PhD Project

Investigation of drugs that modulate ion transport and mucus secretion as a novel treatment of cystic fibrosis.

Background: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is the essential secretory chloride (Cl^-) ion channel in many human epithelial organs [1-3]. The life threatening disease Cystic Fibrosis (CF, mucoviscidosis) is caused by mutations in the gene encoding CFTR. This leads to a severe lung and gastrointestinal disease. The predominant problem is the occlusion of airways and intestine by a thick and highly viscous mucus [4]. However, intensive research in the past years has demonstrated that not only the CFTR Cl^- channel is important for fluid transport and mucus properties. Other Cl^- channels, such as the TMEM16 and the SLC26A9 Cl^- channels also have a large impact on the transport of fluid and mucus [2, 5-7]. The proteins TMEM16A and TMEM16F are different types of ion channels activated by intracellular Ca^{2+} [8-10]. TMEM16A is not only a Cl^- channel. As our own work indicates, TMEM16A supports Cl^- secretion also indirectly, by facilitating intracellular Ca^{2+} signaling required for activation of CFTR [6, 11]. SLC26A9 again is a different type of Cl^- channel that is probably constitutively active.

Objective: The objective of the present PhD project is to investigate drugs that act either directly or indirectly act on these alternative non-CFTR Cl^- channels. By targeting these channels, it might be possible to circumvent the defective CFTR function and to help CF patients to normalize their fluid and mucus transport, and to improve their lung function and intestinal transport. These efforts are part of a long term strategy to restore normal lung and intestinal function in cystic fibrosis [12].

The PhD student will be part of an exciting collaborative European research project that is funded by the UK Cystic Fibrosis Trust. This project will run for 4 years and will start in 2018. It includes research teams from England, Netherlands, Portugal and Germany. The PhD student will be working in Germany, at the Department of Physiology of the University of Regensburg (http://www.biologie.uni-regensburg.de/Physiologie/Kunzelmann/index_en.html). Communication within the international research team at University of Regensburg will be in English. The final PhD thesis and the final defense will also be in English. The student will enroll into the international Graduate Student program of the University (https://www.rigel-regensburg.de/). The highly motivated and skilled selected PhD student will be working in intimate exchange with the other teams. He/she will participate in international conferences, present his/her results at scientific meetings and will report them at yearly progress meetings. Because this project is generously funded by the UK Cystic Fibrosis Trust, a PhD fellowship will be provided throughout the project period.

Methods used within this project: The PhD student will examine modulators of alternative Cl^- channels using *in vitro*, *ex vivo* and *in vivo* techniques in genetically modified tissue-specific knockout mice. The compounds used will be either freely available drugs, novel compounds developed by pharmaceutical industry or novel drugs identified within this consortium. These compounds will be examined regarding their impact on fluid and mucus transport in TMEM16A airway and gut-specific KO mouse models. Compounds will be applied via tracheal instillation or, where appropriate, in a specialized mouse plethysmograph via aerosol. Lung sections will be analyzed by histology/immunocytochemistry. Activation of Cl^- conductance will be also examined on isolated tracheas by Ussing chamber techniques. Additional experiments will be performed using electrophysiological techniques such as patch clamp, or microscopic fluorescence techniques as well as biochemistry. These experiments will be performed on cultured cells.

Supervisor

- Prof Karl Kunzelmann, Dept Physiology, University of Regensburg (karl.kunzelmann@ur.de). Please contact Prof. Kunzelmann directly for further enquiries.

Work place

- Department of Physiology, University of Regensburg (Germany).

Begin

- At any time

References

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