Abstracts of
International Society
for Aerosols
in Medicine e.V.

22nd ISAM Congress

Montreux, Switzerland
May 25–29, 2019
Invited Speaker Abstracts

I-01 GLOBAL NEEDS IN RESPIRATORY DRUG DELIVERY
Anthony J. Hickey
University of North Carolina and RTI International USA

Global technology transfer has increased significantly. Consequently, the opportunity to treat lung diseases has expanded. Beyond asthma and COPD, globalization offers a unique opportunity to address pulmonary infectious disease.

A major effort to explore inhaled therapy for drug-resistant tuberculosi is high burden countries is occurring. Notably these efforts may be facilitated by the efforts to treat drug-resistant non-tuberculous mycobacterial infection with drug aerosols in developed countries.

Convergence of therapeutic strategies may result in more rapid development with benefits accruing to greater patient populations.

I-02 INHALED BACTERIOPHAGES AGAINST RESPIRATORY INFECTION
Nathalie Heuzé-Vourc’h
Inserm U1100 - Research Center for Respiratory Diseases, Tours - France

Lung infections, in particular those due to Pseudomonas aeruginosa (Pa), are increasingly difficult to treat due to evolving antibiotic resistance. Bacteriophages are part of the foreseen complementary/alternative therapies to antibiotics. In this study, a public-private consortium developed a phage cocktail for airway delivery, and assessed its preclinical efficacy and resistance to aerosolization.

The cocktail was developed against a 43-strain Pa reference panel; it displayed 95% efficacy in vitro. In a murine model of acute Pa lung infection, local delivery, two hours post-infection allowed 85% survival of animals at 48h and a drop in bacterial lung count. To assess the impact of nebulization, the phage suspension was aerosolized with 4 different nebulizers. Mesh nebulization was the less deleterious to phages, resulting in 33.4% phage viability. Finally, the best drug & device was tested in a porcine model to mimic ventilator-associated pneumonia (VAP) and aerosol delivery. In larger animals, two aero- sols allowed a high dose of phages to be delivered in the lungs and phage treatment led to a reduced bacterial load in both the tissue and broncho-alveolar lavage.

Overall, the phage cocktail was efficient against Pa, both in vitro and in vivo. Nebulization was associated with 1/3 phage viability, which was sufficient to contain infection but not to resolve it in the VAP model. Further studies are required to evaluate phage in combination to antibiotics in VAP.

I-03 PHARMACOKINETIC COMPARISON OF A Budesonide/Formoterol DPI AND SYMBICORT® TURBUHALER® USING A MULTI-BATCH APPROACH
Dennis Sandell1, Giovanni Caponetti2, Marina Fertek3, Luca Raiteri2, Anders Fuglsang4, and Charlotte Keywood2
1S5 Consulting, Blentarp, Sweden
2Zambon SpA, Milan, Italy
3Independent Consultant, Prague, Czech Republic;
4Fuglsang Pharma, Haderslev, Denmark

A blend of spray dried budesonide (BUD) and formoterol fumarate dihydrate (FFD) produced using the Edry® particle engineering technology is mixed with micronized lactose to create a unique formulation to be delivered using a standard Plastiaxe RS-01 capsule inhaler. The product “Z7200” is intended as an alternative to the originator product, Symbicort Turbohaler (“SymbTBH”, AstraZeneca). Z7200 has a very high fine particle fraction of ~70% and was developed to have the same efficacy with a 50% reduction of the delivered dose. Z7200 80/2.25μg and SymbTBH 160/4.5μg were compared in an open-label, randomized, five-period crossover study in 90 healthy volunteers to assess bioequivalence of a single dose (two inhalations), with and without charcoal. As SymbTBH might have high between batch variability, a multi-batch approach with 9 reference batches was used. The results showed FFD bioequivalence in both AUC0-t and Cmax, both with and without charcoal block. For BUD, bioequivalence was found for AUC0-t, but Cmax failed. As several reference batches were studied in the PK study, it was of interest to assess how different PK parameters correlate to in-vitro data for the same batches. No correlation between BUD AUC0-t and Cmax failed. As several reference batches were compared in an open-label, randomized, five-period crossover study, the results for SymbTBH suggest that this product has high between batch PK variability, and that FPM alone is no reliable predictor of in-vivo performance.

I-04 THE PULMONARY IMMUNE SYSTEM AND ITS INTERACTION WITH THE MICROBIOME
Niki Ubags
CHUV – Service de Pneumologiem, Lausanne - Switzerland

With each breath the lung is exposed to an array of environmental pollutants, particulates, and both pathogenic and non-pathogenic microbes. Nevertheless, the airways have historically been regarded as a “sterile environment”. Over the past few years it has become evident that the lung harbours a diverse array of microbes whose dynamic composition is influenced by both host and environmental factors.

The microbiome plays an essential and indispensable role in the education and maturation of the pulmonary immune system in early life. Colonisation of the lungs at this time is a highly dynamic process.
and can be influenced by external factors, thereby increasing the susceptibility for developing early onset lung disease. Moreover, lung microbial composition can be influenced by environmental exposures and lifestyle factors consequently resulting in an enhanced susceptibility to develop pulmonary disease in adulthood. These factors can also contribute to disease exacerbations and chronicity.

Although there have been global efforts to assess the composition of the microbiome in both healthy and diseased lungs, these studies have been mainly descriptive in nature. Therefore, a priority should be to further focus on developing a comprehensive understanding of the mechanisms underlying the observed alterations in lung microbial composition and their contribution to the pathogenesis of respiratory disease.

I-05 ESTABLISHMENT OF AN ALLERGIC LUNG INFLAMMATION MOUSE MODEL FOR PRE-CLINICAL TESTING OF NOVEL ANTI-HUMAN DRUG CANDIDATES

Alexander Eggel

University Hospital Bern, Switzerland

1Department of Rheumatology, Immunology and Allergology, University of Bern, Switzerland
2Department of Pathology, University of Bern, Switzerland

Upon inhalation of allergens, immunoglobulin E (IgE) sensitized airway mast cells degranulate and release soluble mediators promoting allergic symptoms. We have recently described a novel class of disruptive anti-IgE inhibitors, which not only suppresses IgE binding to its primary receptor FcεRI on mast cells but also actively removes FcεRI-bound IgE from allergic effector cells. While it is not feasible to study such novel anti-human IgE drug candidates in patients, preclinical in vivo model systems that recapitulate allergic manifestations in humans are of highest importance. Here, we describe the establishment of an allergic lung inflammation model using double transgenic mice expressing the human immunoglobulin epsilon heavy chain (huIgε) and the human FcεRI alpha-chain (huFcεRIα).

Double transgenic huIgε/huFcεRIα mice were sensitized on intranasal antigen challenge. In response to airway allergen challenge, increased expression of the mast cell specific protease Mep1 as well as the goblet cell specific mucin Muc5ac were observed in the airways of allergic mice.

In summary, this huIgε/huFcεRIα double transgenic mouse model represents an interesting possibility for the pre-clinical in vivo testing of novel anti-human IgE drug candidates.

I-06 AEROSOL DEVICES AND DELIVERY METHODS FOR CHILDREN REQUIRING RESPIRATORY SUPPORT

Michael D Davis

Children’s Hospital of Richmond at Virginia Commonwealth University, Richmond, United States

Many pediatric patients receiving aerosolized compounds require respiratory support. This can complicate compound delivery since most aerosol devices are not designed for use in conjunction with respiratory support devices. Common complications during delivery of aerosolized compounds to pediatric patients requiring respiratory support are an inconsistent and unpredictable delivered concentration of compound, altered airway deposition of the compound, and interference with the respiratory support device. This session will provide a review of techniques, devices, and delivery considerations for aerosolized compounds to pediatric patients requiring respiratory support.

Respiratory care support devices include non-invasive oxygen delivery devices, non-invasive pressure delivery devices, and invasive ventilatory support devices. Typically, non-invasive oxygen delivery devices do not interfere with delivery of aerosolized compounds. Non-invasive pressure delivery devices include continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) circuit, allowing bias flow to dilute and alter aerosolized compound deposition. Invasive ventilatory support devices can affect aerosol delivery in the same way that CPAP and BiPAP do; moreover, aerosolized compounds can negatively affect the function of these devices. Optimal aerosol device selection and techniques can overcome these issues.

I-07 INHALED ANTIBIOTIC DELIVERY TO CHILDREN

Bruce Robin

Children’s Hospital of Richmond at VCU; Richmond; United States

Aerosol antibiotics can deliver a high concentration to the site of infection with minimal systemic absorption. The ideal patients for receiving aerosol antibiotics are those with chronic airway infection and the ideal antibiotics for aerosolization are the concentration dependent (AUC/MIC90) antimicrobials which increase their killing potential the greater the AUC.

There are limitations to the delivery of aerosol antibiotics. Secretions can limit the diffusion of aerosol antibiotics to the distal airway promoting antibiotic resistance. As a chronically administered therapy given for months or years, poor adherence also increases the likely development of resistance. Antimicrobial resistance to inhaled antibiotics reverses on removal of the antibiotic as maintenance of resistance factors by bacteria carries a metabolic cost.

Difficulties in developing aerosol antibiotics include trial design as decreased sputum bacterial density does not directly translate to clinical benefits. Outcomes such as infectious exacerbations and hospital admissions tend to be rare events, and changes in pulmonary function are not a sensitive outcome. Special issues related to the delivery to young children include when to initiate therapy and dosage needed based on the patient’s age, delivery device being used, the effectiveness of use at different ages, and the relative degree of airway obstruction.

Goals for developing aerosol antibiotics include effective delivery to the sinuses to reduce the risk of reseeding, the adjunctive delivery of medications that may allow deeper penetration of the antibiotic into purulent secretions, and administration of a biofilm disruptor which may improve effectiveness of the antibiotics.

I-08 PULMONARY HYPERTENSION: BACKGROUND AND UNMET NEEDS

Anh Tuan Dinh-Xuan

Paris Descartes University, Cochin Hospital, France

The field of pulmonary hypertension is large and encompasses a broad range of diseases and conditions affecting hundreds of thou-
sands of patients worldwide [1]. For a single but rather rare form of pulmonary hypertension, called pulmonary arterial hypertension (PAH), several classes of drugs are now available. These drugs have a substantial impact on the survival of patients with PAH. For instance, 3-yr survival rates have increased from approximately 40% in the 1980s [2] to nearly 80% in current case series [3–5]. One of the most significant breakthroughs at the turn of this century was the discovery of the role played by bone morphogenetic protein receptor type II (BMPR-II) gene in the pathophysiology of familial pulmonary hypertension [6, 7]. This led to a revival of interest in the use of genetic studies to dissect mechanisms and pathways leading to pulmonary vascular disease [8]. However, it soon became clear that the discovery of genes involved in disease would be of little help if the signalling pathways that are perturbed as a result of gene mutation could not be delineated. Furthermore, considering the variety of different types of pulmonary hypertension, it is probable that several factors are likely to be involved in this complex and intricate biological puzzle [9, 10]. Although understanding the cause of severe pulmonary hypertension is crucial, it is certainly not the ultimate target. The main concern remains how to detect the disease in its early development and how to cure patients of this dreadful condition.

References

agonist, has the potential to dilate pulmonary arteries and to attenuate arterial remodeling in PAH. Here, we sought to test the hypothesis that rosiglitazone can be repurposed as inhaled formulation for the treatment of PAH. We have tested this conjecture by preparing and optimizing poly(lactic-co-glycolic) acid (PLGA) based particles of rosiglitazone, assessing the drug particles for pulmonary absorption, investigating the efficacy of the plain versus particulate drug formulation in improving the respiratory hemodynamics in PAH animals, and finally studying the effect of the drug in regulating the molecular markers associated with PAH pathogenesis. The optimized particles were slightly porous and spherical, and released 87.9% ± 6.7% of the drug in 24 hours. The elimination half-life of the drug formulated in PLGA particles was 2.5-fold greater than that of the plain drug administered via the same route at the same dose. The optimized formulation, given via the pulmonary route, produced pulmonary selective vasodilation in PAH animals, but oral rosiglitazone had no effect in pulmonary hemodynamics. Rosiglitazone ameliorates the pathogenesis of PAH by balancing the molecular regulators involved in vasoconstriction and vasodilation of human pulmonary arterial endothelial and smooth muscle cells. All in all, data generated using intact animal and cellular models point to the conclusion that PLGA particles of an antidiabetic drug can be used for the treatment of a different disease, PAH.

I-12 GLOBAL BURDEN OF CHRONIC RESPIRATORY DISEASES

Giovanni Viegi
CNR Institutes of Biomedicine and Molecular Immunology, Palermo, and of Clinical Physiology, Pisa, Italy

Most recent information derive from the Global Burden of Disease Study 2017 reports. There were 3914200 deaths due to chronic obstructive pulmonary disease (COPD) and 495100 to asthma. COPD was the 7th leading cause of years of life lost (YLLs). Prevalence and incidence of COPD were 299398200 and 18475700, those of asthma 272677500 and 43123400 cases. COPD ranked 6th in females and 9th in males for years lived with disability. COPD accounted for 81600000 – 272677500 and 43123400 cases. COPD ranked 6th in females and 9th in males for years lived with disability. COPD prevalence of 9.1% has been found in a recent general population sample of North-Eastern Italy, whilst in Central Italy a 25 yr follow-up of a general population sample has shown an increased prevalence of COPD and asthma symptoms/diseases. A strategy for measuring health outcomes and evaluating impacts of interventions on asthma and COPD has been recently published by the Global Alliance against chronic Respiratory Diseases (GARD).

I-13 THE FREQUENCY OF NON-ADHERENCE TO INHALER THERAPY AND ITS IMPACT ON OUTCOMES IN PATIENTS WITH COPD

Richard Dekhuijzen
Radboud University Medical Center, The Netherlands

Nonadherence to inhaled treatment regimens for chronic obstructive pulmonary disease (COPD) is well known as a clinical problem with a number of important consequences, such as reduced control of the disease, increased health care consumption and increased costs. Nonadherence for COPD is higher than that for many other chronic diseases (70%-80% vs 50%, respectively). There are numerous causes of nonadherence with inhaler use. Intentional factors include ambivalence to treatment, denial of diagnosis, embarrassment about using inhalers in social situations, and concern about adverse events. Unintentional factors include poor inhaler technique (even though the patient thinks he or she is using it correctly), incorrect inhaler use, lack of understanding about when to use an inhaler, forgetfulness, and language barriers. Other factors that can lead to unintentional nonadherence are the need for multiple devices and/or concomitant conditions requiring polypharmacy. Several strategies are effective in increasing adherence. These include careful matching of patient and device, patient empowerment, education and repeated training, and application of electronic monitoring and digital technologies.

Reference

I-14 CLINICIANS ROLE IN PROMOTING ADHERENCE TO INHALATION THERAPY IN PATIENTS WITH COPD

Fedele Lavorini
Dept. Experimental and Clinical Medicine, University of Florence, Italy

Poor inhaler technique and nonadherence impair the efficacy of medications for COPD. A range of factors, including age, dexterity, inspiratory capacity, and cognitive ability can impact patients’ ability to use their device. Treatment success can also be influenced by patient preferences and perceptions. Therefore, it is important that clinicians effectively match inhaler devices to individual patients’ needs and abilities and empower patients by including them in treatment decisions. General practitioners (GPs) are best placed to address patients’ perceptions and attitudes towards therapy, to individualize treatment choice, and to provide tailored education and device training to maximize adherence to treatment. However, GPs are required to have a full understanding of device characteristics, in addition to knowledge of their patient’s characteristics and comorbidities. Following device selection, patient training and education, including a physical demonstration of the device, are key to eliminate any critical errors that may impact on health outcomes. Also pharmacists must be familiar with the device, as they are usually the last healthcare professionals (HCP) to be seen by patients before a device is used. However, device type is often considered of limited importance when prescribing medication for newly diagnosed patients with COPD. Moreover, HCPs did not uniformly view poor device use as a significant barrier to optimal COPD management. Many HCPs are themselves unable to demonstrate correct inhaler technique. Thus, priority must be given to providing effective training for HCPs to enable them to effectively educate their patients. Integral to training for HCPs should be an awareness of common mistakes and reasons for nonadherence, which can serve as a checklist in the provision of patient education.

I-15 ROLE OF SMART INHALER TECHNOLOGY IN ASTHMA – ADHERENCE AND BEYOND

Omar Usmani
Imperial College London; United Kingdom
As healthcare providers we want patients to persist ‘adhere’ with their prescribed inhaled medication. This requires time and effort to educate patients to correctly engage with their device to achieve confidence in effective delivery of the drug to their lungs. Assessing patient’s ability to achieve an adequate inhalation flow, prepare the dose, and undertake the correct steps in using the device are key factors. However, it is well recognized that adherence levels in patients with asthma remains poor and may impact their daily disease symptom control. Digital solutions ‘trackers’ have been explored to assess dose delivery and determine whether they can improve adherence to medication and identify those patients in need of additional attention in order to help achieve better control of their disease. The EU HORIZON funded project ‘myaircoach’ is investigating the role of smart inhaler technology beyond adherence. Sensors capturing inhaler features, patient physiology and environmental exposures will generate personalized data that will allow the customized and predictive self-management of asthma in that patient. The challenges for digital health include infrastructure to support digital systems, regulation of storage and transfer of data, but most importantly, strong evidence is lacking that digital innovation in asthmatic patients improves clinical outcomes over the long term and is cost effective.

Reference

I-16 CFHEALTHHUB: A DIGITAL PLATFORM INTEGRATING REAL TIME DATA CAPTURE WITH BEHAVIOUR CHANGE TO CREATE HABITS OF SUSTAINED ADHERENCE

Martin Wildman
Sheffield University/Adult Cystic Fibrosis Centre, United Kingdom

Background: Cystic Fibrosis is an inherited life limiting disease in which respiratory failure due to infections is the commonest reason for death. Inhaled therapy is effective in preserving lung function and prolonging survival however median adherence to inhaled therapies is 36% or less. We describe the development of a digital platform linking adherence data to behaviour change strategies to create habits of sustained self-care.

Digital platform development: We carried out qualitative research with people with CF (PWCF) using the theoretical domains framework derived from the COMB model (https://doi.org/10.1186/1748-5908-7-37) and identified barriers and facilitators of sustained adherence. Taking these factors into account we worked with PWCF over 14 months from 2015 using agile software design to create a digital platform, CFHealthHub, which presents time and date stamped data from Pari eTracks. CFHealthHub was evaluated in a 2 centre pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019. Over the past 18 months a learning pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019. Over the past 18 months a learning pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019. Over the past 18 months a learning pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019. Over the past 18 months a learning pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019.

Conclusions: Sustained adherence requires behaviour change in both patients and their clinical teams that must be built on a clear understanding of the factors that support habit formation and routine.

I-17 ARTIFICIAL INTELLIGENCE AND AUGMENTED REALITY IN (RESPIRATORY) HEALTHCARE – PRESENT AND FUTURE

Philipp Kroneberg
VisionHealth GmbH, Germany

For 70% of the world population healthcare is inadequate, expensive and far away. The use of digital healthcare in combination with artificial intelligence (AI) and augmented reality (AR) has the potential to improve that. It enhances the way patients receive their treatment and is beginning to have an impact on medicine in many areas. For example, due to AI clinicians are starting to get supported by rapid, accurate image interpretation. Health systems improve their workflows and medical errors due to insufficient data flow are potentially reduced. Patients get enabled to process their own data and to selfmanage their health.

Augmented reality (AR) is an interactive experience of a real-world environment where the objects that reside in the real-world are “augmented” by computer-generated perceptual information. This new technology is enhancing medicine and healthcare towards more safety and efficiency. For now, AR has already made significant changes in the following medical areas: surgery (minimally invasive surgery); education of future doctors; diagnostics; education of patients in home environment.

In respiratory medicine AI and AR have the potential to improve respiratory drug delivery by novel, innovative smart inhalers, enhanced patient education, training programs and comprehensive patient monitoring programs.

References
Bart de Witte: Künstliche Intelligenz im Gesundheitswesen, Life Science Congress Heilbronn 2018.
Eric Topol, High-performance medicine: the convergence of human and artificial intelligence, nature medicine 2018.

I-18 THERE IS A BIT FOR EVERY ILLNESS - HOW VIDEO GAMES CAN SUPPORT THERAPY IN CHRONIC DISEASE

Marc Kamps
Birds and Trees UG, Hamburg, Germany

Can therapy be fun? How can a digital game idea be implemented despite strong limitations imposed by legal, administrative and medical control mechanisms? How do you deal with different stakeholders such as patients, doctors, practitioners and pharmacists during development? Using the example of Patchie, an interdisciplinary project for the therapeutic support of children suffering from cystic fibrosis, the presentation will show you where to start, how therapy can be fun and which hurdles you have to overcome.
ABSTRACTS

Imaging, Modeling, and Physiology of Aerosols in the Lung

A-001 ADVANCED IN VITRO LUNG-ON-CHIP PLATFORMS FOR INHALATION AEROSOL SCREENING ASSAYS

A Artzy-Schmainer1, P Caruás2, S Elias-Kirma1, H Zidan1, N Schneider-Daum2, C-L Lehr2 and J Sznitman1

1Department of Biomedical Engineering, Technion – Israel Institute of Technology, Haifa, Israel
2Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarbruecken, Germany

With formidable technological progress, lung-on-chips provide new opportunities to probe at true scale the pulmonary environment and deliver biomimetic platforms. Microfluidic airways have transformed the landscape for exploring in vitro respiratory physiology and advance basic research and translational medicine. Since drug screening methods are still overwhelmingly conducted in animal models, lung-on-chips offer the prospect of tangible alternatives. Lined with human cells, within a physiologically-faithful architecture, these can help reduce the need for animal studies and offer more relevant human models. We are leading major developments in lung-on-chips, with the first artificially-breathing acinar networks that capture physiologically-realistic respiratory flows. Our acinus-on-chip represents the first in vitro tool enabling quantitative monitoring of inhaled aerosols at the acinar scales. The size-model lung allows direct and time-resolved observations of airborne particle trajectories and deposition patterns. We are expanding such platforms to recapitulate biological barrier functions of the airway epithelium following inhalation exposure, including pathogenic aggression. Airway cells can be collected from biopsy and cultured in devices allowing for advanced diagnostics in addition to monitoring patient’s cell response to different drugs. Our models may provide off-the-shelf kits geared to end-users for a wide range of toxicity assays and drug screens.

A-028 THE INFLUENCE OF CHANGING INTERFACES ON AEROSOL DELIVERY WITHIN HIGH FLOW OXYGEN SETTING IN ADULTS

Yasmin M. Madney1, Nabilah Ibrahim Laz2, Ahmed A. Elberry3, Hoda Rabea1, and Mohamed E.A. Abdelrahim1

1Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
2Department of Chest diseases, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt
3Clinical Pharmacology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

Oral route has been considered superior for aerosol delivery in adults, including with both low and high flow oxygen therapy (HFT). The aim of the present work was to compare the efficiency of aerosol delivery using different interfaces at different gas flow rates using HFT device.

