

## Stemming the flow toward disease: A research profile of Lee Parry

Originally from the South Wales valleys, Lee's undergraduate training was completed with a B. Sc. (Hons) in Genetics from Cardiff University, Cardiff, UK. This training program secured a Cancer Research Wales funded PhD at the Institute of Medical Genetics at (what was then) the University of Wales College of Medicine. His PhD, entitled the "Molecular and Functional Analysis of the Human Tumor Suppressor Genes TSC1 and TSC2," was obtained under the tutelage of Prof Julian Sampson (orcid.org/0000-0002-2902-2348) and Prof Jeremy Cheadle and. Leading to publications contributing to our understanding of the importance of these genes in sporadic cancers, consequences of pathological mutations and our understanding of their role in development and tumorigenesis. During this period, he acquired his first experience with handling and utilizing *in vivo* animal models. Following his PhD, he used his skills in molecular biology and mutation analysis to pursue a Postdoctoral Fellow position within the Mitochondrial Research group of Prof Henrik Dahl and Prof David Thorburn (orcid.org/0000-0002-7725-9470) at the Murdoch Children's Research Institute (MCRI), based at the Royal Children's Hospital in Melbourne, Australia. His work there was a change of focus from the cancer genetics of his PhD aimed at determining the mutation spectrum of patients with mitochondrial Complex I disorder. Upon completing this post, he returned to Cardiff University and to cancer research, working on a Cancer Research UK funded project in the laboratory of Prof Alan Clarke (orcid.org/0000-0002-4281-426X).

Upon joining Prof Clarke's laboratory, he completed his training in the use of *in vivo* animal models and worked on projects aimed at understanding the role of epigenetic regulation in colorectal cancer (CRC). Using a rodent model, he helped clarify the roles that the global epigenetic regulators *Mbd2* and *Kaiso* (*Zbtb33*) play within the intestinal epithelium and immune compartments. He demonstrated that these proteins operate in a context-dependent manner to balance CRC risk. One of his major findings was that in the intestine the normal function of *Mbd2* is exploited by cancer cells to enable tumorigenesis, while in the immune system it plays a key role in preventing tumor-enabling inflammation. His work

demonstrated that *Mbd2*'s *in vivo* role CRC depends on the inflammation status of the intestine and provided a new epigenetic model for inflammation-associated carcinogenesis. With other findings demonstrating that *Kaiso*'s role in regulating cell spindle polarity is crucial to minimize the window of opportunity for tumorigenesis as cells leave the intestinal crypt. Alongside other work contributing to our understanding of how the Wnt signaling pathway and intestinal cell types interplay to maintain intestinal cellular homeostasis and impact on tumorigenesis. During this period the group of Prof Clarke was part of a wider effort that identified the *Lgr5*+ intestinal stem cells and their importance as the cell of origin for CRC; providing a new set *ex vivo* and *in vivo* tools for understanding CRC. These tools allowed him to demonstrate an impact that environmental factors can have on determining the size of the ISC pool and their potential to alter CRC risk. These moments represented a shift in his research to focussing on understanding the role that diet/lifestyle and the microbiome play in the etiology of CRC. His aim to inform strategies and develop novel approaches to addressing the ~50% of CRC cases that are thought to be preventable.

Taking this approach, he secured a position as an inaugural Research Fellow at the newly established European Cancer Stem Cell Research Institute in Cardiff University. There he has established a research group focussed on unraveling the interplay between environmental factors with the normal, premalignant and malignant ISC population that determines CRC risk. His work aims to take a holistic and reductionist approach to understand the association between dietary components, lifestyle choices, and CRC risk. His new work in this area has demonstrated that the CRC chemopreventative properties of black raspberries are due, at least in part, to their impact on the normal ISC population before malignant transformation. And is currently pursuing other avenues of research examining the crosstalk between the diet, microbiome, immune system and ISCs, considering the newly discovered property of non-ISC epithelial cells that they retain an ability to revert to ISCs if the ISC pool suffers trauma. He believes this new evidence on the plasticity of intestinal cells potentially explains the contradictory

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evidence indicating tumor suppressive and oncogenic roles for components such as eating patterns, anti-inflammatory Treg cells, dietary fiber and its bacterial fermentation to short chain fatty acids for example, butyrate.

Finally, in the UK guidelines recommends that after CRC treatment patients should be offered comprehensive advice on managing the effects of treatment on bowel function that includes information on diet and nutritional education. There is an urgent need to improve clinical practice to ensure colorectal patients receive nutritional advice that is both consistent between healthcare professionals and personalized throughout diagnosis, treatment, and posttreatment. However, the mechanisms that underpin the relationship between nutrition and patient outcomes during and following CRC treatment are poorly understood. A greater understanding of the mechanisms which link nutritional intake to physiological consequences is required. An improved mechanistic understanding would form part of a wider robust evidence base which is important in determining cause-and-effect relationships. Lee aims to

answer fundamental questions about the mechanisms by which diet impacts upon the normal biological processes and how they link through to influences on health and disease. With the aim to provide knowledge that supports public health advice and provides mechanistic understanding that can be exploited to develop nutraceutical/therapeutic chemo-preventative agents.

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