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Targeting PI3Kγ scaffold function to activate airway CFTR, limit lung inflammation and promote bronchorelaxation in cystic fibrosis

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Background. 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 ensuing CFTR hypofunction primarily affects the respiratory system, in which the reduced activity of the channel ultimately leads to respiratory failure and death in 80% of CF patients. A number of CFTR correctors and potentiators, restoring membrane expression and cAMP-mediated gating of the channel, have been developed, but their efficacy appears to be unsatisfactory and to strictly rely on elevated concentrations of intracellular cAMP.

Hypothesis and objectives. Given the well-established role of phosphoinositide 3-kinase γ (PI3Kγ) as negative regulator of cAMP, we intend to explore the therapeutic potential of PI3Kγ inhibition in cell-based and pre-clinical models of CF.

Preliminary results. Our preliminary data indicate that, in airway epithelial cells, PI3Kγ primarily serves as a scaffold protein that anchors cAMP-degrading enzymes (PDE) to their activator, protein kinase A (PKA) and ultimately promotes cAMP clearance. A compound disrupting PI3Kγ scaffold function (Patent pending N°TO2014A001105) lowers PDE4 activity and enhances cAMP-mediated phosphorylation and activation of F508del CFTR. Intriguingly, this molecule also promotes cAMP-mediated inactivation of leukocytes and cAMP-dependent relaxation of airway smooth muscles.

Essential Methods. We intend to investigate whether inhibition of PI3Kγ scaffold activity is a suitable approach to simultaneously enhance cAMP signaling in the multitude of cell types that critically contributes to CF pathogenesis. In particular, we plan to evaluate the effects of the molecule (i) on CFTR conductance in CF rectal biopsies; (ii) on smooth muscle cell relaxation in tracheal explants and (iii) on adhesion/migration of human primary professional phagocytes. Finally, we will explore the ability of the compound to alleviate disease severity in preclinical models of (i) CF-like and (ii) CF lung disease.

Expected results and their significance. We anticipate that a compound targeting PI3Kγ scaffold activity stimulates cAMP-dependent events in airway epithelial, smooth muscle and immune cells and thus provides three independent therapeutic benefits in CF models by: (i) restoring CFTR conductance, (ii) limiting airway obstruction and (iii) reducing lung neutrophilic inflammation.

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