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PROSTATE CANCER BIOLOGY

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Prostate cancer remains a major global health issue. It affects one in eight men in the developed world, and now accounts for more cancer related deaths in men than females dying of breast cancer. Research in our group employs a cross-disciplinary strategy to tackle clinically challenging aspects of aggressive prostate cancer, namely metastasis and treatment resistance. Our current research priorities aim to improve our understanding of the early stage of metastasis including colonisation of regional lymph nodes by prostate cancer. In addition, we are collaborating as part of the RadNet programme to study the molecular basis of radiation resistance in prostate cancer.

Defining the tumour microenvironment in promoting cancer metastasis to the regional lymph nodes in prostate cancer

Patients with high-risk localised disease have an increased risk of residual or recurrent prostate cancer despite radical treatment, and ultimately progressing to regional and distant metastasis, which resulted in shortened patient survivals. Molecular factors controlling the initiation of prostate cancer metastasis in the first instance to their subsequent colonisation in the regional lymph nodes within the pelvis and/or distant metastasis remains to be fully defined. It is well documented that the tumour microenvironment of prostate cancer tends to be immunologically cold, and the successes of immunotherapies in other tumour types have not been observed in prostate cancer. Hence, the relationships between the prostate cancer microenvironment and the respective draining lymph nodes represent a major focus of our multidisciplinary project.

The ORCHESTRATE (acronym for "investigating the tumOuR miCroenvironment of High-risk localisEd proStaTe canceR to identify AcTionablE pathways involved in cancer metastasis") project is a research programme funded through the Prostate Cancer UK Transformative Impact Award scheme. ORCHESTRATE was launched in 2024 and consists of five work packages (Figure 1), benefiting from our extensive translational infrastructure in clinical urology (Hing Leung, Mark Salji, Imran Ahmad), pathology (Jonathan Salmond) and imaging with laboratory expertise in preclinical models (Ed Roberts, Karen Blyth and Imran Ahmad), spatial biology (John Le Quesne and Nigel Jamieson, incorporating contemporary omics technologies) and facilitating informatics methodologies including machine learning (Ke Yuan), Figure 2. We will carry out parallel cross species analysis of clinically resected tumours and tumours derived from our preclinical models of aggressive prostate cancer. Figures 3 and 4 highlight expertise in multiplex phenotyping in both human and murine tumours, respectively. Hence, knowledge gained from our research will help identify better treatment strategies for patients with high-risk localised prostate cancer, with accompanying preclinical models for additional validation of putative mechanisms in cancer progression.

Schlafen family member 5 (SLFN5) and treatment resistant prostate cancer

We recently identified Schlafen family member 5 (SLFN5) as an AR-regulated protein in CRPC, with elevated SLFN5 protein expression (based on semi-quantitative immunohistochemistry analysis) in castration resistant prostate cancer, significantly correlated with poor patient survival outcome (Martinez *et al.*, 2021, *Cancer Res*). Our working model is that SLFN5 regulates the expression of LAT1, an essential AA transporter, and thereby intracellular levels of essential amino acids and mTORC1 signalling. Ongoing focus is to further define the molecular basis of SLFN5 mediated castration resistance, thus identifying novel therapeutic targets.

Besides tumour response to androgen deprivation therapy, SLFN5 has recently been implicated in repair of DNA double-strand-breaks (DSBs) by controlling 53BP1 topological arrangement at DSBs (Huang *et al.*, 2023, *Mol Cell*). Indeed, SLFN5 deficiency disrupts the DSB repair topology and impairs non-homologous end joining, telomere fusions, class switch recombination, and sensitivity to poly (ADP-ribose) polymerase inhibitor. We are therefore collaborating with colleagues within the RadNet Glasgow consortium, led by Anthony Chalmers, to characterise the role of SLFN5 in prostate cancer response to radiation therapy. With pump priming funding from RadNet Glasgow, we are creating a panel of radiation resistant human prostate cancer cell models to support future mechanistic studies.

