iCase Project / AY 2023 -2024

An organoid platform for defining molecular effectors of colorectal cancer malignancy

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Department/Institute: Biochemistry

Industrial Partner: AstraZeneca

Research area: Cancer biology

Project outline:

The Ph.D. project is designed to determine molecular vulnerabilities in colorectal cancer (CRC). In greater than 85% of colorectal cancers, somatic inactivation of the tumour suppressor Adenomatous Polyposis Coli (APC) is an early, if not initiating event in disease aetiology. Previous work by the academic laboratory (Rannikmae et al 2021) has stratified three independent, direct consequences of APC inactivation in the intestinal epithelia, that contribute to malignant transformation – de-regulation of proliferation, compromised morphology of the epithelial monolayer and loss of cellular polarity. The molecular re-circuitry imposed by loss of APC function that drive these malignant phenotypes has not been determined.

The project proposes to identify molecular APC effectors and their interactions in the control of proliferation, cell polarity and epithelial organisation using human colon and CRC organoids as a model system with the following three experimental Objectives:

(1) Establish an engineered organoid model system for reversible APC inactivation and dynamic monitoring of: (a) proliferation (using the genetically encoded Fucci reporter), (b) cell polarity (using a probe of microtubule dynamics compatible with live imaging) and (b) epithelial morphology (through automated image analysis and scoring) – de la Roche laboratory.

(2) Test a series of candidate APC effectors in the control of epithelial phenotypes using targeted CRISPR/Cas9-mediated gene inactivation – de la Roche and AstraZeneca Functional genomics laboratories.

(3) Carry out an CRISPR array-based forward genetics screen to identify APC effectors that control epithelial phenotypes – AstraZeneca Functional Genomics laboratory.

Further validation of effectors will be carried out using a combination of interactions experiments and sufficiency to define mechanism. Ultimately, data sets acquired for the APC effectors will be used to validate actionable targets for attenuating malignant phenotypes of CRC.

BBSRC DTP main strategic theme: Bioscience for an integrated understanding of health

BBSRC DTP secondary strategic theme: Understanding the rules of life, Transformative technologies,