Experiment was conducted using vibrating mesh nebulizer (Aerogen Solo) connected distal to heated humidifier attached with tubing to three interfaces: mouthpiece (MP); facemask (FM); and nasal cannula (NC) through an HFT circuit at 10, 20 and 30 L/min flows of oxygen. Aerosol was collected with simulated quiet adult breathing (Vt 500 mL, 15 bpm). The amount of drug deposited on collecting filter was quantified through the application of High performance liquid chromatography.

Aerosol delivery decreased with increasing oxygen flow rate regardless of the interface used within HFT setting. Facemask interface delivered more aerosol at low flow only.

The total inhalable dose (TID) decreased with increasing oxygen flow rate with each tested interface (nasal cannula, mouthpiece and face mask). At oxygen flow rate 10 L/min TID with FM (15.34% of nominal dose) was higher MP (13.7%) or NC (6.5%). The difference in delivery decreased by increasing flow to 20 L/min and 30 L/min (FM (3.1%, 3.0%), MP (7.2%, 1.3%) or NC (3.9%, 2.1%, respectively).

A-034 TOWARDS PREDICTION OF THE PHARMACOKINETICS OF INHALED NANOMEDICINE FROM PHYSIOLOGICAL CELL MODELS: A CASE STUDY WITH LIPOSOMAL CICLOSPORIN A (L-CSA) USING THE VITROCELL CLOUD SYSTEM

Sezer Orak1,2, Barbara Rothen-Rutishauser3, Corinne Jud1,*, Ali Farnoud1,2, Albert Bucholski1, Roman Egle1, Gerhard Boerner2, Oliver Denk2, and Otmar Schmid1,2

1Comprehensive Pneumology Center (CPC), Munich, Germany
2Institute of Lung Biology and Disease, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany
3Adolphe Merkle Institute, University of Fribourg, Fribourg, Switzerland
4PARI Pharma GmbH, Starnberg, Germany
5Breath Therapeutics GmbH, Munich, Germany
*Present address: Agroscope, Competence Division Method Development and Analytics, Postieux, Switzerland

Pharmacokinetics is an essential aspect of any drug approval process. Currently, this aspect has to be measured in animal models and humans for the lack of standardized in vitro testing systems.

In this project, a cell-based in vitro method is examined for prediction of the clinical pharmacokinetic profile of aerosolized liposomal Ciclosporin A (L-CSA). In brief, an alveolar epithelial cell line (A549) was cultured at the air-liquid interface and exposed to aerosolized L-CSA with the VITROCELL CLOUD system. Subsequently, the biokinetics of L-CSA was monitored with HPLC-MS and corresponding in vitro translocation rates into the basal (blood) compartment were calculated.

A clinically realistic burst-like profile with an initially high transport rate that decreased to zero within 4 hours was observed. Unlike the clinical scenario no L-CSA was retained in the lung cell model at the latest time point (24h). On the other hand, the results from this in vitro method can be converted into in vivo predictions of the L-CSA concentration profile in the blood, which are in good agreement with clinical pharmacokinetics data for L-CSA.

This method holds great promise for reducing animal experiments related to pharmacokinetic studies of inhaled drugs, but needs further validation.

A-036 A METHOD FOR DETERMINATION OF TRACHEOBRONCHIAL AIRWAY GEOMETRIES FROM FOUR DIFFERENT STRAINS OF MICE

C. Foong1,2, M.J. Oldham3, F. Lucci3, S. Cockram4, S. Luke5, D. Yeo6, J. Chua2, J. Hoeng1, M. Peitsch1, and A.K. Kucza1

1PMI R&D, Philip Morris Products S.A., Neuchâtel, Switzerland
2PMI Research Laboratories Pte. Ltd., Singapore
3Altria Client Services LLC, Richmond, USA
4Synopsys, Exeter, United Kingdom
Accurate lung morphometry is fundamental for predicting aerosol dosimetry. A complete process from mouse lung cast preparation to automated measurement was established enabling the determination of the airway geometry for four strains of mice (BALB/c, A/J, ApoE-/- and C57BL/6).

Silicone rubber lung casts were prepared in-situ from 20 ApoE-/- and C57BL/6 mice. The morphometry (generation 1 to 6) was manually measured in a selection of casts which were then Micro-CT scanned together with already existing lung casts from BALB/c and A/J mice. A 3D model was reconstructed from the Micro-CT Images of each cast and the skeleton were created from the centreline of each 3D model. Skeleton exceptions (closed loops, trifurcations and isolated nodes) were automatically detected and subsequently resolved manually. Finally, major airway morphometry characteristics (e.g. airway length, diameter, bifurcations angles, and angle to gravity) were automatically measured.

The automated procedure was verified against previous manual or automatic morphometry measurements from lung casts of identical BALB/c & A/J mice. Not surprisingly, tracheobronchial airway diameters for ApoE-/- and C57BL/6 mice were similar, but were significantly different from the other murine strains examined. It is anticipated that these anatomical differences will effect predictions by available dosimetry codes (NCRP, ICRP, and Multiple-Path Particle Dosimetry Model).

A-045 ISOLATION OF SURFACTANT FROM HUMAN TRACHEOBRONCHIAL MUCUS TO STUDY PARTICLE-INTERACTION AT THE AIR-LIQUID INTERFACE

Huck B. 1,2, Schüer J. 3, Schwudke, D. 5, Murgia X. 1, Loretz B. 1, Schwarzkopf K. 1, 4, Bakowsky, U. 3, Lehr CM 1,2

1Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS) and Helmholtz Centre for Infection Research (HZI), Department of Drug Delivery, Saarbrücken, Germany
2University of Saarland, Department of Pharmacy, Saarbrücken, Germany
3Philips University of Marburg, Department of Pharmacy, Marburg, Germany
4Klinikum Saarbrücken, Department of Anesthesia and Intensive Care, Saarbrücken, Germany
5Research Center Borstel, Leibniz Center, Germany

Introduction: The local delivery of nanoparticulate drug carriers to the deep lungs is a promising approach to treat lung infections. A major challenge is to overcome the sophisticated clearance mechanisms of the lungs such as pulmonary surfactant (PS), a thin monomolecular layer at the air-liquid interface of the lungs. Upon contact with PS, the fate of a particle and the uptake into the target cells is drastically affected. As the assess to native PS is very limited, we anticipated that these anatomical differences will effect predictions by available dosimetry codes (NCRP, ICRP, and Multiple-Path Particle Dosimetry Model).

Conclusion: The organic lipid extract of pulmonary mucus exhibits surfactant-like compositional and biophysical properties, with the potential to investigate particle interactions at the air-liquid interface.

A-046 COMPARISON OF REGIONAL AND WHOLE LUNG MUCOCILIARY CLEARANCE USING IMAGING IN MILD-MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

John S Fleming1, Joy Conway1,2, Michael J Bennett1, Livia Tossici-Bolt1 Matthew Guy1, François-Xavier Bé1, Christopher McCrae4, Mats Carlsson5, and Eva Bondesson6

1University Hospital Southampton NHS Foundation Trust, UK
2University of Southampton, Southampton, UK
3Early Clinical Development, IMED Biotech Unit, AstraZeneca, Cambridge, UK
4Respiratory, Inflammation & Autoimmunity, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden
5Global Medicines Development, AstraZeneca, Gothenburg, Sweden
6Clinical Studies Sweden, Lund, Sweden

Background: The mucociliary clearance (MCC) rate from the lung is reduced in Chronic Obstructive Pulmonary Disease (COPD). This study compares regional with whole lung clearance in assessing MCC in mild-to-moderate disease.

Methods: Lung MCC was measured using planar gamma camera imaging in three groups: (i) healthy non-smoking controls (n = 9), (ii) smoking controls (n = 10) and (iii) smokers with mild-to-moderate COPD and bronchitis (n = 15). Following inhalation of radiolabelled aerosol, imaging was performed over four hours and then at 24 h. Both whole lung and inner and outer regional clearances were normalised to 24 h clearance to give tracheobronchial clearance (TBC). The inner region clearance was corrected for both the contribution of aerosol arriving from the outer zone and for the bronchiolar airway contribution, to give a bronchial airways clearance index (BACI). The normalised change in penetration index was also calculated (NOCCHIP).

Results: The optimal endpoint for MCC assessment was chosen to be 3h. There was no difference in TBC between the three groups at 3h, but both BACI and NOCHIP were reduced significantly, compared to non-smoking controls, in both smoking controls and COPD. Compared to the COPD group, a higher proportion of smoking control subjects had NOCHIP values in the non-smoking control range.

Conclusions: Regional clearance parameters provided a more sensitive measure of MCC than conventional lung clearance in mild-to-moderate COPD.

A-048 AEROSOL DOSIMETRY OF INHALED AEROSOLS: COMPARISON BETWEEN EXPERIMENTAL DATA AND PREDICTIONS FROM THE MULTIPLE PATH PARTICLE DOSIMETRY MODEL

Bahman Asgharian1, Andrew P. Kuprat2, Richard A. Corley3, and Chantal Darquenne4

1Applied Research Associates, Inc., Arlington Division, Raleigh, NC, USA
2Pacific Northwest Natl Lab, Richland, WA USA
3Greek Toxicokinetics Consulting, LLC, Boise, ID USA
4Dept. Medicine, University of California, San Diego, CA USA

The development of predictive aerosol dosimetry models has been a major focus of environmental toxicology and pharmaceutical health research for decades, yet experimental validation of these model
predictions is sparse. We simulated aerosol bolus inhalations of 1 and 3 μm-diameter particles in healthy subjects at a flow rate of 0.5 L/s for penetration volumes ranging 200–1200mL using a modified version of the multiple-path particle deposition model, which accounts for convection, diffusion, dispersion, and deposition of insoluble particles. Particle dispersion was mainly due to acinar mixing where the inhaled bolus of 1 and 3 μm-diameter particles mixed with the particle-free air in the alveoli of each airway generation during inhalation, travelled down the lung airway tree, and subsequently exhaled. Alveolar mixing was assumed to occur instantaneously and uniformly while particle deposition by different mechanisms occurred during transport in the lung. Aerosol bolus dispersion, deposition and mode shift were calculated from these simulations and compared to experimental data obtained in 7 healthy subjects for breathing conditions similar to those used in the model. Comparison showed good agreement, suggesting that the dosimetry model used in this study is a useful tool to estimate the fate of inhaled aerosols in the lung that can provide valuable insights for drug delivery and/or health risk assessment.

This work was supported by grant 1U01ES028669-01A1 from NIEHS (NIH).

A-051 DEPOSITION EFFICIENCY OF CHARGED AEROSOL PARTICLES IN LUNG AIRWAYS BASED ON NEW FORCE EXPRESSION FOR POINT CHARGE IN GROUNDED CYLINDER

Adel Hashish1,2 and Trevor Williams2

1Department of Physics, Faculty of Science, UAE University, Al-Ain, P.O. Box: 15551, UAE
2Formerly of Applied Electrostatics Research Group, Department of Electrical Engineering, University of Southampton, Highfield, Southampton, SO17 1BJ, UK

Processes which generate pollutant or therapeutic aerosols usually create charged particles, the resultant electrostatic effects enhancing particle deposition in lung airways. Of main concern is the image force which, for simple geometries, attracts a charged particle to its image in the collecting surface, dominating mutual repulsion at small separations. Charge induced on a cylindrical surface cannot be represented by a point-charge image but still gives a force of attraction termed an ‘image’ force. The potential and electric field distributions in the cylinder are found using cylindrical coordinates and involve modified Bessel functions. The force can be deduced from the potential energy of the point charge or by integrating the Maxwell stress tensor over the cylinder’s surface, giving different but equivalent mathematical forms. Deposition efficiency is determined from this for a particle suspended in air flowing in an airway with parabolic or plug-flow profile. The mathematical formulation is simplified by considering the force on a point charge in a sphere, of the same radius as the cylinder, which is similar. This has a simple form which can be modified by a polynomial factor to match the cylindrical force. Partial fraction decomposition allows factorization of the polynomial, facilitating analytical integration of the functions involved. This yields a dimensionless time constant which corresponds to a collection radius that is used to determine deposition efficiency.

A-062 PROTEIN CORONAS FORMED IN BALF AND SERUM DIFFERENTIALLY IMPACT NANOPARTICLE STABILITY AND CELL UPTAKE

Benjamin King1 and Jennifer Fiegel1

1Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, IA 52245 USA

Foreign material entering the human body first interacts with the bodily fluids, where proteins in the fluids readily adsorb to the materials’ surface. This thin protein shell, or protein corona, directly interacts with cells and tissues in the body and helps determine the materials’ fate. Studies of protein coronas have generally focused on the blood, which has good clinical relevance for injectable therapies but is compositionally distinct from the lung lining fluid. This study assessed the impact of human serum and concentrated BALF on the aggregation, zeta potential, total protein adsorbed, and cell uptake of polymeric particles. The effect of particle size (200 and 500 nm) and surface functional groups (amine- or carboxylate-modified and plain polystyrene) were analyzed. Particles tended to aggregate when their zeta potentials were close to zero, consistent with electrostatic forces controlling particle stability. The stability of particles were distinct in serum and BALF, suggesting that studies conducted in serum may not be strong predictors of particle stability in BALF. Cell uptake significantly decreased for plain particles in serum or BALF compared to those in saline (from >80% to <20%), whereas no uptake differences were observed for amine- or carboxylate-modified particles. This correlated with total protein adsorbed, but not to particle size or zeta potential, suggesting that particle surface chemistry was the most important factor impacting cell responses.

A-074 NUMERICAL MODELS OF RESPIRATORY DRUG DEPOSITION AND PHARMACOKINETICS: APPLICATION TO LIPOSOMAL CICLOSPORIN A (L-CSA)

Ali Farnoud1,2, Sezer Orak1,2, and Otmar Schmid1,2

1Comprehensive Pneumology Center (CPC), Munich, Germany
2Institute of Lung Biology and Disease, Helmholtz Zentrum Muenchen - German Research for Environmental Health, Neuherberg, Germany

In the present study, a novel physiologically based pharmacokinetic (PBPK) model is developed to assess the biokinetic behavior of inhaled liposomal Ciclosporin A (L-CSA) in different organs. A set of rate balance equations for each investigated organ (lung, liver, remaining organs) is set up and the organs-specific transport rates are determined using experimental data from in vitro and clinical studies. The transport rate of L-CSA from the lung to the blood is assumed to be equal to the experimentally determined L-CSA transport rate across an in vitro air-liquid interface model of the lung barrier. The other transport rates are determined iteratively to match L-CSA concentrations measured in the blood of post-lung-transplantation patients. A system of ordinary differential equations is solved and the least square of modelled and measured L-CSA pharmacokinetics profile (up to 48h) is performed using a Python-based software code. Furthermore, the deposition efficiency of the inhaled drug in the respiratory system is simulated using the software package of OpenFOAM. 3DSlicer is used to reconstruct the geometry from the Computed Tomography (CT) images by identifying the region of interest, removing the artefacts, segmenting and generating the stereolithography (STL) file. Large eddy simulation (LES) with a dynamic sub-grid scale (SGS) model is implemented to simulate the airflow and Lagrangian particle tracking is used to simulate particle dispersion and deposition in patient-specific airway. The results from this study will provide insights into the biokinetics and transport rate coefficients of inhaled liposomal drugs throughout the organism.
A-086 A COMPUTATIONAL ANALYSIS OF AEROSOL DEPOSITION IN LARYNGOTRACHEAL STENOSIS

Dennis O. Frank-Ito1,2,3
1Division of Head and Neck Surgery & Communication Sciences, Duke University Medical Center, Durham, NC, USA
2Computational Biology & Bioinformatics PhD Program, Duke University, Durham, NC, USA
3Department of Mechanical Engineering and Materials Science, Duke University, Durham, NC

Inhaled topical medications are widely prescribed for patients with laryngotracheal stenosis (LTS). However, deposition of particles in the stenotic region of LTS patients is currently not well studied. In this pilot study, anatomically realistic three-dimensional reconstructions of the upper airways from nostril to trachea were created from radiographic images of nine LTS subjects. Five of these subjects had glottic stenosis and the other four had tracheal stenosis. Computational fluid dynamics was used to perform particle transport simulations comprising particle sizes of 1–50 microns at particle velocities of 1m/s, 5m/s and 10m/s with inspiratory pressures of 10Pascal, 25Pascal and 40Pascal. Three particle delivery channels were simulated: mouth only, nostrils only; mouth and nostril. Average stenotic deposition fraction was highest through mouth delivery, at 1m/s particle velocity and 10Pascal inspiratory pressure (glottis stenosis = 0.059% and tracheal stenosis = 0.053%). 6microns-10microns (21.3%) particles had the most stenotic deposition among all LTS subjects, and 11microns-20microns (2.84%) particles had the highest stenotic deposition for tracheal stenosis subjects. These results suggest that a tiny fraction of particles deposit in the stenotic region, and delivery through mouth produced the most stenotic particle deposition. Greater deposition of particles in the stenotic region occurred in glottic stenosis subjects than in tracheal stenosis subjects.

A-091 AIRSPACE DIMENSIONS MEASURED BY NANOPARTICLES IN A GROUP OF 618 SUBJECTS

Madeleine Petersson Sjögren1, Laura Aaltoenen2,3, Veronika Idebühn1, Jonas Jakobsson1, Hanna Nicklasson3, Jenny Rissler1, Per Wollmer2,3, and Jakob Löndahl1
1Department of Design Sciences, Lund University, Lund (Sweden)
2Department of Medical Imaging and Physiology, Skåne University Hospital, Malmö (Sweden)
3Department of Translational Medicine, Diagnostic Radiology, Lund University, Malmö (Sweden)

Airspace Dimension Assessment (AiDA) is a novel method for the assessment of distal airspace geometry by measurement of the deposition of inhaled nanoparticles. Inspired nanoparticles deposit predominantly by diffusion in the distant lung. By measurement of the recovery of particles at expiration, the effective airspace radii rAiDA at dominantly by diffusion in the distant lung. By measurement of the position of inhaled nanoparticles. Inspired nanoparticles deposit pre-assessment of distal airspace geometry by measurement of the de-

A-095 BRONCHIAL AIRWAY DEPOSITION OF NEBULIZED HYPERTONIC SALINE FOR TRANS-NASAL VS. ORAL INHALATION IN HEALTHY, NON-SMOKING ADULTS

William D. Bennett, Kirby L. Zeman, Jihong Wu, and Allison Burbank

Center for Environmental Medicine, Asthma and Lung Biology University of North Carolina, Chapel Hill, NC, United States

Background: Nebulized hypertonic saline (HS) enhances hydration and mucociliary clearance of CF bronchial airway surfaces (BAS). While analysis of aerosol delivery by gamma scintigraphy (GS) provides useful estimates of total lung deposition (TLD) there is uncertainty in resolving regional delivery to the BAS.

Methods: Insoluble, radiolabeled particles (Tc99m-sulfur colloid) were added to nebulized HS to measure TLD (% of delivered aerosol) and estimated BAS deposition (% clearance over 24h) using GS. Comparison of HS delivery using a novel trans-nasal device (14% NaCl iTPAD; Parion Sciences, Inc., Durham, NC) vs. a standard oral nebulizer (% NaCl; Pari LC Star) was performed in healthy adults (3M/3F). Mean particle size for the two delivery methods was 2.3um via iTPAD vs. 2.7um via LC Star.

Results: BAS delivery as a % of aerosol exiting the device was significantly less for the iTPAD vs. LC Star: 4.3%/-2.6% vs. 7.7%/-
2.8%, respectively (P < 0.05). The difference correlated with a smaller TLD for the tPAD vs. LC Star; 29+/−5.9 vs. 40+/−8.5%, respectively (P < 0.05). Accounting for differences in NaCl concentration, an approximately equal mass fraction of salt was delivered to BAS with these methods.

**Conclusions:** Nasal delivery of a smaller aerosol particle with twice the salinity did not significantly enhance BAS deposition of HS. Use of an insoluble, radiolabel tracer improves resolution of nebulized, aerosol delivery to the lungs by GS. NIH P01 HL108808 & Parion Sciences, Inc.

**A-100 DOES ADDING A HOLDING CHAMBER TO A VIBRATING MESH (VM) NEBULIZER AFFECT DRUG DELIVERY: INFLUENCE OF A_TEST MODEL COMPONENT ON DOSE MEASUREMENTS**

**Taciano Rocha**1,2, Rod Rhem1, Armélie Dornelas de Andrade3, James B Fink4, and Myrna B Dolovich1

1McMaster University, Hamilton, ON, Canada
2Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
3Universidade Federal de Pernambuco, Recife, PE, Brazil
4Rush Medical University, Chicago, IL, USA

T.R. * Visiting PhD student at McMaster University (Grants from CNPq-PVE 400801/2015-3 and 201601/2018-4, Brazil).

Holding chambers developed for VM nebulizers may increase aerosolized drug delivered to the lung. Does the inlet geometry selected for in vivo studies affect the dose measured?

**Methods:** 500μg of salbutamol was loaded into a VM nebulizer (Aeroneb Solo, Aerogen Ltd, Galway, IR) and ‘inhaled’ using an adult tidal breathing pattern (15bpm; 500ml tidal vol.; BRS 1000, Copley Scientific, UK). Both the USP Inlet (67cc), and a 3D printed 162cc oropharynx model (3DOR) were used to test output of VM with chamber (VMc) and without a chamber (VM). Drug recovered in USP or the 3DOR, expiratory and inspiratory filters (EF; IF, distal to the inlet exit) were washed with HCl 0.9% and analysed by UV/VIS spectrophotometer (Genesys 10S, Thermo Fisher Scientific, MA, USA), described as mean (SD)% of nominal dose (500μg).

**Results:** When the USP Inlet with VMc was used, the drug on EF reduced from 48(7) to 6(1)%, and with the 3DOR, 52(10) to 14(2)%. The mass in the IF increased from 35(2) to 61(2)%, and 26(3) to 43(2)% for USP and 3DOR respectively. Losses in the USP were 2(0.6) and 3(1)% for VM and VMc, respectively. In contrast 12(4) and 22(4)% in 3DOR. T-test for the IF (USP vs 3DOR) showed a mean diff. of 18% (CI 95% 15–21).

**Conclusion:** VMc significantly increased delivered dose with both inlets. However, a lower deposition in the USP inlet may, due to its lower volume, overestimate drug delivered distal to the inlet, indicating that inlet properties may affect dose measurements.

