The immune system can exert both anti- and pro-tumour activity, depending on many factors. 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 dynamics of immune cells in cancer.

The immune system has been implicated in almost every stage of cancer development, from initiation and growth, to recurrence, invasion and metastasis. The role of immunity in cancer is complicated as immune cells can kill cancer cells and stabilise the primary tumour to help prevent spread but they can also produce factors that suppress anti-cancer immunity and benefit tumour growth and dissemination. The immune compartment of cancer is composed of the resident immune cells of the tissue and leukocytes that infiltrate from the circulation. The development of the cancer immune environment is inherently dynamic, and the processes that regulate immune cell recruitment and function are not well understood. Recent success in directing and strengthening the immune system’s anti-cancer functions (e.g. tumour infiltrating lymphocyte (TIL) therapy and immune checkpoint inhibition) highlight the potential for new therapies that can come from a better understanding of how immune cells are regulated. However, these strategies do not work for all cancers or all patients.

Specialised vasculature and leukocyte dynamics

Our group has a particular interest in the lung and the liver, both as sites of primary tumour development and as targets of metastasis. The extensive capillary network of the lung is unusual in several ways. Alveolar capillaries are of exceptionally small diameter (~5µm) and are in such close proximity to external mucosa that they share a basement membrane with the epithelium. In contrast to other organs, pulmonary capillaries are thought to be a major site of leukocyte extravasation, with markedly different mechanisms to the general paradigm of leukocyte recruitment. The liver is also a highly specialised immune environment consisting of a network of specialised blood vessels with a huge surface area. The liver’s importance in homeostasis makes particular requirements for the way that immunity must function in this organ. Localisation and regulation of leukocytes within the pulmonary capillaries and liver sinusoids is not fully described or well understood.

The work of several groups has suggested that neutrophils are important in onco-immunology, and a high neutrophil-to-lymphocyte ratio is associated with poorer prognosis in many advanced cancers. Neutrophils are crucial in many anti-microbial and tissue damage reactions and play a key role in initiating the host immune response to infection. In addition to potent effector mechanisms, including phagocytosis, degranulation 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 (which also produces and modulates matrix degrading – chemoactive products of matrix degradation). 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 contribute to both tumour antagonism and tumour-promoting inflammation, and recent work has demonstrated that neutrophils actually function in live ex vivo lung slices. Neutrophil motility quantified in live ex vivo lung slices from control and pancreatic cancer models. By looking across multiple, relevant cancer models, we aim to do two things: 1) uncover general mechanisms by which immune cells and their regulation contribute to the cancer microenvironment; and 2) uncover cancers with the strongest or most manipulable interaction with particular immune cells. We continue to collaborate with several groups here at the Institute to investigate this in state-of-the-art models. For example, we are currently investigating the mechanisms that regulate neutrophil dynamics in lung cancer by imaging large areas of optically cleared tissue in a lung adenocarcinoma model (Fig 1A; F. Fercoq and X. Raffo in collaboration with Daniel Murphy’s lab); metastasis to the lung from pancreatic cancer using a combination of high-content imaging and analysis in fixed lung tissue and live ex vivo lung tissue imaging in precision-cut lung slices (Fig 1B,C; A. McFarlane in collaboration with Jim Norman’s and Jennifer Morton’s labs) and metastasis to the liver from colorectal cancer directly in situ by intravitral microscopy (Fig 1D; J Mackey and R. Jackstadt in collaboration with Owerri Sansom’s lab).

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Figure 1

Investigating leukocyte dynamics in cancer using multiscale advanced light microscopy.

A) 3D segmentation and reconstruction of tissue features from an optically cleared model lung adenocarcinoma imaged by multiphoton microscopy.
B) Localisation and quantification of neutrophil localisation in the lung of pancreatic cancer model. i) Cells and anatomical features are segmented and their relationships quantified in whole lung slices.
C) Neutrophil motility quantified in live ex vivo lung slices from control and pancreatic cancer models.
D) Still from an intravitreal timelapse of neutrophil dynamics around a colorectal liver metastasis. All images acquired with the help of the Beatson Advanced Imaging Resource.