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Testing CFTR in epithelial organoids for drug development and diagnosis of cystic fibrosis

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Background. In vivo and ex vivo measurements of CFTR function in human cells and tissues is required for screening and monitoring new therapies and phenotyping controversial CFTR genotypes. We set up a technique enabling intestinal stem cells to expand into closed organoids containing crypt-like structures and an internal lumen lined by differentiated cells (Sato et al Gastroenterology 2011) for measuring CFTR function. 2011).

Hypothesis and objectives. This quantitative method could be useful to detect the effects of CFTR genetic variants/rare mutations as well as of drugs targeting specific CFTR. The combination with other functional tests could support controversial diagnosis and drug development.

Methods. Organoids, obtained from intestinal biopsies of CF and non CF subjects, were processed and tested as reported (J.F. Dekkers et al. Nature Medicine, June 2013). We isolated organoids from 29 subjects (16 males and 13 female): 14 healthy donors and 15 patients affected by CF. Nasal Potential Differences (NPD) and Intestinal Currents measurements (ICM) were performed according to the ECFS SOPs. The membrane depolarization assay was performed on monocytes (Sorio C, et al. PLoS One. 2011).

Results. In non-CF organoids swelling was significantly enhanced following treatment with the potentiator Ivacaftor (VX770) and was completely blocked by the CFTR (inh)-172. Remarkably, in organoids from a CF patient carrying the W1282X/R117H CFTR genotype we observed swelling following exposure for 24h to the premature termination corrector Ataluren (PTC124). We also performed membrane depolarization assay in monocytes and detected restoration of CFTR function following 24h exposure to correctors alone or in combination with potentiators as VX770. ICM results were consistent with organoids swelling.

Spin-off for research & clinical purposes. This study proposes a combination of CFTR functional assays in several human tissues aiming at supporting diagnosis, new drugs development and monitoring of individual patients. This individualized approach can be developed for predicting as well as for monitoring effects of new drugs.

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