Exploiting stem-cell derived epithelia to investigate pharmacological repair of bicarbonate transport in cystic fibrosis.

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Funding: 1 Fully Funded PhD project.
The grant provides a salary of between €36,564-€40,032 per year, and covers the costs of tuition fees, laboratory reagents and materials. Funds are also available for training, travel and conference visits.

Project details:
The cystic fibrosis transmembrane conductance regulator (CFTR) anion channel mediates chloride and bicarbonate secretion across various epithelia in the body. Bicarbonate is essential for optimal function of various luminal secretions. As a result, people with cystic fibrosis (CF), i.e. people with little or no CFTR activity, suffer symptoms affecting many organ systems. The development of CFTR modulator drugs has transformed the care of many people with CF. These drugs are divided in two categories: (1) potentiators that improve the ion-channel function of CFTR, and (2) correctors that increase the amount of CFTR at the plasma membrane. So far, development of these has been driven by assays monitoring compound-induced changes in chloride permeation, whereas restoration of bicarbonate transport is seldom taken into account. However, it is conceivable that CF-causing mutations have distinct consequences for chloride and bicarbonate transport, and that modulators have different effects on CFTR-mediated bicarbonate *vs*. chloride transport. Also, it is largely unclear whether CFTR modulators can restore bicarbonate secretion in all CF-affected tissues, in particular those that are rarely used as model systems in drug development (e.g. biliary epithelium). The aim of this project is to increase our knowledge of CFTR-dependent bicarbonate secretion, in the hope that a better understanding of its role in the pathophysiology of the disease may ultimately improve pharmacological treatment of people with CF. In this project, we will use advanced stem-cell, biochemical, molecular biology and genomics-based technologies to investigate epithelial bicarbonate secretion and luminal pH regulation, and use the organoid platform to develop new methods to assess (CFTR-dependent) bicarbonate secretion in CF-affected gastro-intestinal tissues, and to assess the effect of modulator therapy on CFTR function.

The PhD studentship is available to start in early 2023. Informal enquiries can be sent to Dr Marcel Bijvelds (m.bijvelds@erasmusmc.nl).

References:
Bijvelds, M. J. C., Roos, F. J. M., Meijsen, K. F., Roest, H. P., Verstegen, M. M. A., Janssens, H. M.et al., . . . de Jonge, H. R. (2022) Rescue of chloride and bicarbonate transport by elexacaftor-ivacaftor-tezacaftor in organoid-derived CF intestinal and cholangiocyte monolayers. *J Cyst Fibros* **21**, 537-543

Ciciriello F, Bijvelds MJC, Alghisi F, Meijsen KF, Cristiani L, Sorio C, et al., . . . de Jonge, H. R. (2014). Theratyping of the rare CFTR variants E193K and R334W in rectal organoid-derived epithelial monolayers. *J Pers Med.* **12**, 632.

Application deadline: 11/12/2022

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
- an official University transcript.

See also:
https://www.erasmusmc.nl/en/research/departments/gastroenterology-hepatology