# European Respiratory Society
# Annual Congress 2013

**Abstract Number:** 1050

**Publication Number:** P1583

**Abstract Group:** 5.1. Airway Pharmacology and Treatment

**Keyword 1:** Allergy **Keyword 2:** Anti-inflammatory **Keyword 3:** Immunology

**Title:** Pre-clinical characterization of RP3128, a novel and potent CRAC channel inhibitor for the treatment of respiratory disorders

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**Body:** Introduction: Calcium release activated calcium channels inhibitors have a potent role in treatment of autoimmune disorders mediated dysregulated T-lymphocyte and mast cell functioning. Herein, we describe the pre-clinical profile of RP3128, a novel and potent CRAC channel inhibitor with scope for development as a clinical candidate for asthma. Methods: Inhibition of CRAC channel activity in Jurkat cells, cytokine release from human whole blood or PBMC, and mast cell degranulation were estimated. In vivo efficacy of the compound was determined in experimental models of asthma in guinea pigs including PAF or ovalbumin induced eosinophil infiltration into lungs ovalbumin induced histamine release from mast cells, and airway hyper-responsiveness. Results: RP3128 significantly inhibited $I_{CRAC}$ (103 nM) as well as calcium entry into Jurkat cells (40 nM) besides reducing IL-4 (<400 nM) and IL-5 (<250 nM) release from human whole blood and PBMC and IgE-induced RBL-2H3 cell degranulation (24 nM). Oral administration of RP3128 in guinea pigs resulted in a dramatic reduction in eosinophil infiltration in an acute model of PAF-induced allergic asthma ($ED_{50}$ = 0.4 mg/kg/p.o) as well as in an experimental model of ovalbumin-induced chronic airway inflammation ($ED_{50}$ = 0.6 mg/kg/p.o). Consistent with in vitro findings, the compound caused a significant inhibition of mast cell degranulation in Balb/c mice manifested by a reduction in histamine release ($ED_{50}$ = 0.6 mg/kg/p.o). Conclusions: Results demonstrate the potential of RP3128 as an anti-asthmatic agent as evidenced from pre-clinical data. Toxicological evaluation of the molecule is currently in progress.