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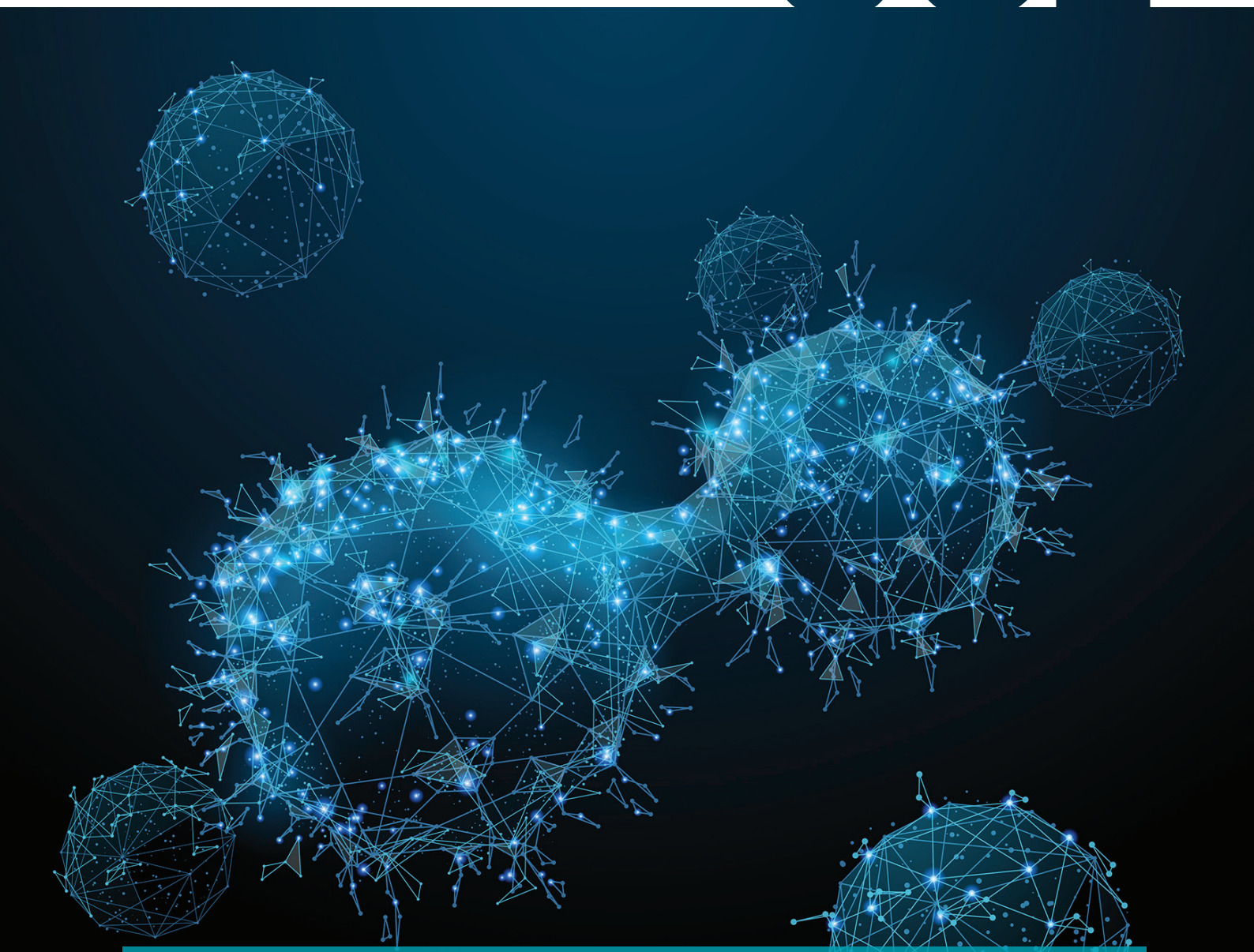

UCL Cancer Symposium

Wednesday 1 May 2024

www.ucl.ac.uk/research/domains/cancer

1. **Huda Alnufaei – Division of Surgery and Interventional Science**

TITLE

The correlation between Boronophenylalanine (BPA) uptake and cell transporters in various human cell lines

ABSTRACT

Boron neutron capture therapy (BNCT) is a radiotherapy modality for cancer. The accumulation of 10B in tumor is the key factor determining the therapeutic efficacy of (BNCT). Improving 10B delivery and distribution can be achieved by investigating specific targets.

Boronophenylalanine (BPA) is transported into the tumour cells through the system L transporters, particularly LAT1. The expression of LAT1 is highly upregulated in various cancers due to its contribution to the tumour growth by increasing the amino acid supply. Furthermore, Transmembrane channel-like 5 (TMC5) belong to a larger trans membrane channel-like (TMC) gene family. TMC proteins are modifiers of ion channels or transporters, directly or indirectly participating in regulating the permeability of cell membrane channels.

Towards understanding the role of LAT1 and TMC5 on BPA accumulation in cancer cells, this study examined their expression levels in various human cancer cell lines (glioma: U87, U251; colorectal cancer: HT29, HCT116; head and neck cancer: PCI30, C666-1) through Western blot analysis.

Then, short hairpin RNA (shRNA) were transduced to knockdown TMC5 in HCT116 colorectal cancer cell line, which exhibited considerable TMC5 expression. The knockdown and control cells were treated with 10B-BPA with a concentration of (25, 50, 100, 200μg/mL). Intracellular 10B levels were quantitatively assessed using inductively coupled mass spectrometry (ICP-MS), sensitive to 10B at concentrations as low as 0.1 ppb. A preliminary study found that the 10B concentration in the TMC5 knockdown group was higher than the control group for all tested BPA concentrations.

Ongoing research aims to clarify the roles of LAT1 and TMC5 in boron uptake and BNCT efficacy in a range of relevant cancer types such as head and neck cancer and glioma. Further research aims to uncover how TMC5 affects BNCT, potentially leading to new BNCT approaches that are more effective and less toxic for cancer patients.

2. **Reem Al-Saadi – Cancer Institute**

TITLE

MULTIMODALITY DETECTION OF TUMOUR RUPTURE IN CHILDREN WITH WILMS TUMOUR

ABSTRACT

Introduction

The IMPORT (Improving Population Outcomes for Renal Tumours of Childhood) study collects amongst other clinical data, radiological, surgical and pathological data pertaining to tumour rupture (TR). Diagnosis of TR signifies stage III disease and requires intensification of treatment, including radiotherapy. This study aims to describe associations between radiologically suspected TR with subsequent surgical and histopathology findings in children with Wilms tumour (WT) registered in the IMPORT study.

Method/Project description

The IMPORT study registered 712 children with renal tumours from 20 centres between September 2012 and March 2021. Data were extracted from case report forms for central radiology review (CRR), surgical forms and central pathology review (CPR).

Results

98 children with newly diagnosed WT had TR identified on CRR at diagnostic abdominal cross-sectional imaging - 63 MRI and 35 CT. TR was limited to renal fossa in 45/98(46%) cases and intra-peritoneal in 53/98(54%). 95/98(97%) had pre-operative chemotherapy for 4-6 weeks before nephrectomy. 87 had TR seen on the pre-operative scan. Among 80/98(82%) cases with TR on CRR and available surgical and pathology forms, TR was not confirmed on either surgery or pathology in 35/80(43%). 1/98(1%)

was upstaged to stage III and received whole abdominal radiotherapy only due to TR suspected on radiology, 5/98(5%) due to radiological TR confirmed at nephrectomy, but not on pathology.

Discussion

Features of TR found at radiology were infrequently confirmed at surgery and/or histopathology and are therefore unreliable for definitive staging and treatment."

3. **Elysse Bautista – UCL Institute of Epidemiology and Health Care**

TITLE

Unraveling Delays in Lung Cancer Care: Insights and Implications for Patient Navigation Programs in Mexico

ABSTRACT

Background:

Delays in lung cancer care are linked to advanced disease and poor patient outcomes. Patient navigation programs offer promise in mitigating these delays. Research is needed to identify delays in lung cancer care in Mexico and to understand the potential of patient navigation programs.

Methods:

Utilizing mixed methods, primary data was collected through lung cancer patient interviews and electronic health records to measure delays. Additionally, interviews with patient navigation programmes were also conducted. As a result, case studies (N=5), qualitative examination of patient narratives (N=46), and quantitative analysis (N=2645) were employed to investigate patient navigation programs and delays in lung cancer care. Results from the qualitative and quantitative streams were independently analysed, and later integrated to generate meta-inferences to confirme, diverge, expand and/or complement results arising from qualitative or quantitative findings.

