Liver cancer is the fourth most common cause of cancer-related death worldwide and is increasing at alarming rates, trebling in the UK in the last 25 years. Working at the interface between clinical care in the NHS and the development of preclinical models to study liver biology, the focus of my group is to understand dysregulated liver regeneration during cancer development with the aim of developing therapy to improve outcomes for patients 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 tremendous 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 been identified in HCC. Understanding why in only a fraction of instances these mutations will lead to cancer formation is central to precision prevention strategies for liver cancer development and can 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 currently no therapy is designed to target molecular forms of the disease. We have developed, and continue to expand, a suite of genetically engineered mouse models (GEMMs) of HCC to study how hepatocytes escape the normal controls governing regulated regeneration. The GEMMs are designed using the genetic blueprint of different human HCCs and aim to identify novel therapeutic targets. The long-term 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.

Mechanisms controlling hepatocyte proliferation
Many pathways control liver proliferation and are dysregulated in HCC. One exemplar is the Wnt/beta-catenin signaling pathway, which is crucial for establishing and maintaining the liver. Activation of the Wnt pathway is sufficient to cause hepatocytes to divide and the liver to grow. Nonetheless, this activation is itself insufficient to lead to tumour formation. A reason for this disconnection between hyper-proliferation and cancer is that upon pathway activation, anti-proliferative pathways are also engaged, preventing perpetual growth. These pathways also engage the immune system and can promote the clearance of potentially malignant cells.

We are investigating numerous signalling pathways in HCC, and how they might be controlled therapeutically. The process of preventing proliferation may result in a state of permanent cell cycle arrest known as senescence. Senescence leaves many of the functional abilities of the hepatocyte preserved but renders them incapable of participating in regeneration. In severe liver injury we described how senescence occurs in response to injury and activates immune cells (Fig. 1). Ongoing work suggests senescent hepatocytes are dynamically altered in their mechanisms of protein production and their interaction with their environment.

Transformation of regenerative hepatocytes into malignancy
We have developed a number of models of HCC utilizing combinations of targeted cancer drivers in a clonal population of hepatocytes based upon the genetic changes most frequently occurring in human HCCs to create avatars-like models of human cancers (Fig. 2). We are then able track the expansion of the altered hepatocyte clones as they progress rapidly from single cells into large nodules and within months into HCC. These tumours model human disease well, including spread (metastasis) to other organs and responses to therapies. Using the CRUK Beatson Institute’s advanced facilities, we are able to track and characterise tumours as they develop using a combination of preclinical imaging and molecular analysis. We study the evolution of tumours as they grow from a single transformed cell with a distinct phenotype to a tumour with a different phenotype. Our aim is to map the evolution of the tumours and test therapies aimed at preventing tumour initiation, expansion and metastasis. We are dissecting these models in collaboration with the CRUK HUNTER Consortium (https://research.ncl.ac.uk/hunter/). This consortium’s aim is to create a network for HCC biomedical research and develop innovative HCC therapies through improved understanding of immune interactions with this cancer.

Ongoing work targeting cancer is examining combinations of therapies to target growth and senescence in HCC. As beta-catenin mutations drive proliferation and are emerging also as a resistance pathway to immune checkpoint anti-cancer therapies, we are investigating how the blockade of beta-catenin can affect both growth and senescence in immunotherapy in this disease subtype. Ongoing work has shown that interactions between immune populations can inhibit successful immune checkpoint anti-cancer therapy in preclinical models of HCC, and we aim to translate this with a clinical trial shortly. Using a pipeline of drug identification, we are examining repurposing existing anti-cancer therapies for subtype-specific treatment in HCC. We have shown that different types of GEMM respond differently to therapy and that therapies identified in this way can be highly effective in the GEMMs at both prolonging survival and eradicating tumours.

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 rescue therapies for those detected with late-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. We hope to provide a rationale for inclusion of these biomarkers in routine NHS practise to facilitate the early treatment and cure of HCC. We are collaborating with experts in public health and statistics to gather and analyse additional deep-sequenced data from across Scotland and have already shown that applying novel statistical analysis of dynamic changes in serum biomarkers for individual patients can detect HCC in its early forms and make even the most advanced screening tests more accurate. With the integration of additional clinical variables and other markers, we aim to improve the accuracy of this approach and move towards clinical trials.

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