246. Animal models of asthma and COPD and late-breaking abstracts on RCT in asthma and COPD

P2121
Umeclidinium (GSK573719) dose response and dosing interval in COPD
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Introduction: Dose differentiation is important in selecting COPD treatments.

Objective: Characterize umclidinium (UMEC), a long-acting muscarinic antagonist, dose response in COPD patients.

Methods: Randomized, double-blind, placebo controlled, crossover study. Subjects were randomized to a sequence of 3 treatments for 7 days separated by a 10- to 14-day washout. Four once-daily (OD) UMEC doses (15.6, 31.25, 62.5, 125mcg) or 2 twice-daily (BID) doses (15.6, 31.25mcg) were administered via dry powder inhaler: Tiotropium (18mcg) was an active control. Primary endpoint was morning trough FEV1; on Day 8; population model analysis was applied with ANCOVA. Serial FEV1, pharmacokinetics and safety were examined. Post hoc analysis of the primary endpoint was performed without one investigative site due to poor study practices.

Results: 163 subjects (mean age 59.5yrs, 52% female) were randomized. Exhaled dose response in trough FEV1 was characterized with OD dose ordering of UMEC 125.6>31.25>15.6mcg. A high potency EED50 (37mcg, 95% CI 18.57, 56 OD regimen) was estimated. Post hoc results were similar. 125mcg OD had more consistent increases in FEV1 from baseline across serial timepoints over 24h compared with other UMEC doses and tiotropium. No advantage of BID over OD dosing was observed. Drug absorption and elimination were rapid. AEIs were highest with UMEC 125mcg OD (18%), placebo (8%), tiotropium (4%), other UMEC doses (5-12%). Two non-drug related, non-fatal SAEs (acute respiratory failure, 15.6mcg OD; myocardial infarction, 31.25mcg OD) were reported.

Conclusions: Dose response for umclidinium was observed in the order 125 > 62.5 > 31.25 > 15.6mcg; a once-daily dosing interval was confirmed.

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P2123
Efficacy and safety of once-daily (OD) fluticasone furoate (FF) in patients with persistent asthma: A 24-week randomised trial
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Introduction: The inhaled corticosteroid (ICS) FF is under development as a OD monotherapy for asthma and in combination with the OD long-acting beta2; agonist for asthma and COPD.

Objectives: To evaluate the efficacy and safety of FF in patients ≥12 years with persistent asthma uncontrolled on a stable low-to-mid dose of ICS (≤500mcg fluticasone pumepon [FP] equivalent total daily dose).

Methods: In this double-blind, double-dummy, placebo-controlled study, patients (N=343; ITT) received FF (100mcg OD in the evening via a new dry powder inhaler; n=114), FP (250mcg twice daily [BD] via DISKUS™; n=114) or placebo (n=115) for 24 weeks. Primary endpoint: trough FEV1 at 24h. Powered secondary endpoint: change from baseline in % rescue-free 24h periods over 24 weeks. Safety assessments included adverse events (AEs), incidence of severe exacerbations and 24h urinary cortisol (UC) excretion.

Results: FF and FP significantly improved trough FEV1 compared with placebo (diff. 146mL; [p=0.009] and 145mL [p=0.011], respectively). Significantly more patients had ≥1 rescue-free 24h periods were reported for FF (14.8) and FP (17.9) than placebo (both p<0.001). Incidence of on-treatment AEs: FF 53%, FP 42%, placebo 40%. Incidence of on-treatment severe asthma exacerbations: FF 3%, FP 2%, placebo 7%. Statistically significant UC suppression was seen with FF (ratio=0.76, p=0.030) and FP (0.77; p=0.036), relative to placebo.

Conclusions: FF 100mcg OD significantly improved trough FEV1 to a similar extent to FP 250mcg BD and reduced rescue use relative to placebo. FF was well tolerated with a similar AE profile and effect on 24h UC to FP. Funded by GSK (FAA12059; NCT01159912).

