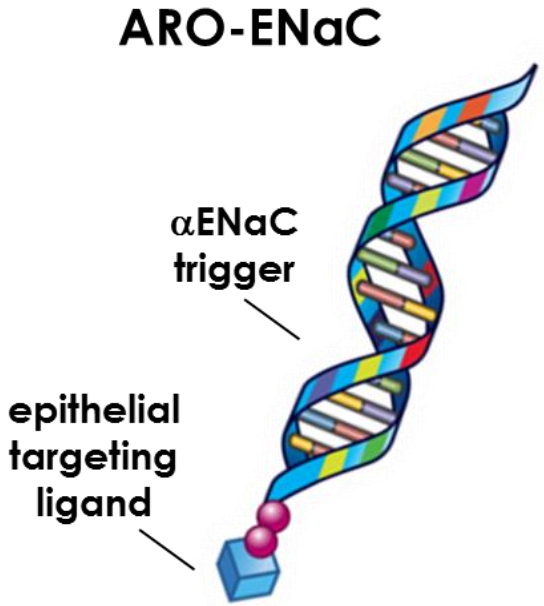
Targeting αENaC with an Epithelial RNAi Trigger Delivery Platform for the Treatment of Cystic Fibrosis

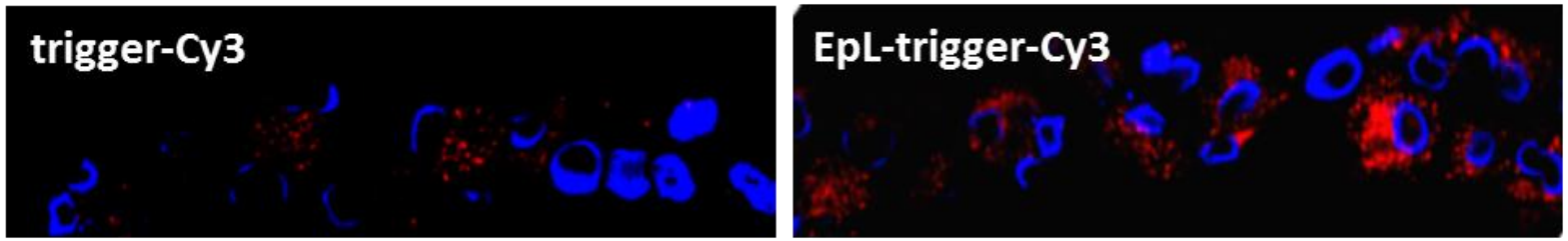
EpL-αENaC RNAi trigger conjugates are internalized by HBE cells *in vitro*, silencing ENaC mRNA expression, reducing amiloride-sensitive current and increasing airway surface liquid