Results:

- 74% of patients were diagnosed in advanced stages, with an average delay of 192 days from symptom presentation to treatment.

- Mexican women experience more delays than men from symptom onset to treatment.

- Diverse patient journeys revealed factors influencing delays, including symptom appraisal, access challenges, regional and demographic disparities, treatment disparities, and financial constraints. However, the institution from referral did not impact delays.

- Various patient navigation implementations were observed, with limited evidence supporting their focus and effectiveness in reducing delays.

Conclusions:

- Calls for rigorous, standardized research on patient navigation to evaluate effectiveness throughout the cancer continuum.

- Understanding patient journeys and addressing delay factors is crucial, especially amidst challenges like fragmented healthcare systems.

- Emphasizes the need for evidence-based interventions to enhance timely access to care for the lung cancer population in Mexico.

4. **Cenk Celik – Research Department of Genetics, Evolution and Environment**

TITLE

Unravelling Internal and External Regulatory Mechanisms of Cell Cycle Arrest in Breast Cancer

ABSTRACT

The cell cycle dysregulation stands as a crucial aspect of cancer progression, demanding a comprehensive understanding of the mechanisms underlying tumorigenesis and therapy resistance. Here, we explore the immune context of cell cycle arrest in breast cancer to elucidate its intricate molecular mechanisms.

We conducted a thorough analysis of 43 primary breast cancer scRNA sequencing datasets, covering diverse subtypes. Our analysis unveiled a complex transcriptional landscape of breast cancer cells, allowing us to identify distinct subsets of highly proliferating and G0 arrested tumour cells.

G0 arrest was observed as a widespread state across all major breast cancer subtypes, with increased prevalence in ER+ tumours and decreased prevalence in TNBC. Moreover, we discovered rewiring of interactions established between tumour cells and their microenvironment when cells were arrested in G0. Specifically, we observed TGFB1-mediated cell cycle arrest actively induced by TAMs, CAFs, B cells and Tregs within the TME, alongside a significant depletion of interactions with T cells. Additionally, we noted immune cell-enriched semaphorin 4D ligand and plexin B1 receptor interactions, impeding T cell infiltration. Exploration of gene regulatory networks in G0 arrested cells revealed a rewiring of modules associated with growth inhibition, unfolded protein response-induced stress and stemness. The G0 arrested cancer cells also exhibited increased EMT hallmarks, with the majority residing in a hybrid E/M state, pointing to metastatic potential. These findings were validated in 12 spatial transcriptomics slides across breast cancer subtypes, where we identified G0 arrest hotspots enriched in EMT hallmarks that appeared to be shielded from cytotoxic T cell recognition by myCAFs and macrophages.

In summary, our study defines a G0 arrested, hybrid E/M state that is actively induced within developing primary tumours as a response to proteostasis-linked stress and appears more successful at evading immune recognition. These insights hold promise for developing therapeutic strategies to overcome immune resistance mechanisms in breast cancer.

5. **Premkamon Chaipanichkul – Division of Surgery and Interventional Science**

TITLE

Effect of hypoxia on Gd-based nanoparticle uptake and distribution in a preclinical spheroid model

ABSTRACT

Oxygen plays a critical role in DNA damage and repair, and its absence in hypoxic tumours leads to radioresistance, increasing the risk of metastasis and complicating radiotherapy. This challenge is quantified by the Oxygen Enhancement Ratio, which shows the need for more than double the radiation doses in hypoxic conditions to achieve the same tumour cell kill as in normoxic conditions. With 90% of solid tumours exhibiting hypoxia, targeted therapies, such as nanoparticle-assisted radiotherapy, offers opportunity to enhance treatment at resistant sites while minimising potential side effects.

Our research employs gadolinium-based nanoparticles (GdBNPs) for their dual roles in image guidance and radiosensitisation. We utilised U87 glioblastoma cell lines in 2D monolayer cultures and a 3D spheroid model which allows for size-tuneable control over the oxygen distribution within spheroids. By varying the culturing time and cell seeding numbers (5, 25, and 50 ×10^3 cells/well), we generated spheroids of 200 to 900 μm in diameter. This variation enabled us to mimic oxygen gradient, simulating in vivo-like hypoxia in spheroids.

Our methodological approach ensured reproducibility, with consistent spheroid size and roundness across different batches. Specifically, we achieved 100% round spheroids when culturing with designated seeding densities over 2 and 3 days. However, at the higher seeding density (50×10^3 cells/well), the percentage of round spheroids slightly decreased. The spheroids were fixed and cryosectioned for high-resolution imaging to map GdBNPs colocalisation with hypoxic markers, HIF1α and HIF2α. Additionally, 2D cultures were exposed to normoxic and hypoxic conditions for various durations to mimic acute and chronic tumour hypoxia. Flow cytometry quantitively measured the expression levels of HIF1α and HIF2α with the uptake of GdBNPs, tagged with Cy5.5 fluorochromes. This detailed analysis offers insights into GdBNPs targeting capability under hypoxic conditions, aiming to enhance radiosensitivity and potentially improve therapeutic outcomes for hypoxic tumours.

6. **Matthew Clarke – UCL Cancer Institute**

TITLE

Predicting Personalised Radio-sensitising Combination Treatments in Non-Small Cell Lung Cancer Using In Silico Modelling

ABSTRACT

Lung cancer is the leading cause of cancer mortality world-wide, with over half of lung cancer patients relying on radiotherapy (RT). Tailoring RT to patient biology remains challenging, despite improved engineering methods allowing more precise RT targeting to patient anatomy. Combining RT with targeted drug therapies allows the personalisation of radiotherapy by radio-sensitising tumours but requires better mechanistic understanding of how different mutational backgrounds drive treatment response. To predict effective radio-sensitising treatment combinations, tailored to different non-small cell lung cancer (NSCLC) mutational backgrounds, we have built a computational model of NSCLC signalling and used it to perform in silico CRISPR screens. This innovative computational approach predicts the effect of RT and drug combinations on tumour and healthy tissue and provides a mechanistic explanation of treatment response in diverse genetic backgrounds. Our model predicts that DNA-damage repair (DDR) inhibitors elicit a broad effect across tumours but also radio-sensitise healthy cells. Conversely, targeting the Myc, WNT and MET pathways is predicted to specifically radio-sensitise tumour cells in a patient-specific manner. The model further predicts drug combinations that target the tumour and spare healthy cells, specifically MYC and ATR inhibition. These results further demonstrate the power of in silico models to predict novel combination therapies for specific mutational backgrounds, paving the way for personalising treatment plans for improved patient outcome.

7. **Helena Coggan – Cancer Institute, Department of Mathematics**

TITLE

An agent-based modelling framework to study cell plasticity in non-small cell lung cancer

ABSTRACT

Recent breakthroughs in phylogenetic analysis of bulk tissue have allowed researchers to reconstruct the evolutionary histories of tumours. The hope is that knowledge of the order and timing of genetic mutations will allow us to characterise the properties of early-stage cancer cells, to better identify and target them. This is complicated by the phenomenon of tumour plasticity, the ability of cells to acquire the hallmarks of cancer via mechanisms other than heritable genetic mutation. In a tumour with only genetic heritability, changes in cell phenotype would occur only as a result of genetic mutations. By contrast, non-genetic heritability could lead to a disconnect between genotype and phenotype. Whilst both mechanisms are likely to impact on cancer development, we ask whether one has a significantly stronger influence than the other by simulating tumour growth under each regime and comparing the distribution of mutations obtained in either case to patient data.

Here, we address this question in a real patient cohort by adapting a mathematical model of lung tumour evolution, which we use to test the validity of two scenarios. In a ‘low-plasticity’ scenario, changes to reproductive fitness occur when cells acquire mutations in the exome. Mutations may be ‘drivers’ (beneficial) or ‘passengers’ (deleterious or neutral). In a ‘high-plasticity’ scenario, mutations have no effect on cell fitness. Cells experience ‘driver-like’ or ‘passenger-like’ cell fitness changes on division, without leaving a genetic mark. The model describes three-dimensional growth of a tumour from a single cell and incorporates biologically-informed death patterns and local competition for space and resources. When the simulation has reached a realistic size, cells on the surface are sampled and sequenced to predict the relatedness of mutations present at detectable frequencies in each of several regions. The outputs are designed to allow comparison with those of the TRACERx cohort of 421 non-small- cell lung cancer patients (NSCLC), comprising multi-region whole-exome (WXS) and bulk RNA sequencing.

