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4th International Workshop on Lung Health Rising Stars Abstracts

For the 4th International Workshop on Lung Health, a call for "Rising Stars" was launched in May 2016. The purpose of the competition was to offer to brilliant young researchers/clinicians the possibility to present their valuable work for the first time in front of an international audience, and also receive feedback of experienced international speakers to help them in their early carrier.

The call was open to researchers/clinicians up to 42 years old. To participate in the competition, they had to submit their abstract with a brief CV. Sixteen abstracts were received from all over the world and were evaluated blindly by the five chairmen of the Workshop on Lung Health—the main criterion being the scientific value of the work presented in connection with the topics of the Workshop. Only in the case of equal scientific score, other parameters were considered to give priority to submitters from low-income countries or, in a second stage, to younger submitters.

The two winners, whose abstracts are given hereafter, have been invited as speakers to the Workshop and have had good visibility both thought the website of the Workshop and the Workshop newsletter.

In 2017, the winner was a young Italian/Croatian clinician, accompanied by a young researcher from Hungary working in the US.

Travel grants were offered to the next three classified submitters, to provide financial means for them to participate as poster presenters to the Workshop. The abstracts of the winners of the travel grants are hereafter reported.

The participation of Rising Stars in the 4th International Workshop on Lung Health, as well as the travel grants, was made possible thanks to grants by Teva Europe.

In April/May 2017 the call for Rising Stars will be open for the 5th International Workshop on Lung Health to be held in Berlin from January 18–20, 2018.

Rising Stars Abstracts

The Role of Bronchodilation on Airway Mechanical Stress, Lung Hyperinflation and NO Production in Stable COPD

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Background: Patients with severe chronic obstructive pulmonary disease (COPD) experience cyclic opening and closure of the airways even at tidal volume (*Pecchiari M* et al. *Respir Physiol Neurobiol 2016*). The effect of this mechanical stress on lung inflammation and its reversibility are still poorly understood. The aim of our study is to investigate the acute effect of long acting beta-agonists (LABAs) on lung inflammation and its relationship with lung function in patients with moderate to very severe COPD. *Methods:* This was a phase IV, multicenter, randomized, interventional, double blind, crossover study. Stable patients with COPD and a forced expiratory volume in 1 second (FEV_1) <60% predicted were consecutively enrolled. Following a pharmacological washout, patients underwent body plethysmography, diffusing capacity for carbon monoxide (DLCO), multi-flow exhaled fraction of nitric oxide (FeNO) at 50, 150 and 350 ml/s, single breath nitrogen washout test (SBN2) at baseline and 30, 60 and 180 minutes after randomization to either formoterol 12 mcg Modulite (FF) or salmeterol 50 mcg (S) metered-dose inhaler. 72 hours after, patients were crossed-over. The distal airway/alveolar NO (C_{alv}) was calculated with the slope-intercept method (*Tsoukias N* et al. *JAP 1998*). Tissue factor (KCO) and ventilation inhomogeneity (VA/TLC) were derived from DLCO. *Results:* The analysis included 45 patients (Table 1). FF and S similarly improved plethysmographic parameters ($P < 0.05$ in all instances, ANOVA). Compared to baseline, FeNO at 350 ml/s and SBN2 phase III slope decreased equally after FF and S ($P < 0.05$ in all instances, ANOVA). C_{alv} was reduced at all time-points (Figure 1A). C_{alv} was correlated with KCO ($r = -0.43$, $P < 0.001$) and residual volume to total lung capacity ratio ($r = 0.38$, $P = 0.013$). ΔC_{alv} was correlated with baseline VA/TLC ($r = 0.48$, $P = 0.001$), ΔKCO (Figure 1B) and changes in functional residual capacity ($r = 0.33$, $P = 0.03$). *Conclusions:* In COPD, the degree of lung inflammation at rest is related to the functional impairment of small airways. In acute conditions, LABAs are able to reduce peripheral FeNO improving hyperinflation and ventilation inhomogeneity.

