SHAREABLE PDF

Correction of CFTR function in intestinal organoids to guide treatment of cystic fibrosis

Anabela S. Ramalho[1], Eva Fürstová[2], Annelotte M. Vonk[3,4], Marc Ferrante[5,6], Catherine Verfaillie[7], Lieven Dupont[8,9], Mieke Boon[1,10], Marijke Proesmans[1,10], Jeffrey M. Beekman[3,4], Ifat Sarouk[11], Carlos Vazquez Cordero[12], Francois Vermeulen[1,10] and Kris De Boeck[1,10] on behalf of the Belgian Organoid Project[13]

Affiliations: [1]Dept of Development and Regeneration, Woman and Child Unit, CF Research Lab, KU Leuven, Leuven, Belgium. [2]Dept of Pediatrics, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic. [3]Dept of Pediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, The Netherlands. [4]Regenerative Medicine Center, University Medical Centre, Utrecht, The Netherlands. [5]Dept of Chronic Diseases, Metabolism and Ageing, Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium. [6]Dept of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium. [7]Dept of Development and Regeneration, Stem Cell Biology and Embryology, KU Leuven, Leuven, Belgium. [8]Dept of Chronic Diseases, Metabolism and Ageing; Pneumology, KU Leuven, Leuven, Belgium. [9]Dept of Respiratory Diseases, University Hospital of Leuven, Leuven, Belgium. [10]Dept of Pediatrics, Pediatric Pulmonology, University Hospital of Leuven, Leuven, Belgium. [11]Pulmonology Pediatrics and National CF Center Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel. [12]Pulmonology and Cystic Fibrosis Unit, Cruces University Hospital, Barakaldo, Spain. [13]A list of members of the Belgian Organoid Project can be found in the acknowledgements section.

Correspondence: Anabela S. Ramalho, O&N IV – 5th floor – bus 804, Herestraat 49, 3000 Leuven, Belgium. E-mail: anabela.ramalho@kuleuven.be

@ERSpublications
Rescue of CFTR function with modulators measured in colon organoids can be used to guide precision medicine in patients with cystic fibrosis. Organoids are an effective model to bring treatment to patients with CF carrying rare *CFTR* mutations. https://bit.ly/2VHHH6s

Cite this article as: Ramalho AS, Fürstová E, Vonk AM, *et al*. Correction of CFTR function in intestinal organoids to guide treatment of cystic fibrosis. *Eur Respir J* 2021; 57: 1902426 [https://doi.org/10.1183/13993003.02426-2019].

ABSTRACT

Rationale: Given the vast number of cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations, biomarkers predicting benefit from CFTR modulator therapies are needed for subjects with cystic fibrosis (CF).

Objectives: To study CFTR function in organoids of subjects with common and rare *CFTR* mutations and evaluate correlations between CFTR function and clinical data.

Methods: Intestinal organoids were grown from rectal biopsies in a cohort of 97 subjects with CF. Residual CFTR function was measured by quantifying organoid swelling induced by forskolin and response to modulators by quantifying organoid swelling induced by CFTR correctors, potentiator and their combination. Organoid data were correlated with clinical data from the literature.

Results: Across 28 genotypes, residual CFTR function correlated (r^2=0.87) with sweat chloride values. When studying the same genotypes, CFTR function rescue by CFTR modulators in organoids correlated tightly with mean improvement in lung function (r^2=0.90) and sweat chloride (r^2=0.95) reported in

clinical trials. We identified candidate genotypes for modulator therapy, such as E92K, Q237E, R334W and L159S. Based on organoid results, two subjects started modulator treatment: one homozygous for complex allele Q359K_T360K, and the second with mutation E60K. Both subjects had major clinical benefit.

Conclusions: Measurements of residual CFTR function and rescue of function by CFTR modulators in intestinal organoids correlate closely with clinical data. Our results for reference genotypes concur with previous results. CFTR function measured in organoids can be used to guide precision medicine in patients with CF, positioning organoids as a potential *in vitro* model to bring treatment to patients carrying rare *CFTR* mutations.