P2124
RC kinase: A novel kinase expressed by alveolar macrophages that may play a role in COPD and IPF
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We have characterized a novel serine/threonine protein kinase, called RC kinase, whose expression is upregulated in COPD patients. Examination of RC kinase mRNA tissue distribution showed a limited expression pattern restricted mainly to the lungs and trachea. Immunohistochemical analysis with a monoclonal antibody revealed expression in CD68+ alveolar macrophage and bronchial epithelial cells. Various cell lines upregulated RC kinase expression upon exposure to cigarette smoke extract, or conditions of oxidative or endoplasmic reticulum stress, and this...
P2125 Statins worse pulmonary fibrosis through enhancing NLRP3 inflammasome activation
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The role of statins is controversial. To evaluate the association between statin use and interstitial lung abnormalities (ILA) in a large cohort of smokers from COPDGene. Next, we evaluated the effect of statin pretreatment on bleomycin-induced fibrosis in mice and explored the mechanism behind these observations in vitro. In COPDGene, 38% of subjects with ILA were taking statins compared to 27% of subjects without ILA. Statin use was positively associated in ILA in multivariable (OR) 1.60, 95% confidence interval [CI] 1.03-2.50, p=0.04 after adjustment for covariates including a history of high cholesterol or coronary artery disease. This association was modified by the hydrophilicity of statin and the age of the subject. Next, we demonstrate that statin administration aggravated lung injury and fibrosis in bleomycin-treated mice. Statin pretreatment enhances caspase-1-mediated immune responses in vivo and in vitro; the latter responses were abolished in bone marrow-derived macrophages (BMDM) isolated from LDLR−/− mice. Finally, we provide further insights by demonstrating that statins enhance NLRP3-inflammasome activation by increasing mitochondrial reactive oxygen species generation in macrophages. Statin use is associated with ILA among smokers in the COPDGene study and enhances bleomycin-induced lung inflammation and fibrosis in the mouse through a mechanism involving enhanced NLRP3-inflammasome activation. Our findings suggest that clinicians should be aware that radiological evidence of ILD can develop in some COPD patients treated with statins.

P2126 Effects of combination of PI3Kδ and δ inhibitors on airway hyperresponsiveness in tobacco smoke-exposed mice
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PI3Kδ and γ are known to be involved in inflammatory cell functions. We recently found upregulation of PI3Kγ in lung tissue of COPD patients and ability of a PI3Kδ inhibitor on restoration of steroid sensitivity in airway inflammation in tobacco-smoke (TS) exposed mice. Superior effects of combination of PI3Kγ and δ inhibitors to each inhibitor alone on airway inflammation in TS-exposed mice were also observed. The aim of this study is to evaluate role of PI3Kδ and δ on airway hyperresponsiveness (AHR) in TS-exposed mice. A2F mice were exposed to TS for 11 days and IC50114 (IC), AS604850 (AS) and/or fluticasone propionate (FP) were administrated intranasally twice a day for 3 days after the last TS exposure. Airway responsiveness was determined as the increment of airway resistance (Δ(Raw/TV)) before and 1 min after histamine administration at 24 h after the last drug dosing. The effects of the PI3K inhibitors on the contractile response to carbachol in guinea-pig tracheal smooth muscle preparation were also evaluated by the isometric tension recording. The concentration-response curve of carbachol was shifted to rightward and reduced the maximal response by AS (10-100 μM) in contrast, the effects of IC (100 μM) was limited in the tracheal smooth muscle. The AHR induced by TS was significantly reduced by AS (4 mg/ml; by 56% inhibition) and IC (4 mg/ml; 43%) alone. The inhibitory effects were enhanced by combination treatment of AS and IC (%). Moreover, the combination of IC and FP showed stronger inhibition (96%) on the AHR. Considering with our previous findings, the combination of a PI3Kδ or PI3Kδ/γ inhibitor with corticosteroid may offer potential treatment of COPD.