**A-101 DEVELOPMENT OF A REALISTIC 3D PRINTED HUMAN OROPHARYNX FOR IN VITRO THERAPEUTIC AEROSOL DELIVERY MEASUREMENTS**

**Taciano Rocha**1,2, Rod Rhem1, Armélie Dornelas de Andrade3, James B Fink4, and Myrna B Dolovich1

1McMaster University, Hamilton, ON, Canada
2Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
3Universidade Federal de Pernambuco, Recife, PE, Brazil
4Rush Medical University, Chicago, IL, USA

†Visiting PhD student at McMaster University (Grants from CNPq-PVE 400801/2015-3 and 201601/2018-4, Brazil).

**Rationale:** Oropharyngeal anatomic characteristics influence the delivery of therapeutic aerosol to targeted lung regions. Realistic upper airways models support in vitro characterization of in vivo therapeutics, device development and quality control.

**Methods:** MATLAB 9.5 (MathWorks) programme was used to convert a CT scan (128 channel Aquilion CXL (Toshiba, Japan)), acquired at end inspiratory pause (healthy male, age 35), into an oropharynx label field with 5 mm walls (smoothing applied). Two connectors, digitally developed, were placed: on the mouth (universal connection to inhalers), and on the base of the trachea (connection to cascade impactors). The model was segmented in three parts (mouth; oropharynx and trachea), printed using the Stratasys Fortus 450mc 3D printer (Stratasys, Eden Prairie, MN, USA) in a Stratasys brand dark grey ABS-M30 material and went through chemical stability analysis using solvents HCl and MeOH.

**Results:** The 3D oropharynx has 162 cc (105 cc, mouth; 16 cc, oropharynx; 41 cc, trachea), and weights 184 g. It is easy to assemble for bench testing, allows a tricompartmental analysis of inhaled aerosolized drug deposition, and no extractables or leachable byproducts were detected. Thus, the material was considered safe for test runs with active pharmaceutical ingredients. The anatomically realistic oropharynx allowed us to perform multiple respiratory tests with different inhalation interventions, for in vitro therapeutic aerosol delivery studies.

**A-105 NIV OR EPAP - WHAT IS THE BEST WAY TO ASSOCIATE POSITIVE PRESSURE TO NEBULIZATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)?**

Catarina Rattes1, Shirley L Campos1, Taciano Rocha2, Renata Pereira2, Érika Andrade1, Caio Morais1, Simone Brandão3, Luciana Alcoforado1, James B. Fink4, and Armélie Dornelas de Andrade1

1Universidade Federal de Pernambuco, Recife, PE, Brazil
2Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil
3Nuclear Medicine Sector, Hospital das Clínicas, UFPE, Recife, Brazil
4Rush Medical University, Chicago, IL, USA

**Rationale:** Positive expiratory pressure (PEP) with nebulization (NBZ) has been associated with improved bronchodilator response. We compared the effects of bronchodilator administration via mesh NBZ during expiratory positive airway valve (EPAP) and non-invasive ventilation (NIV) in patients with moderate to severe COPD.

**Methods:** A crossover study with 9 COPD patients (67.2±7.8 years; average FEV1 (%pred) 43±9.8) randomly assigned to NBZ (control), NBZ+EPAP and NBZ+NIV. Spirometry, radioaerosol deposition (scintigraphy), regional pulmonary ventilation (electrical impedance tomography).

**Results:** Compared to NBZ alone, FEV1 increased on average 110ml (C19% 0.01 to 0.2), and 120ml (C19% 0.03 to 0.21) after EPAP and NIV, respectively, with no difference in radioaerosol lung deposition pattern. During NBZ, NIV had a higher tidal volume (vs. Control; p = 0.002) and a higher minute volume (vs. Control, p = 0.004 and EPAP, p = 0.003). Respiratory effort was greater with EPAP. Bronchodilator aerosol delivery with positive expiratory pressure through EPAP and NIV promotes an improvement in the lung function of patients with stable COPD, but with no difference in the radioaerosol deposition pattern. The data suggest similarity improvement with NBZ with EPAP or NIV.
A-109  NOVEL IMAGING TOOLS FOR DECIPHERING PULMONARY AEROSOL DEPOSITION WITH SINGLE-CELL RESOLUTION IN NON-DISSECTED MURINE LUNGS

L. Yang1, R. Gradi2, A. Feuchtiger3, K. S. Morgan2, D. Kutschke1, T. Stoeger1, D. Razansky4, A. Walch1, F. Pfeiffer2, and O. Schmidt1

1Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Helmholtz Zentrum München, Neuherberg, Germany
2Chair of Biomedical Physics, Department of Physics, Technical University of Munich
3Research Unit Analytical Pathology, Helmholtz Zentrum München, Neuherberg, Germany
4Institute for Biological and Medical Imaging (IBMI), Helmholtz Zentrum München, Neuherberg, Germany

Understanding the dynamic process of aerosolized drug delivery in the context of dose, distribution and biokinetics within intact lungs is essential for therapeutic efficacy. This study first applies in vivo phase-contrast X-ray imaging (PCXI) and ex vivo light sheet fluorescence microscopy (LSFM) to unravel these aspects for two routes of pulmonary delivery (intratracheal instillation and inhalation). PCXI enabled time-resolved in vivo imaging of instillation delivery of the liquid (A mixture of iodine and melamine fluorescent nanoparticles). Aerosol inhalation can only be visualized when the aerosol was sufficiently deposited on the epithelium and a liquid film formed and transported to the lower airways. Tissue-cleared LSFM was used for 3D co-mapping of entire lung morphology and NP distribution. It revealed that aerosol inhalation provides much more homogeneous NP distribution in conducting airways and acini with a central-to-peripheral NP deposition ratio of unity (c/p = 1) versus the more central and patchier deposition pattern for instillation. At cellular resolution NPs were observed in macrophages in the proximal part of the acini at an early time point (2h) and more distal parts at later time points (1 and 14d). Future work will focus on deciphering the whole-lung NP biokinetic profiles including NP deposition, clearance, cellular uptake, and translocation, which could facilitate the development of nanomedicine targeting the diseased sites of the lung.

A-113  ACUTE EFFECTS OF CANNABIS NOSE-ONLY EXPOSURE IN C57BL/6 MICE

Yasmeen Farra1, Dongyang Yi1, Andrew Szendrey2, James Coleman3, Chris Le2, Tom Morrison3, Praveen Kulkarni1, Craig Ferris3, Jessica Oakes1, and Chiara Bellini1

1Department of Bioengineering, Northeastern University, Boston MA
2Department of Pharmaceutical Sciences, Northeastern University, Boston MA
3Department of Psychology, Northeastern University, Boston MA

Cannabis use, both for medical and recreational purposes, is on a sharp rise in the United States and globally. Robust standardized methodologies in animal models of cannabis smoking are needed to further elucidate the impact of cannabis use on overall health. C57BL/6j mice were acutely nose-only exposed to cannabis aerosols generated from the Volcano® vaporizing device. First, we determined the correlation between loaded cannabis (50–450 mg, THC: 13.1%, CBD: 0.001%, National Institute of Drug Abuse) and THC levels in blood serum with an ELISA immunological assay. Next, we quantified the acute physiological, neurological, and behavioural effects of a 450mg optimal dose. Particle count mean diameters, measured with the Engine Exhaust Particle Sizer (EEPS 3090; TSI Inc.), were 280.80±0.003 nm with a geometric standard deviation of 1.42±0.018 nm. THC concentration was 165 ng/mL for a loaded mass of 450 mg. Immediately following exposure to cannabis aerosols, heart rate, diastolic blood pressure (BP), and mean BP decreased on average by 20.5%, 20.0%, and 19.7%, respectively. In-vivo awake fMRI imaging measurements demonstrated that the exposed mice experienced significant BOLD signal changes in the brain, which was supported by behavioural tests in which exposed mice were significantly more anxious overall. These exposure methods generated a reproducible, acute “high” in mice that can be adapted for further studies on the effects of chronic marijuana aerosol exposure.

A-114  THE ROLE OF AEROSOL BOLUS INJECTION TIME ON AEROSOL DOSIMETRY

Kamran Poorbahrami1, David G. Mummy2, Sean Fain3,4, and Jessica M. Oakes5

1Department of Mechanical and Industrial Engineering, Northeastern University, Boston, MA, USA
2Departments of Biomedical Engineering, 3Medical Physics, and Radiology, University of Wisconsin-Madison, WI, USA
3Department of Bioengineering, Northeastern University, Boston, MA, USA

Targeting of inhaled aerosol medications may improve therapeutic response while reducing side effects in asthmatic patients. 10–15% of asthmatic patients do not respond well to maintenance therapy, leading to progressive and uncontrolled symptoms. To understand the correlation between morphometric features, segmental ventilation defects measured from HP3He MRI, and inhaled dosimetry, we apply our in-silico modelling framework to study transport within the conducting airways of two healthy (HS) and four asthmatic subjects (AS). In addition, we investigate the possibility of improving particle delivery to central or peripheral lung regions by altering the time when particles are inhalated. Predictions show similar dosimetry (3 μm diameter particles) in healthy subjects (HS1 = 26.6% and HS2 = 26.6%), but large variability in asthmatics (AS1(mild)= 33.4%, AS2(moderate)= 40.3%, AS3(severe)= 5.9%, AS4(severe)= 56.3%). By releasing particles only at the time of peak flowrate (between 1.2 to 2.5 s), we enhance deposition in HS1, HS2, and AS3 to 36%, 34%, and 11%, respectively. In subjects AS1, AS2, and AS4, we release particles at times of slow flowrate (3.2 to 4.5 s) to reduce central region deposition to 13%, 19%, and 32%, respectively. Particles that do not deposit within the simulated airways are delivered to the peripheral regions. This simulation work highlights the importance of aerosol bolus injection time, which may be leveraged for optimization. Funding Support: NIH-NHLBI HL140436.

A-116  REALIZING LOCALIZED AEROSOL TARGETING: RIGHT AND LEFT LUNG DEPOSITION

Emily L. Kolewec1, Yu Feng2, Jenna Bridell1, and Catherine A Fromen1

1Department of Chemical and Biomolecular Engineering, University of Delaware; USA
2Department of Chemical Engineering, Oklahoma State University; USA
3Division of Otolaryngology, Department of Surgery, Nemours Alfred I. duPont Hospital for Children; USA
ABSTRACTS

A-118 PULMONARY VASOREACTIVITY: EFFECTS OF INHALED OXYGEN AND INHALED NITRIC OXIDE ON PULMONARY VASCULAR CONTROL

G. Kim Prisk

Dept. Medicine, University of California, San Diego, CA USA

Both oxygen and nitric oxide (NO) are known to cause vasodilation in the pulmonary vasculature, but little is known about the spatial or temporal aspects of this effect, how they interact, nor how these effects are altered by pulmonary arterial hypertension (PAH). Arterial Spin Labeling (ASL), an MRI imaging technique, provides dose-free images of the spatial distribution of pulmonary blood flow (PBF), and when performed repeatedly with a repetition rate of 24 images/minute allows exploration of the spatial-temporal response of the pulmonary vasculature to an intervention. In a group of 8 subjects with idiopathic PAH, fluctuation dispersion (FD), a measure of spatial change and temporal variability in PBF, was elevated to ~200% of that seen in 10 normal control subjects (p<0.001) while breathing air and is correlated with the pulmonary vascular resistance. Hyperoxia (30% O2) altered FD by 20% in the normal subjects but there was no corresponding change in the PAH patients. In normal subjects 40 ppm inhaled NO results in a redistribution of PBF to dependent lung in hypoxia (12.5% O2), an effect that is abolished in hyperoxia, and that is absent in some patients with idiopathic PAH. Thus, O2 and NO act in a similar fashion as a pulmonary vasodilator in the normal lung, but this interaction is modified in some patients with PAH, providing a potential probe of the underlying mechanisms involved.

Funding support: NIH grants R01-HL104118, R01-HL119263, and F30-HL110755.

A-120 DEVELOPMENT OF AN EX VIVO RESPIRATORY MODEL OF LUNG FIBROSIS FOR AEROSOL DEPOSITION STUDIES

Yoann Montigaud1, Sophie Péringue2,3, Laurent Plantier4, Lara Leclerc1, Clémence Goy2,3, Anthony Clotagatide2,3, Nathalie Prévôt2,3, Jérémie Pourchez1

1Mines Saint-Etienne, Univ Lyon, Univ Jean Monnet, INSERM, U 1059 Saintbiose, Centre CIS, Saint-Etienne France.
2INSERM U 1059 Saintbiose, Université Jean Monnet, Saint-Etienne, France.
3CHU Saint-Etienne, Saint-Etienne, France.
4CEPR/INSERM UMR1100, Labex MahiImprove & Service de Pneumologie et Explorations Fonctionnelles Respiratoires, Hôpital Bretonneau, Université François Rabelais, Tours, France.

Idiopathic pulmonary fibrosis (IPF) is a progressive disease, which impairs of lung functions. Three-to-five year survival is low and treatments are mostly ineffective due to a narrow therapeutic range. Aerosol drug delivery to the lungs is expected to be an interesting route of administration for IPF.

This work aimed to develop an easy-to-use, ethically less restricted, reliable and relevant ex vivo adult-like respiratory model of lung fibrosis for aerosol deposition studies. This model is composed of a 3D-printed head connected to a sealed enclosure containing a porcine respiratory tract.

Physiological data and pleural-mimicking depressions were measured. We developed a method to induce modifications of mechanical properties of lung parenchyma to mimic the variation of compliance of fibrotic lungs. After modification, tidal volume was 259.4 ± 48.8mL (respectively 298.4 ± 40.6mL before modification), resistances were 10.54 ± 1.39 cmH2O/L.1a and dynamic compliance was 70.27 ± 21.63 mL/cmH2O (respectively 11.66 ± 1.48 cmH2O/L.1a and 99.14 ± 28.79mL/cmH2O before modification). Compared to data on IPF patients, we assumed that we developed an ex vivo respiratory model of IPF.

Lastly, we assessed the feasibility of regional ventilation and aerosol deposition with 81Kr Krypton gas and radioaerosol. Obtained results satisfactorily fit with in vivo data. So, this model could be considered as a valuable tool for regional aerosol deposition studies and to improve inhaled therapies.

New Devices and Emerging Therapies

N-003 INHALABLE LIPOSOMAL NINTEDANIB FORMULATION FOR ENHANCED TREATMENT OF PULMONARY DISEASE

Jonathan Fang1, Wayne Liao1, Keelung Hong1, Ting-Yu Cheng2, Wan-Ni Yu2, Jo-Hsin Tang2, and Yunlong Tseng2

1TLC Biopharmaceuticals, Inc., South San Francisco, California, United States of America
2Taiwan Liposome Company, Ltd., Nangang District, Taipei City, Taiwan

Idiopathic pulmonary fibrosis (IPF) is a debilitating and rapidly fatal disease with devastating symptoms and a median survival time of 2 to 3 years from diagnosis. Ofev® (nintedanib) is one of two FDA-approved drugs used to treat IPF and is taken orally at a recommended dosage of 150 mg twice daily. Unfortunately, nintedanib has a very low oral bioavailability of 4.7% in humans and has adverse effects that include diarrhea, nausea, liver problems, etc. To address these concerns, we have developed a liposomal formulation of nintedanib that can be aerosolized and inhaled. The rationale for developing an inhalable sustained release formulation is direct drug delivery to the lung and prolonged drug retention in the lung, thus reducing toxicity, drug dose, and frequency of administration. A remote loading method was employed to encapsulate significant amounts of nintedanib in liposome. Furthermore, our liposomal nintedanib (~130 nm to 240 nm) was stable during nebulization. Free nintedanib (9 mg/kg) was
intratracheally (IT) instilled into 9 healthy mice, resulting in the deaths of two mice. In contrast, 9 healthy mice that were IT instilled with liposomal nintedanib (9 mg/kg) all remained healthy. Liposomal drug also had longer drug retention in lung than free drug. Finally, our liposomal drug formulation (~5.6 mg/kg IT instilled every two days) demonstrated similar efficacy to that of Ofev® (60 mg/kg/day oral nintedanib) at a lower, less frequent dose in an IPF animal model.

N-005 EFFECT OF OXYGEN ON AEROSOL DELIVERY FROM NEBULIZER AEROGEN ULTRA

Rania M. Sarhan1, Ahmed A. Elberry2, Nada Saed Abdelwahab3, Hoda Rabea1, Mohamed Nabil Salem3, and Mohamed E.A. Abdelrahim3

1Clinical Pharmacy Department, Faculty of Pharmacy, Beni-suef University, Beni-suef, Egypt
2Clinical Pharmacology Department, Faculty of Medicine, Beni-suef University, Beni-suef, Egypt
3Analytical Chemistry Department, Faculty of Pharmacy, Beni-suef University, Beni-suef, Egypt
4Internal Medicine Department, Faculty of Medicine, Beni-suef University, Beni-suef, Egypt

Aim was to compare inhaled dose (in vitro) and urine levels (in vivo) with VMN and spacer (Aerogen Ultra) operated with 6 L/min of oxygen and no oxygen, with T-piece alone. 5000 µg salbutamol in 1 ml was nebulized with breathing simulator adult quiet breathing (500ml, 15 breaths/min and Insp:Exp of 1:1) to determine Total inhaled dose (TID). In vivo, 12 healthy subjects (6 females), >18years (90% of pred were consented, and aerosol was administered during tidal breathing. Urine samples 0.5hr post dosing (USAL0.5) collected urine for 24 hrs (USAL24) and analysed using high-performance liquid chromatography.

Aerogen Ultra without oxygen increased TID (2197.7 ± 470.7) (p = .005), USAL0.5 (110.1 ± 82.7) (p = .034) and USAL24 (906.1 ± 572.6) delivered by VMN compared to T-piece (1351.6 ± 198.8), (84.8 ± 45.3), 517.5 ± 332.6 (respectively, p = .023). When oxygen was introduced in Aerogen Ultra, TID (1081.5 ± 333.9), USAL0.5 (80.4 ± 30.9) and USAL24 (816.5 ± 269.8) were similar to VMN-T-piece. The use of 6 L/min O2 with the Aerogen Ultra reduced aerosol delivery compared to no oxygen.

N-009 IN-VITRO EVALUATION OF DISPOSABLE, HAND-MADE AND TRADITIONAL SPACERS FOR AEROSOL DELIVERY FROM METERED DOSE INHALER

Haitham Saedi1, Hefa B. Salem2, Hoda Rabea1, and Mohamed E. A. Abdelrahim1

1Clinical Pharmacy Department, Faculty of Pharmacy, Beni-suef University, Beni-suef, Egypt
2Pharmaceutics and Industrial Pharmacy Department, University Beni-suef University, Beni-suef, Egypt

Spacers with Metered dose inhaler (MDI) enhance aerosol delivery and overcome lack of hand breath coordination. Hence the aim of the present work was to compare MDI with spacers to the MDI delivery alone.

MDI alone and with five spacers (Homemade, Dolphin, DispozABLE Paper, AeroChamber Max and AeroChamber Plus) were tested (n = 10 for each). Total emitted dose (TED) and aerodynamic characterization was analyzed by Anderson cascade impactor and drug deposition was measured by high-performance liquid chromatography. TED of the MDI alone was 155.16 ± 20.55 µg and the MDI with AeroChamber Max (71.885 ± 5.73 µg), AeroChamber Plus (61.915 ± 8.91 µg) and DispozABLE Paper spacer (76.38 ± 8.57 µg) were higher than Homemade (52.93 ± 9.94 µg) and Dolphin spacers (49.31 ± 9.0 µg; p < 0.00). Fine particle Dose (FPD) (<5µm) emitted from AeroChamber Max, Aero plus and DispozABLE Paper spacer were significantly higher than that of the MDI alone and other spacers. AeroChamber Max, AeroChamber plus and DispozABLE Paper spacer have better TED and FPD than other spacers. DispozABLE Paper spacer was among the best performing device and available at very low cost.

N-012 CURRENT AND EMERGING INHALED THERAPIES OF REPURPOSED DRUGS

David Cipolla, Richard W Chapman, Michel Corboz, Donna Konicek, Franziska Leifer, Zhili Li, Vlad Malinin, Adam Piaunt, Sasha Rose, Jimin Zhang, and Walter Perkins

Insmed Incorporated, Bridgewater, NJ 08807, USA

Many of the early therapies to treat respiratory conditions like asthma and COPD were first given orally or by injection. Repurposing of those therapies for inhalation allowed for improved efficacy and safety by delivering higher drug concentrations to the target organ, the lung, while reducing systemic concentrations that often are responsible for side effects. Surprisingly, this paradigm continues to the present day. A number of inhaled therapies in development are repurposed compounds that have been reformulated, or turned into prodrugs, to improve their tolerability or modify the pharmacokinetic profile in the lung. The disease areas that are being targeted include asthma, COPD, TB, IPF, PAH, CF, lung cancer, inflammatory conditions and respiratory infections. One example is an inhaled liposomal formulation of amikacin that was recently approved by the FDA to treat Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in adults with limited or no alternative treatment options. This formulation was designed to enhance the uptake of amikacin into macrophages, the site of the MAC infection, and in vivo data confirmed a 274-fold increase compared to IV amikacin. Another example in clinical development for pulmonary arterial hypertension (PAH) is an inhaled sustained-release, prodruk formulation of treprostinil that is designed to provide an improved risk/benefit profile in a once- or twice-daily administration profile.

N-015 NOVEL PORTABLE HANDHELD NEBULIZATION PLATFORM FOR PULMONARY DELIVERY OF UNPROTECTED PLASMID DNA FOR EFFECTIVE INFLUENZA VACCINATION

Anushi Rajapaksa1, Jenny Ho1, Aisha Qi1, Tri-Hung Nguyen2, Michelle Tate, Robert Bischof, David Piedrafta, Michelle McIntosh, Els Meeusen, Ross Coppell, James Friend, and Leslie Ye1

1Micro/Nanophysics Research Laboratory, RMIT University, VIC 3001, Australia
2Monash Institute of Pharmaceutical Sciences, Monash University, VIC 3052, Australia
3Faculty of Medicine, Nursing & Health Sciences, Monash University, VIC 3800, Australia

DNA vaccines offer a rapid production route without significant side effects or requiring an extensive cold chain. However, inhaled delivery of macromolecules such as DNA and other biologics remains difficult given their tendency to denature under the large stresses.
accompanied by aerosolization. We demonstrate a new nebulizer platform using high frequency (>10 MHz) vibration in the form of hybrid acoustic waves for delivering unprotected plasmid DNA (pDNA) vaccines against influenza. The efficient energy transfer allows rapid production of a monodispersed mist of 1–5 μm pDNA aerosols at powers <1 W, which, together with the high frequency, minimizes the shear and cavitational forces acting on the pDNA. Consequently, we observe >90% of the aerosolized pDNA remaining viable. Intratracheal instillation in mice subsequently revealed good in vivo transfection, with gene expression concentrated in the epithelial cells around the terminal airways. Moreover, we obtain comparable antibody titer levels in the bronchoalveolar lavage and sera of sheep following inhalation of the nebulized pDNA to that obtained subcutaneously, but with 4x less dose. Given the difficulty of introducing functional immune responses in large animals with DNA vaccination, this constitutes the first successful demonstration of pulmonary vaccination with an unprotected DNA vaccine in a large animal model, particularly with a low-cost, battery-operated, handheld nebulizer suitable for use in the developing world.