In this ongoing work, we show results from a large cohort of simulations under both scenarios and predict corresponding patterns of genetic similarity. This allows us to use approximate Bayesian computation (ABC) to predict the mechanisms at play in the TRACERx cohort of 421 non-small-cell

lung cancer patients (NSCLC). We present a novel 'meta-inference' approach, where evolutionary parameters are fit to each patient's data using well-chosen summary statistics. Given the size of the TRACERx cohort, this enables the evaluation of each scenario by examining the plausibility and similarity of output parameters obtained across patients. We hope that this work will shed light on the role of heritability in lung cancer development and guide future research into therapeutic approaches.

8. **Tishe Coker – UCL Cancer Institute**

TITLE

The proportion of preclinical models characterising Black patients with prostate cancer and how well they represent the biological features of their disease – a systematic review

ABSTRACT

This systematic review aims to address the critical gap in preclinical prostate cancer research resources relevant patients. Despite the higher incidence and mortality rates of prostate cancer among Black men, existing preclinical models predominantly reflect the genetic and physiological characteristics of White patients, or patients of unknown ethnicity. This discrepancy limits the understanding and effectiveness of treatment strategies for Black patients, despite them being a cohort of distinct clinical need.

The primary objective of this review is to systematically assess the proportion of existing preclinical models that include race and/or ethnicity data for Black patients with prostate cancer. Furthermore, it seeks to determine how well these models characterise the biology and pathophysiology of prostate cancer for Black patients within the preclinical research landscape. Through a comprehensive search strategy encompassing both clinical and biological databases, the review will collate and assess the quality of a) clinical omics datasets, b) cell lines and cell line omics datasets, c) 3D models and 3D model omics datasets, in order to identify available preclinical research resources representing Black prostate cancer patients.

This review will employ narrative synthesis and subgroup analysis, given the heterogeneity of study methodologies and outcomes, to present a nuanced understanding of the current state of preclinical models in representing the disease in Black patients.

Although specific results are pending due to ongoing data collection at the time of abstract submission, this review anticipates presenting a comprehensive overview of the availability and representativeness preclinical models in portraying prostate cancer in Black patients. It aims to highlight the need for clinically relevant research practices that address the unmet preclinical needs and racial differences in prostate cancer pathology and treatment responsiveness, ultimately contributing to the reduction of racial disparities in prostate cancer outcomes.

9. **Laura Donovan – Developmental Biology and Cancer, Cancer Institute**

TITLE

MYC-Driven Recurrent Medulloblastoma and CD74: Targeting the Nexus for Effective Treatment

ABSTRACT

Background: One of the most significant unmet clinical challenges in paediatric oncology is the development of novel therapeutic strategies for recurrent medulloblastoma (R-MB). MYC-driven MBs are defined as classically cold tumours with a low incidence of infiltrating immune cells, resulting in a therapeutic challenge. The identification of cell-cell communications, particularly ligand–receptor pairs, allows for the inference of significant intercellular communications based on the expression of corresponding genes. Consequently, we hypothesised that the most influential cell-cell interactions within the tumour immune microenvironment (TME) of MYC-driven MB could unveil prevalent immune-suppressive interactions and potential vulnerabilities for therapeutic exploration.

Methods/Results: Paired primary-recurrent bulk RNA-sequencing data, confirmed myeloid cells as the most infiltrating immune cell type in group3-MB and group4-MB. Comprehensive spatial phenotypic and cell-cell communication analyses corroborated this discovery, validating an increased incidence of macrophages in the matched-recurrent tumours. Subsequently, we used innovative algorithms for 10X MB single-cell data to predict interactions between tumour-cell ligands and immune-cell receptors within

the TME; macrophages emerged as the core immune-cells involved in interactions throughout the TMEs, with the most significant ligand-receptor interaction and inflammatory response between MIF and CD74.

In-depth immunohistochemistry analyses of primary and recurrent group3 and group4 tumours, and exhaustive tissue microarrays demonstrated expression of both CD74 and MIF, with limited expression of CD74 within the brain. To investigate the therapeutic potential of CD74, we developed recurrent, immune competent MYC-driven medulloblastoma mouse models. Comprehensive deconvolution analysis confirmed the TME integrity of our models to mirror that of the human disease. Locoregional delivery and repeat dosing of a bioactive-CD74 peptide demonstrated significant tumour reduction in our immune-competent mouse models, demonstrating the impact of our prediction algorithm and significant therapeutic potential of targeting the CD74-MIF axis in MYC-driven primary and recurrent MB.

Conclusions: Essential cellular interactions and therapeutic vulnerabilities have been identified in the tumour-microenvironment of MYC-driven primary-recurrent MB.

10. **Emily Drabek-Maunder – Institute of Child Health**

TITLE

Pre-treatment evidence of abnormal supratentorial white matter in children with posterior fossa tumours using diffusion MRI

ABSTRACT

Over half of childhood brain tumours originate in the posterior fossa, which includes tumours classified as low-grade (e.g. pilocytic astrocytoma) and high-grade (e.g. medulloblastoma). Even though overall survival rates of paediatric brain tumours have substantially increased, survivors face neuropsychological impairments impacting behaviour, cognition, language and motor skills. Post-treatment outcomes are associated with structural changes within the brain, but it is unclear if observed microstructural damage is caused exclusively by radiotherapy or if there is earlier damage from the tumour and related effects. Diffusion MRI is a non-invasive technique that can be used to better understand white matter microstructure by quantifying water diffusion in the brain. Diffusion tensor imaging (DTI) can be used to assess white matter damage. In this work, we used DTI to better understand white matter microstructure in 8 posterior fossa tumour patients prior to surgery. We compared individual patients to age- and sex-matched healthy controls in a one-against-many approach. We demonstrate the presence of supratentorial white matter abnormalities prior to treatment in 3 patients. Before treatment, all patients are found to have significantly enlarged lateral ventricles relative to total brain volume ($p<0.05$). Patients with ventricle volumes >4% relative to brain volume correspond to significant changes in DTI parameters found in pre-treatment images, suggesting that hydrocephalus impacts white matter microstructure before surgery. Observed white matter changes are complex and patient-dependent, patients demonstrate compression (increased fractional anisotropy; FA) or diffuse oedema and damage (decreased FA). These white matter abnormalities persist over time, which could lead to cumulative damage, for example when adjuvant treatment involves radiotherapy. To improve patient outcome, pre-treatment imaging could be considered during individual treatment planning and risk evaluation to avoid further injury to white matter. Pre-treatment white matter abnormalities may have a bearing on neurocognitive patient outcomes, which will be the focus of future work.

11. **Benjamin Draper – Institute of Child Health**

TITLE

Overcoming Tumour Heterogeneity in Medulloblastoma with Dual-Targeting CAR T-cells

ABSTRACT

Medulloblastoma (MB) is the most common malignant childhood brain tumour. Group 3 MB has the worst prognosis (<10% survival), linked with the highest rate of fatal recurrence with no therapies currently existing for recurrent group 3 MB.

Chimeric Antigen Receptor T-cell (CAR-T) therapy allows highly specific targeting of tumour cells whilst reducing off-target effects seen with current standards-of-care such as radiotherapy and chemotherapy.

CAR-T have shown great promise in haematological malignancies however there has been a failure of translating this success to treating solid tumours. Reasons for this are multifaceted but the two we focus on are overcoming T-cell exhaustion and antigen-negative escape.

We have developed a dual CAR-T to simultaneously target the tumour antigens B7H3 and GPC2 which are expressed across all stages of paediatric medulloblastoma. Dual CAR constructs targeting B7H3 and GPC2 were designed with complementary costimulatory signalling domains and showed greater levels of tumour control over repeated stimulations as well as having a favourable exhaustion profile demonstrated by decreased PD-1 expression compared to single-targeting second-generation (2G) CAR-T over increased restimulations. Furthermore, our dual CAR-T maintained higher Th1 cytokine release over repeated stimulations compared to second-generation CARs. In stress-test assays dual CARs show favourable phenotypes and better tumour cytotoxicity compared to 2G CARs. Our data demonstrates the superiority of dual CAR-T against MB target cell lines and PDXs evaluated in in vitro assays, leading the way to our future work, to establish efficacy in in vivo PDX and immune-competent tumour models of primary and recurrent paediatric medulloblastoma.

12. Peter Embacher – Medical Physics and Biomedical Engineering

TITLE

Stochastic modelling of lineage correlations in glioblastoma cells to capture non-genetic heterogeneity

ABSTRACT

Glioblastoma is one of the most aggressive and difficult to treat cancers. One obstacle to developing successful treatments is the substantial interpatient and intratumour heterogeneity. This variability in treatment response even occurs in genetically identical cells and could be due to inherent randomness in gene expression. However, non-intuitive correlation structures in the division and death dynamics of genealogically related cells imply an unrecognised deterministic process. We developed a mathematical modelling framework to distinguish between multiple different hypotheses governing heterogeneity in cell proliferation and death following radiotherapy.