P2127 A robust translational model of acute exacerbations in the tobacco-smoke and poly IC treated mouse
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Exposure to tobacco smoke (TS) for 4 days induces steroid-insensitive lung inflammation in mice. The effect of adding the viral mimetic poly IC (PIC) to TS-exposed mice was examined. Methods: Mice were exposed daily to either TS or air for 4d. Saline or PIC was administered intra-nasally. The time course of lung inflammation was examined 4-12hrs after the last exposure and cell numbers measured in the BAL fluid. The acute effects of oral Dexamethasone (DEX 0.3mg/kg) or Roflumilast (ROF 5mg/kg) on the peak inflammation were examined. The effects of DEX on the kinetics of the enhanced inflammation were also examined. Results: TS caused a lung inflammation which was inhibited by ROF but not by DEX. PIC alone induced an inflammation that was not inhibited by DEX or ROF. Dosing PIC in addition to TS induced an exaggerated response that was significantly greater than the additive effect of the two stimuli. The enhanced response peaked 24hrs after the last exposure then slowly declined. Neutrophils were predominant over the first 48 hrs. Macrophage numbers increased at 24-72hrs and lymphocyte numbers peaked at 48-72hrs. The peak inflammation after TS/PIC exposure was significantly inhibited by ROF (5%, p<0.05) and DEX (56%, p<0.05), in contrast to the lack of efficacy of DEX against TS or PIC alone. A single dose of DEX after the last exposure reduced the exaggerated response over the entire 120hr study period, but did not fully resolve the inflammation. Conclusions: TS exposure for 4 days induced a steroid-insensitive lung inflammation. Addition of PIC markedly enhanced the inflammatory response which was sensitive to both steroids and roflumilast, mimicking features of human COPD.

P2128 Inhaled cationic salts modulate macrophage function to reduce inflammation during LPS induced lung injury
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Pulmatrix is developing PUR118 as a host-targeted, dry powder therapy based on the inhalation of calcium salts for acute exacerbation (AE) control in chronic obstructive pulmonary disease and other inflammatory lung disease. Preclinical data suggest that this approach is effective against an array of pathogens and also reduces inflammation resulting from environmental stimuli such as tobacco smoke. We hypothesized that this treatment could be effective in reducing lipopolysaccharide (LPS) induced lung inflammation by modulating the function of pulmonary macrophages. Mice were exposed to nebulized LPS (Pseudomonas aeruginosa) and PUR118 was delivered via whole body exposure 1h post-LPS challenge. Four hours after LPS exposure inflammatory cell counts and chemokine and cytokine concentrations were determined in BAL. PUR118 treatment decreased total inflammatory cell counts and neutrophil counts in the BAL fluid of LPS challenged mice and correlated with reduced KC, IL-6 and TNF-a in BAL fluid. Separately, peritoneal macrophages were isolated from naive mice and challenged with LPS in media supplemented with calcium to simulate conditions thought to be found in lung fluid lining after PUR118 treatment. Inflammatory mediator secretion and gene expression were determined 2h post LPS exposure. Macrophages stimulated with LPS in the presence of calcium exhibited a dose dependent decrease in IL-6 and TNF-a secretion and reduced gene expression for these inflammatory mediators. These data suggest that PUR118 can act through macrophages to reduce lung inflammation and may reduce the risk of AE caused by infections during chronic lung disease.

P2129 Inhaled calcium salts reduce expression of inflammatory mediators associated with tobacco smoke exposure to reduce airway inflammation
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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 of 100 μg 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<0.003) 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 independent of IC3P 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 TSS, typical of many key drivers of neutrophilic inflammation at both the gene and protein level as a mechanism to reduce airway inflammation.

P2130 Protection against allergen-induced airway hyperresponsiveness (AHR) by olodaterol in guinea pigs is synergistically enhanced by tiotropium

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The ultra-long acting β2-agonist olodaterol has shown to be effective in asthma and COPD. Increased cholinergic tone, common to these diseases, may reduce β2-agonist responsiveness. In a guinea pig model of asthma, we investigated the protein expression of airway inflammatory cells in combination with the long acting anticholinergic tiotropium. Airway responsiveness (PC100) was assessed at baseline (24h before OA) and after the early (EAR, 6h after OA) and late (LAR, 24h after OA) asthmatic reactions. 10nM OA before, animals were treated with PBS (control), 1nM olodaterol and/or 0.1nM tiotropium (nebulizer concentrations, 3 min). OA induced AHR to histamine after the EAR (4.9-fold decrease in PC100 compared to baseline), which was fully protected by olodaterol (2.3-fold increase in PC100) and tiotropium (1.3-fold increase). When combined, a synergistic 4.8-fold increase in PC100 was observed. After the LAR, AHR (2.8-fold decrease), was also protected by olodaterol, tiotropium and their combination. AHR (1.5-, 1.3- and 1.6-fold increase in PC100, respectively) OA-induced infiltration of inflammatory cells, measured by BAL after the LAR, was not affected by any treatment. In conclusion, in a guinea pig model of asthma olodaterol and tiotropium protect against allergen-induced AHR after the EAR and LAR, without affecting inflammatory cell influx. Synergism between the drugs was found after the EAR, indicating that acetylcholine reduces the effectiveness of the β2-agonist and that the combination of olodaterol and tiotropium may be beneficial in the treatment of allergic asthma (supported by Boehringer Ingelheim Pharma).

