

Targeting PI3K scaffold function to activate airway CFTR, limit lung inflammation and promote bronchorelaxation in cystic fibrosis

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Background and Rationale. The underlying cause of cystic fibrosis (CF) is a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), a cyclic AMP (cAMP)-stimulated chloride channel. The consequent CFTR dysfunction primarily affects the respiratory system, where the reduced activity of the channel results in obstruction of small airways and, together with airway inflammation and infections, eventually leads to respiratory failure. A number of CFTR correctors and potentiators have been developed, but their ability to rescue the basic defect of CF is still unsatisfactory.

Hypothesis and Objectives. We previously showed that phosphoinositide 3-kinase γ (PI3K γ) acts as a scaffold protein and negatively regulates cAMP. Here, we hypothesized that targeting PI3K γ scaffold activity enhances cAMP in airway smooth muscle, immune and epithelial cells, leading to concomitant (i) bronchodilation, (ii) anti-inflammatory effects and (iii) CFTR potentiation.

Methods. We explored the ability of a peptide targeting the scaffold activity of PI3K γ (Patent n° PCT/IB2015/059880 - WO/2016/103176) to function as (i) bronchodilator, (ii) anti-inflammatory and (iii)

CFTR potentiator. A mouse model of chronic lung inflammation (OVA-sensitized mice) and human primary bronchial epithelial cells (F508del) were used.

Results. We found that the peptide significantly elevates cAMP in the airways and limits methacholine-induced airway hyperresponsiveness in OVA mice. In the same model, the peptide reduces neutrophilic lung inflammation and also inhibits human neutrophil adhesion in vitro. Finally, the peptide potentiates F508del currents per se, and in combination with the gold-standard potentiator VX-770, upon pharmacological correction with VX-809.

Spin-off for research & clinical purposes. Overall, the results of this study demonstrate that the PI3K γ targeting peptide may be exploited therapeutically to provide (i) bronchodilation, (ii) anti-inflammation and (iii) CFTR potentiation. This will eventually allow maximizing patients' benefit. Chemical optimization of the peptide is ongoing and will eventually pave the way to a peptide-based aerosol therapy to be used in combination with standard-of-care CFTR correctors/potentiators.

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