**The Institute of Cancer Research**

## PHD STUDENTSHIP PROJECT PROPOSAL

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| **FUNDER DETAILS** | |
| **Studentship funded by:** | Medical Research Council - Doctoral Training Partnership (MRC DTP) |
| **Funder specific requirements:** | All MRC DTP students will attend taught courses one day a week for the first nine months of the PhD. This training will cover computational and thematic science training as well as core and transferable skills. Students will spend the remainder of the four years on their PhD project full time with monthly cohort activities. |
| **PROJECT DETAILS** | |
| **Project Title:** | **Advanced multiparametric MRI for the characterisation of soft tissue sarcoma and response to neoadjuvant therapy** |
| **SUPERVISORY TEAM** | |
| **Primary Supervisor(s):** | Dr Simon Robinson |
| **Associate Supervisor(s):** | Professor James O'Connor<br>Dr Paul Huang |
| **Secondary Supervisor:** | Dr Christina Messiou |
| **DIVISIONAL AFFILIATION** | |
| **Primary Division:** | Radiotherapy & Imaging |
| **Primary Team:** | Pre-Clinical MRI |

**SHORT ABSTRACT**

Imaging technology is required to enable personalised adaptation of treatment for improved outcomes for patients with soft-tissue sarcoma, specifically techniques which can identify those patients who would benefit from neoadjuvant therapy prior to surgery, accurately assess tumour response, and enable expedient switching to a more efficacious agent/treatment regime as necessary. The objective of this project is to use advanced, clinically-translatable multi-parametric MRI strategies, coupled with computational pathology, to define imaging biomarkers associated with the heterogeneous phenotype that develops within patient-derived xenograft models of soft-tissue sarcoma, and for the assessment of tumour response to neoadjuvant therapy.

## BACKGROUND TO THE PROJECT

Soft-tissue sarcomas (STS) are a rare group of highly aggressive malignancies comprised of multiple different histological subtypes. Effective treatment of STS is challenging owing to the highly heterogeneous nature of these tumours, which include varying degrees of cellular tumour, fat, cystic and necrotic tissue components (Du et al., 2020).

First line treatment of localised high-grade STS typically involves surgery with radiotherapy. Conventional imaging is a critical component in the differential diagnosis, radiotherapy treatment planning, surgical planning and treatment response assessment. Neoadjuvant radiotherapy improves local control, but the addition of systemic agents as a means of reducing the incidence of metastatic disease to improve survival is being actively investigated. This has amplified the need for techniques which can identify those STS patients who would benefit from neoadjuvant therapy prior to surgery, accurately assess tumour response, and enable expedient switching to a more efficacious agent/treatment regime as necessary (Wardelmann et al., 2016).

Advances in non-invasive MRI techniques provide a means of defining quantitative imaging biomarkers to visualise spatial variations and temporal evolution of tissue structure-function *in vivo*, which can enable accurate tumour detection, an understanding of the microenvironment, and inform on treatment response. New MRI biomarkers need to be established that provide useful research tools for i) hypothesis-testing in pre-clinical and clinical research, and/or ii) guiding clinical decision-making. Imaging biomarkers must undergo rigorous technical and biological validation before being deployed in the clinic. Early imaging biomarker development demands close imaging-pathology correlation, to understand the tissue components underpinning the imaging measurement, which can be meaningfully studied using animal models and computational pathology (Li et al., 2019, Zormpas-Petridis et al., 2020).

There is a clear need to develop imaging technology to enable personalised adaptation of treatment for improved STS patient outcomes. More sensitive and robust multi-parametric imaging methods are required that accurately inform on the heterogeneous distribution of tissue components, and how they change in response to tumour treatment (Messiou et al., 2016).

## PROJECT AIMS

- Implement advanced multi-parametric MRI protocols to interrogate tumour tissue heterogeneity within patient-derived xenograft (PDX) models of soft-tissue sarcoma *in vivo*.
- Combine MR image analysis with computational pathology to validate and define how MRI biomarkers reflect regional variations in tumour histology.
- Assess STS PDX response to neoadjuvant therapy alone, and in combination with radiotherapy, using multi-parametric MRI and digital pathology.