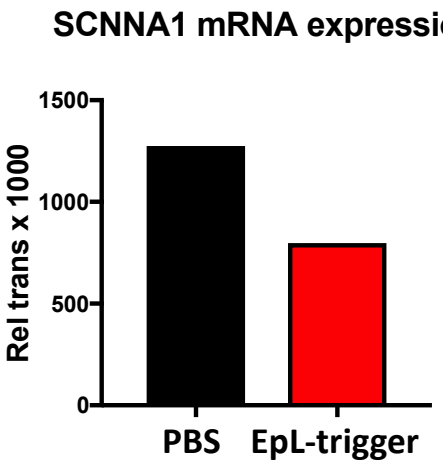


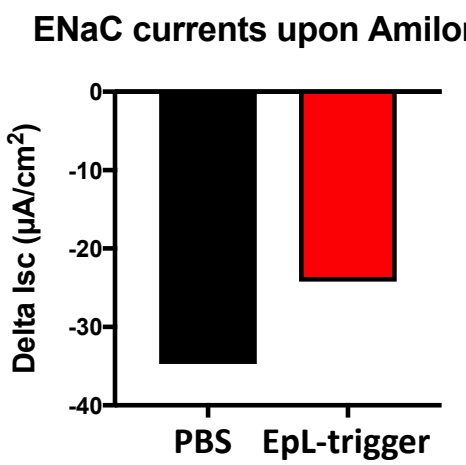
EpL = integrin αvβ6 ligand

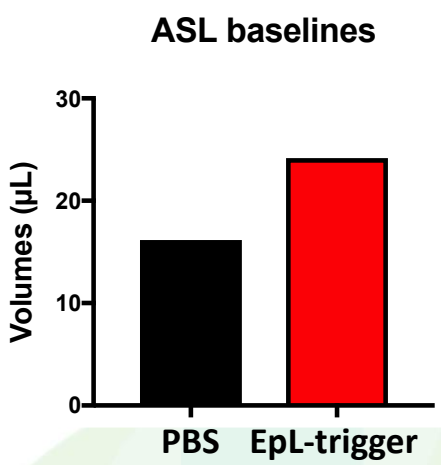
Silencing αENaC mRNA expression in lung is expected to improve airway hydration and increase mucociliary clearance

Fully differentiated HBE cells in ALI culture









