**Title of the project**: Title: Testing pancreatic cancer cell invasion using mesenteries

**Supervisor: Dr. Armando E. Del Río Hernández**

Cellular and Molecular Biomechanics laboratory: http://biomechanicalregulation-lab.org/
Department: Bioengineering/ South Kensington Campus
email: a.del-rio-hernandez@imperial.ac.uk

**Background:**
Pancreatic cancers present symptoms primarily in their late stages and the survival rate is very low. The insidious nature of this cancer defined by high rates of metastasis plays a key role in the associated mortalities. A hallmark of metastasis in malignancies of epithelial origin such as in the pancreas, breast and liver is the invasion of the basement membrane (BM). Aggressive malignant tumour cells, empowered by the epithelial to mesenchymal transition (EMT) program, lose their E-cadherin mediated cell-cell adhesion and adopt a stromal phenotype leading to invasion of the BM. While earlier studies employed animal and tissue models such as the nematode anchor cell, chick heart fragments and the amniotic membrane, recently, synthetically reconstituted matrix components such as Matrigel have been used to characterise invasiveness of carcinomas. In either case, the models lacked rapid experimental turnover or failed to provide a holistic representation of invasion respectively.

In our group, we developed a novel assay to study BM invasion by pancreatic cancer cells using the mouse mesentery as a model. The tissue is excised and affixed to one end of hollow cylindrical moulds such that it acts like a membrane. We find that the mesentery is able to excellently mimic the BM in its key structural components – collagen I and IV, laminin– and provide a rapid and close-to-actual representation of the invasion process when seeded with pancreatic cancer cells.

You can find below examples of images related to this project.