We use live-cell imaging data of different glioblastoma patient-derived cell lines with stably expressed H2B reporters to identify and track their nuclei. We constructed an image analysis pipeline to automatically extract cell fates and construct lineage trees from the microscopy data. We developed multiple mathematical models representing different hypotheses for the inheritance mechanism of cell fate propensities, including single-factor inheritance from mother cells and circadian rhythm-modulated division and death rates. The models are formulated within the Bayesian framework to capture the high levels of stochasticity and allow for a probabilistic interpretation of the results. Model parameters describing proliferation and death rates as well as the correlation structure within a lineage are inferred statistically and a model comparison is carried out to quantify the goodness of fit of the hypotheses for several datasets. Once complete, our parameterised mathematical models could be used to simulate the responses of the cancer cells to different treatment strategies, such as chronotherapy or novel drug-radiation combinations.

13. Andrei Enica – UCL Cancer Institute

TITLE

Informing lung cancer immunoprevention using spatial omics

ABSTRACT

Lung cancer is the leading cause of cancer-related death worldwide. Checkpoint inhibitors have shown significant promise in invasive disease; however, we currently lack clinical strategies for immune-prevention. Understanding the early regulation of immune responses during squamous carcinogenesis could provide novel targets for immune prevention of lung squamous cell carcinoma (LUSC).

Using scRNA-seq, we profiled preinvasive bronchial biopsies from patients with a smoking history, enrolled in a surveillance programme at UCLH. This revealed a subset of highly suppressive OX40hi

GITRhi Helios+ BATF+ regulatory T-cells enriched in carcinoma-in-situ (CIS) relative to normal epithelium. The origin and immune regulatory mechanisms of this subset are unknown in the pre-malignant setting.

To further understand this, we generated a single-cell spatial map of the immune ecosystem in nascent LUSC, for the first time. This allowed us to explore the broader distribution, activation, and interaction of different immune subsets in pre-invasive lesions using the Nanostring CosMx platform. Given the extensive remodelling of MHCII signalling networks during LUSC carcinogenesis (patterned by loss of MHCII on basal airway epithelium and gain on B-cells and cDC2s), a focused analysis has defined the interactions of BATF+Tregs with local antigen-presenting cells, as well as CD8 T-cell dynamics. Key regulatory targets were spatially validated using multiplex immunofluorescence.

Investigating how the nascent TME may be patterned differently during progression vs regression will allow the selection of targetable regulatory axes for interception. These will be functionally validated using mouse models of chemically-induced carcinogenesis and early-stage lung cancer patient-derived explants to make a roadmap of clinical pathways for LUSC immune-interception.

14. Enzo Giardina – Developmental Biology & Cancer

TITLE

Design of retinoid-responsive toxin gene systems for neuroblastoma treatment

ABSTRACT

Retinoic acid (RA) has been shown to improve clinical outcomes for neuroblastoma (NB) patients; however, its use has been limited by toxicity and evolved tumour resistance. To increase RA efficacy, we aim to design a “toxin gene” therapeutic that is highly sensitive to transcriptional activation by RA, that will generate a cytotoxic response in NB cells. We linked the toxin gene, diphtheria toxin A (DTA), to RA-responsive promoters in plasmids and tested their cytotoxic capabilities under a range of RA concentrations. MicroRNA-response-elements (MREs) were also cloned into the plasmids to minimise expression in off-target tissues, primarily the liver. Luciferase assays were used to quantify expression with and without the MREs, while fluorescence-based assays were used to assess cell survival. Plasmids were delivered to NB cells in culture using our previously documented peptide-targeted, liposome-based nanocomplexes (ref 1). The RA-driven DTA vector, after transfection into NB cells, is highly sensitive to RA, requiring minimal exogenous RA (<100 nM) for maximal cytotoxic activity. Compared to RA alone, the vector shows greater toxicity at all concentrations of RA, shown by the complete loss of positively transfected NB cells following RA treatment. Liver-specific MREs knocked down transcription by 98% in the hepatoma-derived Huh7 cell line, and also reduced cytotoxicity in this line; however, decreased activity was seen in some NB cells. Next steps are to improve the tumour-selectivity of the system and to carry out proof of principle testing in vivo using our targeted delivery system. If successful, this novel approach could be developed as a combination treatment alongside RA in patients, as a route to effectively remove residual tumour cells.

15. Amalia Gjerloev – Mathematics

TITLE

Using operational research simulation techniques to inform decision making for cancer pathways

ABSTRACT

With the Covid-19 pandemic, healthcare systems have seen a huge influx of patients, a strain on hospital resources and increased pressure to operate efficiently in order to save patient lives. Cancer services have been particularly impacted and face long waiting times following a dramatic fall in referrals at the start of the pandemic. In order to improve resource allocation, scheduling and understanding of the pandemic's impact on patient care, we developed a flexible model of patient flow along the cancer care pathway. We present a framework for analysing resource management in care pathways that employs Discrete Event Simulation and heavily involves clinical and operational managers. A case study is presented, in which we use our simulation framework to inform operational decisions for lung cancer services at a London-based hospital.

16. **Priyanka Gupta – Division of Surgery & interventional Science**

TITLE

Engineering advanced healthcare models for drug testing: Chemotherapy screening on a novel, dynamic, multicompartmental, multicellular pancreatic cancer model

ABSTRACT

INTRODUCTION: Pancreatic Ductal Adenocarcinoma (PDAC) is considered to be one of the deadliest diseases with very low survival rates. This is partly attributed to the tumour resistance to currently available treatment, resulting from a complex and highly heterogeneous tumour microenvironment (TME). A key challenge in cancer tissue engineering is to mimic the various TME features.

METHODS: In this work we perform drug testing in biologically complex, PDAC biomimetic models which can spatially mimic the fibrosis/desmoplasia of pancreatic cancer as well as the tissue interstitial flow.

We perform drug testing with Gemcitabine (GEM), in polymer-protein based multi-cellular scaffold of pancreatic cancer, pancreatic activated stellate and endothelial cells. Two different two architectural configurations were used: (i) a single scaffold and (ii) a zonal scaffold comprised of an inner (cancer) compartment and an external (stroma) compartment. Furthermore, via using a perfusion bioreactor we achieved mimicry of the interstitial flow, which enables more accurate drug delivery. Imaging of cellular proliferation/spatial organization, apoptosis of the different cell types and Extraceullar Matrix (ECM) secretion was carried out along with q-PCR assessment of various biomarkers, e.g. Epithelial-to-Mesenchymal Transition EMT or metastatic markers both pre- and post-treatment with the drug.

RESULTS: Within our static models, we observed that the dual scaffold showed a higher resistance to GEM in comparison to the single scaffold. These results highlight that the spatial arrangement of the cells, within a 3D model, affect the response to chemotherapy. Furthermore, the introduction of dynamic flow affected the cell spatial organization, and biomarker expression involved with EMT and matrix remodeling highlighting the importance of fluid and its role in PDAC's resistance to chemotherapy. Our work highlights the importance of spatio-temporal cellular arrangement and interstitial fluid flow for accurate in vitro studies of drug screening.

17. **Anna-Dimitra Kataki – Division of Surgery and Interventional Science**

TITLE

Mapping the therapeutic efficiency of novel proton beam therapies on advanced multicellular 3D pancreatic cancer models: Towards building better healthcare delivery models

ABSTRACT

The development of advanced cancer tissue engineered models allows replicating the intricate ecosystems found in tumour tissue microenvironments (TME) enabling a more precise preclinical evaluation of treatment approaches. The high treatment resistance of pancreatic cancer (PC) is directly linked to its' very complex TME. These distinct TME characteristics are not adequately reproduced in conventional preclinical research, despite their significant connection to radiotherapeutic resistance. Progress in radiotherapy, including techniques like image-guided and proton therapy, seeks to improve treatment outcomes while minimizing harm to adjacent healthy tissues, allowing for precise targeting of tumours and increased dose accuracy. These evolving techniques exhibit different radiobiological effectiveness compared to traditional therapies, emphasizing the necessity for reliable biomimetic models to assess delivery strategies.

This work focusses on evaluating the therapeutic efficiency of proton beam therapy versus traditional photon therapy, for the first time, on spatially advanced multicellular PC models.

