Investigating the impact of CF therapeutics beyond the airways using nanosensing technology.

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Funding: 1 Fully Funded PhD project.
As well as funding materials, consumables and use of imaging facilities, the award provides a generous tax-free stipend (£24,093, £26,057 and £26,839 per annum during the PhD years) and covers tuition fees (at home or overseas student rates). Funds are also available for attending specialised training workshops and relevant international scientific conferences to increase awareness of scientific advances, but also to provide opportunities for networking and team building.

Project details:
The cystic fibrosis transmembrane conductance regulator (CFTR) is an anion channel that is important for both chloride (Cl^-) and bicarbonate (HCO_3^-) movement. In CF, this channel becomes defective disrupting the normal flow of anions. The bicarbonate (HCO_3^-) anion is fundamental to our system of pH regulation and together with CO_2 it forms the most important buffering system in the human body, dynamically stabilizing pH in both extracellular and intracellular fluids. As a result, people with cystic fibrosis (CF), who have little or no CFTR activity, suffer problems affecting many different organ systems. However, to date, the main focus of CF research has been in the airways because problems in the lungs have traditionally been the major cause of morbidity and mortality.

Recently new drugs have been developed to restore the activity of CFTR, thus restoring HCO_3^- transport and bringing huge health benefits to CF patients and much-improved lung function. Nonetheless, here lies something of a mystery, because new work now suggests that whilst CF drugs restore CFTR bicarbonate transport in some tissues (e.g. the lungs), they are not fully effective in other tissues where CFTR is also active. This project will examine the causes of the variable effectiveness of these new CF therapies in restoring bicarbonate transport in a variety of tissues using epithelial cells grown initially as organoids. These organoids will be derived from intestinal, pancreatic and cholangiocyte (bile duct) sources, where CF drugs seem to have differing efficacy.

Interestingly, effective HCO_3^- transport is essential for proper mucus secretion, mucus rheology (its fluid properties) and mucus transport by epithelial cells. Consequently, in this project one of the impacts we will examine is that on epithelial cell mucus secretions. Importantly, the effective transport of secreted mucins depends on the rheology of the mucus formed. If the mucus is too thick and sticky or, at the other extreme, too runny, it cannot be transported well and poor transport leads to infection and serious health problems. To assess the rheology of mucus we will examine a measure called spinnability. This is the ability to pull a 'thread' from a sticky solution (akin to pulling a thread when spinning yarn). Spinnability is a very useful measure of epithelial secretions because it combines the two critical properties of viscosity and elasticity. Indeed, spinnability is the only measure of rheology that is reported to be negatively correlated with both predicted mucociliary and cough clearance. Further, it has been used previously to follow changes produced by pharmacological intervention, so it should provide a good measure of drug-induced changes. We will therefore use this approach to understand the relationship between mucus rheology and partial or complete restoration of bicarbonate transport.

In this project you will be working as part of a major international team of researchers, each pursuing complementary aspects of the research programme that starts from the molecular details of CFTR-drug interactions and ends with the clinical implications and approaches for improving patient outcomes.

The PhD studentship is available to start in September 2023. Informal enquiries can be sent to Dr Guy Moss (g.moss@ucl.ac.uk).

References:
1. Ivanova R., Benton D.C.H., Munye M.M., Rangseesorranan S., Hart S.L., Moss G.W.. A Nanosensor Toolbox for Rapid, Label-Free Measurement of Airway Surface Liquid and Epithelial Cell Function. ACS Appl Mater Interfaces. 2019 Mar 6;11(9):8731-8739. doi: 10.1021/acsami.8b14122.

2. Bijvelds M.J.C., Roos F.J.M., Meijsen K.F., Roest H.P., Verstegen M.M.A., Janssens H.M., van der Laan L.J.W., de Jonge H.R. Rescue of chloride and bicarbonate transport by elexacaftor-ivacaftor-tezacaftor in organoid-derived CF intestinal and cholangiocyte monolayers. J Cyst Fibros. 2021 Dec 15:S1569-1993(21)02165-2. doi: 10.1016/j.jcf.2021.12.006.

3. Wilson, D. What is rheology?. *Eye* **32,** 179–183 (2018). https://doi.org/10.1038/eye.2017.267

Application deadline: 31/03/2023

Application details: Please visit https://www.ucl.ac.uk/biosciences/cystic-fibrosis-bicarbonate-centre
The application will include:
- your latest CV with contact details for two referees
- a 2-3 paragraph statement explaining your interest in the project and what you feel you will bring to the role
- official University transcript(s).