To define the toxicity of inhaled DM in a mouse model, using different concentrations of DM solution: normal saline, 60, 90 and 360 mg/kg. Inhalation studies lasted ~ 20 min/day, for 3 weeks. Blood analysis and complete histological evaluations were performed.

**Methods:** Female BALB/c mice, were divided to 4 groups exposed to increasing concentrations of DM solution: normal saline, 60, 90 and 360 mg/kg. Inhalation studies lasted ~ 20 min/day, for 3 weeks. Blood analysis and complete histological evaluations were performed.
Conclusion: The PDE4 inhibitor RNO curbs Plt–leukocyte interactions. Akt phosphorylation, while inducing phosphorylation of Csk, the major negative level of GR nuclear translocation at 24h after 4h FF (10−7M) treatment as seen maintained at 16 and 24h. There was a corresponding decrease in cytosolic GR AKAP79, AKAP250 and AKAP450 (aka AKAP9) are expressed in human airway of AKAPs in regulating inflammatory cytokine release and the responsiveness to AKAP250 (aka AKAP12). Here we studied the expression pattern and functions nuclear localisation for 24 hours after washout in monocytes.

Fluticasone furoate (FF) is a novel corticosteroid (CS) under development. In dose-ranging studies in asthmatics, FF had 24 hour (h) duration of efficacy. The effects of FF on GR nuclear translocation over a 24h time-course could contribute to the pathophysiology of this disease. Supported by Stichting Astma Bestrijding and a Rosalind Franklin Fellowship.

TFNs substantially contribute to the establishment of chronic airway inflammation. The PDE4 inhibitor roflumilast N-oxide (RNO), the active metabolite of roflumilast (ETAR/ETBR antagonist Bosentan with those of the ETAR-selective antagonist Ambriam.R The overall response of cultured HASMCs of n=8 current smokers to TNFs in the absence or presence of Bosentan or Ambriam was investigated by gene expression analysis with the Agilent Whole Genome Oligo Microarray technique (40,000 genes). Results of Asthma- and/or COPD-related cytokines/chemokines were verified by quantitative RT-PCR and ELISA.

The expression of 4.9±0.3±16 genes was induced twofold or more by TNFs. Among them were GM-CSF, G-CSF, 8 CC and 8 CXC family members and 5 interleukins. Bosentan and Ambriamina had comparable effects on 396±63 genes, respectively, in TNFs-exposed HASMCs. Among them were CCL5/7/8/19/20, CXCL6/10, CXCL1, IL-6/7/23 and GM-CSF (all <p<0.05). The release of CCL2, CCL7, CXCL1 and GM-CSF was more efficiently reduced by Bosentan compared with Ambriam (p<0.05). Without the exception of GM-CSF, the effects of ET receptor antagonists on these factors were due to inhibition of gene transcription.

Six genes contribute to the establishment of chronic airway inflammation in asthma and COPD. Particularly none-selective ET receptor antagonists might have therapeutic utility in early stages of chronic airway diseases by counteracting the establishment of inflammatory processes.

Simvastatin selectively inhibits TSLP-production in primary bronchial epithelial cells from COPD donors.

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Simvastatin selectively inhibits TSLP-production in primary bronchial epithelial cells from COPD donors.
Effects of aclidinium on respiratory function in guinea pigs chronically exposed to cigarette smoke
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Introduction: Chronic obstructive pulmonary disease is characterised functionally by decreased respiratory function due to airflow obstruction. Aclidinium, a novel muscarinic antagonist, on respiratory function and signs of bronchial irritation in guinea pigs chronically exposed to cigarette smoke (CS).

Methods: Male guinea pigs (n=46) were divided into 2 groups: control (n=22) and exposed to CS (n=24; 6 cigarettes/day, 5 days/week for 24 weeks). Animals received nebulised vehicle, aclidinium 10 μg/mL or aclidinium 30 μg/mL 60 min before CS exposure. The thickness of the adventitia, muscular layers of the airway wall was measured by planimetry in immunostained sections. Emphysema and goblet cell metaplasia were evaluated using sections stained with haematoxylin-eosin and alcian blue, respectively. The internal luminal perimeter of each airway served as a reference to normalise and stratify the assessments.

Results: Aclidinium prevented thickening of the small airway muscularis layer in animals exposed to CS. Thickness after CS exposure was: aclidinium 10 μg/mL and aclidinium 30 μg/mL 60 min before CS exposure. The thickness of the adventitia, muscular layers of the airway wall was measured by planimetry in immunostained sections. Emphysema and goblet cell metaplasia were evaluated using sections stained with haematoxylin-eosin and alcian blue, respectively. The internal luminal perimeter of each airway served as a reference to normalise and stratify the assessments.

Conclusions: Aclidinium reduces human lung fibroblast activation following CSE exposure in vitro. Aclidinium may reduce lung fibroblast activation in patients with COPD after CS exposure.

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Prevention of adverse pulmonary consequences of myocardial ischaemia in 
P855
imbalance. We propose that inhalation of PC-SOD would be therapeutically
The results suggest that PC-SOD protects against pulmonary emphysema by inhi-
pulmonary inflammation.
We also found that inhalation of PC-SOD suppressed cigarette smoke-induced
induced increase in the pulmonary level of superoxide anions, cell death, activa-
tion of proteases and expression of pro-inflammatory cytokines and chemokines.
We also found that inhalation of PC-SOD suppressed cigarette smoke-induced
pulmonary inflamation.
The results suggest that PC-SOD protects against pulmonary emphysema by inhi-
bition of inflammation and cell death and amelioration of the protease/antiprotease
imbalance. We propose that inhalation of PC-SOD would be therapeutically
beneficial for COPD.

