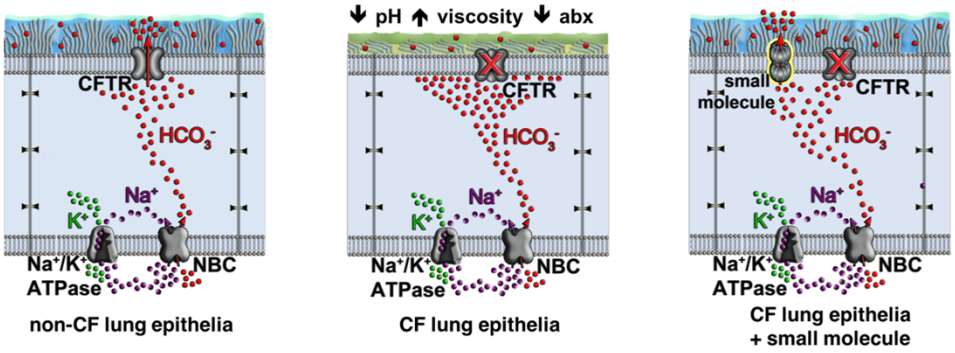
Small molecule ion channel restores host defenses in cystic fibrosis airway epithelia

Rajeev S. Chorghade and Martin D. Burke

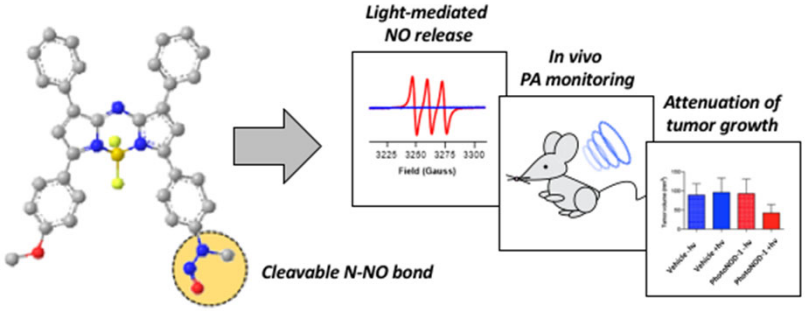
Cystic fibrosis (CF) is caused by loss-of-function mutations in the CFTR anion channel. Loss of CFTR-mediated bicarbonate secretion to the airway surface liquid (ASL) decreases pH and impairs host defenses. We report that the ion channel-forming natural product amphotericin B (AmB) permeabilizes human lung epithelia to bicarbonate, and thereby increases ASL pH. Though AmB is permeable to anions and cations, ASL concentrations of Na+ and K+ were unchanged, suggesting compensatory action of the robust network of pumps and channels in airway epithelia. In genetically diverse CF primary human lung epithelia, AmB increased ASL pH, restored viscosity, and increased antibacterial activity, key components of host defenses. AmBisome®, a clinically approved formulation safely aerosolized to the lung, increased ASL pH in CFTR-/- piglets. Thus, an imperfect small molecule surrogate is sufficient to restore host defenses in CF epithelia, demonstrating a mechanism to address diseases caused by deficient protein function.



Near-Infrared Photoactivatable Nitric Oxide Donors with Integrated Photoacoustic Monitoring

Effie Y. Zhou, Hailey J. Knox, Christopher J. Reinhardt, Gina Partipilo, and Jefferson Chan

Herein, we describe photoNOD-1 and -2, the first organic, NIR-photocontrolled nitric oxide (NO) donors that incorporate a photoacoustic (PA) readout of analyte release. The photoNODs exhibit chemostability to various biological stimuli and negligible cytotoxicity in the absence of irradiation. Upon single-photon NIR irradiation, photoNOD-1 and -2 release NO and PA-active products that enable ratiometric monitoring of NO release. Unlike existing NIR NO donors, the photoNODs do not require encapsulation or multiphoton activation for use in live animals. We use a murine model for breast cancer to show that photoNOD-1 can selectively affect tumor growth rates in the presence of NIR light.



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