N-018 FLO-TONE CR AS A NOVEL MINI-SPACER AND PMDI INHALATION TECHNIQUE TRAINING TOOL: A COMPARATIVE PHARMACOKINETIC STUDY

Wesam G. Ammari1 and Mark Sanders2
1Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University, Jordan;
2Clement Clarke International Limited, United Kingdom

Rationale: Spacers have been developed to help patients who cannot, despite repeated verbal inhaler training (VT), overcome the pressurised metered dose inhaler (pMDI) hand-lung coordination problem. Patients tend to complain that spacers are bulky to carry around. Clement Clarke International (UK) has recently introduced the Flo-Tone° CR (FT) as a mini-spacer and audible feedback trainer to help patients achieve good hand-lung coordination with a slow inhalation. Our aim was to evaluate the relative lung (USAL0.5) and systemic (USAL24) bioavailability, and the oropharyngeal deposition (OD) of salbutamol inhaled from Ventolin° Easihaler° (GSK) either alone after VT, or connected to FT.

Methods: Ten adult, healthy male subjects took part in a two-period, randomized, crossover study. Participants were trained by either VT or FT to inhale 2×100μg salbutamol puffs (1 minute gap). Immediately after inhalation, each subject gargled with water for OD evaluation. USAL0.5 and USAL24 were determined from 0.5hr and 0.5–24hr urinary salbutamol excretion methods, respectively.

Results: Compared with VT, FT significantly (p<0.05) increased USAL0.5 (14.03 vs 5.86 μg) and decreased OD (6.61 vs 12.53 μg). USAL24 for VT and FT were not significantly different (p>0.05).

Conclusions: Compared with VT, FT combines the benefits of a pMDI training tool coaching the inhaler use, and of a spacer on lung dose and OD. The mini-sized FT design is an added value for pMDI therapy acceptance and compliance.

N-019 EXPLORING INHALATION OF NEBULIZED BACTERIOPHAGE D29 TO PROVIDE PROPHYLACTIC PROTECTION AGAINST MYCOBACTERIUM TUBERCULOSIS AEROSOL IN A PRECLINICAL MOUSE MODEL

Nicholas B. Carrigy1, Sasha E. Larsen2, Melissa Harrison3, Philip Kuehl4, Graham Hatfull5, Dominic Sauvageau2, Warren H. Finlay1, Rhea N. Coler2,6,7, and Reinhard Vehring4
1Department of Mechanical Engineering, University of Alberta, Canada
2Infectious Disease Research Institute, USA
3Department of Chemical and Materials Engineering, University of Alberta, Canada
4Lovelace Biomedical, USA
5Department of Biological Sciences, University of Pittsburgh, USA
6Department of Global Health, University of Washington, USA
7PAI Life Sciences Inc., USA

Tuberculosis has led to more deaths worldwide than any other infectious disease for the past four years. The poor protection afforded by the Bacillus Calmette-Guérin vaccine and the emergence of multidrug-resistant and extensively drug-resistant tuberculosis strains warrant the development of alternative interventions. One such alternative is to prophylactically deliver aerosol containing bacteriophage D29, a lytic, parasitic virus receptor-restricted to infecting mycobacteria, including Mycobacterium tuberculosis, the causative agent of tuberculosis. In this study, a nose-only inhalation device is adapted for use with a vibrating mesh nebulizer to deliver large amounts of active bacteriophage D29 aerosol, ~1 pfu/alveolus, to the lungs of mice that subsequently receive either a high exposure, 50–100 cfu, or a low exposure, 5–10 cfu, of M. tuberculosis H37Rv via a whole-body aerosol exposure system. Bacteriophage D29 remained present and active in the lungs for at least 90 minutes after exposure. Interestingly, pre-treatment with bacteriophage D29 aerosol significantly decreased the burden of M. tuberculosis in the lungs of mice (p<0.05) evaluated 24 hours post-challenge. These results suggest that high doses of nebulized bacteriophage D29 aerosol may be worth exploring as a means of providing extra protection to health care professionals regularly exposed to patients with active tuberculosis and to individuals in areas with high rates of tuberculosis transmission.
like Colistin. Co-spray drying Ciprofloxacin with Colistin not only improved physical and aerosol stability but also enhanced antibacterial activity which is a great advantage while treating ‘difficult to cure’ respiratory infections caused by multidrug resistant bacteria.

My research work is a sincere effort to maximise the utility and efficacy of high-dose DPI, an effective delivery tool for controlling severe respiratory infections.

N-021 IMPACT OF ADVANCED PRACTICAL PATIENT COUNSELLING USING A TRAINING DEVICE AND MOBILE APPLICATION

Haitham Saeed1, Heba F. Salem2, Hoda Rabea1, and Mohamed E. A. Abdelrahim1

1Clinical Pharmacy Department, Faculty of Pharmacy, Beni-suef University, Beni-suef, Egypt
2Pharmaceutics and Industrial Pharmacy Department, University Beni-suef University, Beni-suef, Egypt

Low lung deposition from MDI is a result of incorrect inhalation technique. The aim was to demonstrate the effect of a training device (Trainhaler® CR plus Flo-Tone® combined with mobile application in asthma control in comparison to traditional verbal training. 371 asthmatic patients were consented and divided to the Training Device (187) and verbal training (184).

In each of 3 monthly visits, all patients were trained to the correct inhalation technique, inhalation flow through MDI and spirometry (FEV1, FEV/FVC and PEF) measured, and asthma control test (ACT) performed.

Lung functions of Training Device group were significantly (p<0.001) improved between visit 1 and 2 also between 2 and 3, while for verbal group improvement was significant only in visit 3 (p<0.001). The values of the FEV1% of pred at visits 1, 2 and 3 were 63.57±9.36, 65.02±7.70 and 70.05±6.32 respectively for verbal counselling group, 61.57±8.39, 69.62±7.82 and 78.05±8.14 respectively for training device group.

Inhalation flow (IF) through the MDI improved significantly for both groups, but with high extent in Training Device group. The values of the IF at visits 1, 2 and 3 were 107.24±19.42, 70.52±13.13 and 59.74±10.73 respectively for verbal counselling group, and 116.43±12.41, 55.74±13.83 and 37.60±10.59 respectively for training device group.

The percentage of subjects with an ACT that improved by three or more points after one month was higher in the training device group (52.5%) than in the verbal counselling group (34.8%). In the second month this increased to 67.9% and 49.5% for the advanced counselling and verbal counselling groups, respectively.

Addition of a training device combined with mobile application to the normal verbal counselling of MDI with asthmatic patients resulted in significant improvements in asthma control and patients quality of life compared to traditional verbal counselling.

N-024 PATIENT EXPERIENCE WITH CLIP-TONE: ON-DEVICE ACOUSTIC GUIDANCE FOR SUSTAINED INHALER TECHNIQUE IMPROVEMENT

Mark Sanders

Clement Clarke International Limited, Edinburgh Way, Harlow, CM20 2TT, Essex, UK

A pMDI that is intuitive to use would be an advance. Progress has been made with breath-actuation, and training/dummy devices but these do not fully address the core issue of coordination with a slow, deep inhalation. Many healthcare professionals (HCPs) lack the skills to train patients correctly. True competence (training, skill, experience and knowledge to perform a task) is achieved by few.

A different type of pMDI add-on (Clip-Tone®) is now available. This small, ring-shaped device, with tailored-riding, clips to the top of the actuator and emits distinct harmonics, audible to user/HCP and to smartphone app. It is possible to co-ordinate and measure duration accurately. To date, in vitro research has confirmed no effect on the aerosol and an indiscernible effect on pMDI resistance.

A simple six-question survey of Clip-Tone experience has been completed by 53 adult (39–90 years), Ventolin®-using, COPD patients. Responses to practical questions (helpfulness, ease of attachment, volume, continued use, and recommendation) were all positive (98–100%). Two-thirds would use an app to check technique. Unsolicited patient narratives were of particular interest; expressing improved Ventolin performance and confidence in having used correct technique.

Occasional verbal technique training has not demonstrated sustainable improvements but this new type of mHealth-optional on-device guidance may help HCPs to deliver, and patients to attain and sustain pMDI competence.

N-025 IMPACT OF PEG LENGTH AND PEGYLATION SITE ON THE CONFORMATIONAL STABILITY OF ALPHA-1 ANTITRYPsin

Xiao Liu1, Mireille Dumoulin2, T Wlims3, and Rita Vanbever1

1Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2Center For Protein Engineering, University of Liège, Liège, Belgium.

PEGylation of alpha-1 antitrypsin (AAT) might improve its stability and prolong its half-life following inhalation. The impact of PEGylation on AAT was studied by comparing the stability of wild type AAT and PEGylated AAT.

The wild type AAT was purified by size exclusion chromatography (SEC) from Pulmolast®. Linear 30 kDa, linear 40 kDa and 2-armed 40 kDa were conjugated to AAT by either thiol PEGylation or N-terminal PEGylation. The mono-PEGylated AAT was purified by anion exchange chromatography (AEC). The secondary and tertiary structures of the wild type and PEGylated AAT were characterized by fluorescence and far-UV circular dichroism (CD) spectroscopy. The same techniques were used to monitor the chemical-induced and thermal-induced unfolding transitions of wild type and mono-PEGylated AAT. The thermal-induced aggregation was further characterized by SEC and SDS-PAGE.

The chemical-induced and thermal-unfolding transitions of PEGylated AAT are similar to the wild type AAT, indicating that the PEG length and the PEGylation site have both no significant impact on the conformational stability of AAT. However, the thermal denaturation of AAT is an aggregation process rather than an unfolding process, as indicated by SEC analysis of denatured samples. With the increase of PEG length, the stability of PEGylated AAT to thermal-induced aggregation is enhanced. In addition, thiol PEGylated AAT showed higher stability than the N-terminal PEGylated AAT.

N-027 AEROSOL DELIVERY OF INHALED VANCOMYCIN DURING MECHANICAL VENTILATION USING I-VENT SYSTEM, A UNIQUE SMALL VOLUME, BREATH ENHANCED JET NEBULIZER

Rohinton Toddywala1, Vijay Shukla1, Akanksha Hande2, and Gerald Smaldone2

1Inspix Inc., Somerset NJ,
2SUNY, Stony Brook, NY
ABSTRACTS

N-038 LESSONS LEARNED: LAUNCHING A SOFT MIST INHALER FOR HORSES

Herbert Wachtel1, Marcus Rahmel1, Guido Endert2, and Benjamin Franzmann3

1 Boehringer Ingelheim Pharma GmbH & Co KG, Binger Strasse 173, 55216 Ingelheim, Germany,
2 DESIGNquadrat GbR, Schmiedhofweg 1, 50769 Köln, Germany,
3 Boehringer Ingelheim Vetmedica GmbH, Binger Strasse 173, 55216 Ingelheim, Germany

Based on the first commercially available soft mist inhaler (Respimat®), a new inhaler for horses has been designed and scaled up. Unique medicinal aerosol features such as a slowly moving aerosol cloud, a small droplet particle size, high fine particle fractions, as well as an intuitive user interface and simplified user action were integrated in a completely new housing.

The existing Respimat technology motivated Boehringer Ingelheim Vetmedica GmbH to develop an equine inhaler. Keeping in mind the experiences gained with Respimat, human factors engineering has been translated into the horses’ reality. Considering the upper airway geometry of horses and their typical breathing patterns as well as the user habits, an innovative device was built around the functional core units of Respimat. In the stable, first-hand information on use scenarios was obtained. Relevant interfaces and characteristics have been defined. These include: The nostril adapter (connecting the nostril of the horse with the inhaler containing a valve and a breath indicator), and the handle with a dual-functional lever enabling single hand operation.

So far, the Respimat platform has relied on aqueous aerosols but now the inhaler contains an ethanolic solution which provides matched droplet properties. It is used to treat clinical symptoms associated with equine asthma, formerly known as RAO (recurrent airway obstruction) and SPAOPD (summer pasture associated obstructive pulmonary disease).

N-039 THE NEW RE-USABLE RESPIMAT® – SYNERGISM OF CARTRIDGE AND DEVICE

R. Krampe2, M. Frank1, S. Kattenbeck1, S. Leiner1, M. Meisenheimer1, H. Wachtel1, and F. Weiland2

Boehringer Ingelheim’s Respimat has been a well established and user friendly inhaler worldwide for a whole product family since its introduction in 2004. Patients appreciate the easy coordination between actuation and inhalation; physicians appreciate the high inhalable fraction and the fact that the inhaler performance is independent of the patient’s inspiratory flow. However, patients and physicians questioned why such a ‘high tech inhaler’ was not refillable and had to be discarded after 30 doses. HCPs also asked for further simplification of the assembly.

With the re-usable Respimat, Boehringer Ingelheim fulfils the wish for a refillable inhaler and simplification of the assembly when a new cartridge is inserted without changing any of the well-appreciated properties. The re-usable Respimat continues to use the established dosing and soft mist generation. It can be used for up to six cartridges with 30 doses each. Using an iterative design process according to ISO 13485 and ISO 20072, core features of the inhaler like dose counting, have been optimized. Insertion and removal of the cartridges have been assessed in Human Factor studies.

Products with the re-usable inhaler have been approved in the EU starting in late 2018 as a drug-device combination. The poster presents comparative data of the Respimat and the re-usable Respimat in terms of dosing accuracy, particle size distribution and spray duration.

Objective: The present study describes the delivery of a Vancomycin formulation using i-VENT system to reduce aerosol losses during mechanical ventilation.

Methods: The breath enhanced i-VENT nebulizer system, powered by wall gases at 50 PSIG and 3.5 LPM, can generate aerosol continuously or can be inhalation triggered using a unique electronic circuit. The device was connected to the inhalation tubing near the ventilator. The amount of drug delivered (n = 3) to an in vitro lung model was quantified using a commercial ventilator for a short duty cycle (SDC) (15 bpm; Vt 0.46L; 50 LPM; I:E 1:6; PEEP 5 cm H2O) and a long duty cycle (LDC) (20 bpm; Vt 0.65L; 40 LPM; I:E 1:2; PEEP 5 cm H2O). The nebulizer was charged with 6 mL of a Vancomycin formulation (60mg/mL). Inhaled Mass(IM), Exhaled Mass(EM) and residual in the nebulizer were determined using HPLC.

Results: SDC CONTINUOUS(mg): IM – 58.28±2.00; EM - 63.40±3.52; Nebulizer – 117.79±3.15

SDC INHALATION TRIGGERED(mg): IM – 104.66±3.41; EM – 29.00±0.89; Nebulizer – 109.11±5.48

LDC CONTINUOUS(mg): IM – 102.04±5.49; EM – 34.73±3.02; Nebulizer – 135.90±25.95

LDC INHALATION TRIGGERED(mg): IM – 126.21±5.23; EM – 17.22±0.87; Nebulizer – 101.58±17.22

Conclusions: The i-VENT delivered a clinically relevant dose under all conditions. As expected, inhalation triggering resulted in a significantly higher dose of drug compared to the continuous mode.

N-037 THE RE-USABLE RESPIMAT: OPTIMISATION OF A SUCCESSFUL INHALER DESIGN

S. Leiner1, M. Frank1, A. Gardev2, S. Kattenbeck1, R. Krampe2, M. Meisenheimer1, H. Wachtel1, and F. Weiland2

1Boehringer Ingelheim Pharma GmbH & Co KG, D-55218 Ingelheim an Rhein, Germany
2Boehringer Ingelheim microParts GmbH, Hauert 7, D-44227 Dortmund, Germany

Boehringer Ingelheim’s Respimat has been a well established and user friendly inhaler worldwide for a whole product family since its introduction in 2004. Patients appreciate the easy coordination between actuation and inhalation; physicians appreciate the high inhalable fraction and the fact that the inhaler performance is independent of the patient’s inspiratory flow. However, patients and physicians questioned why such a ‘high tech inhaler’ was not refillable and had to be discarded after 30 doses. HCPs also asked for further simplification of the assembly.

With the re-usable Respimat, Boehringer Ingelheim fulfils the wish for a refillable inhaler and simplification of the assembly when a new cartridge is inserted without changing any of the well-appreciated properties. The re-usable Respimat continues to use the established dosing and soft mist generation. It can be used for up to six cartridges with 30 doses each. Using an iterative design process according to ISO 13485 and ISO 20072, core features of the inhaler like dose counting, have been optimized. Insertion and removal of the cartridges have been assessed in Human Factor studies.

Products with the re-usable inhaler have been approved in the EU starting in late 2018 as a drug-device combination. The poster presents comparative data of the Respimat and the re-usable Respimat in terms of dosing accuracy, particle size distribution and spray duration.
Development of the re-usable Respimat showed once again how important the synergistic design of the two parts of Respimat-cartridge and device are. The interfaces also have to be considered in the synergistic production based on well-defined specifications to finally receive a matching drug-device combination.

N-040 THE NEW RE-USABLE RESPIMAT® - TECHNICAL PERFORMANCE AND USABILITY

M. Meisenheimer1, M. Frank1, A. Gardev1, S. Kattenbeck1, R. Krampe2, S. Leiner1, N. Tesch1, H. Wachtel1, and F. Weiland2

1Boehringer Ingelheim Pharma GmbH, Ingelheim, Germany
2Boehringer Ingelheim microParts GmbH, Dortmund, Germany

Respimat is an eco-friendly inhaler with a precise performance and a robust actuation - inhalation coordination. The current Respimat is designed to be used with one cartridge. With respect to environment and improvement of usability, the new re-usable Respimat was developed to be used with up to 6 cartridges. Changes, including a dose counter attached to the cartridge, were implemented to enable the re-usable concept and to improve ease of use. Dosing principle remained unchanged.

Changes mentioned above and overall device performance were assessed in technical tests (design verification) and usability studies (design validation). In particular the interaction between dose counter (cartridge) and device was evaluated, as this systemically designed interface is essential for the re-usable function and improved usability.

Performance of re-usable Respimat over six cartridges was proven to be comparable to the marketed version. Device performance was robust even under stress situations like vibration tests, drop tests and others.

Usability studies (Human Factors) demonstrated simplified handling, in particular by removing the clear base, cartridge insertion and dose counting. Readability of the remaining doses was considered an improvement for the patient - compared to the marketed Respimat.

Finally, technical performance tests and usability studies proved a robust re-usable concept with unchanged spray performance characteristics and improved handling of the re-usable Respimat.

N-047 TREATMENT OF MYCOBACTERIUM AVIUM SUBSP HOMINISSUS (MAH) LUNG INFECTIONS IN MICE WITH INTRANASALLY INSTILLED LIPOSOMAL CIPROFLOXACIN IN COMBINATION WITH CLARITHROMYCIN AND ETHAMBUTOL

Igor Gonda1, Luiz E. Bermudez2, Amy Palmer2, and James D. Blanchard3

1Respides LLC, San Francisco, CA 94107;
2Oregon State University, Corvallis, OR 97331;
3Aradigm Corporation, Hayward, CA 94545

Introduction: MAH lung infections are common in bronchiectasis and cystic fibrosis. Antibiotic resistance and side-effects make the current therapies problematic. We found dosing of liposome-ciprofloxacin (LC) into mouse airways by intranasal instillation (IN) is efficacious for MAH. Since current standards of treatment are combinations, we studied if oral therapy in combination with LC would be efficacious.

Methods: C57 BL/6 mice (n = 12 per group) were infected with MAH 104 by IN aerosol and 3 weeks later baseline infection was measured. Mice were then treated daily for 6 weeks by IN with saline control (S); IN of 1 mg/kg of the following ciprofloxacin treatments: free ciprofloxacin solution (CIS); liposomal ciprofloxacin (CFI); mixture of free ciprofloxacin solution and CFI (DRCFI), and liposomal nanoparticles (CFIN); and 100 mg/kg by gavage clarithromycin+ ethambutol (CE). Combinations of CE with LCs were also used.

Results: Although CIS had little effect on the lung bacterial load, CE alone and all LC preparations alone (CFI, DRCFI, CFIN) had significant reductions of log cfu ≥1 (p < 0.05 vs S). LCs in combination with CE resulted in further significant decreases in MAH lung loads (0.7 to 0.9 log cfu, p < 0.05 vs. treatments not using combinations; p < 0.01 vs. S). There was no emergence of resistance.

Conclusions: Inhaled LC in combination with oral macrolide + ethambutol may add a significant benefit for the treatment of MAH lung infection.

N-050 INVESTIGATING THE MECHANISMS OF RETENTION OF PEGYLATED DORNASE ALFA IN THE LUNGS

Sohaib Mahri1,2, C. Bosquillon3, and R. Vanbever1

1Advanced Drug Delivery & Biomaterials, Louvain Drug Research Institute (LDFR), Université Catholique de Louvain, Brussels 1200, Belgium
2School of Pharmacy, University of Nottingham, Boots Science Building, University Park, Nottingham, NG7 2RD, UK

The attachment of polyethylene glycol (PEG) of high molecular weight (≥20kDa) to proteins has been shown to prolong their local residence time in the lungs following pulmonary delivery. In this work, we investigated the roles of macrophe uptake, transport through lung epithelial cells, and diffusion across tracheal mucus in vitro in the fate of dornase and its PEGylated forms with linear 20 kDa (PEG20-Dornase), linear 30 kDa (PEG30-Dornase), and two-arm 40kDa PEG (PEG40-Dornase).

The uptake by J774 and RAW 264.7 macrophages was assessed by flow cytometry. A significant decrease in the uptake was observed for both cell lines, and more markedly for PEG30-Dornase and PEG40Dornase in J774, where the uptake was 4 times lower compared with the unpegylated dornase after 24h.

The transport across epithelial cells was assessed on a monolayer of calu-3 cells raised at air-liquid interface. The percentage of amount transported from the apical to the basolateral side at 24h was inversely proportional to the molecular weight of the proteins and accounted for 19%, 18%, 11%, and 9% for dornase, PEG20-Dornase, PEG30-Dornase, and PEG40-Dornase in a row.

Similar trend was observed for the transport across a thin layer of porcine tracheal mucus mounted on Transwell® inserts. The half-life times for crossing the mucus layer were 25, 56, 70, and 79 minutes for dornase, PEG20-Dornase, PEG30-Dornase, and PEG40-Dornase respectively.