## RESEARCH PROPOSAL

The objective of this project is to use advanced, clinically-translatable multi-parametric MRI strategies to define imaging biomarkers associated with the heterogeneous phenotype that develops within patient-derived xenograft (PDX) models of STS, and for the assessment of response to neoadjuvant therapy alone, and in combination with radiotherapy. PDX models more closely reflect the clinical complexity and diversity of malignant disease. Initial studies will focus on established PDX models of leiomyosarcoma, one of the more common subtypes of STS seen in the clinic, propagated in immune-deficient mice.

Tumour-bearing mice will then be imaged using established multi-parametric MRI protocols to non-invasively quantify and map imaging biomarkers of the tumour microenvironment (Fig.1). The MRI methods/biomarkers will include:

1) Conventional anatomical $T_2$-weighted MRI for tumour delineation and volumetric analysis.
2) Quantitation of native $T_1$ and $T_2$ relaxation times (ms) using MR relaxometry, used to inform on free, structured or bound tissue water (Zormpas-Petridis et al., 2020).
3) Diffusion-weighted (DW) MRI which provides a biomarker of tissue cellularity, quantified as the apparent diffusion coefficient (ADC, $x10^{-6}$ $mm^2/s$). In viable tumour tissue the movement of water molecules is restricted, resulting in reduced water diffusion. ADC is typically elevated in areas of necrosis and shown to increase following effective treatment/cell death, including radiotherapy (Winfield et al., 2019).
4) Magnetisation transfer ratio (MTR, %) imaging, which informs on the proportion of tissue water bound to macromolecules, and sensitive to the extracellular matrix composition (Reeves et al., 2020). MTR may have value in differentiating myxoid tissue often encountered in STS from necrosis.
5) Magnetic resonance elastography (MRE), an emerging MRI technique used to visualise and quantify (kPa) the mechanical or viscoelastic properties of tumours. Increased tissue stiffness contributes to malignant transformation, tumour progression and metastasis. MRE maps the complex shear modulus G* in terms of its two components, the elasticity modulus $G_d$ and the viscosity modulus $G_l$ (Li et al., 2019).
6) Oxygen-enhanced (OE-) MRI for mapping tumour hypoxia, which relies on quantifying hyperoxia-induced changes in the MRI relaxation rate $R_1$ ($s^{-1}$) induced by excess paramagnetic oxygen molecules dissolved in blood plasma and interstitial fluid (O'Connor et al., 2016).

Both MRE and OE-MRI have the potential to predict, assess and guide treatment response in STS with stromal characteristics associated with increased stiffness and impaired drug delivery (Pepin et al., 2019), and in which hypoxia is known to adversely affect patient prognosis (Nordsmark et al., 2001).

