IMMUNE CELLS AND METASTASIS

Group Leader
Seth Coffelt

Scientific Officer
Heather Spence[1]

Research Scientists
Nadia Iqbal[2]
Abhiram Charan Tej Mallu[3]
Natalie Phinney[4]
Toshiyasu Suzuki[5]
Robert Wiesheu[4]

Graduate Students
David Hamilton[6]
Regan Leaver[7]
Federico Lupo[1]
Febby Ningsih[8]

Interns
Pablo Casado Alonso[9]
Elizabeth Thompson[9]
Lewis Pennie[9]
Vardhini Rajkumar[9]
Nuria Serrano Ribes[10]

[1]CRUK Career Establishment Award
[2]CRUK Discovery Programme Award
[3]Worldwide Cancer Research
[4]MRC Programme Award
[5]CRUK Biology to Prevention Award
[6]NHS Lanarkshire
[7]Medical Research Scotland
[8]Indonesian Government Scholarship
[9]University of Glasgow
[10]University of Barcelona

Our lab focuses on a type of immune cell, called a gamma delta (γδ) T cell. γδ T cell refers to a variety of cell subsets with distinct properties and anatomical locations. There are γδ T cell subsets that kill cancer cells and other subsets that promote cancer progression. Our lab has ongoing projects aimed at understanding when and where these diverse γδ T cell subsets are important. We are exploring the involvement of γδ T cells in breast, colon, liver, and pancreatic cancers. In 2024, our lab published one research article, one commentary, one review article, and we contributed data to four collaborative studies led by other labs. We said good-bye to Rob who moved to Harvard for a postdoc position. We welcomed 10 new members to the lab.

Breast cancer

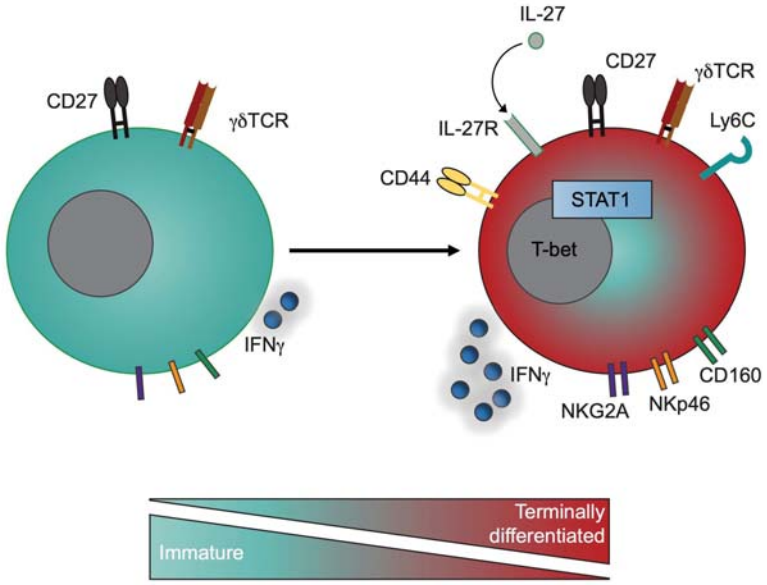
In mice, γδ T cells that express the co-stimulatory molecule, CD27, are committed to the IFNγ-producing lineage during thymic development, and in the periphery, these cells play a critical role in host defence and anti-tumor immunity. Unlike αβ T cells that rely on MHC-presented peptides to drive their terminal differentiation, it is unclear whether MHC-unrestricted γδ T cells undergo further functional maturation after exiting the thymus. This year, we provided evidence of phenotypic and functional diversity within peripheral IFNγ-producing γδ T cells. We found that $CD27^+Ly6C^-$ cells convert into $CD27^+Ly6C^+$ cells, and these $CD27^+Ly6C^+$ cells control cancer progression while the $CD27^+Ly6C^-$ cells cannot. The gene signatures of these two subsets were highly analogous to human immature and mature γδ T cells, indicative of conservation across species. We show that IL-27 supports the cytotoxic phenotype and function of mouse $CD27^+Ly6C^+$ cells and human $Vδ2^+$ cells, while IL-27 is dispensable for mouse $CD27^+Ly6C^-$ cells and human $Vδ1^+$ cells. These data reveal increased complexity within IFNγ-producing γδ T cells, comprising of immature and terminally differentiated subsets, that offer new insights into unconventional T cell biology (Figure 1).

Colorectal cancer

Using mouse models provided by Owen Sansom's lab, we have investigated the role γδ T cell subsets in colon cancer. One project focused on gut-resident cells that express the Vγ7 T cell receptor chain, because our previous work showed that these cells are inherently anti-tumorigenic cells. We have found that deletion of the tumour suppressor *Apc* induces changes in epithelial cells, causing reduced interaction between epithelial cells and Vγ7 cells. However, recent observations this year also broadened our scope to CD8αα αβ T cells of the gut, as it seems these cells may have redundant functions with Vγ7 cells. We are exploring the individual contributions of αβ and γδ T cells to anti-tumour immunity. Another project focused on a group of amphiregulin (AREG)-expressing γδ T cells that express either the Vγ4 or Vγ6 T cell receptor chains. By crossing *Vil1-Cre^{ERT2};$Kras^{G12D}$;$Trp53^{F/F}$;$Nicd1^{+/-}$* mice with γδ T cell knockouts, we found that γδ T cells promote tumour initiation in this model. Our experimentation has revealed specifically that Vγ4 or Vγ6 cells infiltrate tumours and these cells express AREG. We are working with the hypothesis that γδ T cell-derived AREG activates EGF receptor on cancer cells to induce their proliferation.

Pancreatic cancer

We have found that γδ T cells drive metastasis in the *$Kras^{G12D/+}$;$Trp53^{R172H/+}$;Pdx1-Cre* (KPC) mouse model of pancreatic cancer, and our work has been focused on overcovering the mechanism by which γδ T cells promote metastasis. We discovered that macrophages and fibroblasts are reduced in pancreatic tumours from γδ T cell-deficient mice,



indicating that γδ T cells regulate these cells in some way to support metastasis. Currently, we are investigating the mechanisms by which this occurs. At the same time, we are also exploring the role of IFNγ-producing γδ T cells in tumour-bearing KPC mice, as we have data to show that knockout of these cells accelerates cancer progression. We are performing killing assays and other *in vivo* experiments to determine which specific subset is responsible for these actions.

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