Research Interests – Prof. Dr. Erika L. Pearce

Research in my laboratory focusses on understanding the cellular and molecular mechanisms that control immune responses, with a particular emphasis on how metabolism governs this process. The immune system is the organ system that is responsible for controlling infection, cancer and mediating autoimmune diseases. Currently our work is focussed on the role of metabolism in regulating memory T cell development and effector T cell function, as well as function in other immune cell types such as macrophages. My laboratory is committed to using a wide variety of approaches to address key questions in immune cell metabolism *in vitro* and *in vivo*, and how metabolic changes impact protective immunity to infection and cancer. More recently, we have also begun to delve into how aberrant immune cell metabolism and subsequent function underlies autoimmunity. We hope that our work will allow us to develop new ways to target immune cell differentiation, longevity, and activity through metabolism, with a long-term goal of mitigating human disease.

Cells of the immune system are vital for host defence and tissue homeostasis, but also cause immune-mediated disease if not properly controlled. Unlike other cells in the body, immune cells possess the ability to respond to environmental signals and assume a wide variety of distinct functional fates as a consequence. They can morph from dormant sentinels into pathogen killing machines, migrate from one tissue to another, modulate surface receptor expression, vigorously proliferate, secrete copious amounts of effector molecules, or exert controlling effects over neighbouring cells. After the burst of activity following an immune response, these specialised cells can die, creating space and limiting tissue damage in a particular environment, or return to resting states that allow them to persist for extended periods of time in readiness for a secondary insult.

The activation, proliferation, engagement of effector functions and return to homeostasis of immune cells are intimately linked and dependent on dynamic changes in cellular metabolism. The utilisation of particular metabolic pathways is controlled on one level by growth factors and nutrient availability dictated by competition between other interacting cells, and on another level by the balance of internal metabolites. Studying immune cells, has lent deep insight into how cells differentiate and coordinate their behaviours with metabolism under a wide array of settings. We study several areas of research in the lab, including how and why

particular metabolic pathways are engaged in immune cells, as well as these cells use nutrients during infection and cancer.

Mitochondria are powerhouses of the cell, the organelles where the nutrients we eat are made into energy. Every cell in our body needs to make energy to survive and perform their function, including our immune cells. Memory T cells, along with other cells in the immune system, are important for conferring long-term protective immunity against a pathogen or cancer. Long-term immunity is easily observed in people that have received a successful vaccination, as they remain 'protected' from infection with a particular pathogen. We found that memory T cells rely on mitochondrial metabolism to fuel their differentiation, survival, and function and that by modulating their mitochondrial metabolism we could make better, long-lived memory T cells. We have extended these studies to understand how shape changes to the mitochondria influence metabolic pathway engagement in these cells. Mitochondria can exist as round balls, flat or elongated tubes, and even fuse into long thin threads. Our data suggested that structural changes preceded the dynamic metabolic changes that occur during the life of a T cell, and that mitochondrial morphology controls the cellular metabolic state. These findings pointed to the idea that modulating mitochondrial dynamics may create metabolically fit T cells and, therefore, improve adoptive cellular immunotherapy against tumours.

Unlike memory T cells, aerobic glycolysis, a metabolic pathway that occurs outside of mitochondria, is actually required for effector function in T cells, but it is not necessary for the proliferation or survival of these cells. This means that aerobic glycolysis becomes uniquely important for T cells when they need to perform effector functions, e.g. killing infected cells or tumour cells. We more recently built from these results to examine how glucose concentrations in a tumour microenvironment might impact the anti-tumour activity of tumour infiltrating T cells.

On a simple level, both effector T cells and tumour cells use glycolysis as a major metabolic pathway, and cancers are very effective at competing for and using glucose. This can mean that in many situations, a T cell, which needs glucose and glycolysis in order to effectively kill a cancer cell, is in direct competition for this substrate with the cancer cell it tries to kill. We showed that nutrient competition alone, as a distinct mechanism, can mediate tumour progression, even in highly antigenic tumours that are normally recognised and rejected by the immune system. The situation is like a tug-of-war for sugar between tumours and T cells, and the side that can pull in sufficient resources will win the game. We are continuing to assess

how T cells access and use other nutrients beyond glucose during cancer and infection. We hope that by understanding how immune cells meet their metabolic demands, we will learn how to intercede in this process, and provide new ways to convince the immune system to fight cancer and infection.