

EPD/23/01 - The Impact of Genetic Complexity on Drug:Target Engagement in Colorectal Cancer

Cancer is a disease typically driven by abnormal changes in the elements (genes) that control cell behaviour. These changes often lead to uncontrolled cell growth and induce the spread of cells to remote parts of the body. Despite extensive efforts to identify useful anti-cancer drugs, most drugs that are effective in our model systems fail in clinical trials in patients. As a result, most patients with solid tumours lack effective, durable drug treatments and cancer remain a primary source of mortality: currently one in four Scottish citizens will die from cancer. My research looks to expose the nature of the disconnect between pre-clinical drug studies and patient response.

One answer may lie with genetic complexity. For example, in colorectal cancer, a leading cause of cancer-related deaths, we know that many genes are altered ('mutated') in a single tumour and that this complexity impacts response to drug therapies. A continuing challenge for the colorectal cancer field is to identify drugs that are safe and effective for patients, most of whom have genetically complex tumours. Here, I propose to examine the link between genetic complexity and drug response. I address this challenge by using a miniature intestine referred to as an intestinal organoid. By growing a patient's gut cells in a dish with a specialized support system, the result is a gut-like structure. Adding cancer mutations can lead to tumour-like progression including aspects of disease spread. This platform provides an opportunity to understand how genetic complexity impacts drug response and, importantly, to identify pathways responsible for drug resistance.

For each patient-derived organoid model, I will engineer sensors that will allow me to assess the following:

- 1) Whether these organoids show emergent drug resistance, mirroring the experience of most patients
- 2) Whether genetic complexity changes a drug's ability to find and bind its target

This project will provide an invaluable tool for producing insights from the bench that are more relevant for patients and lend themselves to future clinical trials.