N-058 L-LEUCINE COATED INHALABLE TEOICPOLAIN POWDERS PRODUCED BY AEROSOL FLOW REACTOR METHOD

Nurcin Ugur1, Luis M. Bimbo2, Per Saris3, Ville Vartiainen1, Jouni Hirvonen2, Esko I. Kauppinen1, and Janne Raula1

1Department of Applied Physics, Aalto University School of Science, Espoo, 00076, Finland
2Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, 00014, Finland
3Department of Applied Chemistry and Microbiology, Faculty of Agriculture and Forestry, University of Helsinki, 00014, Finland
ABSTRACTS

**N-059 NUMERICAL AND EXPERIMENTAL INVESTIGATIONS ON NASAL SPRAY USAGE STRATEGIES IN CHRONIC RHINOSINUSITIS**

Saikat Basu\(^1\), Zainab Farzal\(^2\), Landon Holbrook\(^3\), Olutade Fasanmade\(^4\), Benjamin Langworthy\(^4\), and Julia S Kimbell\(^2\)

\(^1\)Department of Mechanical Engineering, South Dakota State University, Brookings, SD 57006, USA
\(^2\)Department of Otolaryngology/Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA
\(^3\)School of Business and Technology, Milligan College, TN 37682, USA
\(^4\)Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Ostomatal complex (OMC) is the pathway for mucociliary drainage and airflow exchange between the main nasal airway and sinuses. Therefore, many physicians view OMC as a potent deposition site for topical sprays in the treatment of chronic rhinosinusitis (CRS). We numerically simulated airflow and particle transport in five nasal reconstructions, to identify spray techniques that would amplify drug delivery to the sinuses and OMC. The airflow models were digitally sculpted from pre-surgery CT-scans of CRS patients. Two different spray directions were considered in each: (a) package insert-based Current Use (CU) – an upright spray axis with subject’s head leaning slightly forward (22.5°), and (b) Revised Use (RU) – with spray axis aimed at OMC and through centroid of the visible OMC’s projection on the view-plane for best-possible OMC sighting. In both, sprayer was set at 5-mm insertion. Despite perturbations, RU saw 6-fold increase in targeted delivery, over CU. Furthermore, both parametric t-test and non-parametric Wilcoxon signed rank test returned \( p < 0.05 \), indicating statistically significantly larger RU deposition. Comparisons of simulated deposits (along coronal, axial, sagittal directions) in two representative models with in vitro spray experiments in 3D-prints gave high Pearson correlation, all exceeding 0.85, thus endorsing the reliability of numerical models. The results, if validated via clinical trials, may change topical spray usage paradigm. Supported by NIH R01HL122154.

**N-060 DESIGN OF EXPERIMENTS STUDY TO FORMULATE DRY POWDER AEROSOLS FOR ENHANCED BACTERIAL BIOFILM ERADICATION**

Ojas Pradhan\(^1\), Christine Czarnecki\(^1\), Benjamin King\(^1\), Sachin Gharse\(^2\), Michael Crain-Zamora\(^1\), and Jennifer Fiegel\(^1,2\)

\(^1\)Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, IA 52245 USA
\(^2\)Department of Pharmaceutical Sciences and Experimental Therapeutics, The University of Iowa, Iowa City, IA 52245 USA

Chronic pulmonary bacterial infections are difficult to eradicate due to the formation of bacterial biofilms in the lungs, where colonies of bacteria secrete and are then protected by an extracellular matrix. We are working to develop combination therapies to entice bacteria out of the biofilm communities using dispersion compounds, that then increase bacterial susceptibility to common antibiotics. The objective of this study was to develop dry powder aerosols containing colistin sulfate (antibiotic), sodium citrate (nutrient dispersion compound), and leucine (to increase powder flowability) that exhibit high yield and drug loading and suitable aerodynamic properties, while maintaining good antibacterial properties. Aerosols were generated using a Büchi 190 spray dryer. A two-level central composite design was used to determine the effects of solution flow rate, atomizer flow rate, leucine concentration, and solution concentration on key dry powder characteristics: yield, water content, chemical composition, mass median aerodynamic diameter, and effectiveness against Pseudomonas aeruginosa biofilms. Results from this study revealed that formulation parameters could be tuned to control the yield, water content, and aerodynamic size of the spray dried powders. Under some conditions, spray dried powders maintained their expected chemical composition and were effective in killing 1-day old biofilms of Pseudomonas aeruginosa.

**N-061 ZWITTERIONIC POLYMER COATINGS TO LIMIT PROTEIN ADSORPTION TO NANOCARRIER SURFACES**

Benjamin King\(^1\), Michael Crain-Zamora\(^1\), and Jennifer Fiegel\(^1\)

\(^1\)Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, IA 52245 USA

Nonspecific protein adsorption to drug carriers can cause aggregation, impair the ability of drug carriers to cross biological barriers, and induce clearance as part of the foreign body response. Thus, nonfouling biomaterials can aid the transport and persistence of drug carriers in the body. This study focused on the development of zwitterionic polymers, polymethacryloyloxyethyl phosphorylcholines (pMPC) containing ammonium and phosphate moieties, as a nonfouling coating to enhance nanoparticle uptake in lung cells. Polymers synthesized via photoinitiated polymerization reaction with various RAFT agents were characterized and coated onto 100 nm gold particles. pMPC coatings helped maintain nanoparticle stability in BALF or serum, likely due to strong hydration of the polymer coating. pMPC-coated nanoparticles formulated using the i651 RAFT agent exhibited no measurable protein adsorption, while those formulated with I2959 reduced protein adsorption by about 75%. pMPC-coated particles exposed to serum experienced 3-to-10 fold increase in particle uptake compared to bare gold particles, as measured by ICP-MS. No differences in uptake were observed with particles exposed to BALF, suggesting that certain BALF-specific proteins can adsorb to the particle surface and limit cell interactions. Dose-dependent changes...
in A549 cell viability were observed only with the RAFT agent; however, once incorporated into the polymer no toxicity was observed.

**N-063 IN VITRO COMPARISON OF BREATH SYNCHRONIZED AND CONTINUOUS AEROSOL VIA VIBRATING MESH NEBULIZER WITH DIFFERENT POSITION AND FLOWS IN ADULT TRANS-NASAL AEROSOL DELIVERY**

Jie Li1, Wei Wu2, and James B Fink1,3

1Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, IL, United States;
2Department of Critical Care Medicine, Zhongshan Hospital, Fu Dan University, Shanghai, China;
3Aerogen Pharma Corp, San Mateo, CA, United States

**Introduction:** Breath synchronized (SYNC) aerosol is associated with higher inhaled dose than continuous (CONT) during mechanical ventilation, we aimed to compare SYNC and CONT aerosol by vibrating mesh nebulizer (VMN) via HFNC.

**Method:** An adult manikin (Laerdal) with collecting filter distal to the trachea attached to pump simulating quiet and distressed breathing. Nasal cannula gas flows (GF) of 5, 10, 20, 40 and 60 L/min. VMN was placed at the inlet of humidifier and proximal to patient. SYNC aerosol was set 50% of the inspiratory time. Albuterol (2.5mg in 1mL) was nebulized for each condition (n = 3). Drug was eluted from the filter and assayed with UV spectrophotometry (276 nm).

**Result:** When GF < inspiratory flow (IF), SYNC inhaled dose was higher than that of GF < IF [20.5(12.9, 24.2) vs 4.0(2.2, 6.9) %, p < .001]. Moreover, SYNC inhaled dose was similar with both neb positions, but higher than CONT with neb placed at the inlet of humidifier [20.6(9.8, 27.2) vs 17.4(16.3, 19) %, p = .029]. When GF > IF, SYNC inhaled dose with neb placed proximal was greater than the inlet of humidifier [6.9(4.8, 7.5) vs 2.2(1.2, 3.5) %, p < .001], but similar with CONT at the inlet of humidifier. CONT inhaled dose was higher with VMN placed at the inlet of humidifier than proximal.

**Conclusion:** When gas flow was lower than inspiratory flow, inhaled dose with VMN placed at the inlet of humidifier was higher than close to patient, and inhaled dose with SYNC VMN was higher than continuous aerosol.

**N-064 CLINICAL IMPACT OF REDUCING HFNC GAS FLOW ON INHALED EPOPROSTENOL DELIVERY IN THE ADULT ICU**

Jie Li1, Keith Roberts1, Payal K Gurnani2, David Vines1, and James B Fink1,3

1Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, IL, United States;
2Pharmacy, Rush University, Chicago, IL, United States;
3Aerogen Pharma Corp, San Mateo, CA, United States

**Introduction:** High-flow nasal cannula (HFNC) commonly administers gas flow exceeding patient’s inspiratory demand, which may reduce efficient lung delivery of inhaled epoprostenol (iEPO). We aimed to assess clinical impact of iEPO via HFNC when gas flow was reduced.

**Methods:** A retrospective study identified adults receiving iEPO via HFNC for pulmonary hypertension (pHTN) alone or comorbid with hypoxemia/right heart dysfunction from 2015 through 2018. With IRB approval, patients’ response to iEPO including mean pulmonary arterial pressure (mPAP) and oxygenation (SpO2/FIO2), HFNC flows and length of stay were retrieved from medical records.

**Results:** Of 34 patients, 10 patients (8 of 10 for pHTN) initiated iEPO with HFNC simultaneously, but with no improvement in mPAP. In 24 patients iEPO was initiated following HFNC (22 for pHTN while 15 of 22 patients were comorbid with severe hypoxemia), had decreased mPAP, and improvement in SpO2/FIO2 after iEPO. However, the improvement in mPAP and SpO2/FIO2 only persisted in the 16 patients whose HFNC flows were reduced, their length of stay in ICU [8.5(6.3, 12) vs 17.5(12.3, 23.3) days, p = .011] and hospital [11.5(7.3, 16.5) vs 19.0(12.3, 26.3) days, p = .023] were shorter than the 8 patients whose HFNC flow unchanged.

**Conclusion:** iEPO delivery via HFNC is effective in improving mPAP and oxygenation with reduced stay in the ICU and hospital when HFNC flow is reduced after iEPO initiation. Further studies are recommended.

**N-072 PROTEIN STABILITY DURING NEBULIZATION: HOW TO MANAGE THE COLLECTION STEP?**

Elsa Bodier-Montagutelli1,2,3, Renaud Respaul1,2,3, Philippe Duquenne1, Nathalie Heuzé-Vourc’h1,2,3, and Laurent Vecellio1

1Université de Tours, UMR 1100, 37032 Tours, France
2INSERM, Centre d’Etude des Pathologies Respiratoires, UMR 1100, 37032 Tours, France
3CHRU de Tours, Service de Pharmacie, 37032 Tours, France

**Introduction:** Nebulization is a promising mode of administration for protein therapeutics, but associated with physical stresses, potentially impairing protein stability and activity. Characterizing nebulized proteins implies aerosol collection; by gathering droplets, this step may modify protein behaviour. In this study, we assessed the influence of the aerosol collection method on protein stability and activity.

**Methods:** Monoclonal antibody (mAb) aerosols were produced with a mesh nebulizer (Aerogen Solo) and collected in 15mL or 2mL tubes (PP15, PP2), AGI-4 Impinger (AGI), BioSampler (BS), Cyclone-BC112 (CYC) and Next-Generation Impactor (NGI). For each device, we assessed: (i) aerosol collection efficiency, (ii) mAb aggregation by flowcell microscopy, dynamic light scattering (DLS) and size-exclusion chromatography (SEC), and (iii) mAb affinity to the target antigen with a competition assay.

**Results:** Aerosol collection efficiencies were around 70% for all devices except CYC (10%). The concentration in micronic mAb particles was highly variable, ranging from 6.107 (AGI) to 3.105 (NGI) particles/mL. DLS and SEC showed 0–5% loss of antibody monomer depending on the collector. mAb affinity to its target was similar in all conditions.

**Conclusion:** The aerosol collection method had a strong impact on the aggregation of a nebulized protein, potentially causing pre-analytical bias. Selection of the aerosol collector is critical, but identification of the best one remains questionable.

**N-079 EVALUATION OF AEROSOL DELIVERY ACROSS TREATMENT MODALITIES DURING SIMULATED HIGH FLOW NASAL THERAPY**

Gavin Bennett, Mary Joyce, and Ronan MacLoughlin

Aerogen, IDA Business Park, Dangan, Galway, Ireland
**Introduction:** Current clinical practice for concurrent aerosol delivery during high flow nasal therapy (HFNT) can involve the use of a facemask placed over the nasal cannula. Here, we assess aerosol delivery across combinations of different drug delivery modalities, using two nebulizer types.

**Methods:** A vibrating mesh nebuliser (VMN) (Aerogen Solo, Aerogen, Ireland) was used with the Airvo 2 system (F&P, NZ), at a gas flow rate of 50LPM. A jet nebuliser (JN) was used with a facemask (Cirrus2 at 8LPM driving gas flow rate, Intersurgical, UK). A facemask and/or nasal cannula were positioned on an adult nose-throat model that was connected to a breathing simulator (Ingmar Medical, US) via a filter (Baxter, Ireland) (Vt 500 ml, BPM 15, I:E 1:1). A 2 mL dose of 2mg/mL albuterol sulphate (GSK, Ireland) was nebulised. The mass of drug captured on a filter placed distal to the trachea was quantified using UV spectroscopy at 276 nm.

**Results:**

Table 1. Tracheal dose (%) across modalities.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Tracheal dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMN + HFNT at 50LPM</td>
<td>2.88 ± 0.15</td>
</tr>
<tr>
<td>Facemask + JN + HFNT at 50LPM</td>
<td>0.82 ± 0.16</td>
</tr>
<tr>
<td>Facemask + JN</td>
<td>6.13 ± 0.09</td>
</tr>
</tbody>
</table>

**Conclusion:** Greater aerosol delivery was observed when the VMN was integrated with HFNT (2.88 ± 0.15), as opposed to standard practice JN and facemask, placed over the cannula (0.82 ± 0.16). Increased aerosol delivery was observed when HFNT was discontinued, and a JN with facemask used (6.13 ± 0.09). However in this scenario, the patient would not be receive supplemental oxygen.

**N-087 ON-DEMAND NITRIC OXIDE FOR VENTILATOR-BASED NITRIC OXIDE INHALATION: A RISK-REDUCTION PERSPECTIVE**

Mark Rimkus1,2, Duncan Bathe1, and Frederic Montgomery, 1

AIT Therapeutics, Garden City, NY, USA, 11530.
mark@ait-pharm.com

Inhaled nitric oxide for the treatment of Persistent Pulmonary Hypertension of the Newborn has been delivered by diluting the contents from high-pressure gas cylinders. The AIT Therapeutics system in development uses plasma arc technology to generate a controlled concentration of nitric oxide gas over a wide range of gas flows. The system is being designed to provide reservoir-free, real-time NO generation from a room air gas source and will operate in the same fashion as current cylinder-based nitric oxide (NO) delivery systems for use with mechanical ventilators.

A comparison of the detailed risk profiles for the cylinder- versus NO generator-based systems identified 20 risks to patient (8 total) and health care providers (12 total) directly associated with cylinder-based systems. Of these, the NO-generator based system effectively removed 17 risks (9 ranked as moderate, 8 as minor) and significantly reduced the probability of occurrence of the remaining 3 risks from remote to improbable. Additionally, the NO generator significantly decreases the logistical burden to hospitals compared to the cylinder-based NO delivery systems.

The on-demand, high performance NO generation system developed by AIT Therapeutics will significantly decrease the risks to both the patient receiving NO therapy and the health care workers providing it while making no compromises to the performance specifications of cylinder-based systems while.

**N-092 PH-DEPENDENT ANTIOXIDANT CAPACITIES OF N-ACETYLCYSTEINE AND GLUTATHIONE AQUEOUS NANOAEROSOLS STUDIED BY AEROSOL VALENCE PHOTOELECTRON SPECTROSCOPY: IMPLICATIONS IN NANOSCALED AEROSOL MEDICINES FOR LUNG DISEASES**

Chia C. Wang1

Department of Chemistry1, and Aerosol Science Research Center, National Sun Yat-sen University, Kaohsiung, Taiwan, R.O.C.

N-acetylcysteine (NAC) inhalation has been widely used to treat the chronic obstructive pulmonary disease (COPD) and chronic bronchitis. However, since NAC functions in such a way to elevate the glutathione (GSH) level, it often necessitates long-term high dose treatment of NAC to take effect. On the other hand, GSH is the primary antioxidant in the lung and the direct administration of glutathione aerosol has been suggested as a promising therapeutic strategy in treating lung diseases, including cystic fibrosis, idiopathic pulmonary fibrosis and chronic rhinitis. To get new molecular insights into the antioxidant capacities and therapeutic efficacies of nanoscaled NAC and GSH system equipped with a specially designed chip adaptor. Exposure to aerosolized phosphate buffered saline solution served as control. 24 hours post-exposure, cells were stained with a live/dead dye and supernatants were collected for a comprehensive lactate dehydrogenase activity testing and cytokine measurements. First results are indicating that stretched cells are more susceptible to nanoparticle exposure. Future on-chip exposure experiments, examining different aerosols and exposure protocols, will reveal the utility of the breathing alveolus on-chip as a novel in vitro inhalation tool.
aerosol therapy, we measured the high resolution aerosol valence photoelectron spectroscopy of NAC and GSH aqueous nanoaerosols at varying pH. The photoelectron spectra show that NAC and GSH aerosols with an average size ~100 nm exhibit distinct molecular orbital characters and ionization energies at varying pH. Since the ionization energy is the most direct measure of how readily a species can lose an electron and become oxidized, this study unravels new molecular insights underlying the antioxidant abilities of GSH and NAC in the nanoscaled aqueous aerosol form, shedding new light in formulating aerosols with optimized antioxidant capacities and therefore the highest therapeutic efficacies for treating lung diseases that are induced or associated with excessive metabolic/pathogenic oxidative stress.

N-096 ENHANCED DEPOSITION OF NASAL SPRAYS USING A PATIENT-SPECIFIC POSITIONING TOOL

Alyssa Burke1, Landon T Holbrook1, Saikat Basu1, Chris T Jadelis1, Jihong Wu1, Elizabeth Monaghan1, William D Bennett1, and Julia S Kimbell2

1Center for Environmental Medicine, Asthma, and Lung Biology, and 2Department of Otorhinolaryngology/Head & Neck Surgery, University of North Carolina, Chapel Hill, NC, USA

Introduction: The efficacy of nasal sprays to treat the nasal passages or deliver drugs to the brain is limited by their ability to deliver drug beyond the nostrils and anterior nasal passage. The aim of this study was to evaluate the effects of a new line-of-sight (LOS) delivery method using a patient-specific nozzle positioning tool (NPT) for nasal spray deposition in models derived from individuals with chronic rhinosinusitis (n = 3).

Methods: CT scans of the nasal cavity and anterior nares were used to 3D print models for nasal spray administration. A patient specific NPT was designed to aim the spray bottle at an angle with the best LOS to the osteomeatal complex for comparison to current use (CU) instructions. The nasal spray was spiked with the radioisotope Tc99m to allow deposition to be imaged and analyzed by 2D gamma scintigraphy.

Results: The percent of the drug sprayed in the nostril that delivered drug beyond the nostrils and anterior nasal passage. Conclusions: Nasal deposition can be improved with a patient-specific LOS NPT, but the majority of drug still deposits anterior to the nasal valve. The use of CT-derived models allows for evaluation of other approaches (e.g. nebulized aerosols) to improve delivery to the nasal passages. Supported by NIH HL122154.

N-098 NEW MESH NEBULIZER FOR INHALED PHAGE THERAPY IN VENTILATION-ACQUIRED PNEUMONIA (VAP)

Sandrine Le Guellec1,2, Joëffrey Pardessus2, Laure Saujel1, Nizar Odem2, María Cabrera2, Guillaume L’Hostis3, Elvir Mujic4, Nathalie Heuzé-Vourc’h1, and Laurent Vecellio2

1DTF Aerodrug, Faculty of medicine, University of Tours, Tours; France 2Inserm U1100 – Research Center for Respiratory Diseases, University of Tours, Tours; France 3Pherecydes Pharma, 102 avenue Gaston Roussel, Romainville; France 4DTF medical, 19 rue de la Presse, Saint Etienne, France

Against difficulty to treat lung infections due to antibiotic resistance, a public-private consortium developed a bacteriophage cocktail (CK-phage) for airways delivery, against P. aeruginosa. In this study the new mesh nebulizer (DTFmesh) developed for assisted ventilation was assessed for in vivo lung deposition and in vitro performances.

In vivo, 2mL-saline aerosols of DTPA-99mTc were nebulised in three ventilated macaques, with the Aeroneb Solo and with the DTFmesh (3 days later). Aerosol deposition was imaged and quantified using a γ-camera. In vitro, the European Pharmacopoeia (EP) method was used to evaluate the inhalable mass and particle size distribution of the drug and device (CK-phage).

In vivo, lung deposition of the aerosol was higher with the DTFmesh than the Solo (39±1% vs. 22±0%, in terms of total aerosol deposited). Although deposition in the central region was high with the DTFmesh (33%), peripheral deposition was similar for both devices (5.3% vs. 4.6%). According to the EP, the CK-phage aerosol MMAD was 3.1±0.1 μm with 82±3% of particles <5 μm and 13±1% of particles <2 μm. The drug and device delivered an inhalable mass of 48±1% (in terms of nebulizer charge).

A new mesh nebulizer was developed for VAP and allowed a high lung deposition in a short time (<5min). Results obtained from EP are in accordance with human lung treatment and support the relevance to develop further inhaled phage therapy. The project has received a grant support (rapid) by the DGA (French army).

N-102 THE I-VENT NEBULIZER: CONTROLLED DRUG DELIVERY DURING MECHANICAL VENTILATION

Sunya Ashraf MD1, Ann D. Cuccia2, Michael McPeck1, Vijay Shukla3, and Gerald C. Smaldone1

1Division of Pulmonary, Critical Care and Sleep Medicine, State University of New York at Stony Brook, Stony Brook, NY, United States 2Respiratory Care Program, Stony Brook University, Stony Brook, NY, United States 3InspiRx Inc., Somerset, NJ, United States

Introduction: Aerosol delivery during mechanical ventilation is uncontrolled and a function of duty cycle, bias flow, nebulizer position and humidification. The present study describes a novel system that minimizes these influences with a design that functions independently of ventilator brand and generates aerosol primarily during inspiration (breath enhancement) and minimizes expiratory losses (breath actuation).

Methods: During a treatment, a 3-way valve directs all ventilator flow to the nebulizer. Aerosol is generated during inspiration by activation of a pressure sensitive breath-actuated circuit. O2/air at 50 PSIG powers the nebulizer at a flowrate of 3.5 L/min. In vitro testing was performed using a heated wire circuit with humidification or valve HME on several ventilator brands over a range of breathing patterns and ventilator modes. The nebulizer was charged with 6 mL of radiolabeled saline.

Results: IM (% neb charge) mean ± SE, 29.5 ± 0.91, n = 76.

