460. Late-Breaking Abstracts Session: New treatments and targets for airway disease

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Late-breaking abstract: Inhaled pan-selectin antagonist bimosiamose in COPD: A double-blind, randomized, placebo-controlled phase II study

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Background: Bimosiamose a pan-selectin antagonist, previously attenuated ozone-induced airway-inflammation in healthy volunteers. Here we investigated the safety and efficacy of Bimosiamose in a cross-over, double-blind, randomized, placebo-controlled, multi-center trial in patients with COPD.
Methods: 77 moderate to severe COPD patients (GOLD II-III) were enrolled. Bimosiamose (10 mg) or placebo was inhaled by the breath actuated nebulizer Akita[2] Apixneb™ for 28 days twice daily on top of standard bronchodilator therapy. Efficacy was assessed by cellular and non-cellular parameters in induced sputum at baseline and day 28 of both treatment periods. Lung function (FEV1, FVC, PEF, IC) was measured by standardized spirometry.
Results: The total AE ratio of Bimosiamose compared to placebo treatment was balanced. In induced sputum, as compared to placebo, treatment with Bimosiamose led to a reduction of absolute numbers of non-squamous cells (-23%), neutrophils (-24%), lymphocytes (-44%), eosinophils (-34%) and macrophages (-49%), IL-8 (-27%), MMP-9 (-16%) and MPO (-7%). Treatment difference was statistically significant for IL-8 (p=0.009) and macrophages (p=0.012). Compared to baseline, Bimosiamose improved FEV1 by 50 mL (-15 to 115; 95%CI) and IC by 117 ml (11 to 222; 95%CI) at day 28. Treatment difference was statistically significant for FVC (p=0.036).
Conclusions: Inhalation of Bimosiamose for 28 days was safe and well tolerated. It led to an attenuation of airway inflammation and trend towards lung function improvements. These findings support the potential of Bimosiamose as a new anti-inflammatory therapy for COPD.

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Late-breaking abstract: Local and systemic distribution of the GATA-3-specific DNAzyme hgd40 after inhalative exposure
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DNAzymes represent a new class of antisense molecules that combines the specificity of DNA base pairing with an inherent RNA-cleaving enzymatic activity. We developed the DNAzyme hgd40 which was shown to effectively target the transcription factor GATA-3 that plays an important role in the regulation of Th2-mediated immune mechanisms in allergic bronchial asthma.
The aim of this study was to investigate local and systemic distribution of hgd40 after local exposure in mice, rats and dogs.
Using fluorescently labelled hgd40 we could demonstrate that the DNAzyme was evenly distributed in inflamed mouse lungs after single application. Moreover, hgd40 could be intracellularly detected in T cells, Goblet cells, AE type 1 cells and macrophages 2 h after i.n. application. Systemic distribution was investigated in rats and dogs in the course of toxicological studies following single and subchronic (28 d) exposure. Generally, only very low systemic hgd40 levels were detected. In rats, the highest serum concentration of hgd40 was observed 1 h post application (p.a.) and decreased over time to non-detectable levels at 24 h p.a. After 27 d of subchronic, daily inhalation, no accumulation of hgd40 occurred. The results were similar for both sexes and three different doses. Similar results were observed in dogs. Our results indicate that local hgd40 DNAzyme admimistration can target different lung cells expressing GATA-3 and thus modulate Th2-driven immune responses. Low concentration in blood and lack of accumulation after subchronic inhalative exposure indicate that GATA-3-specific DNAzyme hgd40 leads only to marginal systemic distribution.

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Late-breaking abstract: Pre-clinical characterization of RP3128, a novel and potent CRAC channel inhibitor for the treatment of respiratory disorders
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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 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 as well as ovalbumin induced histamine release from mast cells.
Results: RP3128 significantly inhibited calcium entry into Jurkat cells (33 nM) besides reducing IL-4 (<250 nM) and IL-5 (<50 nM) release from human whole blood and PBMC. Additionally, the compound suppressed IgE-induced mast cell degranulation at low nanomolar concentrations. Guinea pigs treated with low doses (1-3 mg/kg/po) of RP3128 displayed >70% reduction in eosinophil infiltration in an acute model of PAF-induced allergic asthma as well as in an experimental model of ovalbumin-induced chronic airway inflammation. Consistent with *in vitro* findings, the compound caused a significant inhibition of mast cell degranulation manifested by a reduction in histamine release.
Conclusions: Results demonstrate the potential of RP3128 as an antiasthmatic agent as evidenced from pre-clinical data. Further biological profiling in respiratory models is planned in addition to toxicological evaluation prior to Phase 1 clinical trials.

