IMMUNE CELLS AND METASTASIS

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The spread of cancer (or metastasis) from its primary site of origin to distant locations is the major cause of death among cancer patients. Our lab is interested in the involvement of immune cells in metastasis, with the intention of designing novel immunotherapies for patients with metastatic disease.

This was our first full year at the Institute. We expanded our team with the addition of three new people, because we were fortunate to receive funding from the Naito Foundation of Japan, the Wellcome Trust, Pancreatic Cancer UK, the Royal Society and Tenovus. During this year, we continued to build a research programme focused on the role of immune cells in metastasis. We are particularly interested in γδ T cells, which are a rare population of T cell receptor–expressing cells that drive breast cancer metastasis by controlling the function of neutrophils. Our ultimate goal is to understand how γδ T cells participate in metastasis and to uncover the mechanisms regulating the behavior of these cells so that novel immunotherapies may be developed for patients with metastatic disease. While most of our work uses mouse models of breast cancer, new collaborations at the Institute over the past year have allowed us to expand our questions about γδ T cells to other cancer types. Looking forward into 2018, the data generated from these collaborations will lead to new insights into metastasis-associated γδT cell biology.

γδ T cells in breast cancer

In the breast cancer setting, one outstanding question regarding γδ T cells is how these cells are regulated. Our investigations to address this question led us to the NKG2D receptor. We have found that pro-metastatic γδ T cells express high levels of NKG2D. This receptor is normally associated with NK cells; it recognises cancer cells and induces NK cell killing mechanisms. So we were intrigued by the observation that pro-metastatic cells express a receptor that mediates cancer cell killing, and we are currently exploring the function of NKG2D on γδ T cells. We are also interested in developing new treatment strategies for metastatic breast cancer. For these studies, we are using a model of BRCA1-deficient mammary cancer. Tumours arising in these mice contain very few myeloid and lymphoid cells when compared to BRCA1-proficient tumours. Current efforts are underway to boost T cell infiltration into these immunologically 'cold' tumours. All our work in breast cancer is done in collaboration with Karen Blyth and her team.

γδ T cells in colorectal cancer

γδ T cells are a major immune cell population in normal gut tissue, but whether these cells play a role in colorectal cancer initiation and progression is not well understood. Together with Owen Sansom and his lab, we are determining the importance of γδ T cells in several mouse models that recapitulate distinct molecular subtypes of colon cancer. We are crossing γδ T cell–deficient (*Tcrd*$^{-/-}$) mice with these various models, where we will investigate tumour formation and metastasis. Interestingly, we have found that colorectal tumours lose expression of an epithelial-derived molecule, called BTNL1, which is required for the maintenance of Vγ7-expressing γδ T cells. BTNL1 tethers Vγ7 cells specifically to the gut; therefore, Vγ7 cells are likely to be absent from these BTNL1-deficient tumours. We are working with the hypothesis that the loss of Vγ7 cells potentiates tumour formation. This work is funded by a Wellcome Trust Seed Award and is being done in collaboration with Adrian Hayday (Francis Crick Institute).

γδ T cells in pancreatic cancer

Our lab was fortunate to be part of the Pancreatic Cancer UK Future Leaders Academy in 2017, which allows us to investigate γδ T cells in this deadly disease. Our long-term goal for this project is to develop γδ T cell–specific immunotherapies for pancreatic cancer. In collaboration with Jen Morton and her team, using mouse models of metastatic pancreatic cancer, we have found that γδ T cells are virtually absent from normal mouse pancreatic tissue, but they are prevalent in pancreatic ductal carcinoma. The preferential tropism of γδ T cells to tumour tissue opens a window of opportunity to inhibit the migration of these cells and determine whether tumour progression and metastasis is slowed. Our research efforts will focus on the trafficking of tumour-infiltrating γδ T cells, as well as their communication with neutrophils.

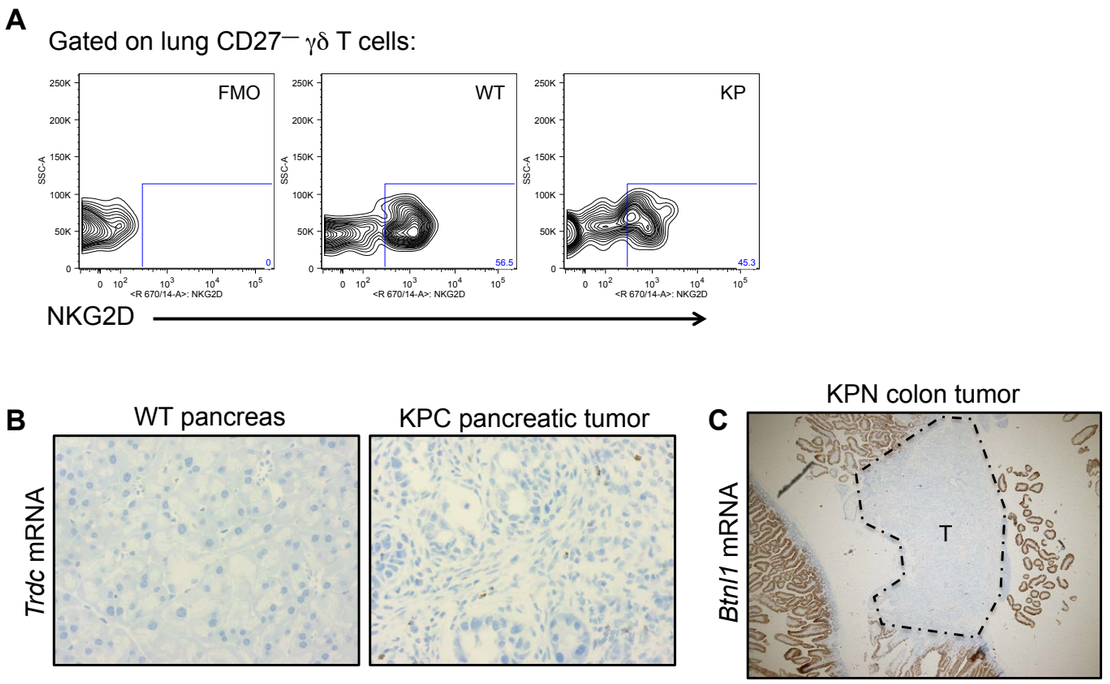

Figure 1
γδ T cells in mammary, pancreatic and colon cancers
(a) Flow cytometry analysis of NKG2D expression on CD27- γδ T cells isolated from the lungs of wild-type (WT) mice or mammary tumour–bearing *K14-Cre;Trp53F/F* (KP) mice. **(b)** γδ T cell abundance in pancreas of WT mice and pancreatic ductal adenocarcinoma of *KrasG12D;Trp53R125H;Pdx1-Cre* (KPC) mice as determined by RNAscope for the Trdc transcript. **(c)** Btnl1 mRNA expression in gut tissue from *Villin-CreER;KrasG12D;Trp53F/F;Nicd1LSL/+* (KPN) mice as determined by RNAscope. T = tumour

γδ T cells in other cancer types

Over the coming year, we will make use of the unique mouse models at the Institute to address the function of γδ T cells in various cancer types. Together with Tom Bird, we will investigate γδ T cells in hepatocellular carcinoma, and Daniel Murphy and his lab will help us study γδ T cell function in lung cancer.

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