Theratyping cystic fibrosis *in vitro* in ALI culture and organoid models generated from patient-derived nasal epithelial conditionally reprogrammed stem cells

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Shareable abstract (@ERSpublications)
Despite approval of Trikafta, a fraction of cystic fibrosis patients with rare genotypes are still lacking modulator therapies. Conditionally reprogrammed nasal cell-based *in vitro* models may allow theratyping for each patient for personalised treatment. https://bit.ly/3ylOJ28

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Abstract

Question Cystic fibrosis (CF) is due to pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Recent improvements have enabled pharmacological therapy aiming at restoring mutated CFTR expression and function. CFTR "modulators" have revolutionised the CF therapeutic landscape, particularly the last approved, Trikafta. This drug combination is indicated by the United States Food and Drug Administration and very recently by the European Medicines Agency for genotypes carrying at least one copy of CFTR with the F508del pathogenic variant. However, several genotypes are not yet eligible for Trikafta treatment.

Materials/patients and methods We exploited an innovative cellular approach allowing highly efficient *in vitro* expansion of airway epithelial stem cells (AESCs) through conditional reprogramming from nasal brushing of CF patients. This approach, coupled to the development of AESC-derived personalised disease models, as organoids and air–liquid interface (ALI) cultures, revealed highly suitable for CFTR pharmacological testing.

Results and answer to the question We fully validated the experimental models and implemented the CFTR functional assays and biochemical CFTR protein characterisation, which allowed the evaluation of the efficacy of clinically available modulators in restoring CFTR maturation and function of each patient-derived "avatar" (theratyping). F508del homozygous genotypes, used as controls, confirmed the higher clinical activity of Trikafta in comparison with older modulators. In addition, Trikafta showed its efficacy on three rare genotypes previously not eligible for treatment with modulators, opening the way to clinical translation. Finally, encouraging results for innovative drug combinations were obtained.