

LIVER CANCER, DISEASE AND REGENERATION



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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. This is driven by underlying liver diseases, including those related to obesity and alcohol consumption. Our group works at the interface of clinical care and the development of preclinical models to study liver biology. We believe that understanding how, within an individual, specific mutational combinations drive a liver cancer will allow us to target that tumour with precision medicine. We want to be part of improving outcomes for these patients, both in Scotland and across the globe.

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 pharmacological therapy for HCC is only minimally effective, and no therapy is currently 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 (Figure 1). 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

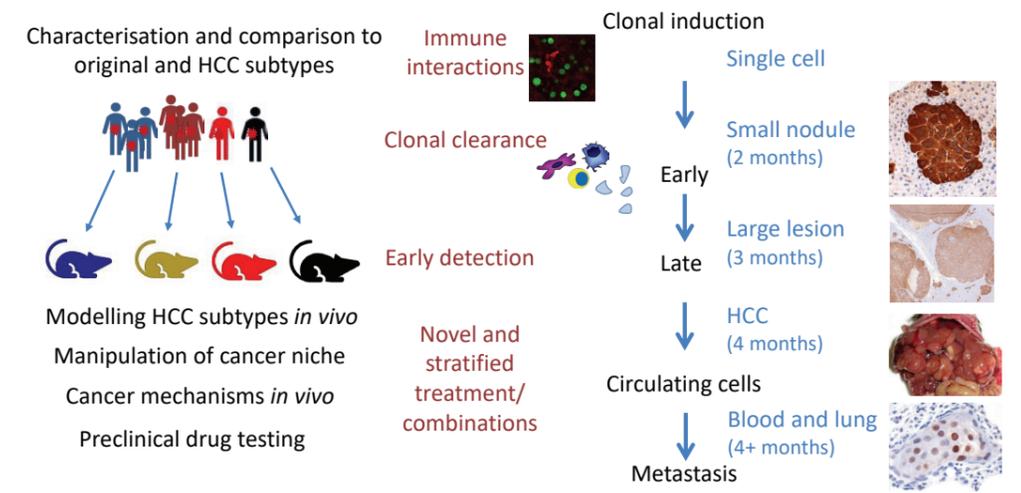
We use GEMMs of HCC to track the expansion of the carcinogenic hepatocyte clones as they progress from single cells, into large tumour nodules and spread to distant sites over months. Using the Institute's advanced facilities, we are able to track and characterise tumours as they develop using preclinical 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 a clinical trial is underway 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 specific therapies identified in this way

Figure 1
Human HCCs can be grouped into different functional and genetic subclasses. We are mimicking the genetic alterations in human HCC subclasses using *in vivo* models in the mouse. Our strategy is to induce clonal hepatocytes and then follow the clones as they develop into metastatic HCC. We aim to dissect and then target the vulnerable mechanisms critical for tumour growth and survival. We focus on stratified therapy for advanced HCC and precision disease prevention taking advantage of senescence in early clones to remove these premalignant cells.



could be highly effective both prolonging survival and eradicating tumours. Our aim is to be able to take these therapies into further clinical trials, targeting specific therapies to specific tumours for precision medicine in liver cancer.

Early detection of hepatocellular carcinoma

Deaths from liver cancer are likely to continue to increase until we are able to identify people at risk of liver disease and HCC, prevent their disease and provide effective rescue therapies for those detected with later stage disease. Using large patient cohorts we are studying how we can improve the use of serum biomarkers to identify patients at risk of liver cancer. This includes work within the CRUK Scotland Centre and a CRUK programme grant, together with the Zanivan lab, collaborating across the UK to uncover novel biomarkers. We hope to provide a rationale for

potential inclusion of these biomarkers in routine NHS practice. We already collaborate with experts in public health and statistics to gather and analyse additional data collected from across Scotland with the aim of making screening tests more accurate. We are very excited about the prospect of working with an industrial partner to explore whether changing the way we do liver tumour surveillance in patients, replacing ultrasound with a state-of-the-art MRI scan, could improve early disease detection. The aim is that through catching and treating these cancers early, and combining this with new and more targeted, therapy we can provide better opportunities and outcomes for patients with liver cancer.

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Figure 2
Cancer prevention in preclinical models by targeting early tumour clones.

We are able to explore specific vulnerability of individual liver cancer subtypes. We have identified pathways which are specifically activated in early disease. When we apply therapies to early disease, we are able to reduce the numbers of cancer clones that become established and improve survival in our multifocal cancer models. Alternatively, using drug screening approaches, we have identified a class of compounds already in clinical use in other forms of cancer which synergise with current HCC therapy to promote highly effective tumour regression in one specific subtype of our models representing approximately 1 in 3 liver tumours.

