Colorectal cancer (CRC) is the second most common cause of cancer related death in the western world. Disease that is localised to the colon can be treated with surgery. Despite this, 40% of patients will suffer from disease recurrence. Recurrence usually occurs at sites distant from the colon, most commonly liver and lungs, and is called metastatic disease. Most patients who die from colorectal cancer do so due to metastatic disease. Unfortunately, treatment options remain limited for these patients, with surgery remaining the best strategy if disease is diagnosed early. My team is focused on understanding why disease recurs following surgery, the patterns of recurrence and whether the disease can be subtyped to permit development of better therapies for patients.

**Assessing the heterogeneity of colorectal liver metastases**

Assessment of human colorectal liver metastases (CRLM) suggests that different subtypes exist. These can be detected histologically and separated into ‘immune’, ‘stromal’ and ‘canonical’ using transcriptomic analysis (Pirola et al., 2018, Nature Comms). Patients from the immune subgroup do very well following surgical resection and can be cured of their disease. It is likely these patients may also respond to commonly used immunotherapies, however, this as yet still to be clearly elucidated. We are making efforts to accurately subtype the disease in our patients (Figure 1) and we have partnered with Nanostag to assess the heterogeneity of these subtyped tumours.

We have identified that CRLM in certain patients are profoundly immunosuppressed with very few activated T cells evident within the microenvironment of these tumours (Figure 1). We observe higher numbers of myeloid cell populations in promoting neutrophil function at metastatic sites (Coffelt et al., 2015 Nature); that neutrophils were key cellular regulators of the metastatic microenvironment in CRC (Jackstadt et al., 2019, Cancer Cell), regulating an immunosuppressed microenvironment as we observed in patients with very poor outcomes. However, the mechanism by which these neutrophils functioned to progress metastatic disease and how to manipulate them in vivo remains unknown. We have performed RNA sequencing of neutrophils from sites within our ‘1P’ model and found differentially expressed genes within neutrophils associated with metastases (Figure 3). We are currently investigating whether inhibition of specific genes expressed by neutrophils in vivo influences their behaviour and progression of metastases. Others have shown cooperation of gamma delta T cell populations in promoting neutrophil function at metastatic sites (Collett et al., 2015 Nature), that production of transferin by neutrophils supports metastatic cells (Liang, Li, & Ferrara, 2018 PNAS); the role of neutrophil extracellular traps in awakening dormant tumour cells. (Albrengues et al., 2018, Science), and that neutrophils can accompany tumour cells to metastatic sites and help them establish (Szczerba et al., 2019, Nature). Our previous work together has revealed that neutrophils have key cellular regulators of the metastatic microenvironment in CRC. Using orthotopic transplantation techniques we can mimic human disease to provide a model of stromal rich metastasis for assessment of anti-metastatic therapies in vivo. Our previous work together has revealed that neutrophils were key cellular regulators of the metastatic microenvironment in CRC (Jackstadt et al., 2019, Cancer Cell), regulating an immunosuppressed microenvironment as we observed in patients with very poor outcomes. However, the mechanism by which these neutrophils functioned to progress metastatic disease and how to manipulate them in vivo remains unknown. We have performed RNA sequencing of neutrophils from sites within our ‘1P’ model and found differentially expressed genes within neutrophils associated with metastases (Figure 3). We are currently investigating whether inhibition of specific genes expressed by neutrophils in vivo influences their behaviour and progression of metastases. Others have shown cooperation of gamma delta T cell populations in promoting neutrophil function at metastatic sites (Collett et al., 2015 Nature), that production of transferin by neutrophils supports metastatic cells (Liang, Li, & Ferrara, 2018 PNAS); the role of neutrophil extracellular traps in awakening dormant tumour cells. (Albrengues et al., 2018, Science), and that neutrophils can accompany tumour cells to metastatic sites and help them establish (Szczerba et al., 2019, Nature). Our previous work together has revealed that neutrophils have key cellular regulators of the metastatic microenvironment in CRC (Jackstadt et al., 2019, Cancer Cell), regulating an immunosuppressed microenvironment as we observed in patients with very poor outcomes. However, the mechanism by which these neutrophils functioned to progress metastatic disease and how to manipulate them in vivo remains unknown. We have performed RNA sequencing of neutrophils from sites within our ‘1P’ model and found differentially expressed genes within neutrophils associated with metastases (Figure 3). We are currently investigating whether inhibition of specific genes expressed by neutrophils in vivo influences their behaviour and progression of metastases. Others have shown cooperation of gamma delta T cell populations in promoting neutrophil function at metastatic sites (Collett et al., 2015 Nature), that production of transferin by neutrophils supports metastatic cells (Liang, Li, & Ferrara, 2018 PNAS); the role of neutrophil extracellular traps in awakening dormant tumour cells. (Albrengues et al., 2018, Science), and that neutrophils can accompany tumour cells to metastatic sites and help them establish (Szczerba et al., 2019, Nature).