Courtesy Matthias Salathe

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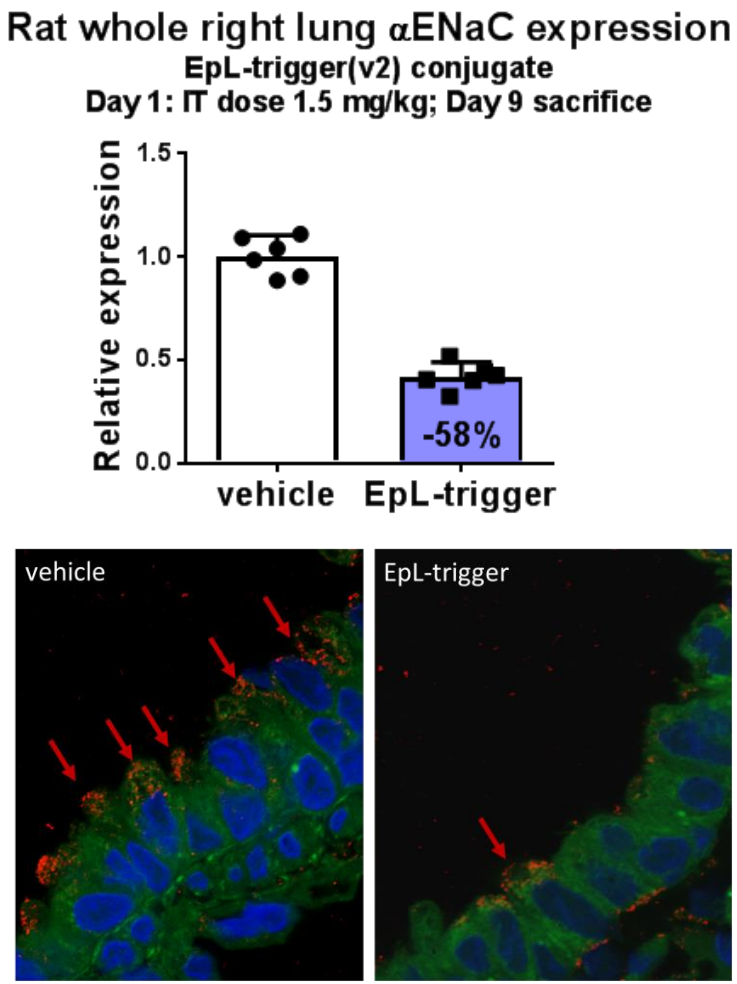
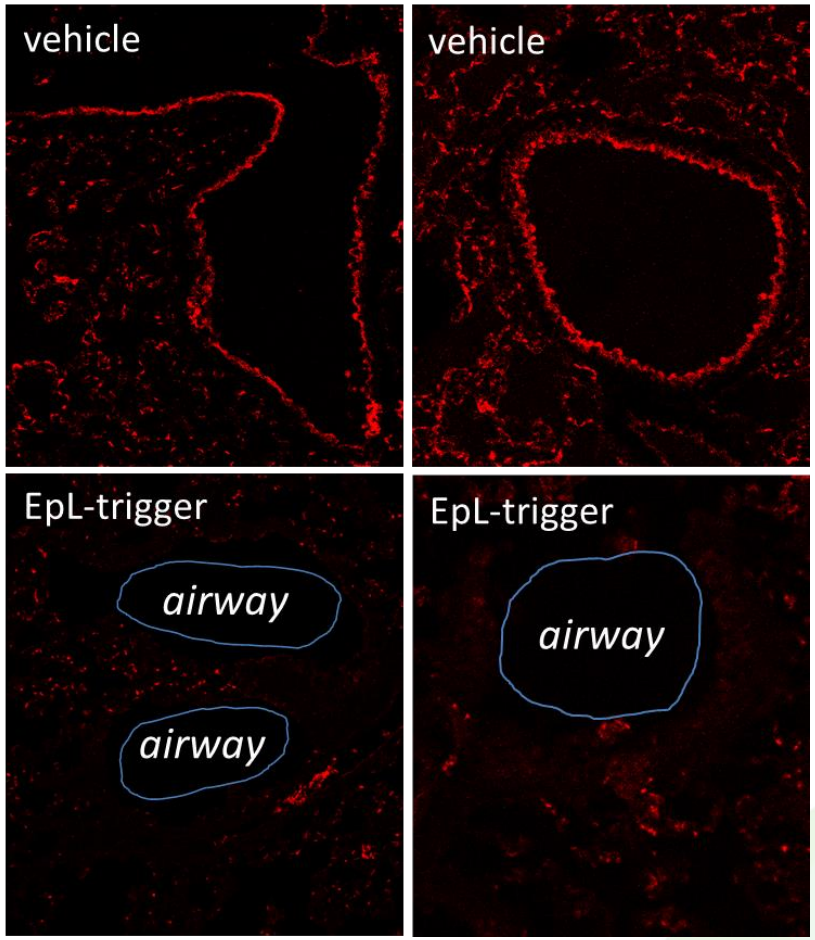
EpL-αENaC RNAi trigger conjugates silence lung αENaC mRNA expression and eliminate airway protein expression after IT dose