More specifically, proton and photon radiotherapy were conducted in polymer-protein based scaffolds, prepared in two architectural configurations: (i) a single scaffold containing cancer cells (monocellular model) and (ii) a zonal scaffold comprised of an inner (cancer) compartment and an external (stroma) compartment (containing activated stellate cell and endothelial cells), which can mimic the fibrotic/desmoplastic reaction of the disease. Thereafter, the radiotherapy cytotoxicity was spatially mapped.

Our study demonstrated that PC is more susceptible to proton beam therapy as opposed to photon therapy. For both scaffold architectures, metastatic PC exhibited higher resistance to both treatment regimens when compared to the non-metastatic PC. Treatment resistance was more pronounced in the multicellular zonal model. More specifically, there was little reduction of cell viability in the zonal model, especially for the cancer mass, indicating the protective effect of the stroma. Our findings show that incorporating zonal/spatial cellular and matrix structures in 3D tissue models lead to better biomimicry of the tumour.

18. Veronika Lachina – Laboratory of molecular and cell biology

TITLE

Investigating the mechanical changes in the fibroblastic reticular network of tumour-raining lymph nodes using a vertex model

ABSTRACT

Lymph nodes provide a specialised niche for immune cell interactions. Fibroblastic reticular cells (FRCs), a crucial stromal component of a lymph node, form a 3-dimentional cellular network that facilitates the immune response. Not only do FRCs produce growth factors, chemokines, and inflammatory cues but they also deposit and enwrap extracellular matrix (ECM) to form a conduit. Laser ablation experiments have shown that the FRC network is under tension, and lymphocyte trapping experiments have demonstrated that lymphocytes generate an outward pressure force. To better understand the effect of these opposing forces on the FRC network, I have adapted a vertex model in which FRCs are represented by connected edges under tension and polygons represent lymphocyte zones which produce an outward pressure force. I am using my model to study how the FRC network changes in a tumour-draining lymph node (TDLN). Preliminary data shows that aSMA is overexpressed in patches in a TDLN and aSMA increases FRC contractility in vitro. Model simulations suggest that a uniform increase in FRC tension isn't disruptive to the network, however, local increases in FRC tension cause the loss of the typical FRC network geometry, which may reduce its ability to support immune cell interactions. Furthermore, TDLN are known to become fibrotic due to ECM over-deposition. I am collecting ex vivo data on the mechanical contribution of ECM to the FRC network, and preliminary data from laser ablation experiments post ECM-digestion, indicate that ECM may act as a viscous material, stabilising the network, and opposing FRC contractility. I have incorporated an ECM parameter into my model, and I plan to investigate how its over-deposition affects the FRC network. Studies have shown that lymph node metastasis is a bad prognostic factor for patients, and it is crucial to understand how changes in TDLNs make them unable to fight cancer.

19. Leticia Meneguello – Cancer Institute/Laboratory for Molecular Cell Biology, UCL

TITLE

Exploring the role of REXO1 in R-loop biology and cellular response to oncogene-induced replication stress

ABSTRACT

The replication stress response is a crucial aspect of cancer biology and treatment. In cancer cells, persistent proliferative signalling can lead to an ongoing state of replication stress (RS), known as oncogene-induced RS. This is a key driver of genomic instability and one of the main events contributing to cancer's onset and progression. To tolerate RS, cells activate a complex cellular response to ensure the completion of genome duplication before mitosis through the coordinated ATR/Chk1/Wee1 axis. Drugs targeting Chk1, ATR and Wee1 exhibit promising potential in selectively targeting cancer cells in pre-clinical models. However, Chk1, ATR and Wee1 also have essential functions for healthy cells, consequently limiting their therapeutic window in clinical contexts. To investigate and explore alternative approaches to target the replication stress response, we carried out a high-content image-based screen to identify new targets involved in RS tolerance in response to oncogene activation. We developed an oncogene-inducible cell system of non-transformed Retinal Pigment Epithelial 1 cells, transformed with stable c-Myc-ER. The induction of c-Myc activity induces replication stress and DNA damage. siRNA Library used included 1357 siRNAs targeting our custom-made list of E2F targets, and a panel of DNA damage proteins and cell cycle regulators. We identified 148 siRNAs with a similar or greater

therapeutic window than our positive control, an siRNA targeting Chk1, for which inhibitors are in clinical trials. Interestingly, we identified the poorly explored protein REXO1 (RNA exonuclease 1), and we have shown that REXO1 depletion increases DNA damage signalling and promotes R-loop accumulation. R-loops are hybrid DNA-RNA structures generated upon transcription perturbation, which are a source of replication stress and genome instability. We are currently exploring REXO1's role in R-loop biology and the cellular response to replication stress.

20. Francesco Moscato – UCL Cancer Institute

TITLE

Computational Modelling of ICB Resistance Mechanisms in Metastatic Melanoma

ABSTRACT

Immune checkpoint blockade (ICB) therapy has revolutionised treatment for metastatic melanoma. By activating the tumour-adjacent immune microenvironment rather than targeting the tumour cells directly, ICB has shown great potential to provide long-term responses in tumours otherwise resistant to traditional lines of therapy. Nonetheless, more than half of melanoma patients treated with ICB do not respond to treatment, raising the need for a better understanding of how to predict and target ICB response. Over a hundred molecular predictors of ICB response have been proposed, such as tumour mutational burden, checkpoint inhibitor ligand expression and T-cell receptor clonality, however, taken individually their predictive power has proven highly variable across patients and cancer types. Executable models provide a means to represent complex cell-to-cell interactions within the tumour microenvironment and mechanistically predict how different tumour mutational backgrounds and gene expression profiles can impact on therapy response. We have built an executable model of the interaction between melanoma cells and cytotoxic T lymphocytes within the tumour microenvironment that recapitulates at a fine molecular detail the events leading to T-cell exhaustion and T-cell re-activation in response to ICB therapy. Using this model, we run in silico CRISPR screens to predict ICB response and highlight potential resistance mechanisms and novel therapeutic strategies to restore ICB response in non-responding tumours. Finally, we validate our predictions using in vivo models.

21. Callum Nattress – Department of Oncology, UCL

TITLE

Multimodal γδ T Cell Cytotoxicity Overcomes Cellular Therapy Reprogramming

ABSTRACT

Colorectal cancer (CRC) is a devastating disease that kills ~700,000 people worldwide annually. Current immunotherapies struggle against both microsatellite stable (MSS) disease and the immunosuppressive CRC tumor microenvironment (TME). Despite these challenges, tumor infiltrating γδ T cells confer a prognostic benefit to CRC patients and can kill cancer via antibody independent cytotoxicity (AIC) and antibody-dependent cellular cytotoxicity (ADCC). We hypothesized that γδ T cells can be exploited as an 'off-the-shelf' anti-CRC biotherapeutic but their complex interactions within the CRC TME need to be elucidated. To explore the patient-, donor-, and mechanism-specific interactions of γδ T cells with CRC, we performed single-cell profiling of >1,000 CRC patient-derived organoid (PDO) and human Vγ9Vδ2 T cell cultures. γδ T cells from multiple donors were used either unmodified or engineered to secrete a modified IL-15 cytokine (stIL15-γδs). The addition of anti-tumour IgG further allowed us to study anti-PDO ADCC, with antigen specificity assessed with antigenKO PDO models. Using 126-plex Thiol Organoid Barcoding in situ (TOBis) mass cytometry (MC) (Qin et al., Nature Methods, 2020) (Sufi and Qin et al., Nature Protocols, 2021), we measured cell-type specific signaling across multiple γδ donors and CRC PDOs, including post-translational modifications (PTMs), cell-state, and immunological phenotype. We found that stIL15-γδs exhibit superior proliferation, purity and viability both in vitro and in vivo. stIL15-γδs demonstrated significant cytotoxicity against all CRC PDOs tested, commonly outperforming standard-of-care chemotherapies even when challenged against our previously-defined chemorefractory MSS patients (Zapatero et al., Cell, 2023). The susceptibility of PDOs to ADCC differs substantially and is not associated with antigen density and %positivity or PDO tumor mutational burden. Minimal differences in ADCC capability were seen between stIL15-γδs donors which were not associated with γδ phenotype or pre- and post-experiment FcγR CD16 expression.