Background: Chronic exposure to ozone in mice induces chronic lung inflammation and emphysema, features of COPD. We determined to examine the preventive and therapeutic effects of N-acetylcysteine (NAC) on airway inflammation, airway hyperresponsiveness (AHR) and abnormal lung function. Methods: BALB/c mice were exposed to air or ozone (3ppm, 3h), twice a week for 6 weeks and then ozone exposure was discontinued for 6 weeks. NAC treatment (100mg/kg, i.p. twice a week) was started on the 6th week. NAC treatment during exposure period or cessation period did not inhibit or reverse abnormal lung function. AHR was induced in ozone exposed mice and persisted after ozone cessation. NAC treatment during exposure period or cessation period did not inhibit or reverse abnormal lung function. AHR induced by ozone in Balb/c mice and persisted after ozone withdrawal. NAC inhibited AHR during cessation period. Total cells and neutrophils in BALF were increased in ozone exposed mice and returned to normal after ozone cessation. NAC given during exposure period reduced the total cell counts, but not the neutrophil counts.

Conclusions: AHR and abnormal lung function persisted in ozone induced COPD model despite cessation of ozone exposure. Though NAC had no effect on neutrophilic inflammation or abnormal lung function in ozone-exposed mice, it did inhibit AHR during cessation period. NAC interferes with airway smooth muscle dysfunction caused by chronic oxidative stress.

P2132 Interaction of the glutamatergic and nitrergic signaling system in the airway hyperactivity (AHR) model

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It is only little information regarding a possible interaction of glutamatergic and nitrergic system in the airways hyperactivity (AHR). We investigated the effect of agents modulating the activity of these systems on the experimental ovulaminium-induced AHR as well as on the changes of exhaled nitric oxide (eNO) levels. We used the agonists of NMDA receptors - N-methyl-D-aspartic acid (NMDA) and monosodium glutamate (MSG), selective competitive antagonist (D-2-amino-5-phosphonovascular acid – AP-5) and selective non-competitive antagonist (dizocilpine - MK-801) of these receptors. We used also non-specific inhibitor of NO syntheses N-omega-nitro-L-arginine methyl ester (L-NAME). Effect of AHR to histamine or acetylcholine was evaluated in vitro conditions. NMDA administration caused the increase of tracheal smooth muscle response in ovulaminium-induced HR to acetylcholine. The effect of MSG was less pronounced. MK-801 as well as AP-5 provoked the decrease of reactivity mainly to acetylcholine in tracheal smooth muscle, while the former, non-competitive antagonist was more effective. We recorded the changes in eNO levels. The activation of NMDA receptor with NMDA or MSG increased eNO levels. The inhibition of NO synthase with L-NAME caused the fall of eNO levels. We suppose here the participation of constitutive isoforms of NO syntheses mainly. MK-801 shows the more expressive effect on the eNO levels during sensitisation than AP-5 group. We results bring a whole new look regarding the relationship of the glutamatergic and nitrergic system in the airway inflammatory diseases.