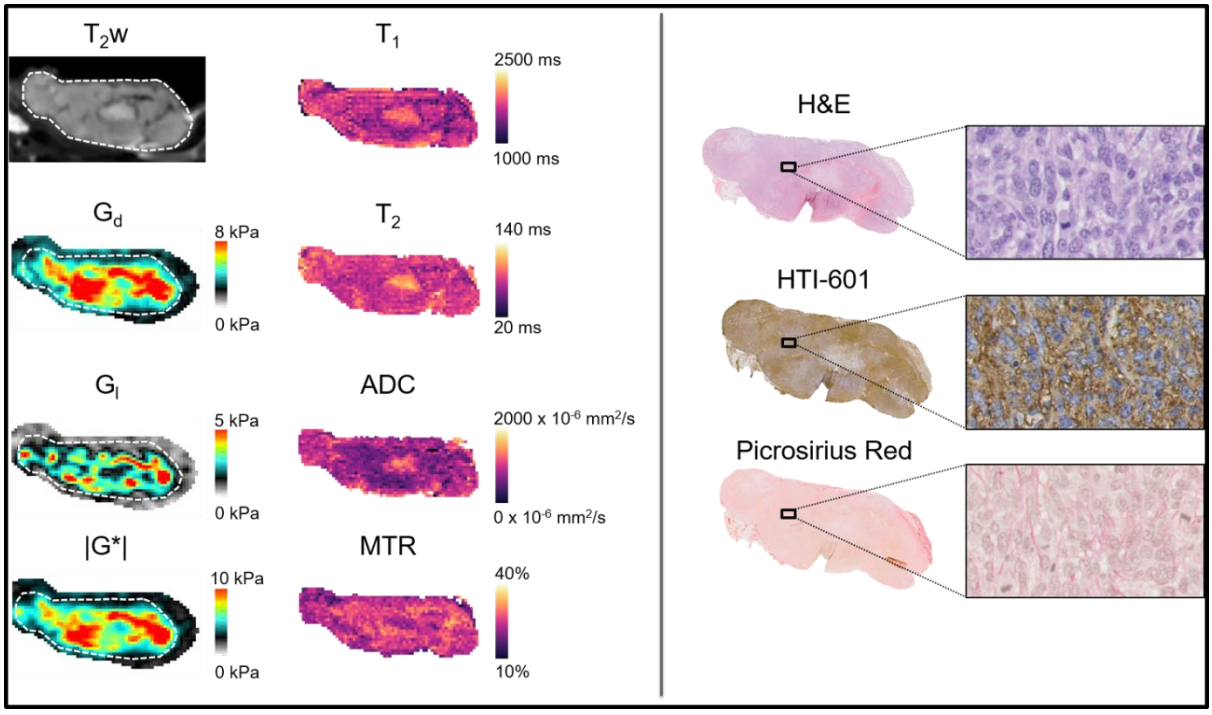


*Fig.1 - Anatomical $T_2$-weighted ($T_2w$) MRI, and maps of native $T_1$, native $T_2$, ADC, MTR, the complex shear modulus G*, the elasticity modulus $G_d$ and the viscosity modulus $G_l$, all calculated from data acquired during a single multi-parametric imaging session performed on a mouse bearing a breast cancer xenograft. Also shown are aligned tissue*

*sections from the same tumour stained with haematoxylin and eosin (H&E), HTI-601 for hyaluronan, and picrosirius red for collagen I and III (Reeves et al., 2020).*

Computational pathology techniques will be applied to objectively and consistently identify and assess whether spatial heterogeneity seen in the multiparametric MRI data acquired *in vivo* is directly linked to regional variations in tumour phenotypic aberrations and microenvironmental components at cellular resolution (Zormpas-Petridis et al., 2020, Li et al., 2019). This approach will be used to assess microenvironmental properties and qualify MRI biomarkers observed within and between STS PDXs. To enable this, for any experimental endpoint, high-resolution $T_2$-weighted MR images will be used to guide the careful excision of the tumour, ensuring that subsequent tissue sections are orientated in the same plane as the MRI data. Aligned tissue sections will then be processed for the histological antigen(s)/marker(s) of interest (e.g. H&E for cellularity, endomucin for vasculature, caspase 3 and Ki67 for cell death and proliferation, picrosirius red for collagen I and III, pimonidazole for hypoxia, γH2AX for DNA damage), and digitised whole tumour section images then acquired. Histological feature(s) of interest will then be automatically or semi-automatically extracted using image processing and machine learning algorithms adapted for each tinctorial stain/chromogen, quantified, and the images processed to match the MRI resolution (Fig.2). Establishing such an imaging/computational pathology pipeline enables the evaluation of any individual MRI biomarker and imaging-defined subregion or "habitat" with histopathology and spatial statistics.