Crucially, we found that stIL15-γδ signaling is reciprocally regulated in a PDO-specific manner, with significant regulation of stIL15-γδ cell-state, PTM signaling and immunological phenotype observed. Increased dysregulation of stIL15-γδs during AIC negatively correlates with PDO cytotoxicity — indicating PDOs negatively reprogram γδ T cellular therapies. However, when γδ T cells engage in ADCC (via anti-tumour IgG), stIL15-γδ signaling recovers, leading to substantial anti-PDO cytotoxicity. Furthermore, stIL15-γδs could perform significant cytotoxicity against all chemoresistant MSS PDOs tested, representing the patient population with greatest unmet clinical need. These results demonstrate that multimodal γδ T cell cytotoxicity can overcome tumor-specific cellular therapy reprogramming.

22. Callum Oddy – Department of Pathology, UCL

TITLE

Studying the development and clonal heterogeneity of gastric intestinal metaplasia (GIM) in human biopsy-derived organoids.

ABSTRACT

Gastric stem cells (GSCs) are responsible for maintaining a healthy gastric epithelium. A single GSC proliferates and differentiates to form a gland, making each gland clonal. Genetic and epigenetic changes can interfere with this tightly regulated process and result in inappropriate activation of pre-malignant phenotypes. Evidence from our team suggests that intestinal metaplasia, the replacement of patches of normal gastric mucosa by pre-malignant intestinal-like epithelium, is driven by individual GSCs switching their normal gastric differentiation lineage to an intestinal-like lineage.

My aim is dissect the evolutionary processes behind metaplasia, which drive further progression to this intestinal precursor and drive further progression to cancer.

At present I have developed a translational pipeline which established patient-matched normal and metaplastic organoids from patients biopsies, totalling 22 organoid lines. Utilising rt-PCR and confocal microscopy I have characterized the organoids, highlighting expression of appropriate gastric/intestinal markers. I have begun methylation analysis of the organoids to study the differentially methylated states between phenotypes. To date, I have illustrated that the organoids can be clustered together based on their methylation profile, suggesting a strong epigenetic influence on phenotype.

Whilst promising progress has been made, in order to answer my aim, several objectives must be met. I will complete the methylation analysis to study differential methylation between the normal and pathological conditions. Using sc-RNA sequencing, I will deeper characterize the organoids, providing information on the transcriptional processes behind GSCs lineage decisions. Finally, using thiol-reactive organoid barcoding in situ (TOBis) and cytometry by time-of-flight (CyTOF) in combination with genetic-editing, the post-translational signalling profile of GIM that could be promoting a cancerous phenotype will be demonstrated.

Together these data will illustrate the strong scientific potential that GIM organoids have to delineate metaplastic evolutionary processes, in addition to providing key evidence for future risk prediction models of gastric cancer.

23. Shi Pan – Research Department of Genetics, Evolution and Environment, UCL

TITLE

Understanding the epithelial-to-mesenchymal transition in cancer with a single-cell language model

ABSTRACT

The epithelial-to-mesenchymal transition (EMT) is pivotal in tumour progression and resistance to treatment, yet its heterogeneity complicates the precise assessment of EMT status of individual tumour cells in different cancer types. Furthermore, while key epithelial and mesenchymal genes driving the transformation are well characterised, other regulators, especially at intermediate stages of the process, are less well understood.

In this study, we employ RNA-seq data from single cells profiled at 0 hours, 8 hours, 1 day, 3 days and 7 days during EMT transformation from xx et al, and leverage a pre-trained single-cell language model (scLLM) to develop a generalisable classifier of EMT status in single cell cancer data. Our method,

scMultiNet, demonstrates an average prediction accuracy of EMT state of 90% AUROC across various cancers. scMultiNet incorporates a simple yet efficient multiplication mechanism and widely considered Parameter-Efficient Fine-Tuning (PEFT) strategy, offering an effective way to adapt the self-supervised pre-trained language model for specific EMT processes. Our approach enables the model to achieve good performance even with limited training data. We further propose a Attention-Driven Expression Significance Index (ADESI), which considers both attention scores from our model and the original gene expression values, to uncover genes that are critical in regulating the entire timeline of EMT transformation. The top regulators uncovered include genes involved in mitochondrial function (e.g., NDUFB10, MRPL51) and oxidative stress response (e.g., PRDX1) suggesting a metabolic reprogramming during EMT. Other genes such as TUBA1B and TUBB, which form microtubules crucial for cell shape and transport during migration, have not been specifically linked with EMT previously. Finally, we employ the derived gene signatures to explore the association of distinct EMT states with survival outcomes and disease recurrence in the METABRIC dataset and find that that patients exhibiting the 8h and 3d EMT signatures, as identified by genes with high attention scores in these categories, showed a notable decrease in survival rates.

In conclusion, scMultiNet exemplifies the effective application of language models in cancer biology research, offering a novel approach to EMT status prediction and identifying clinically relevant gene signatures reflecting the plasticity of the EMT programme.

24. Stephen Patrick – Division of Medicine, UCL

TITLE

Improved Tumour Delivery of Iron-Oxide Nanoparticles for Magnetic Hyperthermia Therapy of Melanoma via Ultrasound Guidance and 111In SPECT Quantification

ABSTRACT

Intro

Magnetic Field Hyperthermia offers a potential route to treat drug-resistant tumours for which current treatment options are limited, such as late-stage melanoma. Yet to be clinically feasible, improved nanoparticle delivery strategies are needed to maximise intratumoural particle delivery and heating, while minimising off-target uptake and damage to surrounding healthy tissue. Quantifying nanoparticle biodistribution is an additional challenge, but necessary to evaluate the performance of improved delivery techniques including ultrasound guidance and controlled infusion rate.

Methods

Tumours were formed in the contralateral rear flanks of (SCID) mice from Human A-375 malignant melanoma cells. Chelate-free, heat-induced radiolabelling was used to attach 111In to a clinical grade 140nm iron oxide nanoparticle (RCL-01, Resonant Circuits Limited), giving radiochemical yields of 96.3% (n = 3, SD = 2.5%). Nanoparticle distribution was quantified following intratumoural injection using SPECT for each delivery strategy: manual injection, ultrasound guided (US) delivery, and US-guidance plus syringe-pump-controlled infusion. For treatment AMF heating was applied for 20 minutes at 5.47 kA/m and 940 kHz, and tumour volume measured pre- and post- treatment with CT. Autoradiography and H+E staining confirmed co-localisation of 111In, iron oxide nanoparticles, and tumour damage.

Results

111In-labelled nanoparticles retained their magnetic properties as measured by SQUID, with labelling stable over 1 week at 37°oC in human serum. Compared to manual injection, ultrasound US guidance together with syringe-pump-controlled infusion significantly improved both nanoparticle concentration within the tumour, and accuracy of delivery as measured by SPECT analysis of tumour and peri-tumour ROIs.

After optimising delivery, AMF heating was applied, with injected melanomas significantly shrinking compared to controls (decrease of 58% vs increase of 64% at 3 days). No significant difference in tumour growth was seen with either AMF heating or nanoparticle delivery alone. Treatment response correlated well with both quantified tumour nanoparticle content, and heating measured with an infrared camera.

Systemic off-target delivery was quantified and extrapolated to clinical doses to predict off-target energy absorbance within safe limits for the main sites of background accumulation.

Conclusion

Ultrasound guidance and controlled infusion rate (10μL/min) were found to give enhanced quantity of nanoparticle delivery compared to manual injection, as well as improved accuracy as measured by tumour to peri-tumour ratio, as compared to manual injection. This resulted in a large, and significant decrease in tumour size post treatment in a model of malignant melanoma, a disease where resistance typically emerges in most advanced stage (IV) patients.

25. Piotr Pawlik – UCL Cancer Institute

TITLE

A novel algorithm for deconvolving cancer allele-specific clone copy number and copy number evolution

ABSTRACT

Tumorigenesis involves the accumulation of both single nucleotide variants (SNVs) and somatic copy number alterations (SCNAs). However, accurately inferring their coevolutionary history from bulk DNA sequencing data remains challenging. We introduce ALPACA (ALlele specific Phylogenetic Analysis of Copy-number Alterations), a novel algorithm that facilitates the practical inference of SNV-SCNA coevolution.

ALPACA formulates the problem as an optimization task, deconvolving the optimal integer copy number profiles for each tumor clone based on bulk tumor copy number data and the inferred phylogenetic tree derived from SNVs. To address the challenges of joint SNV/SCNA inference, ALPACA leverages two key principles:

Leveraging high-mutation burden: In tumors with high mutation rates, all relevant SCNA-containing clones are assumed to be identifiable by their unique SNV mutations. ALPACA thus capitalizes on phylogenetic trees constructed from multi-sample bulk tumor sequencing data using SNVs.

Incorporating multi-sample constraints: The search space for clone-specific copy numbers is restricted by leveraging constraints imposed by multi-sample sequencing data. These constraints include identifying clones present across multiple samples and establishing phylogenetic relationships between clones from different samples.