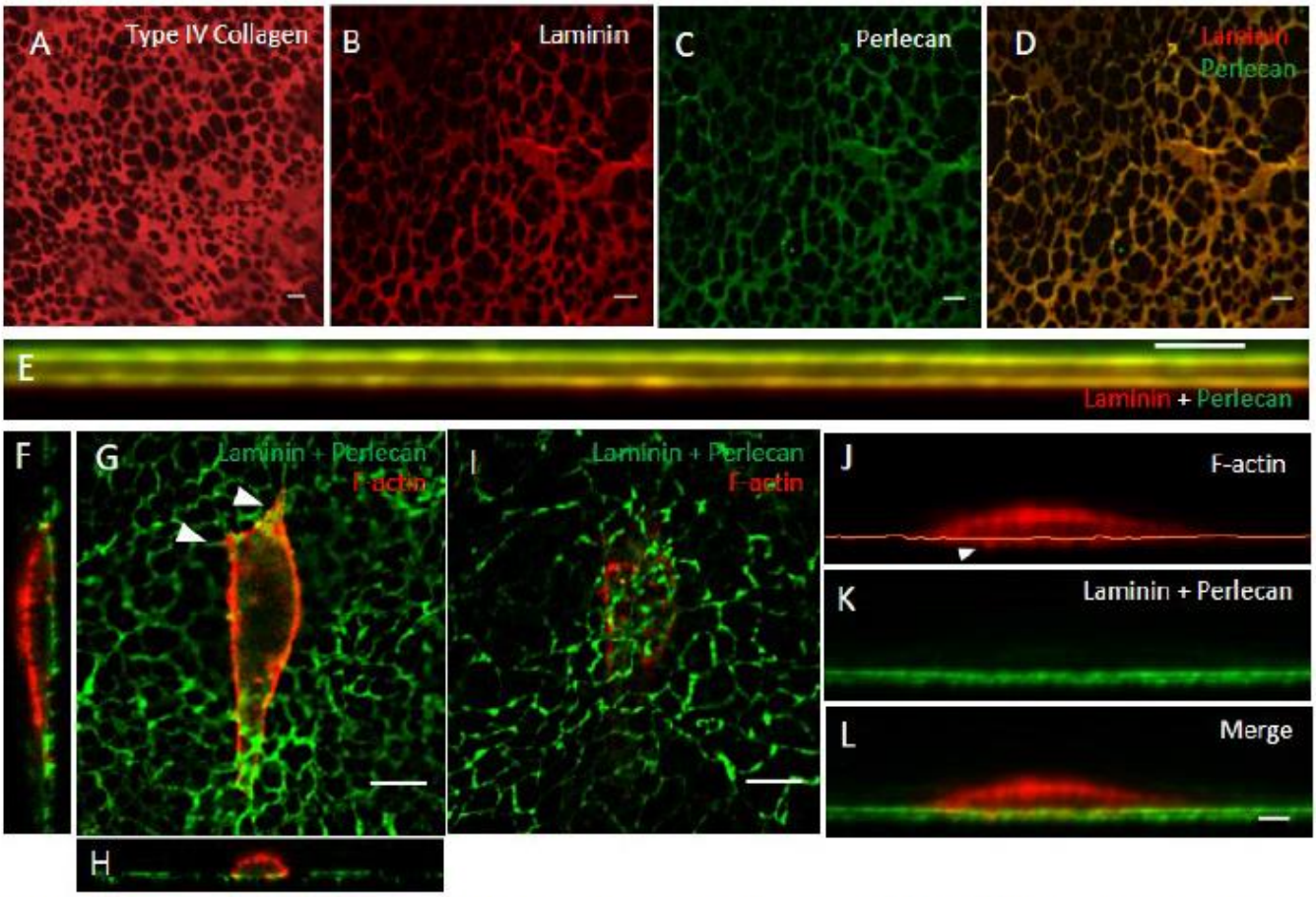


**Figure 3. Visualisation of key mesentery components and cell-mesentery interactions.** (A) Type IV collagen. (B) Laminin, (C) Perlecan, and (D) Laminin and perlecan merge showing co-localisation of the two proteins. (E) Laminin-perlecan bilayer (F-H) Seeded cell on laminin and perlecan bilayer. (G) Top view (XY plane) showing PDAC Suit2-007 cell present on top of the membrane with cell extensions (arrowheads). (F) Condensed z-tack view of cell in G, on the YZ plane. (H) Condensed z-tack view of cell in G, on the XZ plane. (I) Bottom view of the cell in G. (J) Visualisation of cell cytoskeleton from G showing invadopodia (arrowhead), (K) mesentery, and (L) cell invading mesentery. All scale bars are 5 μm.

**Project Description:**

Our group (CMBL) has recently shown that All trans retinoic acid [ATRA] (the active metabolite of vitamin A) induces mechanical quiescence in the chief stromal cells in liver (Cortes et al, Hepatology 2018) and pancreas (Chronopoulos et al, Nature Communications 2016). ATRA induces the RAR-beta dependent negative transcriptional regulation of the myosin molecule that controls cells mechanics and therefore processes such as forces generation and mechanosensing, which are essential to maintain the activated phenotype in these stromal cells. These induced quiescence affects tumour progression.

**Project Aim**

This project aims to investigate the effect of activating the RAR-beta receptor in pancreatic **cancer cells**, with special focus on using these mesentery assays.

**Research Plan**

There are alternatives research plans (tailored to the student's interest) to be discussed in the first one to one meeting with the PI.

Techniques to be used include: (1) Elastic pillars sensor to measure force generation and (2) invasion assays using a novel mesentery methodology. No previous biophysical background is required for the project.

Skills that students will develop during the project:

-Set of experimental techniques including: elastic pillar, novel invasion assays, western blot and qPCR.

-Work in a team with strong disciplinary background

-Deliver research hypothesis and results in a sharp and concise manner

-Active participation in group meetings – development of strong analytical thinking

-Exposure to a wide variety of biophysical techniques highly demanded in the field of cancer biology

**References:**

Cortes E, Lachowski D, Rice A, Robinson B, Thorpe S, Lee DA, Possamai LA, Wang H, Pinato D, and del Río Hernández A. RAR-β is downregulated in HCC & cirrhosis and its expression inhibits myosin-driven activation and durotaxis in hepatic stellate cells. Hepatology 2018.

Chronopoulos A, Robinson B, Sarper M, Cortes E, Auernheimer V, Lachowski D, Attwood S, García R, Ghassemi S, Fabry B & del Río Hernández A. ATRA mechanically reprograms pancreatic stellate cells to suppress matrix remodelling and inhibit cancer cell invasion. Nature Comms 2016

Haining AWM, Rahikainen R, Cortes E, Lachowski D, Rice AJ, von Essen M, Hytönen VP, del Río Hernández A. Mechanotransduction in talin through the interaction of the R8 domain with DLC1. PLoS Biology 2018