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Late-breaking abstract: Pre-clinical efficacy of RP5090 in PI3Kδ mediated airway disorders
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Introduction: PI3Kδ plays a pivotal role in airway remodelling processes that include recruitment and activation of inflammatory cells, cytokine release, mast cell activation and vascular permeability. Given the established criticality of PI3Kδ in airway inflammation, inhibitors specifically targeting this isoform would attenuate progression of asthma and COPD.
Methods: Specificity of RP5090 towards PI3Kδ, suppression of pAKT in THP-1 cells, elastase exocytosis and migration in neutrophils, and IgE-induced mast cell degranulation were determined. Pre-clinical efficacy of RP5090 was confirmed in animal models of airway disorders, namely, LPS-induced pulmonary neutrophilia in rat as well as in acute and chronic eosinophilia models in Guinea Pig.
Results: RP5090 demonstrated significant potency against PI3Kδ (18.5 nM) with several fold selectivity over other isoforms with subsequent inhibition of pAKT. Additionally, the compound inhibited neutrophil functionality and mast-cell degranulation at nanomolar concentrations. RP5090 displayed excellent efficacy in inhibiting LPS-induced neutrophilia in SD rat (65% at 20 mg/kg b.wt). Besides, the compound decreased eosinophil infiltration into the lungs upon induction by PAF (>80% @ 10 mg/kg) or OVA (>60% @ 1 mg/kg) in Guinea pigs. Consistent with *in vitro* findings, the compound caused a significant inhibition of mast cell degranulation manifested by a reduction in histamine release.
Conclusions: Results demonstrate the therapeutic potential of RP5090 in asthma and related airway disorders acting via the PI3Kδ pathway. Further in vivo studies are in progress to evaluate the efficacy of the compound in airway hyperresponsiveness prior to the initiation of clinical trials.

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Late-breaking abstract: The effects of roxithromycin as anti-inflammatoy agent on clinical outcomes in patient with bronchiectasis: A double blinded randomized controlled study
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Bronchiectasis is an inflammatory airway disease with vicious cycle of infection and inflammation. Macrolides have been reported for improve clinical outcomes, we study the effects of macrolide on clinical outcomes such as symptom scores and quality of life in patient with bronchiectasis
Material and methods: Randomized double blinded placebo controlled trials of roxithromycin 300 mg or placebo once daily for 8 weeks in patient with bronchiectasis. Clinical examination, pulmonary function test, St George's Respiratory Questionaire (SGRQ) and sputum culture for aerobic bacteria were done each visits.
Results: 20 bronchiectatic patients, mean age of 56 years, were participated in this study. Nine patients has randomized to roxithromicin 300 mg and 11 patients received placebo once daily. Roxithromycin was shown to improve symptoms scores (mean difference of symptom scores = -2.11, p=0.04) compare with placebo (mean difference of symptom scores = 0.00, p=0.50). Quality of life which assessed by SGRQ was significant improved in the intervention group (p=0.04), but not in placebo (p=0.73). Pulmonary function tests (FEV1, FVC and KCO) were not improved in both groups. No patient in intervention group reported any adverse effect.
Conclusion: Once daily roxithromycin showed benefit on clinical outcomes as well as quality of life. Larger studies of the effects of macrolide in bronchiectasis treatment with longer follow-up times should be done.

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Late-breaking abstract: Once-daily NVA237 improves exercise endurance from first dose in patients with COPD: The GLOW3 trial
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Introduction: Exercise limitation, dynamic hyperinflation and exertional dyspnea

are key features of COPD. We investigated the effects of NVA237, a once-daily (OD) inhaled long-acting muscarinic antagonist, on exercise endurance in pts with COPD.
Methods: 108 pts with moderate-to-severe COPD were randomized to a cross-over design of NVA237 50 μg or placebo OD for 3 weeks, with a 14-day washout. The primary outcome was endurance time during submaximal exercise tolerance test on Day 21 of treatment. Endurance time after first dose, dynamic hyperinflation (inspiratory capacity [IC] at isotime during exercise), and morning trough FEV_1 were also measured.
Results: On Day 21, endurance time significantly increased by 21% with NVA237 compared with placebo; this effect was significant from Day 1, with an increase of 10% (Table). Dynamic IC at exercise isotime and trough FEV_1 showed significant and clinically relevant improvements from Day 1 that were sustained throughout the study (Table). The safety profile of NVA237 was similar to that of placebo.