P2133 Effect of muscarinic receptors inhibition on cytokine release and inflammatory cells infiltration in the airway of cat as an animal model for COPD

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COPD is currently ranked high as the leading cause of death in the world. In this study, fifteen healthy adult male cats were randomly categorized into three groups of each with five in each: I) control, II) exposure to cigarette (COPD model) and III) exposure to cigarette (COPD model) treated with tiotropium. They were exposed to cigarette smoke for four days, using 190 cigarettes for each one totally. In group III, cats were treated with one capsule of tiotropium once a day using endotracheal tubes. On the fifth day, the animals in all groups were killed by exsanguination and the lungs were lavaged. In BAL fluid, total inflammatory cell number, neutrophil and lymphocyte are all increased in exposure to cigarette smoke COPD model. Similar to the effect on total cell number, increase in differential cell numbers was reduced by administration of tiotropium. Experimental cigarette smoke-induced COPD causes were found to increase cytokine release and cells infiltration in the airway of cat as an animal model for COPD. It seems that treatment with antimuscarinic agent like tiotropium may attenuate inflammatory events in the airway of this animal model.

P2134 Anti-inflammatory activity of doxofylline and theophylline in LPS-induced lung inflammation

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Doxofylline and theophylline are two xanthine drugs that show both bronchodilator and anti-inflammatory actions. Data has suggested that doxofylline has a wider therapeutic window than theophylline however, the precise mechanism of action of doxofylline is unknown and its anti-inflammatory activity has not been widely investigated.

Methods: Doxofylline (0.3 mg/kg, i.p.) and Theophylline (10 mg/kg, i.p.) were given -24, -1 and 6 h after LPS (10 μg/mice, i.n.) in Balb/c mice. Lung lavage was performed 24 h later. In other experiments, doxofylline (0.3 mg/kg, i.p.) was given 24 h before LPS (10 μg) into the scrotal sac. Mice were prepared for intravital microscopy 24 h later.

Results: LPS recruited significantly higher number of neutrophils (PMN) to the lung (mean ± SEM) compared to saline (saline:0 ± SEM, n = 4; LPS:5 ± SEM, n = 4), p = 0.05 vs LPS alone). Theophylline (Theo) did not alter the recruitment of PMN in response to LPS (LPS:2 ± SEM, n = 8). Mice showed an accumulation of cells in the tissue (cells/50μm2) (saline:0 ± SEM, LPS:3 ± SEM, n = 4; p = 0.05) and higher number of cells rolling (cells/100μm) in 30 sec saline:0 ± SEM, LPS:5 ± SEM, n = 4; p = 0.05). Theophylline significantly inhibited cell migration in response to LPS.
Corticosteroid resistance in COPD is an urgent problem so the search for drugs that have bronchodilatory and anti-inflammatory effect at all stages of COPD is needed.

**Aim:** To study effect of non-corticosteroid drug fenospiride (F) on contractility of bronchial smooth muscle (SM) in rats with COPD.

**Methods:** Model of COPD was induced in rats by nitrogen dioxide (NO2) exposure (15 ppm, 1.5 h/day, 60 days). F (0,15 or 15 mg/kg) was administered per os daily before exposure to NO2. Control rats received 0.9% NaCl. Isometric contraction of bronchial segments caused by electrical stimulation (st) of preganglionic nerve or SM was recorded by displacement electromechanical transducer.

**Results:** Treatment with F at the acute stage of COPD (15 days) prevented the bronchial constrictor effect of NO2. Contractile reactions of bronchi were lower than in control with st both nerve (89±4%; 107±2% for 0.15 and 15 mg/kg, control 118±5%, p < 0.05) and SM (89±3%; 88.4±4%; 103.3±3% respectively, p < 0.05). Dilatation effect of low dose F was mediated by interaction with capsaicin sensitive C-dermat that prevented the initiation of neurogenic inflammation as evidenced by lack of COPD structural changes in lungs. At stage of COPD (60 days) bronchiatric effect of low dose F did not appear; high dose F caused a greater SM relaxation with st muscle (70±3%) than with nerve (81±2%, p < 0.05).

**Conclusion:** Effect of high dose F was mediated not only the allfferent component but due to its direct relaxing effect on SM.

**References:**

**P2138**

**Effect of CCR3 inhibitors on allergic airway responses in ascaris-sensitized cynomolgus monkeys.**

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**Aim:** CCR3 has historically been associated with the functional responses of eosinophils in various models of allergic disease. The goal of this study was to determine whether pre-treatment with CCR3 inhibitors via oral and inhaled routes attenuates asthma responses in ascaris sensitized Cynomolgus monkeys.

