Liver cancer is now the third most common cause of cancer-related death worldwide, with a trebling in incidence in the UK in the last 25 years. Our group works at the interface of clinical care and the development of preclinical models to study liver biology. Our focus is to understand dysregulated liver regeneration, particularly during cancer development, with the aim of taking novel therapies from the bench to the clinic to improve patient outcome, both with liver cancer, and those at risk of this devastating disease.

Hepatocytes are the key target for regenerative therapy for patients with liver disease and are the source of most liver cancers (specifically hepatocellular carcinoma - HCC). These cells show immense regenerative capacity, but are also prone to mutations during chronic disease and aging, leading to dysregulated regeneration and cancer formation. A range of specific oncogenic driver mutations have now been identified in HCC. Understanding why, in only some instances, these mutations lead to cancer is central to precision prevention strategies for liver cancer development and may aid the early detection of disease. Similarly, understanding how specific combinations of mutations sustain cancer may provide unique therapeutic strategies which could be applied to precision medicine in HCC.

Current pharmaceutical therapy for HCC is only minimally effective, and currently no therapy is directed to specific molecular forms of the disease. We have developed, and continue to expand a suite of genetically engineered mouse models (GEMMs) of HCC. The GEMMs are designed using the genetic blueprint of different human HCCs. The aim of our lab is to use the GEMMs to understand HCC disease biology and guide human clinical trials to target specific therapies to specific subtypes of HCC.

Transformation of regenerative cells into malignancy - prevention and therapy

We use GEMMs of HCC to track the expansion of the carcinogenic hepatocyte clones as they progress from single cells, into large tumour nodules and spread over months. Using the Institute’s advanced facilities, we are able to track and characterise tumours as they develop using preclinical imaging and molecular analysis. We study how these tumours evolve as they grow and have identified specific pathways that can be targeted to aid removal of early cancer cells or kill specific types of cancer in models of late stage disease (Figure 2). We are aiming to understand whether specific forms of background liver disease, e.g. hepatic steatosis, can be targeted directly and how they impinge upon potential prevention strategies.

We collaborate widely to explore tumour biology using our models. We are dissecting the range of models as part of the CRUK HUNTER Consortium. The consortium’s aim is to create a network for HCC research and develop HCC therapies through improved understanding of immune interactions with this cancer. We are also working with a number of industrial pharmaceutical partners to explore drug repurposing and novel drug development.

Ongoing work targeting cancer is examining combinations of therapies to target growth in HCC. As β-catenin mutations drive proliferation and are emerging also as a resistance pathway to immune checkpoint therapies, we are investigating how the blockade of β-catenin can affect both growth and sensitisation to immunotherapy in this disease subtype. Ongoing work has shown that interactions between immune populations could inhibit successful immune checkpoint anti-cancer therapy in preclinical models of HCC and we are commencing a clinical trial in patients to explore promising drug combinations uncovered in our models. Additionally, we are examining repurposing existing anticancer therapies for subtype specific treatment in HCC. We have shown that different types of HCC responded differently to therapy and that therapies identified in this way could be highly effective both prolonging survival and eradicating tumours. Our aim is to be able to take these therapies into clinical trials, targeting specific therapies to specific tumours for precision medicine in liver cancer.

Hepatocytes can be removed from mice using a gene which is normally expressed in these cells only. These genetically engineered hepatocytes then divide in the absence of the gene, and are then killed using a drug. This drug is then used to target similar cells in patients.

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