A novel thiol-saccharide mucolytic for the treatment of muco-obstructive lung diseases

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MUC-031, a novel thiol-saccharide mucolytic drug, is potent and fast acting in rheology-based sputum assays and improves mucus obstruction, airway inflammation and survival in a mouse model of muco-obstructive lung disease http://bit.ly/3Z2UIVQ

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Abstract

Background Mucin disulfide cross-links mediate pathologic mucus formation in muco-obstructive lung diseases. MUC-031, a novel thiol-modified carbohydrate compound, cleaves disulfides to cause mucolysis. The aim of this study was to determine the mucolytic and therapeutic effects of MUC-031 in sputum from patients with cystic fibrosis (CF) and mice with muco-obstructive lung disease (βENaC-Tg mice).

Methods We compared the mucolytic efficacy of MUC-031 and existing mucolytics (N-acetylcysteine (NAC) and recombinant human deoxyribonuclease I (rhDNase)) using rheology to measure the elastic modulus (G′) of CF sputum, and we tested effects of MUC-031 on airway mucus plugging, inflammation and survival in βENaC-Tg mice to determine its mucolytic efficacy *in vivo*.

Results In CF sputum, compared to the effects of rhDNase and NAC, MUC-031 caused a larger decrease in sputum G′, was faster in decreasing sputum G′ by 50% and caused mucolysis of a larger proportion of sputum samples within 15 min of drug addition. Compared to vehicle control, three treatments with MUC-031 in 1 day in adult βENaC-Tg mice decreased airway mucus content (16.8±3.2 *versus* 7.5±1.2 nL·mm^{-2}, p<0.01) and bronchoalveolar lavage cells (73 833±6930 *versus* 47 679±7736 cells·mL^{-1}, p<0.05). Twice-daily treatment with MUC-031 for 2 weeks also caused decreases in these outcomes in adult and neonatal βENaC-Tg mice and reduced mortality from 37% in vehicle-treated βENaC-Tg neonates to 21% in those treated with MUC-031 (p<0.05).

Conclusion MUC-031 is a potent and fast-acting mucolytic that decreases airway mucus plugging, lessens airway inflammation and improves survival in βENaC-Tg mice. These data provide rationale for human trials of MUC-031 in muco-obstructive lung diseases.