Using Optical Coherence Tomography to Evaluate Airway Dynamics in Vivo

Margit V. Szabari[a,d]; Vanessa J Kelly[a]; Matthew Applegate[a]; David C Adams[a,d]; Lida P Hariri[c,d]; Chunmin Chee[a,d]; Khay Tan[a,d]; Robert S Harris[a]; Tilo Winkler[b]; Melissa J Suter[a,d]

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Background/Aims: Airway hyperresponsiveness is a hallmark feature of asthma. To better understand this condition, it is essential to visualize airway behavior *in vivo*. Optical coherence tomography (OCT) is a high-resolution imaging modality that can be used to provide real-time visualization of airway dynamics *in vivo*. Our aim was to use OCT to investigate the structure and function of airways in the healthy and constricted lung in both dependent and non-dependent airway regions during mechanical ventilation. *Methods:* N = 3 sheep were anesthetized and mechanically ventilated. A total of 6 dependent and 6 non-dependent airways were imaged at baseline and following Methacholine administration (Mch: 1 mg/hr). OCT imaging was used to acquire cross-sectional images during Regular Tidal Breathing (RTB) (tidal volume (TV): 10 ml/kg) and in a response to one minute of Double TV ventilation (DTV). The airway-areas during the breathing cycle and pre- and post-DTV maneuvers were calculated from the OCT images using semi-automated image processing algorithms. *Results:* Dependent airway-area increased more than non-dependent airway-area during RTB in the healthy airways ($p < 0.001$). This difference was most prominent in the expiratory phase of the breathing cycle (maximum change in dependent vs. non-dependent airway-area: +13.8% vs. +3.9%). In the constricted airways this difference disappeared during RTB. DTV maneuver had no effect on post-DTV airway-area in healthy airways in both dependent and non-dependent regions. However, the constricted post-DTV airway-area increased compared to the pre-DTV airway-area by +15.5% in the dependent and by +44% in the non-dependent regions (Figure 1). *Conclusions:* OCT provided unprecedented insight into the behavior of airway structure and function of a sheep asthma model. Under normal healthy conditions during RTB dependent airways were more distensible than non-dependent airways. This behavior was reversed after the DTV maneuver during airway constriction, which may be explained by the dependent lung area receiving a higher local Mch dose.

Abstracts of Travel Grants Winners

Amiko®: The Cornerstone Role of Adherence in Obstructive Diseases

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Asthma and COPD are the chronic respiratory diseases with the highest incidence and prevalence. One of the critical point of their management is the adherence to long term-treatment. The weak or bad utilization of prescribed therapy is related to patient's symptoms but also to health care burden. More in details poor medication use is associated to more frequent exacerbations, need to rescue medications prescriptions, unscheduled GP od specialist visit, up to hospitalization. For theabove mentioned reasons seems useful a better attention to correct administration of prescribed therapy, but also to the recording of the real adherence to the treatment. Some methods having the aim of monitoring adherence have been developed, with mixed results. Amiko®, commercialised by Amiko Digital Health Limited (Salisbury House 31, Finsbury Circus, London UK) and developed by the R&D subsidiary Amiko Srl (Piazzale Aquileia 6, Milano Italy – R&D labs- Milano Italy), is developed as an add-on to be positioned on drugs' devices. The technology of Amiko® permits not only to register the real number of administrated doses, but also the used inhalation technique, the inspiratory effort and the orientation of the inhaler. All the data are, in real time, transmitted to a smartphone, tablet or compatible PC and stored. The potential of Amiko® are really many, it can offer many insights for the best individual patient management starting from the objective adherence, going on with data about inhalation duration, orientation of the device and peak inspiratory flow (PIF). The management of these data can help clinician to better control patients' care and, if necessary, to adopt strategies (such as training, education etc) aimed to improve adherence. A study to observe all these fact is now understudy in our clinic, associating Amiko® to a range of currently available dry powder inhalers (DPI) (Ellipta®, Spiromax® and Nexthaler®).

