The role and regulation of membrane electric potential in migratory cells

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Principal supervisor's CRUK CC theme: Cell and Molecular Biology Programme

Department for student registration: Department of Physiology, Development and Neuroscience
Department or institute where research will take place: Gurdon institute

Co-supervisor's name (if applicable): Prof. Shery Y.Y. Huang
Co-supervisor's email address (if applicable): yysh2@cam.ac.uk

Postgraduate scheme: **MRes + PhD (1 + 3-year non-clinical applicants only)**

MRes project outline:

Cells undergo physiological changes to initiate migration in metastatic cancer. One understudied physiological factor in migration is the cell membrane electrical potential (Vmem), which modulates cell-environment interactions via ion channels (ref 1). Recent studies suggest that both normal and cancer cells use extracellular acidification (the Warburg effect) to promote movement (ref 2,3), raising the possibility that Vmem regulates cell migration. To test this hypothesis, we will develop a 3D bio-electronic integrated platform for Vmem modulation in cancer cell lines.

The project objectives are:
1. Generate an organic electronic scaffold of individually addressable conductive micro-fibres to control the electric-field microenvironment of cells.
2. Measure and alter Vmem in a spatially-temporally accurate, non-invasive manner, approaching single cell precision.

In the MRes phase, the student will develop a prototype fibre culture chamber and perform culture and measurements with an initial system

MRes experimental plan:

The student will learn to create micro fibres in Dr. Huang's lab and construct an electronic control system for the printed fibre network (ref 4) on a culture chamber (~5 weeks), the student will then seed a cancer cell line with media and Matrigel onto the fibre structures and observe cell behaviors over time while recording and altering the electronic signals in Dr. Xiong's lab (~10 weeks). Optional: incorporating genetic and chemical reporters of pH and Vmem in the cells using transfection and culture addition.

PhD project outline:

Cells undergo physiological changes to initiate migration in metastatic cancer. One understudied physiological factor in migration is the cell membrane electrical potential (Vmem), which modulates cell-environment interactions via ion channels (ref 1). Recent studies suggest that both normal and cancer cells use extracellular acidification (the Warburg effect) to promote movement (ref 2,3), raising the possibility that Vmem regulates cell migration. To test this hypothesis, we will develop a 3D bio-electronic integrated platform for Vmem modulation in cancer cell lines.

In the PhD phase, the student will complete and refine the novel experimental setup to achieve the following goals:
1. Defining the role of Vmem in initiating and sustaining cell migration;
2. Elucidating the mechanisms of Vmem misregulation in cancer, pointing to potential drug targets and novel treatment options via 'bioelectronic' regulation.

PhD experimental plan:

