iCase Project / AY 2023 -2024

Developing an organ-on-a-chip platform for identifying potent AAV with improved cell targeting for delivery of gene therapy

Supervisor: Prof Róisín M. Owens (rmo37@cam.ac.uk)

Department/Institute: Chemical Engineering and Biotechnology

Industrial Partner: AstraZeneca

Project outline:

Recombinant adeno-associated viruses (rAAVs) are the most commonly used vehicles for in vivo gene therapy in preclinical and clinical studies. Wild-type AAV benefit from infecting as many cells types as possible, however, rAAVs should target a particular cell type. Although capsid engineering has been around for over 25 years, to date none has reached late-stage clinical trials despite distinct intellectual property incentives. This is because the improved targeting has seldom transferred from the screening host species (most often mouse) to humans or nonhuman primates.

Microphysiological systems, also known as organ-on-chips, are microfluidic cell culture devices that recapitulate the structure, function and physiology of tissues and organs in vitro. Connecting multiple organ-on-chips in a single platform allows tissues to grow independently while allowing the organs to interact with each other. Using this system for AAV engineering would enable 1) screening novel virus capsid libraries to de-target from the liver (where the majority of AAV is sequestered) and target a tissue/cell-type of choice (e.g. heart, blood-brain-barrier) and 2) follow the journey of AAV after delivery, e.g. monitor in real time how it: enters the lung/gut, transduces the target tissue, and is metabolized in the liver

AAV capsids with improved and specific tropism will prevent off-target toxicity, allow more efficient transduction at lower doses and therefore result in better therapeutic efficacy while lowering safety issues such as immunotoxicity. Using multi-organ-on-chips systems could enable identification of species-cross-reactive AAVs, circumventing the current issue in the field of lack of translatability from mouse screening models to human. Furthermore, current AAV library screening methods often require multiple generations of in vivo library enrichment in mice, followed by non-human primates. Developing organ-on-chip technology will reduce the numbers of animals required and sacrificed when developing these new capsids.

AZ can provide the AAV variants and train the student in viral engineering, AAV capsid library creation and AAV packaging and production. We also can access a multi-organ system (the HUMIMIC Chip, TissUse) which enables integration of up to 4 different organ models.

BBSRC DTP main strategic theme: Transformative technologies