Conclusion: Breath enhancement with breath actuation overcomes much of the variability in aerosol delivery providing a predictable dose at any ventilator setting or type of humidification. The use of wall gases and stand-alone breath actuation standardizes conditions driving the nebulizer independent of ventilator design. Nebulizer placement at humidifier outlet allows delivery without introducing aerosol into the humidification chamber and circuit design allows nebulizer servicing without circuit interruption.
N-103 CONTROLLING DEEP LUNG DEPOSITION IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

Sunaya Ashraf1, Joshua Samuel1, Vijay Shukla2, and Gerald C. Smaldone1
1State University of New York at Stony Brook, Department of Medicine, Pulmonary, Critical Care and Sleep Division
2InspiRx Inc., Somerset, NJ, United States

Background: In IPF, therapy with inhaled Interferon-γ is safe and may improve pulmonary function. Coughing was, however, often reported. To address this, a small particle, breath enhanced jet nebulizer (i-NEB Mini, InspiRx, Inc) was developed and tested in healthy and IPF subjects. Regional deposition in lung and Airways were studied.

Methods: Four healthy and nine IPF subjects were enrolled. The nebulizer was filled with 2mL of radiolabeled saline and operated at 3.4 L/min for 10 min. To maximize deposition, patients were encouraged to inhale slowly via an audible resistance (~6 sec). Each subject underwent deposition imaging via gamma scintigraphy. Mass balance and regions of interest determined upper airway and regional lung deposition as a percent of nebulizer charge.

Results: MMAD by cascade impaction was (mean ±SE) 1.0 ± 0.03 μm. Lung deposition in healthy subjects was 26% ± 1.8, in IPF 23% ± 1.6 (pNS). Upper airway deposition was 1.4% ± 0.83 and 2.3% ± 0.48 respectively (pNS). In both groups, deposition was primarily peripheral (1.27 ± 0.05, vs 1.28 ± 0.05, pNS).

Conclusion: i-NEB Mini produced small particles resulting in minimal upper airway deposition. Using slow deep breathing, 53% of the inhaled particles deposited in the peripheral lung in all subjects. For future clinical trials, controlled lung dose of small particles, designed to avoid coughing is possible even in subjects with advanced disease.

N-104 BIOAEROSOL VIABILITY AND PARTICLE DYNAMICS OF AEROSOLIZED BCG VACCINE USING JET AND CLINICAL NEBULIZERS

Rachel Redmann1, Deepak Kaushal2, Philip Kuehl3, and Chad J. Roy4,6

1Infectious Disease Aerobiology, Division of Microbiology, Tulane National Primate Research Center, Covington, Louisiana USA
2Southwest National Primate Research Center, Fort Lauderdale, Florida USA
3Lovelace Biomedical Research Institute, Albuquerque, New Mexico, USA
4Department of Microbiology and Immunology, Tulane School of Medicine, New Orleans, Louisiana, USA

Background: Bacillus Calmette–Guérin (BCG) is a vaccine used to protect against tuberculosis to stop early infection. Normally administered as a percutaneous injection, BCG is a live, significantly attenuated bacteria that is now being investigated as an inhalable vaccine formulation. This work investigates the feasibility and performance of four jet and ultrasonic nebulizers aerosolizing BCG and the resulting particle characteristics and residual viability of the bacteria post-aerosolization. A jet nebulizer (Collision) outfitted either with a 3- or 6-jet head, was compared to two clinical nebulizers, the vibrating mesh Orona MicroAir and Aerogen solo. Particle characteristics, including aerodynamic particle sizing, was performed on all devices using comparable BCG inocula concentrations. Integrated aerosol samples were collected and assayed for bacterial viability. A batch lot of BCG (Danish) was used in all generator assessments. Aerosol particles within the respirable range were generated from all nebulizers at four different concentrations of BCG. The jet nebulizers produced a uniformly smaller particle size than the ultrasonic devices, although particle concentration by mass were similar across all devices tested. The resulting measured viable BCG aerosol concentration fraction produced by each device approximated one another, however a measurable decrease of efficiency and overall viability reduction in the jet nebulizer was observed in higher BCG inoculum starting concentrations whereas the vibrating mesh nebulizer returned a remarkably stable viable aerosol fraction irrespective of inoculum concentration.

N-107 NOSE TO BRAIN DELIVERY – EVALUATION OF A NON-HUMAN PRIMATE MODEL WITH THE MODEL COMPOUND SUMATRIPTAN

Meghan Vermillion1, Edward G. Barrett1, Jason Cox1, Badre Hammond2, Larry Mallis3, Bianca Myers1, Karin Rudolph1, Tyler Sniegowski1, Julie Suma2, Gerrall Williams2, and Philip J. Kuehl1

1Lovelace Biomedical Research Institute, Albuquerque, New Mexico, USA
2Aptar Pharma, Le Vaudreuil, France

Background: At the current time there are no less than 30 companies in non-clinical and clinical development of therapeutics for delivery to the brain via nasal deposition. There is a paucity of peer reviewed literature describing non-clinical models to evaluate nose-to-brain drug delivery. Therefore, a non-clinical model has been developed in non-human primates (NHP) to deliver liquid and nasal aerosols, collect serial blood and cerebrospinal fluid (CSF) samples and perform quantifications for the model compound.

Methods: A non-terminal cross over study in cynomolgous macaques (age 6–10 years ~ 3.5 kg) was conducted with dry powder nasal delivery (Aptar Unit Dose Powder device, 10 mg dose), liquid aerosol delivery (Imetrex in Aptar Unit Dose device, 10 mg dose) and subcutaneous (SubQ) injection (Imetrex, 0.1 mg/kg). CSF was collected via cisternal puncture at 7 timepoints out to 4 hours. Blood was collected via venipuncture at 8 timepoints out to 8 hours. Samples were assayed via a qualified LCMS assay. A non-compartmental analysis (NCA) was performed (WinNonlin) to quantify the T_max, C_max, AUC, half-life and bioavailability in each matrix.

Results: The nasal delivery, for both devices, was well adapted to the NHP without modification. Serial sampling of both CSF (100 μL per sample) and plasma (2 mL per sample) was performed without issue. The NCA showed that the nasal powder resulted in increased AUC and C_max and reduced T_max compared to the aqueous nasal spray and the SubQ injection. Additionally the nasal dry powder resulted in increased plasma bioavailability. These data support the use of the NHP as a non-clinical model to evaluate nasal drug delivery, and suggest that the nasal powder may have resulted in direct nose to brain delivery.

N-108 NOVEL INSULIN INHALATION POWDER: BIOAVAILABILITY IN RATS

Francesca Buttini1, Eride Quarta1, Veronica Chierici1, Elisabetta Barocelli1, Massimiliano Tognolini1, Lisa Flammini1, and Paolo Colombo1

1Food and Drug Department, University of Parma, Italy
In this study the storage stability, i.e., drug content, and respirability of pure insulin pulmonary powder (Ins_SD) loaded in Quali-V®-I capsules packed in blister were investigated. The aerodynamic behaviour of Ins_SD was compared to Afrezza®. Ins_SD was prepared by spray drying and HPMC capsules size 3 were filled with 2 mg of Ins_SD powder. The in vitro respirability was assessed using the RS01® at 65 L/min by the Next Generation Impactor. The in vivo study was conducted in male Wistar rats. To load the animal dose (10 IU/Kg) in the DP-4 insufflator TM, Ins_SD and Afrezza® powders (4% w/w) were diluted with mannitol spray dried powder. After intratracheal administration (n = 9) of insulin powders, insulin and glucosyl plasma profiles were determined. As control, subcutaneous administration (SC) was performed. The results showed that Ins_SD exhibited a respirability higher with FPF of 91% than 70% of Afrezza®. Ins_SD powder possessed six month stability at RT. In vivo data showed that Ins_SD was promptly absorbed, reaching the maximum concentration (Cmax 4.9±1.5 mU/ml) 15 minutes post-dosing. Afrezza® had a slower absorption (tmax 30 min), a lower Cmax 1.8±0.37 mU/ml. Following the glucose injection, Ins_SD determined a rapid glucose reduction, similar to Afrezza®. SC injection showed a longer lasting hypoglycaemic effect due to the prolonged insulin concentration in the plasma. There was no inflammation in the lung tissue by BALF and histological analysis.

N-117 NOVEL METHODS FOR THE ASSESSMENT OF SAFETY PHARMACOLOGY AND TOXICOLOGY PARAMETERS IN ANESTHETIZED AND VENTILATED DOGS RECEIVING INHALED EPOPROSTENOL WITH PH 12

J B Fink, K Bujold, J Pfeiffer, S. Authier

1Aerogen Pharma, USA
2Citoslab North America, Canada
3Scientific Research Partners
4Tepper Nonclinical Consulting, USA

Introduction: Inhaled epoprostenol with high pH (12) are commonly administered during mechanical ventilation with little evidence of safety with prolonged exposure. The <4 min half-life requires continuous nebulization over 48 hours to achieve the 6x doses for toxicity studies. We performed a GLP inhalation toxicity study in anesthetized, intubated and mechanically ventilated dogs, requiring establishment of a canine intensive care unit (ICU) capable of providing prolonged anesthesia (propofol infusion and morphine titration) and partial parenteral nutrition (dextrose, amino acids and lipids) while safety parameters were monitored.

Method: Aerosols of epoprostenol (Flolan pH 12, 30000ng/ml) were administered at several dose rates, continuously over 48 hours using a mesh nebulizer (Aerogen Solo) fed by a syringe pump into a humidified circuit of a critical care ventilator (LTV® 1000) ending in an endotracheal tube placed in the trachea. Animals were ventilated with pressure control ventilation (2.0–3.5 PM min venti. 10ip 17 cm H2O PIP and 1 sec insp time with 1:2 I:E. As aerosol could not be monitored during exposure novel methods were developed to determine emitted dose and particle size in vitro.

Results and Discussion: Acceptable baseline measurements were established for all parameters over the 48-hour evaluation period, Flolan with pH 12 was well tolerated with no untoward path observations. Finding suggest that Flolan pH 12 is safe for inhalation.

P-002 CFHEALTHHUB: A DIGITAL PLATFORM INTEGRATING REAL TIME DATA CAPTURE WITH BEHAVIOUR CHANGE TO CREATE HABITS OF SUSTAINED ADHERENCE

Martin Wildman

Affiliations1, Sheffield Adult Cystic Fibrosis Centre, School of Health and Related Research, University of Sheffield, United Kingdom

Background: Cystic Fibrosis is an inherited life limiting disease in which respiratory failure due to infections is the commonest reason for death. Inhaled therapy is effective in preserving lung function and prolonging survival however median adherence to inhaled therapies is 36% or less. We describe the development of a digital platform linking adherence data to behaviour change strategies to create habits of sustained self-care.

Digital platform development: Qualitative research with people with CF (PWCF) using the theoretical domains framework derived from the COMB model (https://doi.org/10.1186/1748-5908-7-37) identified barriers and facilitators of sustained adherence. Taking these factors into account we worked with PWCF over 14 months from 2015 using agile software design to create a digital platform, CFHealthHub, which presents time and date stamped data from a wireless connected nebulizer. CFHealthHub was evaluated in a 2 centre pilot study completed in 2017 and a 600 patient 19 centre RCT will be completed in June 2019. Over the past 18 months a learning health system in 3 adult CF centres has recruited 400 patients to CFHealthHub and involved in the co-production of a clinician facing dashboard emphasising behaviour change supporting the move from rescue to prevention.

Conclusions: Sustained adherence requires behaviour change in both patients and their clinical teams that must be built on a clear understanding of the factors that support habit formation and routine.

P-031 DELIVERY OF AEROSOLIZED SURFACTANT TO PRETERM INFANTS

Andrew R Clark, Ronan J MacLoughlin, James B Fink, and Jeanette Asselin

1Aerogen Pharma Corporation, San Mateo, CA, USA
2Presenting Author
3Aerogen Limited, Galway, Ireland

Aerosol delivery to the lungs of preterm infants is difficult; they are obligate nasal breathers, their airways and tidal volumes are small, their respiratory rates are high and they have unfavorable inhalation to expiratory ratios. In vitro delivery of surfactant via nCPAP was assessed and lung deposition was modelled, based on infant nasal replicas, prior to the design and execution of a clinical study in preterm infants. Delivery efficiency from a novel nCPAP prong adaptor was measured over a range of neonatal inhalation profiles. The collection efficiencies of two human infant nasal replicas were obtained using a surrogate aerosol. These data were combined with a modification of a published theoretical deposition model to estimate lung delivery. The modeling computations indicated that interpatient variability would be high and that to maximize lung dose an aerosol of ~2 μm MMAD was needed. This was followed by a Phase 2a clinical study to eval-
P-041 DEPOSITION STUDIES OF AEROSOL DELIVERY BY NASAL CANNULA TO INFANTS

Timothy E. Corcoran1,2,3, Al Saville4, Philip Adams5, Darrah J. Johnston2, Michael R. Czachowski,4 Yuliya A. Dommina6, Juiana-Huyi Lin6, Daniel J. Weiner7, Alex S. Huber2, Joan Sanchez De Toledo6, and Cecilia Lo8

1Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA
2Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA
3Bioengineering, University of Pittsburgh, Pittsburgh, PA
4Children’s Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA
5Anesthesiology and Perioperative Medicine, University of Pittsburgh, Pittsburgh, PA
6Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA
7Pulmonary, Allergy, and Immunology, Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA
8Developmental Biology, University of Pittsburgh, Pittsburgh, PA

Nasal cannulas provide oxygen support for infants and have been considered for delivering aerosols to the lungs. In order to measure mucociliary clearance in the lungs of infants with congenital heart defects we delivered radiopharmaceutical aerosols via nasal cannula. Here we report on the pulmonary and nasal deposition of these aerosols. Eighteen infants (median age = 26 days) performed clearance measurements soon before or after corrective cardiac surgery. Regional aerosol deposition was assessed using gamma camera imaging. Cannula flowrates significantly affected pulmonary dosing. Flowrates useful for oxygen support were associated with low pulmonary deposition (2 L/min, mean 4.5% of deposited dose, range 2–9%, n = 7) and high nasal deposition. Much lower cannula flowrates increased pulmonary deposition (0.2 L/min, mean 33.5% of deposited dose, range 15–51%, n = 5, p = 0.005 vs. 2 L/min). The ratio of nose/lung dosing was approximately 26:1 at 2 L/min and 2:1 at 0.2 L/min. Bench studies demonstrated cannula output rates of 10.2±1.7% (2 L/min) and 3.3±0.4% (0.2 L/min) of loaded nebulizer dose during a 2-minute delivery. With the delivery system used here, pulmonary aerosol delivery via nasal cannula was very inefficient at the flowrates required to provide oxygen support. Even at low flows, nasal deposition was substantial and local toxicity must be considered.

P-042 MULTI-PROBE NUCLEAR IMAGING OF THE CYSTIC FIBROSIS LUNG

Timothy E. Corcoran1,2,3, Alex S. Huber2, Michael M. Myerburg1, Daniel J. Weiner4, Landon W. Locke5, Ryan T. Lacy5, Lawrence Weber6, Michael R. Czachowski5, Darragh J. Johnston2, Ashok Muthukrishnan6, Alison T. Lennox1, and Joseph M. Pilewski1,4,7

Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA;
2Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA;
3Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA;
4Pulmonary Medicine, Allergy, and Immunology, Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA;
5University of Pittsburgh Medical Center, Pittsburgh, PA;
6Department of Radiology, University of Pittsburgh, Pittsburgh, PA;
7Department of Cell Biology, University of Pittsburgh, Pittsburgh, PA;
8Department of Microbial Infection and Immunity, Ohio State University, Columbus, OH;

Nuclear imaging biomarkers illustrate unique aspects of lung physiology and are useful for assessing therapeutic effects in cystic fibrosis (CF) lung disease. We have developed a multi-probe method to simultaneously measure mucociliary clearance (MCC) and paracellular absorption (ABS). MCC is a direct measure of mucus clearance. ABS has been related to airway surface liquid (ASL) absorption through previous in vitro studies. We describe baseline factors affecting MCC and ABS using data from a retrospective baseline group (n = 22) and the response of the measures to inhaled 7% hypertonic saline (HS) and dry-powder mannitol using data from a prospective response group (n = 7). A retrospective healthy control group (n = 15) is also described. The baseline and control groups performed single measurements of MCC/ABS. The response group performed baseline measurements of MCC/ABS and measurements after each intervention. ABS was correlated to sweat chloride, a systemic measure of CFTR function, while MCC was not. Baseline MCC was depressed after Pseudomonas aeruginosa (PA) infection. MCC provided a more sensitive indication of therapeutic effect and indicated improved clearance with mannitol compared to HS. MCC provides a useful and well-established means of testing therapies directed at improving mucus clearance in the lung. ABS may provide a means of detecting local changes in ASL absorption and CFTR function in the lung.

P-045 EVALUATION OF AN ADAPTER AND MASK FOR USE WITH RESPIMAT INHALER

Ariel Berlinski, and Mary K Tucker

University of Arkansas for Medical Sciences. Pediatric Aerosol Research Laboratory at Arkansas Children’s Research Institute. Little Rock, Arkansas, USA

Introduction: The Respimat device is used to deliver several pulmonary drugs. It’s delivery efficacy may be aided in young and elderly populations by the use of a mask. We evaluated albuterol delivery from the Combivent Respimat alone, with an adapter, and with 2 different mask sizes. We hypothesize that adding a mask will reduce drug delivery but adding a mask will not, irrespective of their dead space volume.

Methods: A breathing simulator (VT 400 ml, I-time 1.2 s, I:E 1:2) was connected to a filter followed by an anatomically correct facial-airway model (www.rddonline.com). Albuterol was delivered via 4 individual actuators of the Combivent Respimat followed by 4 breaths after each actuation. The amount of albuterol delivered to the filter was measured (spectrophotometry at 276 nm) for the inhaler alone, with a commercially available adapter (ODAPT™) alone and with 2 different masks (dead space volume of 90 and 130 ml respectively). Lung dose was calculated as filter dose expressed as % of the nominal dose.
**Results:** Lung dose was 31.5 ± 2.3%, 26.3 ± 1.1%, 23.1 ± 3.5%, and 24.6 ± 1.5% for inhaler alone, inhaler with adapter and small and large mask respectively (p = 0.005).

**Conclusions:** The use of an adapter resulted in 16.5% decrease in albuterol delivery from Respimat inhaler. Adding a mask reduced albuterol delivery further by 6.5 – 12.2% irrespective of the dead space volume of the mask.

**P-049** DEVELOPMENT OF A LONG-ACTING VERSION OF DORNASE ALFA FOR THE TREATMENT OF CYSTIC FIBROSIS

M-J. Guichard¹, T. Wilms¹, B. Ucakar¹, T. Leal², and R. Vanbever¹

¹Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
²Louvain center for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium

Dornase alfa is the mucolytic agent most commonly used for the symptomatic treatment of cystic fibrosis (CF). However, a time-consuming administration of dornase alfa is required daily as it is rapidly cleared from the lungs, thereby contributing to the high therapeutic burden of CF patients. The purpose of this study is to develop a PEGylated version of dornase alfa with a preserved enzymatic activity and an increased residence time in the lungs.

Mono-PEGylation of dornase alfa on its N-terminus was associated with a full preservation of its enzymatic activity, independent of the PEG size. In agreement with this, PEGylation did not alter the secondary or tertiary structure of dornase alfa. In vivo disposition studies in healthy mice demonstrated that PEGylation of dornase alfa greatly increased its residency within the lungs from a few hours (native protein) to more than 15 days. This increased residence time was associated with an improved efficacy as a single dose of PEGylated dornase alfa was as successful as five daily doses of dornase alfa in associated with an improved efficacy as a single dose of PEGylated protein) to more than 15 days. This increased residence time was associated with an improved efficacy as a single dose of PEGylated dornase alfa was as successful as five daily doses of dornase alfa in hydrolyzing DNA in the respiratory tract of β-epithelial Na+ channel–overexpressing mice. Finally, ex vivo evaluation of CF sputa showed that dornase alfa and PEG-dornase alfa induced a similar decrease of elastic and viscous moduli of the sputa. At the moment, a non-GLP toxicity study is being conducted in order to establish the safety of PEGylated dornase alfa.

**P-065** PSEUDOMONAS AERUGINOSA-INFECTED COCULTURE MODEL OF HUMAN AIRWAY CELLS AND MACROPHAGES FOR PRECLINICAL EVALUATION OF INHALED ANTIMicrobIOTICS

Carlos V. Montefusco-Pereira¹,², Thomas Ebensen³, Christoph Beisswenger⁴, Robert Bals⁵, Carlos A. Guzmán⁶, Cristiane de Souza Carvalho-Wodarz⁷, and Claus-Michael Lehr¹,²

¹Department of Drug Delivery, Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken, Germany.
²Department of Biopharmaceutics and Pharmaceutical Technology, Department of Pharmacy, Saarland University, Saarbrücken, Germany.
³Department of Internal Medicine V – Pulmonology, Allergology, Respiratory Intensive Care Medicine, Saarland University Hospital, Homburg, Germany.
⁴Department of Vaccinology and Applied Microbiology, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany

P. aeruginosa is a persistent bacteria in human cystic fibrosis (CF) lungs, and the transition from the planktonic stage to biofilm is a challenge in CF. While animal models have been greatly used in CF research, they failed to reproduce the acute lung disease, resulting in less predictability of new drugs tests. Aiming for a predictive human infected in vitro system for CF lung infection, we established an airliquid interface (ALI) cell culture model with human cystic fibrosis bronchial epithelial cells (CFBE14o-) in the apical side of a transwell and human macrophages (THP-1) in the basolateral side. Similar transepithelial resistance (TEER >300 Ω·cm²) was observed in both, CFBE14o- mono- or co-cultures with THP-1 cells. In the 3D co-cultures early P. aeruginosa-biofilm aggregates were observed after 6 hours, as well as THP-1 transmigration to the site of infection, and a higher level of IL-8, IL-1β, and IL-6. Upon tobramycin treatment, the bacterial killing was higher on an abiotic surface (plastic plates) than on cell surface, which suggests an overestimation of the drug efficacy in cell-free assays. As expected the infection disrupted the epithelial barrier (TEER <300 Ω·cm²), which was similarly restored after tobramycin treatment, in both CFBE14o- mono- and co-culture. In conclusion, such 3D human-based co-culture cell model allows for investigation of cellular and immune responses upon infection and thus appears valuable for preclinical tests of inhaled medicines.

**P-073** A MATHEMATICAL MODEL TO UNDERSTAND THE CLEARANCE OF THE LUNG IN CYSTIC FIBROSIS

P. Anagnostopoulou¹, D. Hasler³, P. Latzin³, D. Obrit¹, and J.C. Schittny¹

¹Institute of Anatomy, Bern, Switzerland
²ARTORG Center for Biomedical Engineering Research, Bern, Switzerland
³Pediatric Respiratory Medicine, Department of Pediatrics, Inselspital - Bern University Hospital, University of Bern, Bern, Switzerland

Cystic fibrosis (CF) is characterized by increased ventilation inhomogeneity (VI). The multiple breath washout (MBW) is a lung function test that measures the degree of VI. However, the mechanisms that produce VI in CF are not well understood. Lung computational models that mimic lung anatomy and physiology are available, but only few of them have dealt in depth with the airway clearance. Our aim was to create a lung model with structural and functional characteristics of the CF lung that simulates the entire MBW test.

