Project Details	
Project Code	CMD27Ba Caixeiro
Title	Decoding the Cellular Origin of Barrett's Metaplasia Using Microlasers and Lab-on-a-Chip Technologies
Research Theme	Cardiometabolic Disease
Project Type	Wet lab
Summary	Barrett's Metaplasia (BM), the only known precursor to oesophageal adenocarcinoma, arises when chronic acid reflux causes the normal oesophageal lining to transform into intestinal-like tissue. Despite its clinical significance, its cellular origins and the mechanisms driving this metaplastic transition remain poorly understood. This interdisciplinary project combines organ-on-a-chip models to investigate cellular responses to molecular drivers of BM. Individual cells will be labelled with microlasers for longitudinal optical tracking, enabling detailed analysis of migration and phenotypic behaviour. Cells will then be isolated using microfluidic lab-on-a-chip platforms and subjected to single-cell transcriptomic profiling to identify pathways underlying BM initiation and progression.
Description	Project Overview Barrett's Metaplasia (BM) is the only established precursor to oesophageal adenocarcinoma, a malignancy with a dismal prognosis and rapidly increasing incidence in Western populations. BM arises in the setting of chronic Gastro-Oesophageal Reflux Disease, where the normal oesophageal stratified squamous epithelium (SSQE) is replaced by intestinal-like columnar epithelium (ICE). Despite its clinical importance, the cellular switch remains unresolved, hindering understanding of disease pathology and the development of early diagnostics and targeted therapies. Several mechanisms have been proposed: (i) stem cell migration from the squamocolumnar epithelium (between the oesophagus and the stomach) to repair the damage caused by acid and bile reflux, thus converting to ICE and (ii) direct transdifferentiation of cells in the SSQE to ICE. However, distinguishing between these possibilities requires high-resolution tools capable of tracking individual cell fates and molecular changes in a physiologically relevant context. Disease-relevant stimulation combined with established biomarkers will enable monitoring of cellular responses to reflux-induced injury and early metaplastic transformation. However, while these approaches reveal what changes occur, they cannot determine which specific cells initiate these changes or how their descendants contribute to disease progression over time. Microlasers offer an unprecedented solution to this challenge. These tiny optical devices (<1 μm) can be internalised by cells and emit exceptionally narrow and stable spectral signatures. Generating thousands of distinct optical labels, they enable individual cells and their descendants to be uniquely identified through successive rounds of cell division. By combining microlaser-based lineage tracing, biomarker analysis, environmental stimulation and microfluidic sorting, disease-associated cells can be isolated for genomic and transcriptomic

	sequencing. This will link lineage history to molecular state, providing insight into the earliest events driving BM. Aims & Objectives This project will integrate 3D organoid models, microlaser-based cell tagging and microscopy, and a bespoke lab-on-a-chip single-cell analysis platform to sort and analyse the cellular and molecular origins of BM. The approach combines stem cell biology, bioengineering, and computational analysis to reconstruct the earliest events of metaplastic transformation Objective 1 - Establish and Characterise Organoid Models of BM Origins The student will culture and maintain 3D epithelial organoid models derived from pluripotent stem cells representing adult oesophageal SSQE and the squamocolumnar junctional epithelium, two of the most likely sites of origin for BM. Organoids will be validated using microscopy, immunofluorescence, and lineage-specific molecular markers to confirm cellular identity. This will establish a robust and reproducible platform for downstream perturbation and tracking experiments. Objective 2 – Develop Microlaser Tagging and Optical Cell Tracking Microlaser cell integration will be adapted for use in epithelial organoids, based on methodologies previously developed in cardiac organoids. Microlasers will be introduced during early differentiation to maximise uptake. Surface coatings will be optimised to enhance uptake and retention. Optical detection systems will be refined to track microlaser signatures in real time, enabling monitoring of individual cells and their progeny. Objective 3- Induce BM-like Changes Using Molecular Drivers Following establishment of baseline cellular behaviours, organoids will be exposed to known molecular drivers of BM, including overexpression of the transcription factor HNF4α, bille acid exposure to mimic chronic reflux conditions. Microlaser-tagged cells will be tracked throughout the induction process to monitor changes in proliferation, migration, and spatial organisation. Immunostaining for cell type and early metaplastic markers will be used to correlate phenotypic shifts. Objective 4- Lab-on-a-Chip Sorting and Single-Cell Analysis A custom lab-on-a-chip platform will be developed to isolate and analyse individual cells based on microlaser tags and immunostaining markers. Organoids will be dissociated into single-cells and encapsulated within water-in-oil droplets for high-throughput analysis. This will build on existing microfluidic and optical detection technologies but will require integration of spectroscopy imaging methods with high-throughput droplet sorting. The system will enable sorting of cells based on lineage history and phenotype. Sorted cells will be subjected to targeted gene expression profiling to uncover transcriptional programs associated with early metaplastic transformation. Objective 5- Data Integration and Interpretation Imaging, behavioural, and transcriptomic data will be integrated to reconstruct cellular trajectories and identify early markers of metaplastic commitment. Findings will be compared with known markers of candidate cell-of-origin populations. Computational pipelines will analyse lineage relationships, migration, proliferation, and responses to

	environmental perturbations. Computational approaches such as clustering will be used to map the transition from normal epithelium to BM, providing mechanistic insights into disease initiation. Student Ownership From the outset, the student will be encouraged and supported in taking full intellectual ownership of their research. The supervisory team will foster an environment where the student is empowered to shape the direction of the work, particularly in designing experiments and shaping project direction. During the initial preparation phase, tailored training and will equip the student to define precise research questions and select appropriate methodologies. This groundwork will position them to independently lead the development and execution of experiments that test the hypotheses they generate.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
Name	Dr Soraya Caixeiro
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Physics
Email Address	scc201@bath.ac.uk
Co-Supervisor 1	
Name	Dr Fabrice Gielen
Affiliation	Exeter
College/Faculty	Faculty of Environment, Science and Economy
Department/School	Physics/Living Systems Institute
Co-Supervisor 2	
Name	Professor David Tosh
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Department of Life science
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	