	NVA237-placebo (LS means, 95% CI)	*p*
Endurance time (sec)		
Day 1	43.1 (10.9–75.4)	<0.001
Day 21	88.9 (44.7–133.2)	<0.001
IC at isotime (L)		
Day 1	0.23 (0.17–0.28)	<0.001
Day 21	0.20 (0.13–0.28)	<0.001
Trough FEV_1 (L)		
Day 1	0.11 (0.06–0.16)	<0.001
Day 21	0.11 (0.06–0.16)	<0.001

Conclusion: NVA237 OD produced immediate and significant improvement in exercise endurance from Day 1, accompanied by sustained and significant improvements in IC at isotime and meaningful improvements in trough FEV_1. Improvement in endurance time increased over the study period, suggesting that mechanisms beyond improved lung function play a role in enhanced exercise tolerance.

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Late-breaking abstract: Preclinical evaluation of an inhibitor of cytosolic phospholipase $A_2\alpha$ for the treatment of asthma
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Asthma is an inflammatory lung disease with considerable requirement for new and effective therapies. Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) is the rate-limiting enzyme responsible for production of eicosanoids implicated in asthma. We investigated a novel $cPLA_2\alpha$ inhibitor, PF-5212372, to establish the preclinical rationale for asthma. PF-5212372 potently and effectively inhibited prostaglandin D_2 (PGD_2) and cysteinyl leukotriene release from human lung mast cells (IC_{50}s 0.29nM and 0.45nM, respectively). In a mixed human lung cell population, PF-5212372 effectively inhibited leukotriene B_4, thromboxane A_2 and PGD_2 (IC_{50}s 2.6nM, 2.6nM and 4.0nM, respectively), but was less effective against PGE_2 release (IC_{50} >301nM, $p<0.05$). In an in vitro cell retention assay, PF-5212372 retained potency up to 24 h post wash-off. Inhaled PF-5212372 effectively inhibited late-phase bronchoconstriction (78% inhibition, $p<0.001$) and airway hyperresponsiveness (94% inhibition, $p<0.001$) in a sheep model of allergic asthma and demonstrated good sheep:human translation in sheep lung mast cells (PGD_2 IC_{50} 0.78nM). PF-5212372 was shown to inhibit AMP-induced constriction of ex vivo human bronchial sections (81% inhibition, $p<0.01$). PF-5212372 was safe and well tolerated in PhI studies.
These data show that inhibition of $cPLA_2\alpha$ using PF-5212372 is effective in a wide-range of pre-clinical asthma models and demonstrates cell retention that may yield clinical duration of action. PF-5212372 may represent a new therapeutic option for the treatment of asthma.

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Late-breaking abstract: Inhaled calcium salts reduce tobacco smoke induced airway inflammation and improve lung pathology
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Rationale: Acute exacerbations (AE) of COPD are associated with bacterial and viral infection, however no available therapy broadly targets infection to prevent AEs. We have developed a novel host-targeted therapy based on the inhalation of dry powder (DP) calcium (Ca) salts that is broadly anti-infective and applicable to AE control. The goal of this study was to evaluate the impact of inhaled Ca salts on inflammation in an acute model of tobacco smoke (TS) exposure.
Methods: C57BL6 mice were exposed to TS for 4d or 11d. Treatments with salt-based DP (40μmol/kg) were delivered by inhalation exposure. A p38 MAP kinase inhibitor (100μg/kg) was used as a positive control. Mice were euthanized 24h after the last TS exposure, BAL cells were quantified and histopathology performed.
Results: In a 4d exposure model, treatment with Ca-based DP (PUR118) once daily 1h or 6h before TS reduced inflammatory cells [for 1h, macrophages (52%) and neutrophils (62%)] compared to control DP ($p<0.01$). Treatment with magnesium (Mg)-based DP 1h before TS reduced macrophages 21% ($p<0.05$); however, neither Mg nor sodium treatment reduced neutrophils. In an 11d exposure model, PUR118 reduced inflammation in prophylactic or therapeutic dosing regimes and markedly reduced the severity and incidence of peri-vascular and peri-bronchiolar inflammation, bronchiolitis, alveolitis, and pneumonitis by histopathological analysis.
Conclusions: Ca-based DP reduced TS induced inflammation and improved lung pathology with equivalent efficacy to the p38 MAP kinase inhibitor. By targeting the infectious cause of AEs and baseline airway inflammation, inhaled Ca DP provides a novel multi-pronged approach for AE control.