

Biophysics of human placental morphogenesis: coupling cell fate, collective migration and tissue mechanics

Use human trophoblast stem-cell systems and quantitative imaging to uncover how cell fate is coupled to the dynamic cellular and mechanical landscape of morphogenesis.

Location: IBDM, Turing Centre for Living Systems
Aix-Marseille University / CNRS, Marseille

Level / duration: M2 internship; duration adapted to the curriculum

Team: Physical Approaches to Cell Dynamics and Tissue Morphogenesis
Supervisor: Sham Tlili (CNRS researcher, biophysics)

Collaboration: Olivier Théodoly, Laboratoire Adhésion et Inflammation (LAI), Marseille, for micropatterning and controlled microenvironments

SCIENTIFIC CONTEXT Placental morphogenesis lies at the interface of developmental biology, biophysics and active-matter physics. Trophoblast cells proliferate, differentiate, migrate collectively and invade maternal tissues while reshaping their cellular and mechanical environment. The placenta is therefore a rich system in which cell fate decisions occur within a dynamic landscape generated and remodeled by the cells themselves during morphogenesis. Understanding this reciprocal coupling - how differentiation affects collective behaviour and tissue state, and how position, neighbours, migration and mechanics feedback on differentiation - is a fundamental and still largely open question. Placental development is also a historically underexplored problem in women's health: abnormal early morphogenesis is associated with disorders such as pre-eclampsia and fetal growth restriction, with major consequences for maternal and fetal health. Recent advances in human trophoblast stem-cell and organoid systems now make these questions experimentally accessible. They provide self-organizing 3D tissues in which the main trophoblast identities - proliferative cytotrophoblast/TSC-like cells (CTB), syncytiotrophoblasts (STB) and invasive extravillous trophoblasts (EVT) - emerge in vitro while geometry, migration and the extracellular environment can be manipulated. This still-emerging field offers a timely opportunity for biophysicists and quantitative biologists to address fundamental questions of fate-morphogenesis coupling in a human system directly relevant to women's health.

INTERNSHIP PROJECT The student will combine two complementary experimental systems. First, a 3D trophoblast organoid model will be used to study how the main placental cell types emerge, organize and change over time within a self-organizing tissue. Second, we will investigate how trophoblast cells migrate and reorganize when they are placed in controlled environments, using both 2D adhesive substrates and 3D extracellular-matrix gels. By varying geometry, confinement and matrix properties, these experiments will test how decisions to differentiate are coupled to cell migration and to the local cellular environment, including cell position, density, neighbourhood and tissue organization.

- use long-term live imaging together with quantitative image analysis, segmentation and single-cell tracking to extract migration fields, cell trajectories and rearrangements, proliferation, local density and differentiation patterns;
- relate CTB, STB and EVT identities to cell position, neighbourhood, migration speed and local tissue organization, and determine whether migrating fronts and crowded regions generate reproducibly different cellular states;
- test whether transitions between more jammed epithelial-like states and more fluid or invasive states correlate with trophoblast differentiation, and address the bidirectional question: does differentiation modify tissue mechanics and collective dynamics, and can the mechanical state of the tissue in turn bias fate?
- use micropattern geometry and controlled culture environments to perturb effective confinement and collective organization reproducibly, building a quantitative bridge between local cell behaviours, tissue-scale migration and the spatial emergence of trophoblast identities.

Conceptually, the system will be viewed as an information-processing active tissue in which cells integrate position, neighbours and mechanical constraints to make fate decisions that feed back onto collective behaviour. The analysis will deliberately combine coarse-grained tissue observables - spreading, front motion, density, velocity fields and global organization - with selected cell-scale measurements from tracking and segmentation. Depending on the student's interests, the experiments can be connected to minimal active-matter or mechano-chemical models of fate-mechanics coupling. A medium-term extension will develop 3D collagen invasion in microfluidic devices, ultimately allowing oxygen and nutrient gradients to be controlled while invasion and differentiation are monitored. A long-term extension of the project (over a PhD thesis timescale) is to quantitatively study the interaction between trophoblast organoids and endometrial organoids (that recapitulate key biological aspects of the maternal uterine environment).

TRAINING ENVIRONMENT The project will be carried out in the team Physical Approaches to Cell Dynamics and Tissue Morphogenesis at IBDM, in collaboration with Olivier Théodoly at the Laboratoire Adhésion et Inflammation (LAI) for micropatterning and controlled microenvironments. The intern will also benefit from the team's expertise in stem-cell-derived embryonic organoids, especially gastruloids, which share related experimental approaches and quantitative challenges, and collaborations with specialists in placenta biology. As this is a new project in the team, the intern will strongly benefit from direct experimental and technical help from the main supervisor, Sham Tlili. The project is embedded in CENTURI - the Turing Centre for Living Systems, an interdisciplinary environment connecting physics, mathematics, computer science and biology. A central objective is to train versatile scientists able to perform experiments, analyse them quantitatively and connect the results to mechanistic or theoretical models of collective behaviour.

CANDIDATE PROFILE M2 student in biophysics/quantitative biology/physics, enthusiastic about experiments and interdisciplinarity. Curiosity, autonomy and motivation to help open a new research direction are particularly valued. The balance between experiments, imaging and modelling can be adapted to the student's background.

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