**Methods:** Animals received a CCR3 antagonist given orally (AP0), or by inhalation (AR1) once or twice a day for 10 or up to 21 days prior to inhaled ascaris challenge. Changes in airway function (immediate and methacholine [MCH]) and airway inflammation (BAL & blood cells) were evaluated.

**Results:** Oral (AP0 5 mg/kg, BID 10 days) or inhaled (AR1 860 µg; BID 7 days) treatment showed a trend towards a reduced immediate ascaris and MCH response but did not reach statistical significance. A longer oral treatment (AP0 3 mg/kg; QD 30 days) resulted in a significant reduction of CCR3 expression in airway function but did lead to a greater reduction in BAL and blood eosinophils than AP0 or fluticasone alone.

**Conclusion:** Treatment with a CCR3 inhibitor in the non-human primates, Ascaris model of asthma, shows that a number of critical parameters can be affected which are significantly different to alterations in the recruitment of eosinophils. Overall, these observations suggest that CCR3 inhibition may have more globally-beneficial responses in an asthmatic setting than previously appreciated.

**P2139**

**PK/PD profiles of the CXCL8 decoy protein PA401 after intravenous and intratracheal administration in saline and LPS exposed mice.**

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Neutrophils play a crucial role in acute and chronic lung diseases including ALL COPD, CF and severe asthma, and their presence in the lung has been correlated to disease severity and progression. Among the mediators of neutrophil recruitment to the lung CXCL8 exerts its chemotactic activity by binding to glycosaminoglycan (GAG) co-receptors on inhaled cells, thus creating a solid-phase haptotropic gradient and being properly presented to GPC receptors CXCR1/2 on neutrophils.

We have engineered higher affinity for GAGs into human CXCL8 obtaining a protein-based competitor for the CXCL8/GAG interaction. By further knocking-out the GPCR domain, we have obtained a decoy protein (PA401) with potent anti-inflammatory characteristics.

PA401 has been tested in murine models of lung inflammation induced by lipopolysaccharide (LPS) showing strong dose-dependent neutrophil reduction in bronchoalveolar lavage fluid (BALF) after intravenous (IV) and subcutaneous (SC) administration.

In the present study we have compared PA401 activity after IV and intratracheal (IT) administration in the same model, using saline exposed mice as control. PA401 plasma levels were also measured to assess pharmacokinetic profiles.

PA401 has strongly reduced BALF neutrophils number after IV and IT administration (up to >70%). The blood cells increase due to LPS exposure was also partly normalized by IV, but not IT treatment, possibly due to the differences in plasma exposure.

PA401 is a new biotherapeutic with a unique mode of action interfering with lung neutrophilic inflammation and with activity after systemic and local delivery being better.
Targeting the IL-1β – IL-17A inflammatory axis for the treatment of viral-induced exacerbations of COPD

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Chronic obstructive pulmonary disease (COPD) is one of the world’s leading respiratory diseases, projected to be the 3rd leading cause of death by 2030. Acute worsening of the disease can be caused by bacterial and viral infections and is often associated with hospitalization. Although COPD exacerbations have been linked to enhanced recruitment of inflammatory cells, such as neutrophils, and to dysregulation of several inflammatory mediators, treatment predominantly relies on corticosteroid therapy with no therapeutic options available to stop disease progression. IL-1β levels are increased in COPD patients during acute exacerbation (Gessner, C. et al. Respir Med 2005; vol. 99 (10) pp. 1229-40); however, it remains to be determined if this is causative of lung dysfunction and exaggerated inflammation or simply associated with the disease.

We found that the severity of COPD exacerbations, characterized by influx of neutrophils to the bronchoalveolar fluid (BALF) and by measurement of lung function, was reduced in mice lacking IL-1β. At early time points after infection this protective effect was mediated by decreased production of IL-17A by Th17 and γδ T cells. However, at the peak of viral infection, neutrophilic inflammation was independent of IL-17A but dependent on IL-1β signaling. Indeed, neutrophil recruitment at late time points during infection could be abrogated by treatment with the IL-1R antagonist Anakinra (Kineret). These data highlight IL-17A and IL-1β as targets for therapeutic intervention during viral-induced exacerbations of COPD.