Oncogenic signalling profoundly alters how cells respond to their environment, typically putting tumour cells under tremendous pressure to reconcile conflicting cues. For example, tumour cells must re-organise their metabolic pathways to balance competing needs for biosynthetic precursors with energetic homeostasis, commonly while surviving in a milieu of limiting oxygen and nutrients.

Our overarching hypothesis is that oncogene-induced biological perturbations can be exploited for cancer therapy, even in the absence of direct suppression of driver oncogenes. We use deregulated MYC as our paradigm oncogene coupled with a mixture of candidate and RNA-based approaches to identify induced vulnerabilities in vivo and in vitro, and are actively exploring several strategies for selective elimination of cells that overexpress MYC.

MYC in cancer
Overexpression of the transcription factor MYC occurs in a huge number of human cancers, arising from almost every tissue type. In many in vivo settings, MYC overexpression is sufficient to initiate or exacerbate tumourigenicity and MYC is therefore typically required to sustain the cancerous phenotype. A successful therapeutic strategy that exploits MYC overexpression is likely to have a tremendous impact on human health.

Our lab has targeted MYC and MYC-related vulnerabilities in a number of cancer models across epithelial and mesothelial cell systems. We have developed mouse models of epithelial and mesothelial cancer and leveraged mathematical and computational tools to guide our experimental design. Recent work has highlighted the importance of MYC overexpression in tumourigenesis and progression of a number of cancer types.

The main strategy we have pursued is to target MYC and KRAS in mutual pathways, exploiting the known oncogenic cooperation between these two drivers. By targeting MYC and KRAS, we have identified a variety of vulnerabilities in these pathways, including those related to the citric acid cycle. The energetic strain that MYC puts on the cell can promote aerobic glycolysis and glutamine metabolism, which are hallmarks of cancer metabolism.

Suppression of NUAK1 thus impairs the ability of MYC-overexpressing cells to respond to declining ATP production. Importantly, the AMPK-related kinase AKT/Nuak1 is also required for maintenance of ATP homeostasis in cells wherein MYC is overexpressed. NUAK1 plays a specific role in MYC-dependent activation of AMPK and also maintains mitochondrial respiratory capacity. Suppression of NUAK1 thus impairs the ability of MYC-overexpressing cells to respond to declining ATP levels while simultaneously depriving cells of ATP-generating capacity, suggesting that suppression of NUAK1 may be an effective means to selectively kill cancer cells with high levels of MYC expression.

Oncogene cooperation during lung cancer progression
Lung cancer remains one of the deadliest forms of cancer worldwide, accounting for some 15% of all cancer-related deaths, and the incidence of lung cancer is on the rise, especially in the increasingly industrialised and densely populated cities of emerging economies. Poor prognosis arises in large part from the combination of late disease detection and limited matching of patients with emerging targeted therapies. We have found that modestly elevating MYC levels in a KRAS-driven model of lung cancer is sufficient to drive progression to metastatic disease. This progression arises in part through increased transcription of the coiled-coil protein family ligands. We have identified a requirement for signal transduction through the ERBB receptor tyrosine kinase network for both establishment and maintenance of KRAS-mutant lung cancer. Our data suggest that KRAS-driven tumours actively seek ways to amplify signalling through the RAS pathway in order to sustain the tumour phenotype. As there are presently no clinically proven inhibitors of KRAS, our observation raises the exciting possibility that simultaneously inhibiting signaling components upstream and downstream of KRAS with existing therapeutic agents may benefit lung cancer patients whose disease is driven by mutant KRAS.

Inflammation and genetics of mesothelioma
Mesothelioma is a lethal tumour of the lining of the chest cavity that arises in people chronically exposed to asbestos. There are no effective therapies and patient survival is typically less than 15 months from diagnosis. My lab has teamed up with respiratory physician Kevin Blath to build an international network of clinicians and researchers, with the goal of improving patient outcomes for this dreadful disease. We have developed a new mouse model that will enable us to investigate the interplay between asbestos-driven chronic inflammation and the major mutations that are commonly found in human mesothelioma. Significantly, intraperitoneal injection of asbestos dramatically accelerates onset and severity of mesothelioma in our mice, even after homozgyous deletion of 3 major tumour suppressor genes, indicating that chronic inflammatory infections contribute to the development of mesothelioma beyond the acquisition of mutations.

This observation suggests that patients may benefit from interventions that aim to reduce inflammation, in addition to those directly targeting the tumour population.

Major developments in 2021
Although COVID-19 continued to limit benchwork throughout 2021, my lab successfully achieved success in securing competitive funding from multiple sources. I led a successful team bid for programme funding from the CRUK Early Detection and Diagnosis Committee, securing over £2.1m in funding for IMMEDI-Meson (Integrated Analysis in Mouse and Man for Early Detection of Mesothelioma), bolstered by an additional £500K from Asthma UK/British Lung Foundation for DEBIT-Meso (Differential Gene Expression in Bystander Transcripts). This funding will enable a deep-dive characterisation of the cellular and molecular content of patient and mouse model pleural effusions to identify biomarkers that may either predict progression to mesothelioma from benign disease or more accurately diagnose occult malignancy from seemingly benign disease. This work is fully integrated within the PREdict-T-Meson umbrella group led by Kevin Blath by maximising the potential for rapid translation of our research into the clinic. In a separate project, in collaboration with CRUK Translational Discovery Labs and Merc Pharmaceuticals was extended for an additional year. Additionally, contributed as a named co-Investigator and co-author on successful team bids for the CRUK Scotland Centre and the MRC National Mouse Genetics Network Cancer Cluster.

Our development of mouse models of Mesothelioma started to yield dividends with our first major publication in this field. In collaboration with the Wills, Macfarlane, Le Quereins lab of MRC Toxicology, we demonstrated a potential for rapid translation of our research into the clinic. In a separate project, in collaboration with CRUK Translational Discovery Labs and Merc Pharmaceuticals was extended for an additional year. Additionally, contributed as a named co-Investigator and co-author on successful team bids for the CRUK Scotland Centre and the MRC National Mouse Genetics Network Cancer Cluster.

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