Anion-selective molecular prosthetics for CFTR outperform Amphotericin B in cultured CF epithelia

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The channel-forming natural product Amphotericin B (AmB) has shown promise as a molecular prosthetic (MP) for replacing missing or dysfunctional anion-selective cystic fibrosis transmembrane conductance regulator (CFTR) channels in cultured cystic fibrosis (CF) airway epithelia. The efficacy of this MP is hypothesized to be improved by fine tuning the small molecule to allow for more selective efflux of Cl^- and HCO_3^-. Here, we designed an AmB derivative, AmB-AA, that has an additional positively charged amine at the C41 carboxylate and forms anion-selective channels when tested in electrophysiological studies. At high concentrations, channels formed by AmB have been shown to stimulate the upregulation of a proton-potassium antiporter, ATP12a, increasing H^+ secretion and thereby causing a loss of airway surface liquid (ASL) pH recovery. In contrast, the anion-selective variant, AmB-AA, mitigates this undesired effect and thereby restores ASL pH at both low and high concentrations. These results demonstrate that increasing anion selectivity improves the capacity for MPs to functionally replace CFTR.