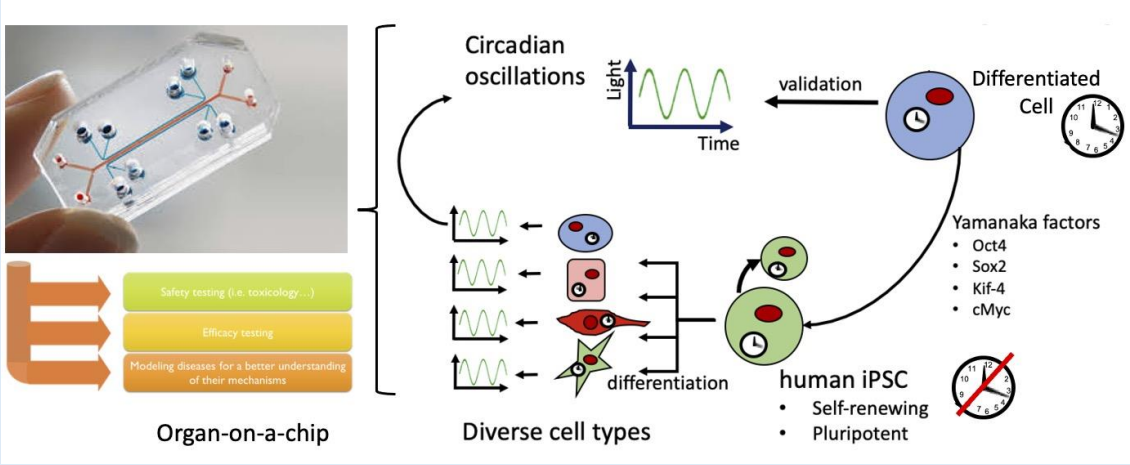
SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

Engineering Circadian Biology into Induced Pluripotent Stem Cell Organ-on-a-Chip models

Organ-on-a-chip (OOAC) technologies are important emerging tools for evaluating the efficacy and safety of novel therapies and may ultimately reduce the requirement for animals in research. OOAC systems incorporate combinations of human cells to recapitulate normal physiology or pathology. There is increasing interest in the use of induced pluripotent stem (IPS) cell-derived differentiated cell models as validated OOAC systems for drug discovery, which would allow personalised systems to be developed.

Physiological processes are co-ordinated by circadian clocks, that endow tissues with endogenous oscillations in gene expression and activity with a period of ~24hr. Circadian rhythms are controlled by a range of chemical and mechanical environmental timing cues, known as zeitgebers (time-givers). The response of cells to zeitgebers is linked to cell differentiation with embryonic stem cells and IPS cells lacking circadian rhythmicity, which only develops following differentiation.



Circadian biology is important in the development of therapeutic agents. Over 80% of proteins that are druggable targets are circadian and likely to benefit from timed administration. However, OOAC technologies do not currently incorporate circadian rhythmicity, which limits their physiological relevance and value as platforms for *ex-vivo* therapeutic evaluation. Overall, **this project will generate iPS cell-OOAC technologies with circadian physiology, as a novel and powerful research tool for use as disease models and to evaluate investigative therapies**.

2. Project Scope

Project aim: To create IPS cell-derived model systems expressing robust and sustained circadian rhythmicity achieved via the following objectives:

- Determine the relationship between IPS cell differentiation and response to zeitgebers using both experimental and mathematical models
- Develop OOAC models involving IPS cell-derived co-culture systems
- Define chemical and mechanical parameters that induce robust and sustained circadian rhythmicity within OOAC technology
- Determine the optimal time of day for the administration of exemplar therapeutic agents, as proof of concept of the technology application

3. Desired Skills from the Student

The ideal candidate should have experience of Cell culture; Microscopy/imaging techniques to monitor cell behaviour; Molecular biology techniques.

4. Supervisory Team

Primary: Professor David Lee – School of Engineering & Materials Science.
Prof David Lee *is Professor of Cell & Tissue Engineering at QMUL. His research employs novel in vitro physiological systems to study the effects of mechanical stimuli on cells. Career funding >£30M, including from the MRC, BBSRC, ESPRC, Wellcome Trust, BHF and an international HFSP grant [RGP0025-2009] investigating mechanoregulation of nuclear organisation/genome function.*

Secondary: Dr Yung-Yao Lin - Blizard Institute – School of Medicine & Dentistry
Yung-Yao Lin *is a lecturer in the Blizard Institute, QMUL with expertise in human iPSCs and CRISPR-based genome manipulation. His group has developed patient-derived microphysiological models for studying neuromuscular disorders, testing candidate drugs and regenerative medicine, with funding (>£1.4M) from industry (Pfizer), charities and NC3Rs.*

Additional: ***Dr John O'Neill (Co-I)*** *is group-leader at the MRC Laboratory for Molecular Biology, Cambridge, and a leading circadian biologist. He studies the molecular basis and consequences of circadian timekeeping and employs a wide range of molecular biology, proteomic, metabolomic and biochemical techniques, including real-time bioluminescent reporters of molecular clock function.*