We developed a multi-scale fractal lung model based on anatomical data including big and small airways. We applied systematically changes in parameters that can produce VI (compliance, residual airway volume, flow resistance, airway transmissibility), and assessed their effects on the pattern of the MBW curve and on the MBW results.

Variabilities in compliance and residual volume of the airways have a direct influence on the MBW pattern and outcomes (lung clearance index changes up to 27% and 24%, respectively). To mimic the increased VI in CF lung disease, systematic reduction in airway transmissibility, in compliance, and in residual volume were applied in the model.

We describe an easy-to-apply whole lung model that simulates the MBW test. By applying proper changes in physiological parameters, this model can mimic the MBW test in CF lung disease, which can be used for our better understanding of mechanisms that produce VI in CF.
P-090  EVALUATION OF USE OF MOUTHPIECE WITH THE VR647 INHALATION SYSTEM IN CHILDREN AGED 1 TO 4 YEARS

Leonard B. Bacharier1, Gary Burgess2, Bernhard Müllinger3, and Sue Snape3
1Department of Pediatrics, Washington University in St Louis School of Medicine, St Louis, MO, USA
2Vectura Ltd, Chippenham, UK
3Vectura GmbH, Goettingen, Germany

Rationale: It is perceived that young children have difficulty inhaling with a mouthpiece. The VR647 inhalation system (VR647IS) is a novel, breath-actuated device for pediatric patients that guides inhalation flow rate and volume to optimise delivery to the lungs and provides real-time feedback to improve patient’s inhalation technique. In this study inhalation success was assessed in children aged 1–4 years using VR647IS with a mouthpiece.

Methods: Children aged 1–4 years with cough and/or recurrent wheeze in the past year, and who had used either a MDI with a spacer or a nebulizer, were included in this open-label study. Patients inhaled isotonic saline for nebulization using VR647IS with a mouthpiece, during two clinic visits (V1/V2), 4–8 days apart. Inhalation success was assessed at the third attempt at each visit.

Results: Overall, 40/41 patients attempted at least one inhalation. Most patients used VR647IS with a mouthpiece successfully (65% and 70% at V1 and V2, respectively); 90% of patients aged 3–4 years, 64% aged 2 years and 17% aged 1 year were successful at using VR647IS with a mouthpiece at V2. Most patients (89%) aged 4 years inhaled with a mouthpiece without hands-on assistance at V2 and 43% of children aged 2 years could use it without assistance.

Conclusions: 90% of children aged 2 years and above were able to use VR647IS with a mouthpiece, and 89% of children aged 4 years could use VR647IS without assistance.

P-099  IN VITRO EVALUATION OF PEDIATRIC NASAL AND PARANASAL DRUG DELIVERY

Laleh Golshahi1 and Sana Hosseini1
1Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University (VCU), Richmond, VA, United States

Intranasal drug delivery devices have mainly been developed for adults. Children are expected to receive a different local dose compared to adults due to their different airway morphology and inhalation patterns. We aimed to compare the efficiency of most common nasal drug delivery devices in terms of regional delivery of suspension patterns. We aimed to compare the efficiency of most common nasal drug delivery devices in terms of regional delivery of suspension patterns.

P-097  FROM THE CORRESPONDING IN VITRO DATA OBTAINED USING COMPENDIAL METHODS TO THE IN VIVO PERFORMANCE OF OIPs

Anders Fuglsang4 and Charlotte Keywood2
1Department of Pediatrics, University of Liverpool, Liverpool, UK
2Vera Novakova3, 4Independent Consultant, Prague, Czech Republic;
3Zambon SpA, Milan, Italy;
4Fuglsang Pharma, Haderslev, Denmark

A blend of spray dried budesonide (BUD) and formoterol fumarate dihydrate (FFD) produced using the Edry® technology is mixed with micronized lactose to create a unique formulation to be delivered using a standard Plastistape RS-01 capsule inhaler. The product “Z7200” is intended as an alternative to the originator product, Symbicort Turbuhaler (“SymbTBH”). AstraZeneca). Z7200 has a very fine particle fraction of ~70%, and was developed to have the same efficacy with a 50% reduction of the delivered dose. Z7200 80/2.25 µg and SymbTBH 160/4.5 µg were compared in an open-label, randomized, five-period crossover study in 90 healthy volunteers to assess bioequivalence of a single dose (two inhalations), with and without charcoal. As SymbTBH might have high between batch variability, a multi-batch approach with 9 reference batches was used. The results showed FFD bioequivalence in both AUC0-t and Cmax, both with and without charcoal block. For

Regulatory and Standardization Issues

R-014  SHOULD MORE CLINICALLY RELEVANT APSD METHODS BE INTRODUCED INTO THE PHARMACOPEIAL COMPENDIA

Jolyon P Mitchell1
Jolyon Mitchell Inhaler Consulting Services Inc., London, Canada1

Historically, pharmacopeial methods have been developed to provide the ‘how to’ for testing a medicinal product for quality. As such, the methods in both European and United States pharmacopoeias for determination of APSD by cascade impactor are robust, with optimal precision and accuracy. This goal has come at a cost that these procedures are too simplified to be able to mimic patient use. Patients frequently have sub-optimal technique for OIP use. There is increasing pressure from stakeholders to provide laboratory-generated measures of performance that are more informative of how these products function in use. Furthermore, in the context of assessing product equivalence, there have been instances where pharmacokinetic data for OIP batches have shown differences that were not evident from the corresponding in vitro data obtained using compendial methods. A group of parallel methods has evolved that are more clinically realistic, but at the same time are more complex to implement. These incorporate (a) an age-appropriate anatomically correct/idealized inlet; (b) a laminar flow mixing device located between the inhaler and the cascade impactor so that the inhaler can be subjected to age and disease-specific flow rate-time profiles, whilst the impactor operates at constant flow rate. It is timely to ask whether the scope of the compendial methods could be widened beyond quality control.
BUD, bioequivalence was found for AUC\textsubscript{0-\texttau}, but C\textsubscript{max} failed. As several reference batches were studied in the PK study, it was of interest to assess how different PK parameters correlate to in-vitro data for the same batches. No correlation between BUD AUC\textsubscript{0-\texttau}, and fine particle mass (FPM) was seen. The between batch RSD in FPM and AUC\textsubscript{0-\texttau} was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between batch PK variability, and was 16% and 11%, respectively. Thus, the results for SymbTBH suggest that this product has high between bath PK variability, and that FPM alone is no reliable predictor of in-vivo performance.

**R-017 IN VIVO REALISTIC IN VITRO TESTING OF OINDPS**

Märten Svensson, Peter Elfman, and Elna Berg

Emmace Consulting AB, Medicon Village, Lund, Sweden

More patient realistic in vitro testing on OINDPs has attracted much interest in recent years. The main driver is to better predict (or explain) the clinical outcome and therefore avoid unwanted surprises and the need to repeat costly studies. The more in vivo realistic testing can also be applied in the development phase of new inhalers/formulations and can for instance be used in addition, and as a complement, to the more traditional standard pharmacopeia tests.

Two major method parameters are important to define and implement when moving towards a clinically relevant method to predict the lung deposition from inhalers and nebulizers. The first one to consider is the throat geometry which can be a significant “hurdle” and filter for the aerosol particles/droplets prior transportation to the lung region. The second parameter is the inhalation air flow profile that can be expected from the patient group in question. By a combination of these two method parameters, vital information is generated how the product will behave when exposed in the hands of patients.

This presentation will focus on these important parameters and how these can be implemented in the lab, how the experiments can be performed from a practical viewpoint, and finally also mention some real case findings.

**R-106 EXPLORING IN VITRO DEPOSITION OF PHARMACEUTICAL AEROSOLS IN THE ALBERTA IDEALIZED THROAT**

Conor A. Ruzzycki, Andrew R. Martin, and Warren H. Finlay

University of Alberta, Edmonton, Alberta, Canada

The development of accurate in vitro correlations requires the careful consideration of a number of issues. Here we explore the effects of inhaler insertion angle and relative humidity on deposition in the Alberta Idealized Throat and a downstream filter. Deposition from three dry powder inhalers (Pulmicort Turbuhaler, Budelin Novolizer, and Easyhaler Budesonide) was examined using inhaler-formulations and can for instance be used in addition, and as a complement, to the more traditional standard pharmacopeia tests.

Two major method parameters are important to define and implement when moving towards a clinically relevant method to predict the lung deposition from inhalers and nebulizers. The first one to consider is the throat geometry which can be a significant “hurdle” and filter for the aerosol particles/droplets prior transportation to the lung region. The second parameter is the inhalation air flow profile that can be expected from the patient group in question. By a combination of these two method parameters, vital information is generated how the product will behave when exposed in the hands of patients.

This presentation will focus on these important parameters and how these can be implemented in the lab, how the experiments can be performed from a practical viewpoint, and finally also mention some real case findings.

**Environmental/Occupational Health/Toxicology**

**E-022 APPLICATION OF NANO-SILVER/CHITOSAN COMPOSITE STERILIZATION MATERIAL FOR THE REMOVAL OF VIRAL AEROSOLS**

Kuo-Pin Yu\textsuperscript{1*}, I-Jen Wang\textsuperscript{1,2*}, I Fan Chang\textsuperscript{2}, Chien Su\textsuperscript{1}, Wan-Tien Shen\textsuperscript{2}, Chun-Hsuan Bai\textsuperscript{1}

\textsuperscript{1}Institute of Environmental and Occupational Health Sciences, National Yang-Ming University, Taiwan

\textsuperscript{2}Department of Pediatrics, Taipei Hospital, Ministry of Health and Welfare, Taiwan

In this study, we applied nano-silver/chitosan-TiO\textsubscript{2} composite (nano-Ag/CS-TiO\textsubscript{2}) filter for the removal of viral aerosols to reduce the risk of virus transmission and infection in hospital wards. The photochemical deposition method was used to synthesize nano-Ag/CS-TiO\textsubscript{2}. The surface and elemental characteristics of the nano-Ag/CS-TiO\textsubscript{2} were analyzed by the scanning and transmission electron microscopy (SEM and TEM). The MS2 phage was used as surrogate viral aerosols. The MS2 plaque reduction (PR) assay found that in 4 mL of liquid culture solution, 2 g of 2wt% nano-Ag/CS-TiO\textsubscript{2} deactivated 91% of MS2 phage within 4 hours. In the air-purification experiments, the generated MS2 phage aerosols will pass through the nano-Ag/CS-TiO\textsubscript{2} filter, and then will be collected by a bioaerosol sampler. According to the activity of the virus collected in the sampler, the bed filter packed with 2wt% nano-Ag/CS-TiO\textsubscript{2} can remove as much as 93% of MS2 phage aerosols. MS2 phage on the surface of nano-Ag/CS-TiO\textsubscript{2} can be deactivated within 20 minutes, and the activation efficiency could up to 95%. In accordance with the simulation of Wells-Riley model, in best situation the airborne infection rate in the room installed with nano-Ag/CS-TiO\textsubscript{2} filter can be reduce from 99% to 34.6%. The technique proposed in this study would effectively reduce the risk of airborne infection, but the results may be different depending on the virus strain tested (virus with capsule or un-capsule).

**E-026 REPEATED LONG-TERM EXPOSURES OF MULTI-WALLED CARBON NANO TUBES TO THE 3D HUMAN LUNG MODEL EPIALVEOLAR\textsuperscript{TM} TO PREDICT THE ONSET OF FIBROSIS**

Hana Barosova\textsuperscript{1}, Anna G. Maione\textsuperscript{2}, Dedy Septiadi\textsuperscript{1}, Monita Sharma\textsuperscript{2}, Amy J. Clippinger\textsuperscript{3}, Alke Petri-Fink\textsuperscript{1}, Patrick Hayden\textsuperscript{2}, and Barbara Rothen-Rutishauser\textsuperscript{1}

\textsuperscript{1}Adolphe Merkle Institute, University of Fribourg, Fribourg, CH

\textsuperscript{2}MatTek Corporation, Ashland, Massachusetts, USA

\textsuperscript{3}PETA International Science Consortium Ltd., London, UK

The use of multi-walled carbon nanotubes (MWCNTs) in commercial products is extensive. Human exposure to MWCNTs can occur throughout their life-cycle via inhalation causing potential adverse effects such as pulmonary fibrosis. Therefore, there is a need to design human-relevant in vitro testing and exposure strategies to assess the biological effects of MWCNTs.
Human-based co-cultures (EpiAlveolar™, MatTek Corporation) consisting of human primary cells, e.g. lung endothelial and alveolar epithelial cells and fibroblasts, were exposed to aerosolized Mitsui-7 MWCNTs at the air-liquid interface using the VITROCELL® Cloud system. Repeated, low doses exposures were performed every working day (5 days per week) for 3 weeks.

Repeated exposures to transforming growth factor-β, used as a positive control for fibrosis, showed a statistically significant (p<0.05) increase in fibronectin production after 1, 4, 18, and 21 days. Repeated exposures to MWCNTs (range of 1 – 30 μg/cm²) caused statistically significant increase in fibronectin release at days 4, 14, 18, and 21. Other (pro-)fibrotic and (pro-)inflammatory biomarkers are currently being investigated.

The EpiAlveolar™ model is a promising tool for predicting the development of pulmonary fibrosis, however, further investigation with additional fibrotic markers and materials is warranted. In the future, the model can be used in combination with other in vitro and in silico methods for hazard assessment of aerosolized nanomaterials.

**E-029 DEVELOPMENT AND TESTING OF THE INDEPENDENT HOLISTIC AIR-LIQUID AEROSOL EXPOSURE SYSTEM (INHALES)**

S. Steiner1, P. Hervey1, S. Majied1, C. Pak1, A. Kuczaj1, and J. Hoeng1

1PMI R&D, Philip Morris Products S.A., Switzerland

The human respiratory tract is functionally and structurally heterogeneous, and the kinetics governing the transfer of gas or aerosol constituents from an inhaled volume of air to its epithelia are highly complex. As a consequence, the physical conditions that the epithelia of different respiratory tract regions experience as well as the amount and composition of an inhaled aerosol they perceive vary strongly. Simulating this complexity for the purpose of in vitro aerosol exposure experiments poses a significant technical challenge.

We developed a novel aerosol exposure system, the Independent Holistic Air-Liquid Exposure System (InHALES). It mimics the complete human respiratory tract from the oropharyngeal cavity down to the lung lumen and allows exposures of tissue cultures of all respiratory tract regions to be conducted in one single experiment. The structural similarity to the respiratory tract translates into functional similarity; critical parameters, such as flow velocities or aerosol dilution, are therefore close to in vivo conditions by default.

We present the results of functional testing of a prototype of the system. Tests were conducted in cell culture exposures and cell-free experiments using cigarette smoke and fluorescently labelled glycerol aerosols as test atmospheres. Currently, we are improving the geometry of the airway model. In particular, a 3D-printed model of the bronchial tree reaching down to the transitional bronchioles is being developed.

**E-032 EXPERIMENTAL AND COMPUTATIONAL MODELLING OF FLOW OF FIBRES IN HUMAN AIRWAYS**

Frantisek Lízal1, Jakub Elcner1, Jan Jedelsky1, Arpad Farkas1, Milan Maly1, Ondrej Pech1, Ondrej Misik1, and Miroslav Jicha1

1Brno University of Technology, Faculty of Mechanical Engineering, Department of Thermodynamics and Environmental Engineering, Technická 2896/2, Brno, the Czech republic

The ability of fibres to align with the flow has been identified as a reason for higher penetration of fibres into the lungs compared to spherical particles by many studies. However, prediction of the fate of inhaled fibres by computational methods is complicated due to the necessary mathematical apparatus and the lack of experimental data for validation. It is common to apply coefficients accounting for the preferential orientation of the fibre flowing through the airways. A new experimental rig has been built to visualize the flow of micron-sized fibres and record the angles of their rotation upstream and downstream of a single bifurcation. The recorded angles are statistically analysed and improved coefficients of fibre orientation will be calculated. The experimental rig consists of a dielectrophoretic classifier of fibres, the model of human trachea and first bronchi, a breathing simulator and a high-speed camera with appropriate illumination. These experiments are supplemented with computational simulations and experimental measurement of deposition of fibres in a replica of human lungs comprising of the upper airways and first seven generations of tracheobronchial tree branching.

**E-035 METAGENOMIC CHARACTERIZATION OF MICROBIAL CONTAMINATION IN NEBULIZERS**

Clifford Swanson1, Qi He1, Kristen Wyckoff2, Jennifer Ferris3, Scott Elder4, Daniel Church5, Lee Ann Holbert5, and Rajiv Dhand6

1The University of Tennessee, Department of Civil Engineering, Environmental Engineering, Knoxville, Tennessee, USA
2Institute for a Secure and Sustainable Environment, The University of Tennessee, Knoxville, TN, USA
3The University of Tennessee Graduate School of Medicine, Department of Medicine, Knoxville, Tennessee, USA
4Respiratory Therapy Department, University of Tennessee Medical Center, Knoxville, Tennessee, USA

With nebulizers being widely employed to deliver respiratory medicines, understanding the occurrence of microbial contamination in these devices is critical for the development of effective protocols to reduce the transfer of contaminants during treatment. The aims of this study were to determine the extent of microbial contamination, factors influencing microbial contamination, and the type of microorganisms contaminating nebulizer devices. Nebulizer kits (Westmed, reference # 0210) were collected from adult patients suffering from pneumonia or COPD exacerbation during their stay at UT Medical Center in Knoxville, TN, with IRB approval. Baseline samples were collected within 24 hours of patient admission, followed by samples every couple of days until patient discharge. Bacterial plate counts showed that contamination was detected on all used nebulizers and contamination rates varied among parts, with mouthpieces testing positive at the highest rate, 74%. High-throughput sequencing of the microbial community present identified several potential pathogens as highly abundant microbial contaminants including Stenotrophomonas, Burkholderia, and Pseudomonas representing up to 26%, 10%, and 8.5% of the sequences retrieved from nebulizers respectively. These findings revealed the high frequency of contamination in nebulizers by microorganisms, particularly with known pathogens, emphasizing the need to develop effective protocols for preventing bacterial transmission.
The liquid impingers are widely used to sampling bioaerosols. But the lowest cutoff diameter of currently commercial impingers was about 0.3 μm, and their physical collection efficiency for nano-bioaerosol is only about 10–20%. Here, we used a modified all glass impinger-30 (mAGI-30) to collect the nano-size MS2 bacteriophage aerosols with different collection media (1% peptone, PBS buffer solution, and deionized water). The mAGI-30 was an AGI30 packed with 3-mm glass beads (with 10 cm depth) and has a collection efficiency of >99% for nanoparticles. The effects of different sampling flow rates (4, 6, and 12.5 lpm) and different sampling time (10, 20 and 30 min) on the collection efficiency of MS2 aerosols were also tested. The results showed the optimal sampling condition of mAGI-30 for nano-size MS2 aerosols was: 1% peptone collection media, operating at 12.5 lpm for 20 minutes, and those variables had a statistically significant effect on increasing the collection efficiency (0.24 ~ 2.04%) and recovery (0.62 to 0.79%) of MS2. Moreover, the mAGI-30 can increase from 9.06 to 1.46% than AGI-30 without packed with glass beads.

E-053 REDUCTION OF (PRO-)INFLAMMATORY RESPONSES BY STEROID DRUGS IN AN INFLAMED HUMAN LUNG MODEL IN VITRO

Barbara Drasler1, Hana Barosova1, Mauro Sousa de Almeida1, Christoph Bisig1, Alke Fink1, and Barbara Rothen-Rutishauser1

1BioNanomaterials group, Adolphe Merkle Institute, University of Fribourg, Fribourg, Switzerland
2Department of Chemistry, University of Fribourg, Fribourg, Switzerland

Various lung diseases are associated with inflammation of the lung tissue. There are emerging strategies and formulations being developed to overcome side effects of conventional anti-inflammatory drugs. In vitro multicellular human lung models can be powerful tools for an early stage efficacy evaluation of newly developed therapies; however their responsiveness to known stimuli needs first to be investigated. Therefore, an advanced human lung model, composed of alveolar epithelial cells and human monocyte-derived macrophages and dendritic cells, was employed to test efficacy of anti-inflammatory agents. Bacterial endotoxin lipopolysaccharide (LPS) was used to trigger pro-inflammatory response of the co-culture model, followed by application of anti-inflammatory steroidal drugs, such as methylprednisolone (MP). Pro-inflammatory reactions were compared before and upon addition of the treatment via secretion of pro-inflammatory cytokines and on gene expression levels (real time quantitative polymerase chain reaction). LPS induced pro-inflammatory response in the model as observed via increased cytokine secretion and increased expression of the related genes. Further treatments with steroidal drugs reduced release of pro-inflammatory markers compared to negative control; this was also confirmed at the gene expression levels. The outcomes suggest that MP is a promising treatment, which can also serve as positive control for reduction of inflammation in lung tissue in vitro.

E-055 MULTI-WALLED CARBON NANOTUBES AFFECT ACTIVATION AND POLARIZATION OF PULMONARY MACROPHAGES AND DENDRITIC CELLS IN AN IN VIVO MODEL OF COPD

Seraina Beyeler1,2, Carlos Wotzke1, Selina Steiner1, Amanuel Adhanom Sengal1,2, Peter Wick3, Stefan Tschanz3, Beat Haenni4, Christophe von Garnier1,2, and Fabian Blank1,2

1Department of Biomedical Research, University of Bern, Bern, Switzerland
2Department of Pulmonary Medicine, Inselspital, University Hospital of Bern, University of Bern, Bern, Switzerland
3Empa Materials, Science and Technology, St. Gallen, Switzerland
4Institute of Anatomy, University of Bern, Bern, Switzerland

Introduction: With progress of nanotechnology there is concern about adverse health-effects of inhaled occupational nanoparticles, such as multi-walled carbon nanotubes (MWCNT), particularly in the respiratory tract in individuals suffering from chronic obstructive pulmonary disease (COPD).

Methods: We employed an Elastase/LPS COPD mouse model in which animals received 0.08μg/cm2 of MWCNT by intratracheal instillation. Lung function, morphometry, differential counts of broncho-alveolar lavage fluid (BALF), as well as phenotype of alveolar macrophages (AM) and dendritic cells (DC) were monitored in the respiratory tract.

Results: Treatment with MWCNT caused accumulation of AM in BALF from COPD groups that increased from 24h to 7d. In the COPD group, MWCNT treatment shifted AM polarization towards a M1-like predominant phenotype, as measured by the ratio of markers CD38 to CD206, and increased AM activation with upregulation of co-stimulatory markers CD40 and CD80. Moreover, MWCNT treatment increased frequencies of DC, leading to an expansion of the CD11b+CD103+ DC subset. Though MWCNT did not trigger lung functional or structural changes, they induced increased expression of muc5AC RNA in COPD animals.