Furthermore, ALPACA employs parsimony principles and biologically informed constraints to guide the deconvolution process. Clone-level results obtained with ALPACA offer valuable clinical insights and enable novel analyses, such as copy-number signature analysis or temporal ordering of SCNA acquisition.

We demonstrate that ALPACA surpasses current state-of-the-art methods in inferring the copy-number evolution of complex simulated tumors. Applying ALPACA to a large multi-sample cohort of non-small cell lung cancer (NSCLC) from the TRACERx421 study revealed elevated chromosomal instability at metastasis-seeding clones. Additionally, ALPACA identified common patterns of copy number alterations across the genome, characterizing metastatic seeding clones and highlighting their increased SCNA burden compared to non-metastasizing clones.

26. Zofia Piszka – UCL Cancer Institute

TITLE

Studying genomic evolution in colonic cell line models of mismatch repair deficiency

ABSTRACT

Mismatch repair deficiency (MMRd) occurs in ~15% of colorectal cancers (CRC) in a sporadic or familial form (Lynch syndrome). MMRd results in a high burden of single nucleotide variants and indels and microsatellite instability. MMRd CRC demonstrate profound clonal complexity and evolvability under immune selection. High mutational load translates into elevated neoantigen numbers which is thought

to be the basis of their excellent response to immune checkpoint inhibitors (ICIs). However, for reasons yet unclear, ~50% of MMRd CRC do not respond to ICIs. Therefore, improved biomarkers for patient stratification are required.

The aim of my project is to understand genomic differences between MMRd genotypes that likely contribute to the variable clinical outcomes. I used CRISPR-Cas9 to knock out four MMR genes (MLH1, MSH6, MSH3, MBD4) in different combinations in human colonic epithelium cells, thus producing 29 cell lines representing eight clinically observed MMRd genotypes. I established through live-cell fluorescent imaging and flow cytometry that the knockouts did not alter cell doubling time and cell cycle profiles. Western blotting and qPCR revealed a decrease in MSH2 expression following MSH6 knockout. The cell lines were subjected to 3-4 weeks' mutation accumulation period, followed by whole genome sequencing (WGS) at 30x. The sequencing data will be used to derive mutation burdens, rates and signatures for each MMRd genotype. Moreover, combining the WGS data with CUT&TAG experiments and replication timing data from the ENCODE database will provide insight into mutation distribution across the genome. Finally, my cell models offer an opportunity to assess hypermutator adaptability to stress such as temozolomide treatment under highly controlled in vitro conditions. The results of this project will be interpreted together with the organoid work and clinical data from the NEOPRISM trial to yield a holistic outlook on MMRd as a multifaceted genetic phenomenon.

27. Ahmed Rokan – UCL Division of Infection and Immunity

TITLE

The Evolution of a Transplantable Tumour

ABSTRACT

One of the hallmarks of cancer is the ability to evade the host immune system. Remarkably, there are non-human cancers that completely evade the immune system and transmit as clonal allografts. These are known as transmissible tumours. A well-known example is the Canine Transmissible Venereal Tumour (CTVT) whereby the cancerous cell itself is transmitted to the new host, irrespective of the dog leukocyte antigen haplotype. To understand how a mammalian cancer might evolve the ability to escape allogeneic recognition, we have passaged a mouse melanoma cell line from syngeneic C57BL/6 mice into progressively more allogeneic mice. After each passage, we have performed flow cytometry analysis on dissociated tumours and RNA-seq analysis on tumour cells. The results showed a progressive adaptation to evade allogeneic recognition. At the N2 (F2 x BALB/c) passage, the tumour take ratio was low but additional rounds of passaging significantly improved it to a point where these tumours not only were able to grow into N2 mice with a >90% take but also grew in BALB/c mice with around 90% take. Flow cytometry showed increased intratumoural immune infiltrate in the early passages, followed by progressive loss of CD4, CD8 and NK cells in the late passages. RNAseq data indicated that tumour gene expression was changing in response to passaging. In conclusion, these data suggest that our experimental model can successfully evolve tumours that grow irrespective of the MHC haplotype. Our model will provide key mechanistic insights into cancer escape from allogeneic rejection that may be used to blunt organ transplant rejection.

28. Hugh Selway-Clarke – Division of Medicine, UCL

TITLE

In Silico Testing of Hypotheses for the Effect of Smoking on Somatic Evolution in the Healthy Human Lung

ABSTRACT

Recent single-cell genomic analysis of healthy lung tissue (Yoshida et al, Nature 2020) has shown remarkable intra-tissue heterogeneity in the degree of effect smoking has on mutational burden, as well as an expansion of less-mutated basal cell sub-populations after smoking cessation. These two findings suggest potential mechanisms for somatic evolution in the healthy lung, which forms the backdrop for lung cancer formation. Here, we use computational modelling, based on a model of lung homeostasis previously verified by lineage tracing (Teixeira et al, eLife 2013), to assess the ability of these hypotheses to reproduce observations. Applying a Bayesian inference framework to simulations of

basal lung cell populations over the course of patients' lifetimes, we find preliminary evidence for a protected sub-population of basal cells in the lung which are less affected by smoking. The simulations suggest that this protected sub-population, in combination with immune targeting of highly mutated cells being dampened during smoking, can best reproduce the unexpected dynamics seen in the data. With further testing and validation in epidemiological datasets, this mechanistic understanding will allow for better public engagement on smoking and streamline future research into the early detection and prevention of lung cancer.

29. Daniel Shewring – Laboratory for Molecular Cellular Biology, UCL

TITLE

Harnessing the Lymphoid Tissue Niche to enhance anti-tumour immunity

ABSTRACT

Chronic inflammation within the tumour microenvironment (TME) often results in T cell exhaustion, loss of effector functions, and an inability to suppress tumour growth. Recent findings highlight the crucial role of stem-like CD8+ T cells, acting as stable reservoirs that replenish tumour-infiltrating cytotoxic T cells, orchestrating a durable antitumour response. While these cells circulate through tumours, they do not accumulate, cycling back to tumour-draining lymph nodes (TDLNs), indicating dependence on the lymphoid stromal tissue for niche survival factors.

My PhD project aims to examine how the TDLN niche sustains stem-like CD8+ T cell populations during tumour progression. I hypothesise that immune-stromal crosstalk in the TDLN coordinates the release of niche growth factors for stem-like CD8+ T cell survival. Our goal is to manipulate the tumour stroma to enhance the recruitment and retainment of stem-like CD8+ T cells in situ. Comparative analysis of TDLNs to distal lymph nodes reveals gene expression changes affecting key growth factors required by stem-like CD8+ T cells. Flow cytometric analysis indicates small, systemically circulating populations of these cells, while histological examination of primary tumours reveals colocalization with dendritic cell/stromal niches.

To elucidate trafficking kinetic and quantify cell retention in tumours versus lymphoid tissues, we will use a novel photoconvertible reporter mouse model. Temporal labelling of immune cells within TDLNs or tumour sites allows tracking of dynamic trafficking of stem-like CD8+ T cells. Using genetic models, we will conditionally alter gene expression in stromal cells and quantify changes in T-cell trafficking in response to changes in stromal-derived signalling factors. Uncovering the interplay between stem-like CD8+ T cells and their survival niche within tissues will offer potential avenues for targeted manipulation and improved antitumour immune responses.

30. Emmi Suonpera – Institute for Global Health, Centre for Clinical Research in Infection & Sexual Health

TITLE

Screening and early detection to prevent anal cancer (SEPAC): protocol and progress report

ABSTRACT

Background

Limitations of methods for anal pre-cancer screening have prevented their implementation, even among high-risk populations such as men-who-have-sex-with-men (MSM) living with HIV. High-resolution anoscopy (HRA) and biopsy, the gold standard for the detection of anal high grade squamous intraepithelial lesions (HSIL), are too expensive and impractical for primary screening. We aim to develop a screening strategy based on liquid-based cytology (LBC) and a biomarker panel, with HRA confirmation for those who screen positive. The study will complete recruitment at 6 London sites by September 2024.

Methods

The study will determine the sensitivity and specificity of a panel of biomarkers to detect persistent HSIL among MSM with HIV aged >40 (n=1000). All will have anal LBC followed by HRA. Participants with HSIL on HRA/biopsy have repeat examination at 6 months to define presence of persistent HSIL. LBC samples will be assessed for cytology, p16/Ki-67 dual-staining, hrHPV, HPV-E6/E7-ratio, DNA methylation of host/HPV genes. Topographic records and images, and histology will be secondarily reviewed for quality assurance. Baseline clinical data and pre/post screening quality of life will be recorded.

