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**Title:** Inhaled calcium salts reduce expression of inflammatory mediators associated with tobacco smoke exposure to reduce airway inflammation

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**Body:** PUR118, an inhaled calcium based dry powder (DP) formulation exhibits preclinical anti-inflammatory and anti-infective activity. PUR118 may provide a novel approach for acute exacerbation control in patients with COPD and CF where the combination of underlying inflammation and pathogen infection result in reduced lung function and quality of life. The goal of this study was to evaluate the impact of PUR118 on gene expression in lung samples from a tobacco smoke (TS) exposure model. Mice were exposed to TS for 4d and treated with PUR118 or DP control 1h prior to TS. Mice were euthanized 4h after the last TS exposure and BAL and lung RNA were collected for cell counts, protein levels and QPCR analyses. Expression of 336 genes was evaluated using targeted QPCR arrays. TS exposure increased BAL cell counts that were reduced with PUR118 (79% reduction in neutrophils;  $p < 0.001$ ) to similar levels as a p38 MAPK inhibitor. TS exposure upregulated 21 genes more than 2-fold compared to control mice not exposed to TS and PUR118 treatment inhibited the expression of 11 of these 21 genes. Ten out of the 11 downregulated genes were validated using independent QPCR with 5 significantly inhibited by PUR118 ( $p < 0.05$ ). Among genes found downregulated with PUR118 treatment, many were associated with neutrophilic inflammation including: KC, MIP2, ENA78, IL-6, and MCP-1. BAL protein levels of several of these were similarly reduced by PUR118 compared to controls. Thus, PUR118 diminishes the inflammatory signals induced by TS exposure including many key drivers of neutrophilic inflammation at both the gene and protein level as a mechanism to reduce airway inflammation.