Prevention of adverse pulmonary consequences of myocardial ischaemia in 
rats
P855
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The efficiency of treatment strategies against airway hyperresponsiveness (AHR) were compared following chronic postcapillary pulmonary hypertension induced by myocardial ischaemia (MI). Airway resistance (Raw) was measured in four groups of rats under baseline conditions, and following iv infusions of 2-18 μg/kg/min methacholine (MCh). Sham surgery was then performed in Group C, while the left interventricular coronary artery was ligated in the other groups with-
out treatment (Group I), or daily treatments with combined angiotensin enzyme 
activator inhibitor-1 (PAI-1) in the myocardium and the renal cortex was attenuated
markedly attenuated systemic hypertension, improved systolic heart function and
survival in experimental malignant hypertension. Mortality, hemodynamics and biomarkers of tissue remodeling and degeneration were assessed in Dahl salt-sensitive rats maintained on a high salt diet and treated with riociguat (3 or 10 mg/kg/d) for 14 weeks. Riociguat markedly improved survival and increased survival. Histological examination of the heart and kidneys revealed that riociguat significantly ameliorated fibrotic tissue remodeling and degeneration. Correspondingly, mRNA expression of the pro-fibrotic biomarkers osteopontin (OPN), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and plasminogen activator inhibitor-1 (PAI-1) in the myocardium and the renal cortex was attenuated by riociguat. In addition, riociguat reduced plasma and urinary levels of OPN, TIMP-1, and PAI-1. Riociguat markedly improves survival and attenuates systemic hypertension and systolic dysfunction, as well as fibrotic tissue remodeling in the myocardium and the renal cortex in a rodent model of pressure and volume over-
load. These findings suggest a therapeutic potential of sGC stimulators in providing
organ protection in diseases associated with impaired cardio-renal functions.

AZD3199: A fast acting β2-receptor agonist with long duration of action
P888
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Background: AZD3199 is a novel, ultra long acting β2 -agonist (uLABA) de-
designed to combine 24 hour duration of action with a fast onset of action similar to
formoterol, as well as low systemic exposure. Its in vivo profile was evaluated in the
guinea pig. Methods: Bronchoconstriction was elicited in anesthetised guinea pigs by his-
tamine administration. Dose-response curves for AZD3199 given via the inhala-
tion and intra-tracheal (i.t.) routes were constructed and sub-maximal doses used to de-
fine duration of action from 2–72 hours. The b-agonist propranolol was ad-
ministered after histamine-challenge to show the level of β2 efficacy at each dose
and time point. Blood samples were taken throughout and plasma β2 concen-
trations used as a marker of systemic β2 effects. Satellite groups were used to monitor

These findings suggest the efficiency of combined ACE inhibitor and diuretics to

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lung and plasma AZD3199 levels. The pharmacodynamic and pharmacokinetic profiles of AZD3199 were compared to formoterol and salmeterol.

**Results:** Sub-maximal doses of AZD3199 given i.t. inhibited bronchoconstriction for 24 hours; equi-effective doses of formoterol and salmeterol had significant effects for 12 hours. AZD3199 had the longest lung PK half-life. Inhalation of sub-maximal doses of nebulized AZD3199 gave bronchoprotection lasting 24 hours, with no significant effects on blood K⁺ levels. An equi-effective inhaled dose of formoterol bronchoprotected for 8 hours with decreases in blood K⁺ seen at 2 hours. The reduced systemic effects for AZD3199 relative to formoterol are consistent with its high lung to plasma concentration ratio.

**Conclusion:** AZD3199 is a novel uLABA with a fast onset of action and a longer duration of action than conventional LABAs, and also has a low potential for systemic effects.

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**An assessment of the functional profile of aclidinium in human bronchi and left atria**

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**Introduction:** Aclidinium bromide is a novel, long-acting muscarinic antagonist, currently in development for the treatment of chronic obstructive pulmonary disease.

**Aims:** To assess the functional profile of aclidinium in isolated human bronchi and left atria, the organs responsible for efficacy and systemic side effects, respectively.

**Methods:** The smooth muscle relaxant effects of aclidinium, tiotropium and ipratropium were measured in isolated human bronchial rings by determining potency, onset (time to 50% inhibition) and offset (time to 50% recovery). The effects of the muscarinic antagonists were assessed in human left-atria strips pre-treated with carbachol 10 μM to inhibit electrically-induced contractions via the M₂ receptor. Duration of action was defined as the time required to recover 50% of the carbachol effect.

**Results:** Aclidinium had similar potency to tiotropium and ipratropium in human bronchi. Aclidinium onset (4.4±0.7 min) was faster than tiotropium (7.4±1.3 min; p<0.05) and similar to ipratropium (3.3±0.6 min). Aclidinium offset (334±49 min) was longer than ipratropium (76±9 min; p<0.05). Tiotropium did not recover within 10 h. Aclidinium inhibited the bradycardiac effect of carbachol in human left atria, with a shorter half life (110.2 min; 95% confidence interval [CI] 103.0, 117.3) than tiotropium (159.3 min; 95% CI 148.2, 171.7) but longer than ipratropium (16.6 min; 95% CI 16.4, 16.8).

**Conclusions:** Aclidinium has similar potency but faster onset of action than tiotropium in human bronchi. In human left atria, aclidinium had a shorter duration of action than tiotropium at M₂ receptors, suggesting a lower potential for cardiovascular side effects.