Differential Capacity of Rhinovirus and Influenza Virus to Cause Asthma Exacerbations; Clinical Characterization of the Acute Viral Conditions on an Asthmatic Background

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Background: Rhinovirus (RV) infection is an established trigger of asthma exacerbations, whereas evidence of such capacity of influenza virus (IFV) is not as consistent. In this context, we hypothesized that IFV infection may cause a condition that is different from RV, in that it is less prone to asthma exacerbations. We opted to test this hypothesis by evaluating the associations between IFV/RV positivity and clinical characteristics in children hospitalized for a flu-like illness. *Methods:* The participants were 1207

children, 6-months to 13-years old, hospitalized for respiratory symptoms/fever. The information collected included demographics, medical history, symptoms/physical findings/diagnosis at presentation and treatment. Nasal secretions were tested via PCR for IFV/RV. Associations were evaluated with logistic regression models controlled for several confounders. *Results:* RV positivity was associated with an asthma-like presentation, including increased wheeze/effort of breathing/diagnosis of an asthma exacerbation, and decreased fever/vomiting. Conversely, IFV^+ children presented with decreased wheeze/effort of breathing/diagnosis of an asthma exacerbation, while they had more often fever. In the subgroup of children with an asthma history, both viruses induced wheeze that required asthma medication, however, IFV was uniquely associated with a more generalised and severe clinical presentation including fever, rales, intercostal muscle retractions and lymphadenopathy. These symptoms were not seen in RV^+ asthmatics, who had less fever and more cough. *Conclusions:* In children with respiratory symptoms/fever, RV but not IFV is associated with wheeze and an asthma-like presentation. In the subgroup of children with asthma history, IFV causes a more generalised and severe disease which, however, when compared to the RV-induced condition lacks salient clinical characteristics of an asthma exacerbation. This clinical distinction in the acute infections caused by these viruses highlights the remarkable potential of RV to induce asthma attacks, and provides a clearer characterization of these viral conditions on an asthmatic background.

Identifying a Novel Therapeutic Strategy for Asthma: Aiding Airway Epithelial Cell Repair

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Introduction/Aims: Recent advances have implicated the airway epithelium as a key driver in asthma pathogenesis, partly due to its dysregulated response to damage. Novel therapies focusing on protecting and repairing vulnerable airways, particularly in early life, could transform asthma treatment by preventing disease development/progression. (1) To analyse primary airway epithelial cells (pAEC) migration patterns post-wounding *in-vitro*. (2) To identify mechanisms and potential therapeutic targets enhancing wound repair processes. *Methods:* pAEC were obtained from non-asthmatic and asthmatic paediatric airways. Scratch wounds were performed on pAEC monolayers to assess repair and imaged every 30 minutes (IncuCyte ZOOM®, Essen Bioscience). Migration trajectories of leading-edge pAEC were analysed using ImageJ. Integrin gene and protein expression were investigated by qPCR and In-Cell™ Western, respectively. Total RNA was sequenced (Illumina Hi-Seq2500) and differential gene-expression analysis was performed (DESeq2 and Ingenuity Systems (QIAGEN)). *Results:* Response to wounding in asthmatic children was deficient and lacked specificity with significantly lower mean migration distance(non-asthma and asthma; 256.9 ± 7.1 and $152.3 \pm 8.6\mu$m (mean $\pm$ SEM)), velocity (0.42 ± 0.02 and $0.22 \pm 0.01\mu$m/min), directionality (91.3 ± 0.1 and $61.1 \pm 0.1\%$) and forward migration index (95.3 ± 0.1 and $64.6 \pm 0.1\%$). A major regulator of cell migration, i.e. integrin $\alpha5\beta1$, was investigated in pAEC. Lower gene ($\alpha5$, 5.9-fold, $p < 0.0001$;$\beta1$, 1.5-fold, $p < 0.05$). and protein ($\alpha5$, 2.8-fold, $p<0.05$; $\beta1$, 3.1-fold, $p<0.05$) levels in pAEC from asthmatic children ($n \geq 11$) compared to control ($n \geq 23$). RNA-seq analysis identified 1,153 differentially expressed genes in asthmatic children ($n = 6$) relative to control ($n = 4$) with overrepresented gene ontologies related to integrins and extracellular matrix. Drug database screening identified several clinically safe drugs that are now being examined for drug repurposing potential to restore integrin expression and aid wound repair. *Conclusion:* These novel experiments demonstrate abnormal migration behaviour of asthmatic airway epithelium post-wounding. Some mechanisms controlling this disease phenomenon were identified like decreased integrin $\alpha5\beta1$, and multiple transcriptional mechanisms were dysregulated in asthmatics, some of which are targetable by existing drugs. Supporting airway epithelial repair and barrier integrity may be a novel therapeutic avenue for asthma.