patient in neoadjuvant clinical trials to isotope infusion at time of (a) biopsy (interventional radiology suite) and (b) theatre during nephrectomy following neoadjuvant therapy
• Establish patient derived models (PDXs and organoids) + imaging as the experimental platform synergistic to the human tracer work.

Main techniques:

1. Metabolomic profiling using LCMS and RNAseq to determine the metabolic pathways that are altered in RCC. Spatial heteroheterogeneity of metabolism will be assessed within the tumour using RNAscope, DESI and nanoSIMS.
2. Metabolic imaging will be undertaken as part of the research pathway for these patients to evaluate imaging changes with biosample metabolism and finally tumour organoids and animal-based models (including animal imaging) where metabolism and drug treatment interactions will be studied as part of co-clinical studies including hyperpolarised 13C-pyruvate MRI. Experimental approaches will also be developed including deuterium metabolic imaging with 2H-labelled glucose to complement the infusion studies.
3. In vivo infusions.
4. PDX/Organoids
5. Data integration (clinical, imaging, metabolite)

Key references:

1. C. Frezza, G.D. Stewart, C. Yong. Oncometabolites in renal cancer: Warburg's hypothesis re-examined. Nature Reviews Nephrology. 2020;16:156-172.
2. B. Faubert, et al. Lactate Metabolism in Human Lung Tumors. Cell. 2017; 171: 358-371.
3. S. Ursprung, et al. Hyperpolarized 13 C-Pyruvate Metabolism as a Surrogate for Tumor Grade and Poor Outcome in Renal Cell Carcinoma-A Proof of Principle Study. Cancers. 2022; 335.