The immune system can exert both anti- and pro-tumour activity, therefore, understanding the role of immune cells in the cancer microenvironment is of critical importance. Our lab uses cutting-edge light microscopy and other techniques to investigate the spatiotemporal dynamics of immune cells in cancer.

The immune system has been implicated in several ways. Alveolar capillaries are of particular interest in the lung with its huge surface area, extensive capillary network and role in gas exchange. In addition, the lung is a major lymphoid organ where lymphocytes circulate and can be influenced by interactions with alveolar macrophages, contributing to the inflammatory milieu in a number of ways. Alveolar macrophages can phagocytose, degranulate and the recently described process of NETosis, neutrophils can contribute to the inflammatory milieu in a number of ways. Neutrophils can produce and consume chemokines, cytokines and growth factors and can modify the extracellular matrix. Additionally, the accumulation of apoptotic neutrophils and their subsequent clearance is thought to directly contribute to anti-inflammatory programmes at the end of acute inflammatory responses. Taken together, these features mean neutrophils have the potential to both antagonise and promote tumour progression.

Neutrophils are crucial in the process of lung and liver metastasis. Because of this diversity of actions and importance in the host defence, we need more mechanistic detail in order to interact with neutrophils in a way that would inhibit cancer but not leave the patient at risk of serious infection. Neutrophils can be regulated by – and can regulate the function of – other immune cells, so an important goal is to see how a number of different cell types simultaneously glean more information about the way that they interact and to uncover potential pathways to modify.

By looking across multiple, relevant, cancer models, we aim to do three things: 1) uncover general mechanisms by which immune cells and their regulation contribute to the cancer microenvironment, 2) uncover cancers with the strongest or most manipulable interaction with particular immune cells, 3) monitor how treatment with immunom- and chemotherapeutic agents affects leukocyte localisation to develop better treatment schedules and combinations. We continue to collaborate with several groups here at the Institute to investigate this in state-of-the-art pre-clinical models. We were excited to contribute to a major collaboration (Leo Carlin as co-senior author with Tom Bird, Owen Sansom, and Derek Mann) that addressed the role of neutrophils in the response of hepatocellular carcinoma on a non-alcoholic steatohepatitis background (NASH-HCC) to immunotherapy. In this context neutrophils were thought to be tumour promoting via their suppression of anti-tumour immunity. We found that by targeting the major neutrophil chemokine receptor CCR2, we could make our models of NASH-HCC vulnerable to immune checkpoint inhibitors. Intriguingly, there were more, rather than fewer neutrophils in the tumours, but they had changed phenotype, suggesting the possibility of reprogramming neutrophil activity in the tumour microenvironment (Leslie, Mackey, Jamesson et al., Gut 2022). We were excited to see the opening of a clinical trial based on this combination (CUBIC) and also received funding via a CRUK programme grant renewal to continue this highly productive collaboration.

Publications listed on page 103

J Clin Invest, and recent work has demonstrated that neutrophils actually benefit cancer spread in the process of lung and liver metastasis. Because of this diversity of actions and importance in the host defence, we need more mechanistic detail in order to interact with neutrophils in a way that would inhibit cancer but not leave the patient at risk of serious infection. Neutrophils can be regulated by – and can regulate the function of – other immune cells, so an important goal is to see how a number of different cell types simultaneously glean more information about the way that they interact and to uncover potential pathways to modify.

By looking across multiple, relevant, cancer models, we aim to do three things: 1) uncover general mechanisms by which immune cells and their regulation contribute to the cancer microenvironment, 2) uncover cancers with the strongest or most manipulable interaction with particular immune cells, 3) monitor how treatment with immunom- and chemotherapeutic agents affects leukocyte localisation to develop better treatment schedules and combinations. We continue to collaborate with several groups here at the Institute to investigate this in state-of-the-art pre-clinical models. We were excited to contribute to a major collaboration (Leo Carlin as co-senior author with Tom Bird, Owen Sansom, and Derek Mann) that addressed the role of neutrophils in the response of hepatocellular carcinoma on a non-alcoholic steatohepatitis background (NASH-HCC) to immunotherapy. In this context neutrophils were thought to be tumour promoting via their suppression of anti-tumour immunity. We found that by targeting the major neutrophil chemokine receptor CCR2, we could make our models of NASH-HCC vulnerable to immune checkpoint inhibitors. Intriguingly, there were more, rather than fewer neutrophils in the tumours, but they had changed phenotype, suggesting the possibility of reprogramming neutrophil activity in the tumour microenvironment (Leslie, Mackey, Jamesson et al., Gut 2022). We were excited to see the opening of a clinical trial based on this combination (CUBIC) and also received funding via a CRUK programme grant renewal to continue this highly productive collaboration.

Publications listed on page 103