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I am a foundation doctor, with career aspirations in pathology and oncology. As a third year medical student, I became interested in the dynamic relationship between a cancer and the immune system. In order to survive, cancer cells must acquire the ability to evade immune detection and destruction. At the time, I remember reading about the amazing responses to humanised monoclonal PD-1 antibodies, most notably amongst patients with melanoma and non-small-cell lung cancer. The successes of PD-1 inhibitors (and other immunotherapies) reflect their ability to reverse immune quiescence and re-invigorate anti-tumour cytotoxicity.

In unselected colorectal cancer cases, treatment benefit from PD-1 checkpoint inhibitors was initially modest (Brahmer *et al.*, 2010; Lipson *et al.*, 2013). However, one patient with refractory, metastatic colorectal cancer developed a durable, complete response. After analysing the tumour tissue, it soon became apparent that the genome was unique; due to mutations in one of the DNA mismatch repair (MMR) genes, it displayed a very high mutation rate resulting in microsatellite instability. This was the first demonstrated benefit of immunotherapies in microsatellite instability-high (MSI-H) tumours, and was the building block for further phase II and III clinical trials, which confirmed the results.

MSI-H tumours contribute to approximately 15-20% of colorectal cancers (Vilar & Gruber, 2010), and 30-40% of endometrial cancers (Morice *et al.*, 2016). These tumours largely arise sporadically; a subset (2-5%) is caused by Lynch Syndrome (previously termed hereditary non-polyposis colorectal cancer, or HNPCC), whereby patients inherit a pathological mutation in one of the DNA mismatch repair (MMR) genes (Boland *et al.*, 2008). Up until recently, research has largely focused on colorectal cancers associated with the syndrome. Women with Lynch Syndrome are at an equally high risk of acquiring endometrial cancer, and endometrial cancer is often their sentinel malignancy (Lu *et al.*, 2005).

Under the supervision of Professor Crosbie and Professor McMahon, I defined a pilot research study comparing the expression of beta-2-microglobulin (an essential component of the MHC class I antigen presentation machinery) in Lynch Syndrome-associated MMR-deficient, and MMR-proficient endometrial cancers (wild-type). I received an educational scholarship from the British Department of the International Association of Pathologists for this research project. During this time, I had the opportunity to immerse myself in the complexities of immune evasion, immune quiescence, the hypothesis of immunoediting, and the principals of immunohistochemistry.

Like most research, our results prompted further questions. I chose to undertake an intercalated Masters degree to build on this work. Under the supervision of Professor Crosbie, I constructed a research proposal to fully explore the immune characteristics of Lynch Syndrome-associated MMR-deficient, sporadic MMR-deficient, and MMR-proficient (wild-type) endometrial cancers. We confirmed that MMR-deficient tumours were much more immunogenic than MMR-proficient

tumours. Importantly, we also obtained unequivocal proof that germline-proven Lynch Syndrome-associated tumours are much more immunogenic than their sporadic MMR-deficient counterparts, likely reflecting a lifetime of exposure to tumour neoantigen (Figure 1). Based on this fundamental difference, we propose that Lynch Syndrome-associated tumours should be considered as a distinct immunological entity. Our results have critical implications for potential response to immunotherapy within endometrial cancer as well as other MMR-deficient cancers. We recently published these results in *Frontiers of Immunology* (Ramchander & Ryan *et al.*, 2020)

As a third year medic, I did not expect my pilot study would translate into a large-scale multi-centre research project that set out to address an important question. It is through the support and mentorship from established academics, and organisations like the BDIAP that foster an investigative spirit, that I have had the opportunity to develop as a young researcher. I am truly grateful for the support I have received from the BDIAP; it has undoubtedly helped me find my footing in oncology, and has fuelled my aspirations to pursue an academic career in the field.

Figure 1. The immune signatures of endometrial cancer