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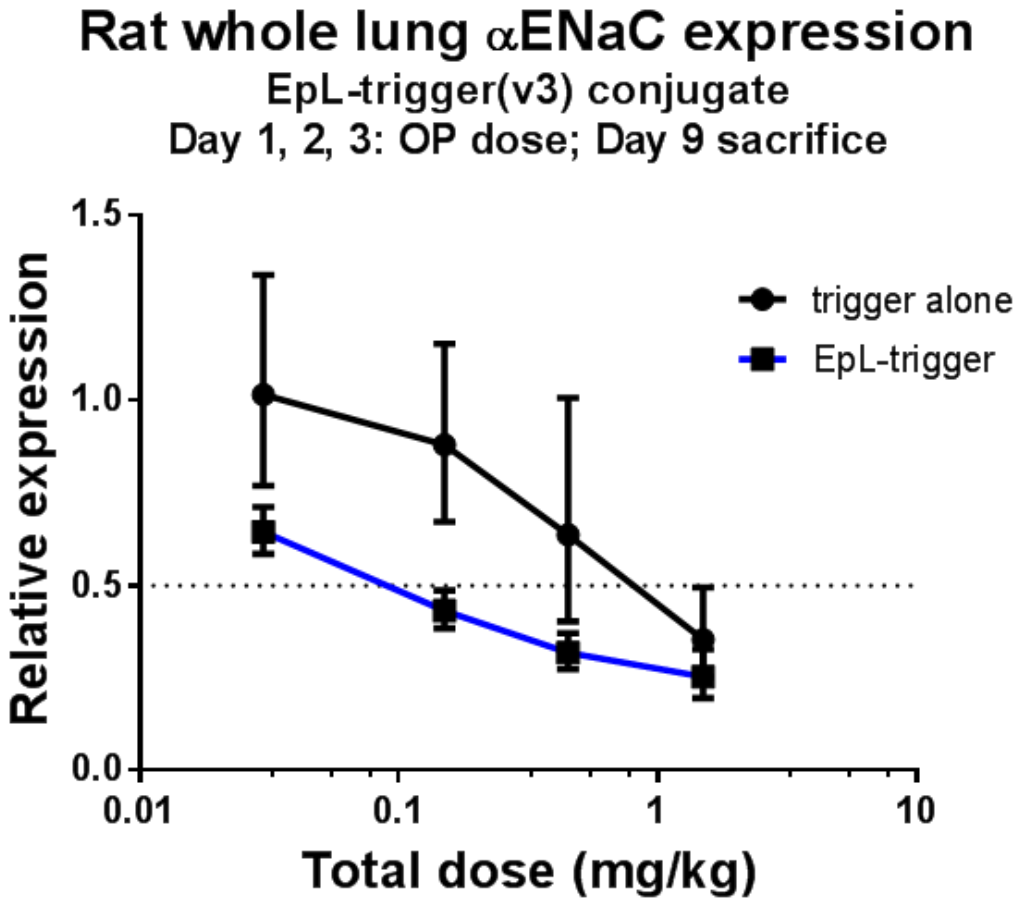
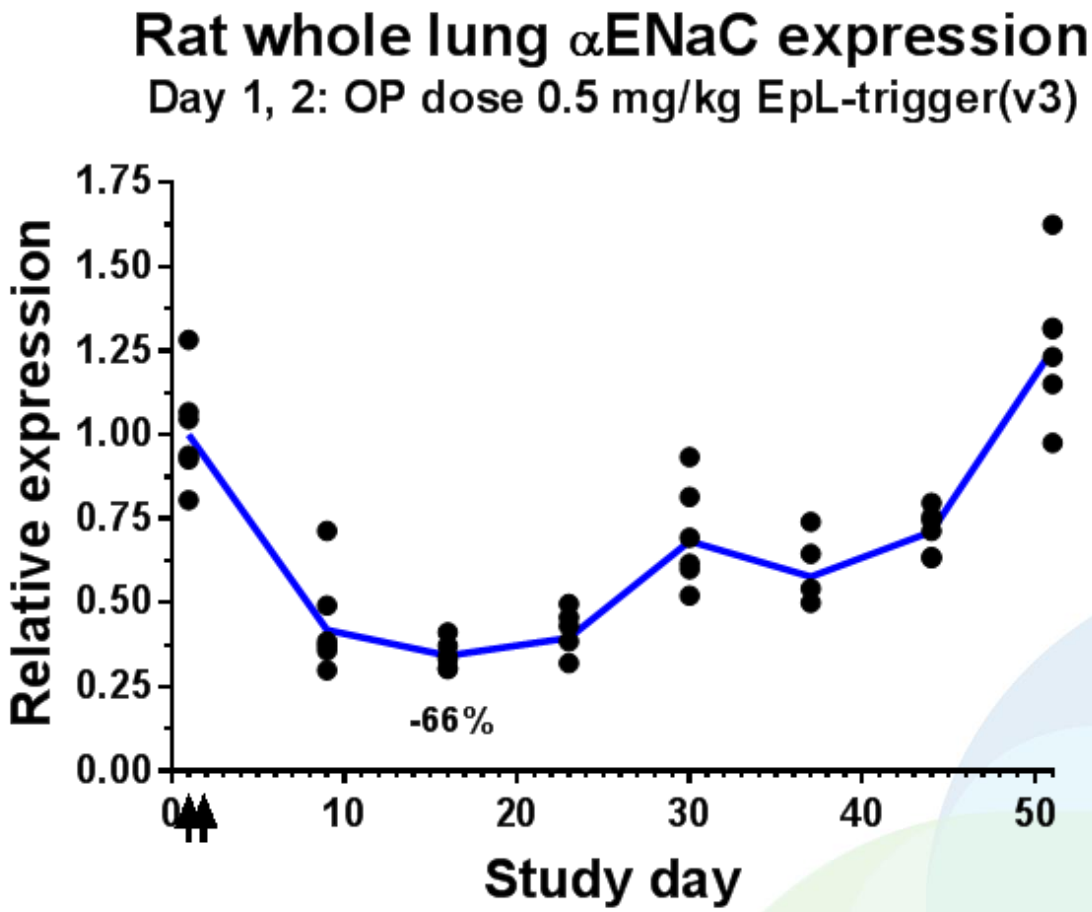
EpL trigger delivery platform increases potency and uniformity of target mRNA silencing in the lung, producing durable reduction in αENaC mRNA expression