Results

To date, n=557 enrolled and screened; of those with first screen results available (n=518), 161 (31%) had HSIL on biopsy; 325 (63%) were negative. Four suspected cases of early anal cancer were detected of which 2 were confirmed. Twenty-eight (5%) have had repeat examination due to inconsistent initial cytology and histology results. Five withdrew from the study following their 1st HRA examination.

Conclusions

SEPAC is expected to provide further evidence to support the design and implementation of practical screening programmes in selected populations at increased risk of anal cancer.

31. Vithurran Thavarajah – UCL Division of Surgery and Interventional Science

TITLE

Spatial characterisation of an explant model of localised prostate cancer

ABSTRACT

Understanding cancer biology in a manner tailored towards patient cohorts is a challenging concept with a low yield of positive results, owing to traditional research methods of reliance on 2D cultures and animal models that lack complexity and clinical relevance. 3D in vitro/ex vivo modelling has been touted as a feasible way to bridge this gap via tumour reconstruction of critical cell-cell and cell-protein interactions which drive native tumour survival and progression. However, despite a myriad of 3D cancer models being available, none have successfully phased out animal-based research. A reasonable explanation would be that industry demands a model that mimics the native complexity of tumour tissue but is relatively simple to implement with minimal expertise, set up cost and a quick turnaround time from set up to analysis. In literature, patient-derived explant cultures have existed since 1986, claiming the benefits of preserving native cellular spatial organisation, heterogeneity and function. This project involves the characterisation of a 72hr prostate cancer explant gelatin culture using a basic tissue culture protocol to assess the preservation of tissue architecture along with cellular and protein composition. The GeoMx Spatial Transcriptomics platform was utilised to delineate epithelial and stromal-specific expression profiles, elucidating tumour interaction with the surrounding extra cellular matrix. The dissection of region of interest-based profiles across cultured tissue gave further insights into intra tumour heterogeneity and established gradients of molecular expression. Correlating these with tissue architecture information acquired from imaging allowed the identification of spatially refined niches in cellular compositions and how they compare to control uncultured tissue. The spatially-refined characterisation of this explant model helped identify areas where the current culture protocol captured native tissue properties and where improvements were needed.

32. Rebecca Todd – Centre for Behavioural Medicine (Department of Practice & Policy, School of Pharmacy)

TITLE

An introduction to the TRANSFORM and REFORM projects: Addressing racial inequalities in treatment and survivorship for Black patients with prostate or breast cancer.

ABSTRACT

Racial inequalities have been demonstrated to have severe consequences for both prostate and breast cancer, with Black patients often shown to have worse clinical outcomes. One possible contributing factor could be Black patients' access or engagement with treatment. Limited research on this area in the UK currently exists, however, existing studies have suggested Black cancer patients are less likely to take their treatment as prescribed and more likely to stop early. Potential barriers or perceptions could understandably lead to these patients wanting to disengage with treatment, such as culturally specific concerns about side effects and distrust of healthcare systems. Therefore, this is a crucial avenue to explore; if patients can make more informed treatment decisions, it may potentially lead to improved treatment engagement. This is what the TRANSFORM and REFORM projects hope to achieve. Both studies aim to understand and tackle inequalities in treatment and survivorship for Black cancer patients, with TRANSFORM focusing on Black men with prostate cancer and REFORM focusing on Black women with breast cancer. The projects will start with qualitative patient interviews to delve into their experiences of cancer and associated treatment. Quantitative questionnaire studies in NHS clinics will follow, comparing both Black and white patients' engagement with treatment, alongside any relevant associated factors. Questionnaires will include validated measures investigating adherence to treatment, illness and treatment beliefs, physician-patient communication, and perceived discrimination in healthcare. It is hoped that these projects will help to provide better support for Black patients on treatment, by enabling the development of targeted support materials for both healthcare staff and patients. Black voices are historically underrepresented in research, often leading to healthcare practices not being designed with their needs in mind. Consequently, studies such as these are vital to ensuring that Black patient voices are heard and considered when tackling health inequalities.

33. Yuchen Yang – LDH

TITLE

Advancing Early Cancer Diagnosis: The ADEPTS Study for pancreatic cancer and other pancreaticobiliary disease.

ABSTRACT

Early detection strategies for pancreatic cancer have been prioritised by the NHS and UK healthcare providers to improve the persistently poor outcomes linked with late-stage diagnosis. Aligning with these, the Accelerated Diagnosis of neuro Endocrine Pancreatic TumourS (ADEPTS) project was created to establish a liquid biopsy biobank, and accelerate the detection of pancreaticobiliary diseases, by two main arms of research: (i) identifying a set of red flag symptoms, and (ii) validating non-invasive biomarkers and tests. ADEPTS is unique in using symptomatic and healthy cases as control groups simultaneously, avoiding the potential bias caused by inflammatory conditions.

Patient recruitment is conducted at the Royal Free Hospital and UCLH Trusts via endoscopy, oncology, and surgery clinics. ADEPTS aims to recruit 2500 participants by the end of 2024. The study is designed to recruit four main cohorts: pancreatic cancer patients (PDAC and PNET), other pancreatic conditions (e.g. pancreatitis, cystic lesions), symptomatic patients (e.g. biliary and bowel conditions, stones), and healthy participants. ADEPTS collects blood, urine, and recently tissue samples from these clinics which are available for collaborators and a variety of ongoing studies.

The study has recruited 2030 participants so far, including 133 PDAC and 35 PNET patients, more than 400 patients with other pancreatic conditions, and more than 1000 symptomatic patients. The biobank has been established with 1360 serum, 1298 plasma, 1179 urine and 54 tissue samples. Access to clinical information for these patients is also available. A real-time cohort analysis is being conducted regarding age/gender distribution, geographical distribution, diabetic status, BMI status, smoking/drinking factor analysis. Symptom analysis among different cohorts has been performed with 17 common gastrointestinal symptoms.

The ADEPTS biobank is a representative sample of patients coming into London clinics for gastrointestinal symptoms and cancers. This, and the accompanying clinical data, have supported over 10 ongoing studies and collaborations.

34. **Fatimah Zachariah Ali – Division of Surgery and Interventional Science**

TITLE

A platform for quantitative mapping of boron uptake and microdistribution in a preclinical cancer model to inform boron neutron capture therapy (BNCT) drug studies

ABSTRACT

In this study, we focused on refining the delivery of Boronophenylanine (BPA), a widely used boron agent in clinical applications for Boron Neutron Capture Therapy (BNCT). BPA is recognized for its active transport into tumor cells via the L-type amino acid transporter (LAT1) found in malignant cells. However, existing clinical practices fall short in optimizing the 10B microdistribution and intracellular uptake concentration. To discern the influence of drug and cell characteristics on BPA uptake and microdistribution, we innovatively crafted a preclinical spheroid platform. Specifically, colorectal cancer spheroids (HT29 and HCT116) were engineered to emulate hypoxic/normoxic and proliferative/quiescent zones within metastases. Following treatment with clinical-grade 10B-BPA, we subjected these spheroids to meticulous analysis of 10B uptake and microdistribution. Our refined cryo-fixation and cryo-sectioning techniques effectively preserved cellular morphology, ensuring precise 10B localization. Leveraging Nanoscale Secondary Ion Mass Spectroscopy (NanoSIMS), we achieved spatial resolution and semi-quantification of 10B isotopes within cells with exceptional precision. Simultaneously, other isotopes were mapped to delineate cellular structures. Consecutive spheroid sections were stained with Ki67 and HIF1α, complemented by scanning electron microscopy (SEM) to facilitate precise identification of cell morphology. Laser ablation inductively coupled mass spectrometry (LA-ICP-MS) played a pivotal role in delineating intraspheroid 10B distribution, overlaying it onto a widefield image for accurate cell status identification. Our innovative platform facilitated cross-comparison of 10B uptake across diverse cell lines, potentially unveiling normoxic/hypoxic and proliferating/quiescent zones. The findings underscored NanoSIMS' accuracy in mapping 10B distribution within cells, revealing significantly higher signals in treated cells compared to controls. This comprehensive drug uptake and mapping platform provides invaluable insights into optimized BNCT drug solutions, shedding light on the nuanced interplay of boron drug features, incubation parameters, and cell/tumor characteristics on 10B microdistribution and uptake concentrations. Ongoing efforts are directed towards co-localizing intratumoral 10B microdistribution with subsequent biological responses post-neutron irradiation.