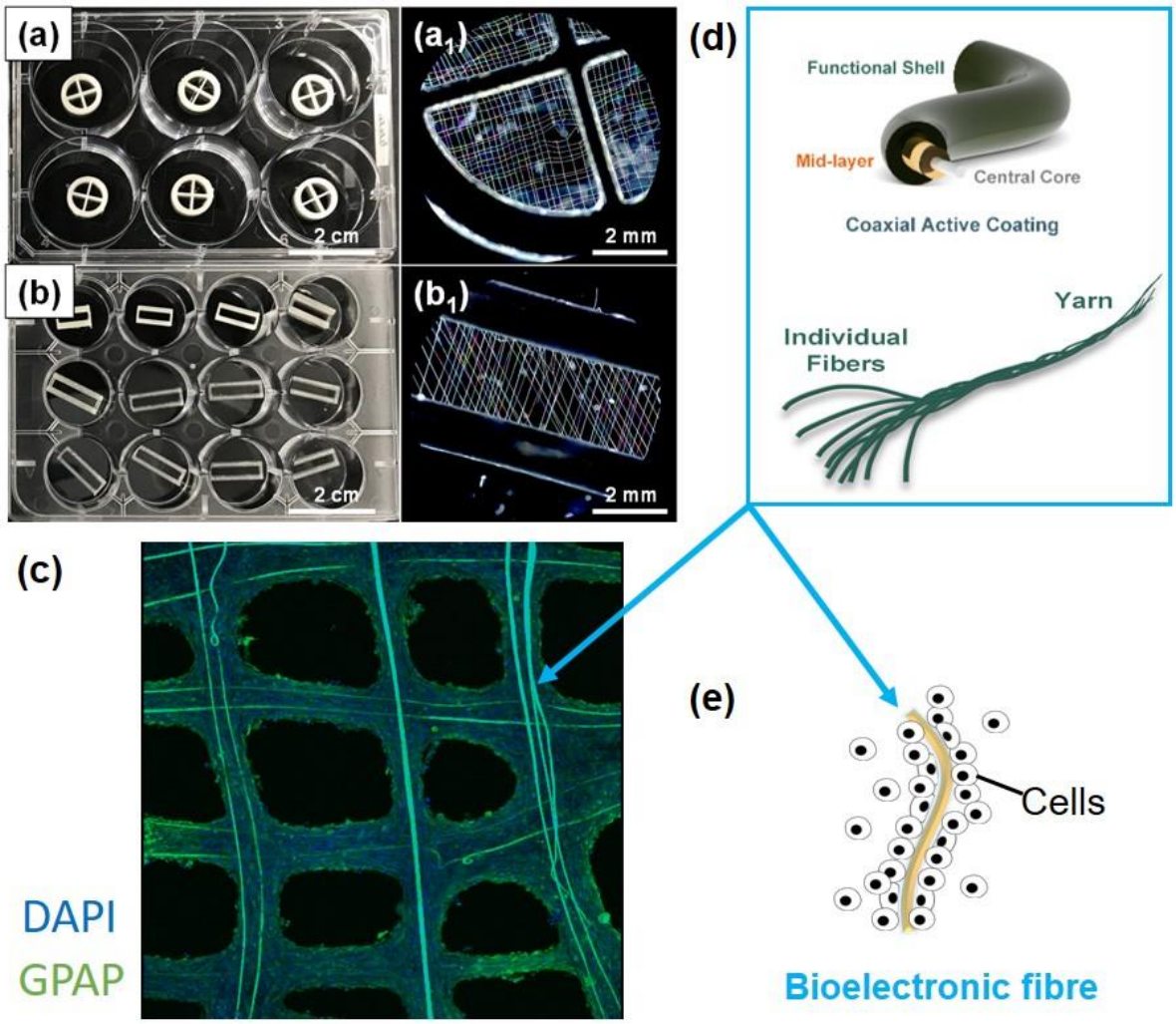
Year 1: The student optimizes the fibre culture chamber manufacture and cell culture process, establishes the microscopy and image analysis pipelines that allow identification of cell migration dynamics. The student also establishes analysis protocol for the bioelectric signals captured by the fibre network. Year 2: The student tests cells of different migratory properties and associate them to the observed spatial temporal electric signals. The student also utilizes stable lines of pH and other reporters to relate cell dynamics to the electric state of the cells using live imaging. The student also tests the possibility of applying voltage changes through fibres to alter cell behaviors. Year 3: The student tests specific molecular hypotheses that arise from work in Year 2, discovers major mechanistic links between Vmem and cell migration and relates the findings to cancer metastasis.

Main techniques:

Cell culture, 3D printing, Microscopy, Image analysis, Modeling

Key references:

1. Levin, M. Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Cell 184, 1971–1989 (2021).
2. Oginuma, M. et al. A Gradient of Glycolytic Activity Coordinates FGF and Wnt Signaling during Elongation of the Body Axis in Amniote Embryos. Dev. Cell 40, 342-353.e10 (2017).
3. Oginuma, M. et al. Intracellular pH controls WNT downstream of glycolysis in amniote embryos. Nature 584, 98–101 (2020).
4. Wang, W. et al. Inflight fiber printing toward array and 3D optoelectronic and sensing architectures. Sci. Adv. 6, eaba0931 (2020).


(a)
(a1)
2 cm
2 mm
(b)
(b1)
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2 mm
(d)
Functional Shell
Mid-layer
Central Core
Coaxial Active Coating
Yarn
Individual Fibers
(c)
DAPI
GPAP
(e)
Cells
Bioelectronic fibre