Therapeutic manipulation of our immune systems is a new and potentially ground-breaking way of treating diverse diseases. For instance, it is now clear that, if given proper instruction, the immune systems of cancer patients can find and destroy tumours. The emergence of ‘check-point’ inhibitors as a revolutionary cancer treatment is evidence of this.

My research over the past eight years has contributed to an exciting transformation of classical immunology to reveal the importance of metabolic processes in shaping immune responses. There is now a new understanding that the fuels available to immune cells and the ways that these fuels are used have a substantial impact on immune cell function. We are now revealing novel and exciting strategies to control immune cells through changing their metabolism - this has potential towards treating a range of diseases.

**Natural Killer Cells** — Natural Killer (NK) cells are a type of cytotoxic immune cell, “immune assassins”, with important roles in defending our bodies from cancer and viral infection. NK cells operate through directly killing their targets by injecting cytotoxic poisons. When NK cells become activated they ramp up their metabolic processes to allow them to generate sufficient energy and to make the tools they need to be effective killers.

However, these metabolic processes can be disrupted during disease, leading to NK cells that do not work properly. For instance, our work in collaboration with Lydia Lynch and Andrew Hogan shows that NK cells from individuals with obesity cannot increase their metabolism when activated and fail to kill tumour cells.

In partnership with Clair Gardiner’s lab, our research teams at TBSI have revealed that NK cells from patients with metastatic breast cancer have abnormalities in the cellular powerhouses called mitochondria. Normally mitochondria form elongated structures, but the mitochondria in patient NK cells are shortened and have reduced energy production (Figure 1). We are investigating how these metabolic processes are disrupted in NK cells in these diseases. The ultimate goal is to develop strategies to provide NK cells with robust and irrepressible metabolism and therefore enhanced abilities to protect us from cancer and viral infection.

**Can nutrients shape immune responses?**

I’m also interested in the different ways that metabolic fuels, or nutrients, control our immune systems. For instance, in many immune cells glucose is important in fuelling metabolic processes to make energy. But glucose can also act as an immunological signal because cells contain glucose sensors that detect the presence or absence of glucose and change their behaviour accordingly. The EU has funded an ERC Consolidator award to allow my lab to investigate the new concept that nutrients are important signals that can shape immune responses.

My research has made the interesting discovery that starving Dendritic cells (DC) of glucose enhances their ability to activate other immune cells. This starvation can result from competition for glucose with neighbouring cells. When a DC is surrounded by glucose-hungry cells the DC can become starved and the nutrient switch called mTORC1 is turned off leading to a change in DC behaviour (Figure 2). My lab is now studying the complex relationship between the local availability of nutrients and the control of our immune responses.

NK cells operate through directly killing their targets by injecting cytotoxic poisons. When NK cells become activated they ramp up their metabolic processes to allow them to generate sufficient energy and to make the tools they need to be effective killers.

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**Fig 1.** Competition for nutrients controls Dendritic cells (DC): T cells (green) clustering around a DC (purple) consume all the available nutrients, such as glucose, leading to the inhibition of nutrient sensing signaling pathways like mTORC1 (red). Inhibition of mTORC1 alters the function of DC leading to enhanced T cell immune responses. Dashed lines outline DCs of interest.

**Fig 2.** NK cells from the blood of healthy individuals (left) and patients with metastatic breast cancer were analysed for mitochondria (red) structure. The structure of mitochondria from breast cancer patients is altered and they are not making energy efficiently.