

## Resolvin D1 for Targeting Chronic Lung Inflammation and Infection in cystic fibrosis

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**Background.** Endogenous resolution mechanisms that promote return to homeostasis are defective in cystic fibrosis (CF) leaving inflammation unrestrained with consequent loss of respiratory function, disability, and premature death of patients. Resolvin (Rv) D1 is an endogenous pro-resolution mediator that has entered clinical trials for the treatment of inflammatory diseases. Therefore, its therapeutic potential in CF is of wide interest.

**Hypothesis and Objectives.** Overarching hypotheses tested in this project are that RvD1 represents a potent therapeutic candidate for limiting lung inflammation and enhancing resolution of *P. aeruginosa* infection in CF. Main objectives are to determine, in preclinical models of CF, if RvD1 a) dampens lung inflammation and damage, b) promotes resolution and clearance of bacterial infection.

**Methods.** To achieve the research goals, we infected CFTR<sup>-/-</sup> and wild type mice with the RP73 clinical strain of *P. aeruginosa* and assessed the actions of RvD1 on airway inflammation, lung damage, and bacterial titer.

**Results.** Oral administration of RvD1 significantly reduced death, lung infection, and neutrophil infiltration in CF and wild type mice infected with RP73 immobilized in agar beads that gave a persistent infection and a non resolving inflammation reminiscent pathology of CF patients. Also, RvD1 diminished histological signs of lung damage (i.e., parenchymal inflammation, mucus metaplasia, and epithelial hyperplasia). In isolated human cells, RvD1 dampened expression of adhesion molecules on human endothelial cells, stopped leukocyte recruitment, and

enhanced phagocytosis of RP73 by neutrophils and macrophages, recapitulating its *in vivo* actions. In murine lung macrophages sorted during *P. aeruginosa* chronic infection, RvD1 regulated expression of Toll-like receptors and microRNAs (miR-21 and 155) that lower the inflammatory signaling in macrophages. These results unveil roles and mechanisms of action of RvD1 in chronic *P. aeruginosa* infection in CF mice, providing evidence for potent anti-inflammatory, pro-resolution, and tissue protective properties in preclinical models of CF 6.

**Spin-off for Research & Clinical Purposes.** These results give proof of concepts for the therapeutic use of RvD1 to limit inflammation, promote resolution, and potentiate microbial clearance in CF.

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