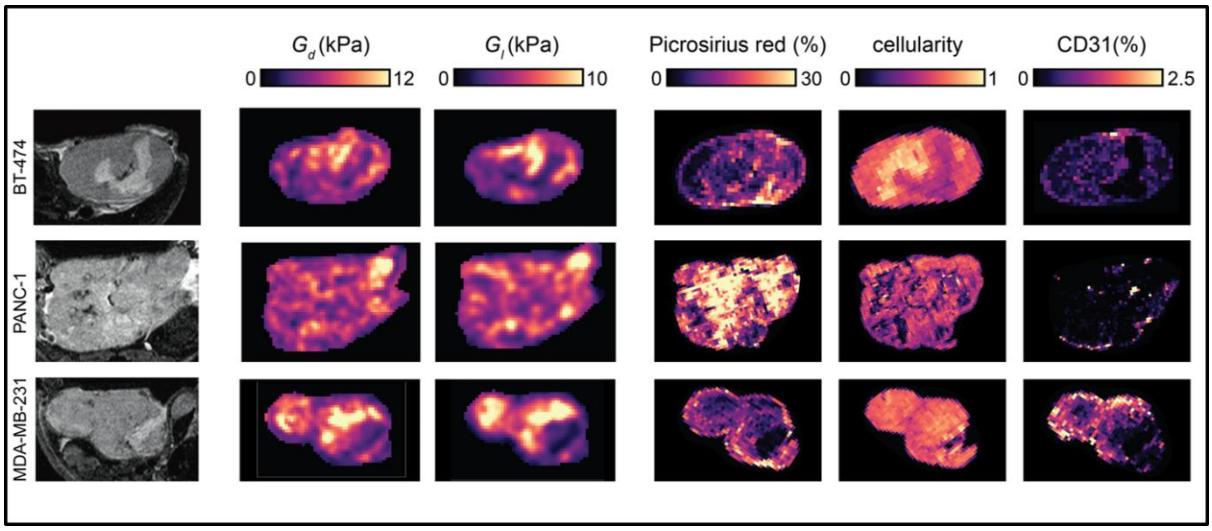


*Fig.2 – Computational pathology pipeline used to assess the spatial relationship of MRE-derived biomarkers with microenvironmental components. The figure shows representative anatomical $T_2$-weighted MRI images and parametric maps of elasticity ($G_d$) and viscosity ($G_l$), and corresponding computed maps of picrosirius red staining (collagen I and III), haematoxylin and eosin staining (cellularity), and IHC detection of Cd31 (vascular density) extracted from high-resolution images of tissue sections from orthotopic BT-474, luc-PANC-1, and luc-MDA-MB-231 LM2-4 breast and pancreatic cancer xenografts (Li et al., 2019).*

The most informative MRI imaging biomarkers of heterogeneity in the STS PDX models will then be investigated for assessing tumour response to neoadjuvant therapy. Guidance on current and appropriate neoadjuvant treatment regimes will be sought from Prof. Robin Jones (Team Leader in Sarcoma Clinical Trials). Tumour-bearing mice will undergo multiparametric MRI prior to and following neoadjuvant therapy, and computational pathology will be performed to assess histopathological response. Subsequently, tumour response to NAC combined with

radiotherapy, administered using a small animal radiation research platform (SARRP) system, will be similarly investigated.

The project will be based within Dr. Robinson's Pre-Clinical MRI team located in the Centre for Cancer Imaging (CCI) in Sutton, which provides a state of the art, collaborative, multi-disciplinary pre-clinical research environment, with imaging (7T MRI) and therapy (SARRP) equipment located adjacent to each other. A panel of STS PDX models have been established in Dr. Huang's laboratory. Prof. O'Connor's team will provide expertise in mathematical modelling of MRI data for imaging biomarker validation and, together with Dr. Messiou, support translation into aligned clinical imaging investigations of STS.

**LITERATURE REFERENCES**


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| **CANDIDATE PROFILE** | |
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| **Note:** the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1) | |
| **Pre-requisite qualifications of applicants:** | Candidates must have a first class or upper second class honours BSc Honours/MSc in Biological Sciences, Physics or Engineering, or Computer Science. |
| **Intended learning outcomes:** | - Secure a Home Office licence, become a responsible licensee and gain proficiency in the propagation of PDX models *in vivo*.<br>- Expertise in the use of a Bruker pre-clinical MRI scanner and an excellent understanding of advanced MRI techniques.<br>- Experience in developing image analysis tools and applying spatial statistical methods to cancer imaging data.<br>- A deep understanding of the pathophysiology of soft tissue sarcoma and current treatment strategies.<br>- An appreciation of clinical imaging approaches for the assessment of soft tissue sarcoma.<br>- Develop strong and confident communication skills through regular presentations of their work at lab meetings, departmental seminars and report writing, and at national/international conferences.<br>- Training within a stimulating research environment in which many projects are of a multi-disciplinary or collaborative nature, providing an insight into a wide range of imaging techniques and expertise. |
| **ADVERTISING DETAILS** | |
| **Project suitable for a student with a background in:** | ☒ Biological Sciences<br>☒ Physics or Engineering<br>☐ Chemistry<br>☐ Maths, Statistics or Epidemiology<br>☒ Computer Science<br>☐ Other (provide details) |

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| **Keywords:** | 1. Magnetic resonance imaging |
| | 2. Soft tissue sarcoma |
| | 3. Radiotherapy |
| | 4. Computational pathology |
| | 5. Image analysis |
| | 6. PhD London |