Prostate Specific Membrane Antigen (PSMA) related Neuronal Metabolites in Treatment Resistant Prostate Cancer

PSMA converts NAAG (N-Acetylaspartylglutamic acid or N-Acetylaspartylglutamate), a highly prevalent neurotransmitter, to NAA (N-acetylaspartic acid) and Glutamate and may be important in radioresistance. We hypothesise that PSMA activity can be determined by NAA/NAAG measurement in urine. These neuronal metabolites may promote survival as a local acetate and glutamate source for sphingolipid dependent survival mechanisms driven by activation of glucocorticoid receptor.

A combined pre-clinical and clinical approach is being undertaken to investigate NAA/NAAG biology. Urinary NAA/NAAG pre and post radiotherapy may be clinically useful to explain differences in radiosensitivity related to PSMA activity. Surgical explant models of CRPC including bone metastasis will visualise NAA and NAAG within the tissue microenvironment using Mass Spec Imaging (MALDI / DESI).

Publications listed on page 123

Figure 1

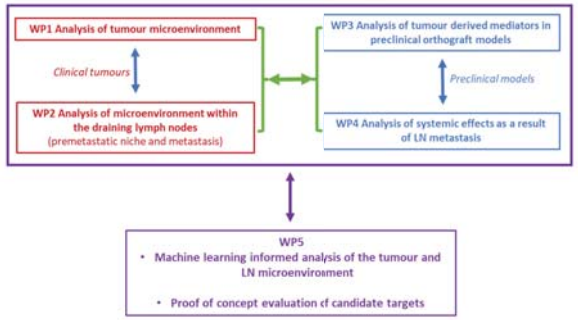

Figure 2

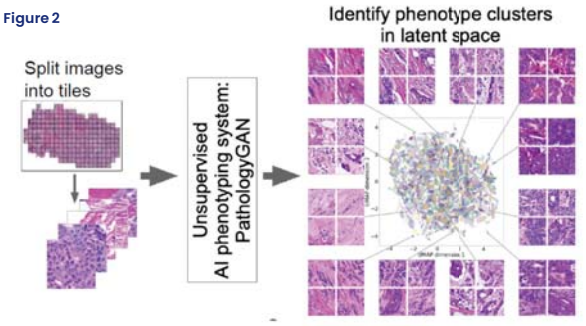

Figure 1. Overview of the five interconnecting work packages of the ORCHESTRATE project, leveraging the ability to carry out cross-species analysis on clinical resected tumours and tumours from pre-clinical models of aggressive prostate cancer.

Figure 2. Illustration of workflow to find phenotype clusters which could be used to refine histopathological classifications associated with lymph node metastasis.

Figure 3

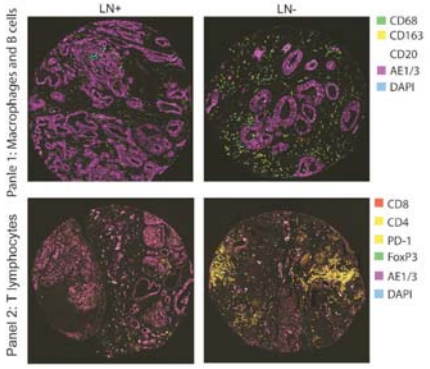

Figure 4

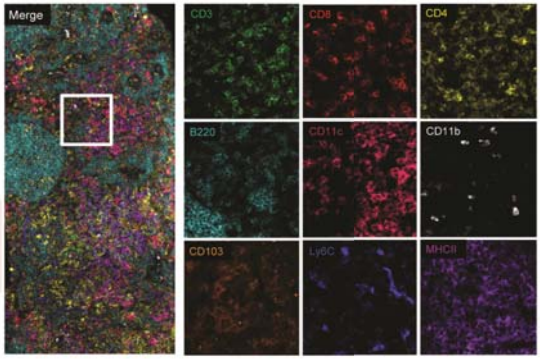

Figure 3. Representative multiplex immunofluorescence images showing reduced immune cell infiltration in patients with (left) compared to patients without (right) LN metastasis. Images are spectrally unmixed for Panel 1: macrophage & B cell (top) and panel 2: T lymphocyte (bottom). (Data generated in collaboration with Leah Officer-Jones and John Le Quesne)

Figure 4. Multiplex high resolution imaging of sections of murine lymph nodes, with subsequent segmentation and identification of key cell types carried out in HALO to support spatial statistical analysis. Images shows data from nine markers (identity provided in inserts) for illustration. (Data generated by Ed Roberts' research group.)