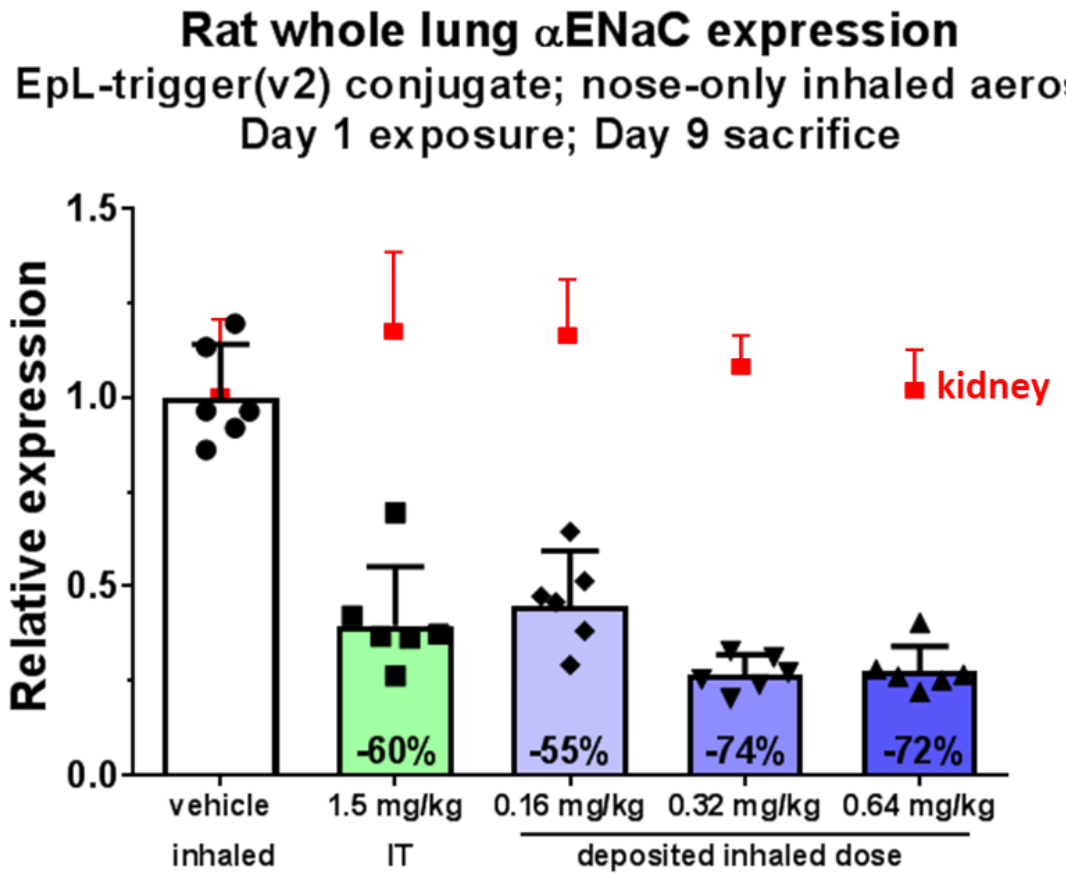




Durable mRNA silencing supports every other week (or less frequent) dose regimens

Targeting αENaC with an Epithelial RNAi Trigger Delivery Platform for the Treatment of Cystic Fibrosis

Aerosol inhalation improves delivery efficiency of EpL-αENaC RNAi trigger conjugates



- Inhaled EpL-αENaC RNAi trigger conjugates produce durable silencing in the lung with no changes in renal αENaC mRNA expression or serum potassium levels
- ARO-ENaC for cystic fibrosis is Arrowhead's first therapeutic candidate to employ the pulmonary epithelial delivery platform
- The platform may be adapted to additional therapeutic targets in the pulmonary epithelium, particularly those that are currently inaccessible to traditional small molecule or antibody approaches