Falk Foundation/Guts UK Awards 2025

MEDICAL STUDENT ESSAY PRIZE WINNER:
Dr Nat Peckett

Plasticity in the gastrointestinal tract in health and disease: The role of ATRX in colorectal cancer metastasis

Dr Peckett undertook this project whilst intercalating for a PhD in colorectal cancer research at the Institute of Genetics and Cancer at the University of Edinburgh. She will return to her fourth-year medical studies at the University of Edinburgh this August.

Dr Peckett explains:

'ATRX is a chromatin-remodelling helicase, implicated in regulating both Epithelial-mesenchymal transition (EMT) and metastasis in Colorectal Cancer (CRC) and is one of the most commonly mutated genes in the cancer process. The aim of my project was to focus on determining the mechanism by which ATRX loss regulates cell plasticity and metastasis.

'Undertaking this project really appealed to me as I had a strong desire to gain hands-on research experience and was particularly interested in cancer biology and cell plasticity. As a result of this work, I have become competent in a wide range of research techniques, building a strong foundation for developing a research interest as part of my future clinical career.

'Using both wet lab and computational research techniques, I investigated the effects of ATRX loss on the chromatin landscape and how this was associated with ATRX loss phenotype and behaviour, along with the co-regulatory roles of other transcription factors in this process. We found that ATRX mutation occurs in 7% of CRCs and is associated with late-stage metastatic disease and poor survival in patients, particularly in the highly aggressive CRIS-B subtype. We also discovered that the deletion of ATRX in a mouse CRC organoid model resulted in an aggressive phenotype, including increased propensity to induction of epithelial-to-mesenchymal transition (EMT), tumour invasion and metastasis. We further observed a loss of transcriptional colonic epithelial identity and emergence of highly plastic mesenchymal and squamous-like cell states.

'We believe that ATRX loss results in loss of chromatin accessibility at key colonic epithelial gene loci, thus preventing epithelial transcription factors from binding, and resulting in the softening of colonic epithelial identity which is central to the ATRX loss phenotype. It is this loss of identity that allows for increased cellular plasticity and supports the gain of unorthodox gene expression.

'I further explored the role of an EMT programme in our metastatic CRC models. We wanted to determine whether the EMT process is fundamental to metastasis, or whether it is just one example of phenotypic plasticity. My findings challenge the classical view of EMT and suggest that it is cellular plasticity, rather than the adoption of any particular cell state(s), that is critical for metastatic progression.

'As a result of this work, which has been included in a paper currently in the process of being published, I established that the loss of colonic epithelial identity on its own is associated with poor prognosis, and there is evidence of loss of HNF4A activity as a possible mechanism for this. Additionally, that a full EMT programme is not fundamental to metastasis.

'Further, the prominent role of the HNF4A gene in maintaining lineage identity in the gastrointestinal tract cannot be ignored. It seems the loss of lineage integrity is the key to disease development in progression of aggressive pancreatic and CRC disease, as well as the transition from Barret's oesophagus to oesophageal adenocarcinoma. Is HNF4A the master regulator of loyalty to gastrointestinal epithelial cell lineages?'

Dr Peckett's Project Supervisor, Mr Kevin Myant, Principle Investigator, Colorectal Stem Cell Transformation at the Institute of Genetics and Cancer at the University of Edinburgh comments:

'Nat's project worked on identifying the mechanism by which loss of ATRX influences cell identity and plasticity in colorectal cancer. This work contributed to a publication which is currently in press identifying ATRX loss as a mediator of cell plasticity and metastasis in colorectal cancer. This will hopefully pave the way to better understanding and targeting of ATRX mutant disease in patients. Nat has gained invaluable skills and experience from this project to take forward into a future clinical career which I'm pleased to see recognised by this award.'

Dr Peckett states:

'This award has encouraged me to think about how my research fits more broadly into the gastroenterology field, outside of being specific to cancer and oncology. It has also provided me with the opportunity to attend the annual BSG conference to learn more about gastroenterology as a speciality and what career opportunities it holds.'

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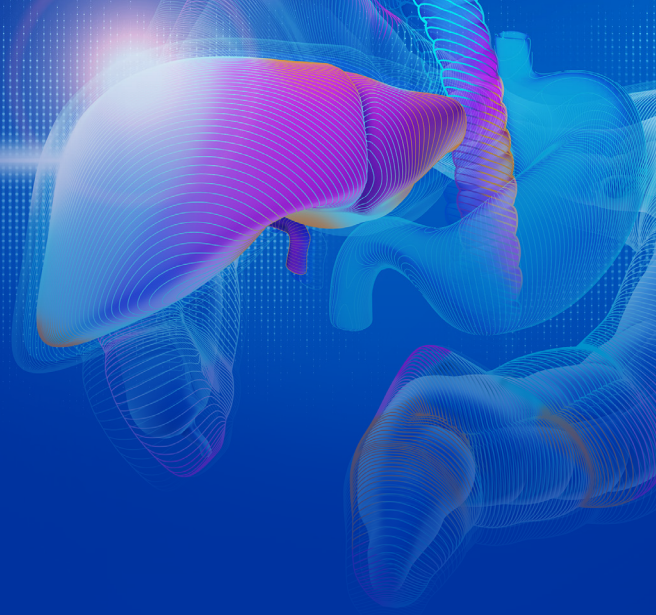

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