Project Details	
Project Code	MRCIIAR26Ba Caixeiro
Title	Decoding the Cellular Origin of Barrett's Metaplasia Using Microlasers and Lab-on-a-Chip Technologies
Research Theme	IIAR
Project Type	Wet lab
Summary	Barrett's Metaplasia (BM), the only known precursor to oesophageal adenocarcinoma, arises from chronic acid reflux. It involves the transformation of the oesophageal lining into an intestinal-like tissue, though its cellular origin and underlying mechanisms remain unclear. This project uses organ-on-a-chip models to study how cells respond to molecular drivers of BM. Individual cells will be tagged with microlasers for optical tracking, enabling detailed analysis of migration and behaviour over time. Lab-on-a-chip devices will then be used to sort cells in a microfluidic device and perform single-cell genetic profiling. These insights aim to reveal BM's origins and inform future therapeutic strategies.
Description	**Background** 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 and is pivotal in understanding disease pathology and identifying therapeutic targets for BM limiting the development of early diagnostics and targeted interventions. 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. Microlasers provide a uniquely powerful approach to this challenge. These standalone lasing particles can be internalised by non-phagocytic cells and emit unique wavelengths, effectively functioning as optical barcodes. Once incorporated, they allow for the precise tagging and re-identification of individual cells across multiple generations. **Aims & Objectives** This project will integrate 3D organoid models, microlaser-based cell tagging, and a bespoke lab-on-a-chip single-cell analysis platform to uncover 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 both adult oesophageal SSQE and the squamocolumnar junctional epithelium—the two most likely sites of origin for BM. These organoids will be validated using microscopy and immunofluorescence staining for lineage-specific

	marker. 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, starting from similar protocols developed for uptake in cells in cardiac organoids. Microlasers will be introduced during early differentiation to ensure stable incorporation. Surface coatings will be optimised to enhance uptake and retention. Optical tracking systems will be refined to detect microlaser emission spectra in real time, enabling longitudinal tracking of individual cells. Computational tools will be developed to analyse cell trajectories, motility, and behavioural responses to environmental cues. Objective 3- Induce BM-like Changes Using Molecular Drivers Once baseline cell behaviours are established, organoids will be exposed to known molecular drivers of BM, including overexpression of the transcription factor HNF4α, Bille acid perturbations will be applied 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. We will dissociate organoids into single-cells and encapsulate them into water-in-oil droplets. This will build on existing microfluidic and optical detection technologies but will require integration of fluorescence imaging methods with high-throughput droplet sorting. The system will enable real-time identification and sorting of cells based on lineage history and molecular 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 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 beginning of the project, the student will be encourage 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 refining the focus within each objective. During the initial preparation phase, tailored training and foundational activities 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.

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