Conclusion: Data show that MWCNT affect the pulmonary immune system by altering both phenotype and activation of antigen-presenting cell populations. Extrapolating these in vivo findings to human pulmonary exposure, caution is warranted when handling inhalable nanofibers.

E-076 ANALYSING FUGITIVE EMISSIONS FROM A BREATHE ACTUATED NEBULISER

Ciaraí O’Toole1, Gavin Bennett2, James McGrath1, Mary Joyce1, Roman Mac Loughlin2, and Miriam Byrne1

1Centre for Climate & Air Pollution Studies (C-CAPS), School of Physics, National University of Ireland Galway, Galway, Ireland
2Aerogen, IDA Business Park, Dangan, Galway, Ireland

Introduction: Studies to date have identified the potential for fugitive emissions to be released during standard nebulisation treatments. Here we characterise fugitive emissions from a breath actuated jet nebuliser designed to reduce emissions.

Methodology: A breath actuated jet nebuliser with mouthpiece (Aeroeclipse2, Monaghan Medical, Canada) was operated at 8 L/min. Two modes on the nebuliser were tested during simulated adult breathing (Vt 500 mL, 15 BPM, E:R ratio 1:1); breath actuated nebulisation (BAN) and continuous nebulisation (CN) (n = 4). 3mL of 2mg/mL salbutamol was nebulised. Two Aerodynamic Particle Sizer
(APS) (TSI Inc., US) devices at 0.8 m and 2.2 m from the nebuliser were used to characterise the fugitive aerosol concentration (mg drug/m³). The study duration was 45 minutes for each run.

**Results:** Fugitive emissions were released during both CN and BAN modes. CN mode on the nebuliser at 0.8 m had higher fugitive aerosol concentrations compared with 2.2 m (0.051 ± 0.018 mg/m³ vs 0.039 ± 0.010 mg/m³). CN mode fugitive higher aerosol concentrations with BAN mode (0.051 ± 0.018 mg/m³ vs 0.028 ± 0.007 mg/m³).

**Conclusion:** Our findings confirm that fugitive emissions are released into the environment during respiratory therapy during both continuous and breath actuated jet nebulisation. When using the breath actuated mode, lower but detectable fugitive emissions were released into the environment suggesting bystander exposure to medical aerosol is still a risk.

**E-078 A SIMPLE MICROFLUIDIC PLATFORM FOR TESTING AEROSOL DEPOSITION ON ALVEOLAR EPITHELIAL MODELS**

Carius P.1,2, Artzy-Schnirman A.3, Szmitman J.3, Schneider-Daum N.1, and Lehr C.-M.1,2

1 Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Helmholtz Center for Infection Research (HZI), Saarland University, Saarbrücken, Germany

2 Biopharmaceutics and Pharmaceutical Technology, Department of Pharmacy, Saarland University, Saarbrücken, Germany

3 Department of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa, Israel

hAELVi, a novel human alveolar epithelium lentivirus immortalized cell line, could help to standardize the transport of inhalable substances across the air-blood barrier in vitro. Tight barrier properties have been characterized and showed high transepithelial electrical resistance (TEER) of >1000 Ω·cm² under air-liquid interface (ALI) as well as submerged culture conditions. This model, like other in vitro models of the lung, however, is based on cells grown on permeable growth supports (e.g., Transwell®) in static culture conditions. Static conditions restrict the supply of fresh culture medium, thus hindering optimal oxygenation, nutrient transport and removal of metabolic by-products. Microfluidic systems could bypass these issues, by allowing the implementation of dynamic flow. However, the design and the morphology of current microfluidic channels limit the particle sizes of deposited aerosols down to a narrow range. Here, we present preliminary data from a self-made microfluidic platform that combines the benefits of filter supports with the advantages of microfluidic flow at a low cost. Fluorescein sodium was nebulized by the use of an Aerogen Solo nebulizer and a customized nebulisation chamber onto hAELVi cell monolayers cultured under ALI conditions. Samples were taken from the receiver chamber under flow conditions. This setup could allow for the investigation of the transport of aerosols by the introduction of permanent sink conditions through flow.

**E-088 CHARACTERIZATION OF THE PHYSICAL AND THERMAL PROPERTIES OF NEW AND EMERGING TOBACCO PRODUCT (NETP) EMISSIONS**

Phillip W. Clapp1, Christopher T. Jadelis1, Jihong Wu1, Kirby L. Zeman1, John T. Minges2, Alyssa Burke1, Landon T. Holbrook1, and William D. Bennett1

1Center for Environmental Medicine, Asthma, and Lung Biology, 2Marisco Lung Institute, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; USA

**Background:** New and Emerging Tobacco Products (NETPs), such as pod vapes and heat-not-burn cigarettes fuel a growing multibillion-dollar industry. As NETPs evolve, it is unclear to what degree device geometry, power settings, and mechanisms of aerosolization affect aerosol properties.

**Methods:** To address this, we evaluated the physical and thermal properties of emissions from 5 popular NETPs with differing designs and aerosolization methods. Particle size and mass output were measured by cascade impactor, and temperature (temp) profiles were collected using a K-type thermocouple positioned 1mm from the mouthpiece of each device.

**Results:** Mean particle sizes ranged from 0.5 μm – 1.2 μm when sampling the entire puff. Aerosols from 3rd generation e-cigarettes reached temps greater than 150°C using manufacturer-suggested power settings while aerosols from the JUUL (pod vape) and USONICIG (ultrasonic vape) did not exceed 54°C; the peak temp of smoke produced by a standard 3R4F research cigarette. IQOS (heat-not-burn cigarette) emissions reached a peak temp of 70°C. However, 1 IQOS smoking session (14 puffs) did not provide sufficient particle output for accurate sizing by cascade impaction.

**Conclusions:** These data demonstrate the variability between popular NETPs and highlight the similarities and differences between NETP emissions. Importantly, our findings suggest that aerosols from 3rd generation e-cigarettes may put users at risk for thermal injury to the respiratory tract.

**E-083 AEROSOL GENERATION, COMPOUND UPTAKE, AND DISEASE-MODIFYING EFFICACY FOLLOWING INHALATION ADMINISTRATION OF NEBULIZED ALKALOIDS IN A MURINE MODEL OF ULCERATIVE COLITIS**

Wei Teck Tan1, Blaine Phillips1, Giuseppe Lo Sasso2, Subash Krishnan1, Arkadiusz Kuczaj2, Patrick Vanscheeuwijk2, Julia Hoeng2, and Manuel C Peitsch2

1 PMI R&D, Philip Morris International Research Laboratories Pte. Ltd., Science Park II, Singapore

2 PMI R&D, Philip Morris Products S.A., Neuchâtel, Switzerland

In order to support pre-clinical studies demonstrating in vivo efficacy of inhaled compound delivery, we have evaluated a small whole-body exposure chamber (sWBEC, inExpose, Sciex) as a means to effectively deliver alkaloids to rodents. An aerosol was supplied to the sWBEC by nebulizing nicotine and tobacco alkaloids using Blaustein Atomizing Modules (BLAM, CH Technologies, USA). The BLAM functions by breaking up the liquid test item into tiny droplets using pressure generated when compressed dry air is expanded through small orifices. Spatial variation of the aerosol was measured at different locations within the sWBEC and found to be very low. The time to reach 95% of the equilibrium nicotine concentration was estimated to be ~82 minutes; it remained stable for up to six hours, demonstrating temporal homogeneity. To determine in vivo tolerance, C57Bl/6 mice were exposed for six hours per day to a nicotine-containing aerosol (50 μg/l). Plasma collected immediately after the exposure period demonstrated effective uptake of nicotine. Finally, nicotine and a related tobacco alkaloid, both with potential anti-inflammatory properties, were assessed in the DSS-induced colitis model in C57Bl/6 mice following inhalation exposure. While nicotine had minimal efficacy in the DSS-induced colitis model, exposure with the related alkaloid was associated with reduced colonic inflammation and less weight loss compared to control animals, indicative of a mild disease-modifying effect.
E-089 AN INEXPENSIVE IN VITRO EXPOSURE SYSTEM FOR UNIFORM SEDIMENTATION OF LIQUID AEROSOLS GENERATED BY NEW AND EMERGING TOBACCO PRODUCTS (NETPS)

Phillip W. Clapp1, Christopher T. Jadelis1, Kirby L. Zeman1, JiHong Wu1, John T. Minges2, Ilona Jaspers1, and William D. Bennett1

1Center for Environmental Medicine, Asthma, and Lung Biology, 2Marsico Lung Institute, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Background: Most commercially available multiwell in vitro aerosol exposure systems rely on impaction or electrostatic manipulation of diluted aerosol to achieve particle deposition at cell culture surfaces. However, reported particle sizes of NETP emissions suggest these methods may not produce adequate deposition for toxicity testing.

Methods: To address this, we developed and validated an inexpensive gravimetric sedimentation exposure system for puff-actuated NETPs. Our system, which can be housed within a standard cell culture incubator, uses microcontroller-based automation to deliver aerosols to a small (16 cm x 9 cm x 7 cm) chamber containing a single Transwell multiwell plate. To quantify particle deposition, fiberglass filters were placed into 6.5 mm Transwells and filter weights were recorded before and after a JUUL e-cigarette vapor session (40, 5-second, puffs and 9-minute inter-puff settling time). A direct comparison was made with a Vitrocell VC10 using the same experiment design and JUUL vapor protocol.

Results: Sedimentation of JUUL aerosols in our system resulted in uniform particle deposition of 253 ± 9 µg onto 24, 6.5 mm Transwells. The Vitrocell VC10 achieved 36 µg ± 21 µg deposition by impact; significantly less than the deposition achieved by sedimentation and with greater inter-well variability.

Conclusions: Based on these data, we believe our sedimentation exposure system may provide an effective and inexpensive means for in vitro toxicity testing of NETPs.

E-097 IN VITRO OXIDATIVE STRESS RESPONSE CHARACTERIZATION AND ANTIOXIDANT PROTECTION IN HUMAN PULMONARY CELLS

Jordan A. Hoops1 and Timothy M. Brenza1

1Department of Chemical and Biological Engineering, South Dakota School of Mines & Technology

Exposure to pollutants and particulate matter cause oxidative stress through the direct introduction of exogenous ROS and compounds that drive free radical reactions, or indirectly through the recruitment and activation of inflammatory cells which release free radicals. The large surface area of the lungs and direct contact with inhaled air make the respiratory system highly susceptible to oxidative stress related injury, including DNA damage, cellular barrier dysfunction, and direct tissue damage. More susceptible populations include immunodeficient individuals, infants, elderly and those with pulmonary diseases such as asthma.

Previous groups have investigated the acute and subchronic exposure responses of human pulmonary cell line A549 to particulate exposure, including production of reactive oxygen species and cell viability. Antioxidant supplementation with Trolox, a commercially available vitamin E analog, has been investigated by various groups to decrease DNA damage and cell cycle arrest in A549s when acutely exposed to oxidants, including particulate matter (PM10).

The goal of this work was to characterize acute and chronic oxidative stress response parameters of the A549 cell line by the ratio of reduced and oxidized glutathione, chemokine production, DNA integrity, and surfactant secretion. The capacity of antioxidants to attenuate acute and chronic oxidative stress damage was also evaluated.

E-110 OPTIMIZATION AND VALIDATION OF VITROCELL® 24/48 IN VITRO INHALATION EXPOSURE SYSTEM READY FOR PHARMA APPLICATIONS

Evelien Frijns1, Jo Van Laer1, An Jacobs1, Karen Hollanders1, Sven Vercauteren1, and Sandra Verstraelen1

1VITO NV (Flemish Institute for Technological Research), Unit HEALTH, Boeretang 200, 2400 Mol, Belgium

Epidemiological and animal studies are used to investigate adverse effects on inhaled compounds. However, results are not always easy to interpret and experiments are expensive, time consuming and use large numbers of animals. For this, there is an increasing demand for the development of alternative approaches existing of realistic lung cell models (e.g. 3D), realistic inhalation exposure systems (i.e. air-liquid interface) and proper dosimetry techniques to increase the predictive ability of in vitro cell models and therefore accelerate the shift from in vivo towards in vitro testing.

The VITROCELL® 24/48 exposure system is designed to perform a dose-response profile in one run. Six dilutions with 6 inserts are used for exposure to compounds and 6 inserts in the same system are used for negative and positive control exposure, respectively.

Experiments with the VITROCELL® 24/48 system were performed to test different humidification systems, trumpet heights, flows and cell models (A549, MucilAirTM) to find the most optimal settings. Quality control charts for cell viability of negative and positive control exposures were established. It is shown that the exposure system is ready for testing pharmaceutical compounds.

E-115 BRONCHIAL HYPER-RESPONSIVENESS FOLLOWING CHRONIC CIGARETTE EXPOSURE IN APOE-/- MICE

Dongyang Yi1, Yasmine Farra1, Emma Lloyd1, Chiara Bellini1, and Jessica M. Oakes1

1Department of Bioengineering, Northeastern University, Boston, MA 02115, USA

Chronic exposure to cigarette smoke is linked to inflammation, oxidative stress, and development of cardiopulmonary functional abnormalities. Apolipoprotein E prevents lipid accumulation in the tissues and is a negative regulator of airway hyperreactivity and mucin gene expression in house dust mite treated mice. The aim of our study was to investigate the impact of chronic cigarette exposure on inflammation, tissue destruction, and airway responsiveness in female ApoE−/− mice. Mice (n = 6) were nose-only exposed to smoke for one hour a day over six months; particulate matter concentrations: 1.2–1.6 g/mL. Following exposure, we quantified inflammatory cells from bronchial alveolar lavage (BAL) fluid, tissue structure from perfusion-fixed lungs, and respiratory mechanics following increasing amounts of nebulized methacholine (0–50 mg/mL of PBS, of 2–3 µm diameter particles). Here, we employed a single and low-frequency forced oscillation technique (FlexiVent, SCIREQ Inc.). Normalized by baseline...
values, airway resistances ($R_a$) were larger in cig-exposed (2.54±1.13) compared to age-matched (1.45±0.48) mice and respiratory compliance was higher in the cig-exposed mice ($C_{rs, exposed} = 2.85E-2±0.19E-2$, $C_{rs, control} = 2.17E-2±0.04E-2$ mL/cmH$_2$O). The importance of Apolipoprotein E to lung degradation is further evidenced by the enhanced bronchial hyper-responsiveness shown in ApoE$^-$ mice, particularly when coupled with exposure to inhaled toxins.

### Other

**O-023  ATMOSPHERIC SPRAY FREEZE DRYING OF BACTERIOPHAGE D29 WITH SUGARS**

Alvin Ly, Nicholas B. Carrigy, Hui Wang, Melissa Harrison, Dominic Sauvageau, Andrew R. Martin, Reinhard Vehring, and Warren H. Finlay

University of Alberta, Edmonton, Alberta, Canada

Bacteriophage are potential therapeutic agents for treating multiple drug resistant bacterial infections. Bacteriophage D29 is of interest since it is a parasitic virus to *Mycobacterium tuberculosis*, however many challenges remain to enable the use of D29 as a prophylactic agent. In this study, atmospheric spray freeze drying is used to process bacteriophage D29 into a dry powder. Mixtures of trehalose and mannitol at varying mass ratios were used as preservation excipients. The feedstock was atomized into a cold chamber where the solution spray was rapidly frozen and conveyed onto a filter. Cold gas was passed through the filter at atmospheric pressure to desiccate the powder. The combination of low temperature and low partial pressure resulted in sublimation. The trehalose and mannitol feedstock at a mass ratio of 7:3 and a combined mass concentration of 100 mg/mL had an average titer reduction of 0.7 log(pfu/mL) due to atmospheric spray freeze drying and a moisture content of 4.9±0.1%. In contrast, pure trehalose and 1:1 trehalose and mannitol solutions both had titer reductions greater than 1.5 log(pfu/mL) and moisture contents unacceptable for phase storage. Raman spectroscopy showed that trehalose in all cases remained amorphous while mannitol completely crystallized, leading to solid phases desirable for protein preservation. The results highlight the potential of atmospheric spray freeze-drying as a processing technique in preserving biopharmaceutical products.

**O-030  THE CONFUSING WORLD OF DRY POWDER INHALERS; IT IS ALL ABOUT INSPIRATORY Pressures NOT INSPIRATORY FLOW RATES**

A.R. Clark$^1$, J.G. Weers$^2$, and R. Dhand$^3$

$^1$Aerogen Pharma Corporation
$^2$Respira Therapeutics Inc.
$^3$Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Tennessee Graduate School of Medicine

DPIs differ in design; formulation, dose storage, powder dispersion, dosing mechanisms and resistance to inhaled airflow. There is a growing misconception that a single Peak Inspiratory Flow Rate (PIFR) can be employed as the sole criterion to determine a patient’s ability to use a DPI effectively, regardless of airflow resistance. In this abstract, we clarify that the controlling parameter for DPI performance is the pressure drop generated by the patient’s inspiratory effort and not the PIFR. The minimum pressure below which a particular inhaler will not deliver an adequate therapeutic dose is difficult to define. DPIs gradually lose their ability to deliver and disperse medication as pressure drops (flow rates) decline. However, a pressure-drop equal to, or greater, than ~1 kPa with any DPI is a reasonable threshold above which a patient should receive an adequate therapeutic dose. This minimum pressure drop could be employed as a criterion to determine which patients are likely/unlikely to be able to use any DPI effectively.

It should be noted that several other factors influence lung deposition and therapeutic effectiveness: the patient’s cognitive ability, device training and oropharyngeal and airway geometry. Also, for most DPIs higher inspiratory pressures (flow rates) usually mean better powder dispersion and a higher fine particle dose, but higher inhaled flow rates can result in higher oropharyngeal deposition and less uniform drug deposition in the airways.

**O-033  SOBITX$^TM$, AN INEXPENSIVE, RAPID, EFFICIENT, SIMULTANEOUS, O$_2$ AND MDI BRONCHODILATOR ADMINISTRATION DEVICE, OPTIMIZED FOR USE IN FIRST-AID, EMS AND HOSPITAL EMERGENCY**

Michael T Newhouse and Pete Goldman

Background: Inexpensive SVNs used in ambulances and emergency departments for administering bronchodilators are inefficient and initiation/therapy takes 15–30'', delaying recovery. Oxygenation (6–8pm) is limited by SVN requirements; ~50% of dose is lost during continuous nebulization. Except in USA, MDI+VHCs are commonly used worldwide, but require alternating the O2 mask and MDI+VHC for bronchodilation.

Method: With MDI ExtendRx$^{TM}$ inserted through the 22mm opening in CPR-O2 mask sealed to the face, 7 studies with O2 of 0–25 lpm, 12 albuterol puffs (90µg; 1080µg over 5'') were targeted into a subject’s open mouth at 30 sec intervals during tidal inhalation. Results: Typical β agonist symptoms of mild tremor/ tachycardia-no other adverse effects (e.g. arrhythmia). LRT dose = PK Tmax at 25’ averaged 2–3ng/mL, similar to 12 normals with optimal technique (GSK Ventolin pkg insert). Mask % O2 stable throughout.

Conclusion: Unique SOBITx System rapidly provides both bronchodilator Tx and, independently, oxygenation within 1–2 min of ambulance arrival, in ED, or at first-aid scene, to patients with e.g. severe asthma, thus speeding recovery and reducing cost.

**O-052  DOSATOR-BASED CAPSULE FILLING PROCESS – STATISTICAL ANALYSIS ON THE KEY PARAMETERS IMPACTING IN-VITRO AERODYNAMIC PERFORMANCE OF CARRIER-BASED AND SPRAY-DRIED POWDERS**

Nuno Neves$^1$, Maria Braga$^1$, and Eunice Costa$^1$

$^1$Hovione FarmaCiencia SA, Loures, Portugal

Multiple capsule filling (CF) experiments were performed using a pilot scale MG2 FlexaLab capsule filler varying several input parameters. A carrier-based formulation and a carrier-free spray dried powder were used. Statistical analysis was performed for each powder individually to quantify the impact of each input variable on a capsule based dry powder inhaler emitted dose (label claim) ($\text{ED}_{50,c}$) (%) and fine particle dose (FPD) ($\mu$g/capsule). The impact of several CF parameters was studied through a statistical analysis. Two models were generated separately for carrier-based ($M_\lambda$ and SD formulations ($M_\beta$). $M_\lambda$ showed that chamber/layer ratio and layer depth are the variables impacting $\text{ED}_{50,c}$ and FPD the most – higher the chamber/layer ratio and the powder bed layer depth, the better the aerodynamic performance observed. Concerning $M_\beta$, the model that better fitted the data was obtained with the dosator diameter and filling speed as input.
variables. Dosator diameter is the dominant factor on both ED\textsubscript{L,C} and FPD — larger the dosator, higher the ED\textsubscript{L,C} and FPD. This effect is likely related with the lower compaction of the powder inside the dosator. On the opposite side, CF speed has a negative impact on ED\textsubscript{L,C} with higher speeds mostly leading to lower ED\textsubscript{L,C}. Regarding FPD, the contribution of filling speed was less significant as in ED; nevertheless, the same negative trend is observed.

This study highlights the need for including capsule filling process assessment on overall process development.

O-056 EFFECT OF RECORDED INHALATION WAVEFORMS ON THE IN VITRO AERODYNAMIC PERFORMANCE OF A PASSIVE DRY POWDER INHALER (DPI)

Mark W. Nagel\textsuperscript{1}, Jason A Suggett\textsuperscript{1}, and Jolyon P. Mitchell\textsuperscript{2}

\textsuperscript{1}Trudell Medical International, London, Canada
\textsuperscript{2}Jolyon Mitchell Inhaler Consulting Services Inc., London, Canada

Patients can readily access on-line training videos demonstrating correct inhaler use. This proof-of-concept study explored the impact on patient waveforms and potential drug delivery if patients used such instruction without clinician support. Consent was obtained from three DPI naïve adult volunteers, each of whom was asked to inhale from a Diskus\textsuperscript{®} DPI, modified to prevent delivery of medication. Apart from being told to inhale “quick and deep”, the volunteer received no further instruction before inhaling. Breathing profiles were obtained using SmartLab\textsuperscript{™} instrumentation with Insight\textsuperscript{™} recording software (Hans Rudolph Inc). Volunteers then watched a training video and followed the instruction for inhalation. The “untrained” and “trained” inspiratory flow rate waveforms were re-created by breathing simulator coupled to the mouthpiece of an Advair\textsuperscript{®} Diskus\textsuperscript{®} DPI (250 µg fluticasone propionate/50 µg salmeterol xinafoate). In each case, the resulting aerosol was size-analyzed by a Next Generation Impactor equipped with pre-separator, mixing inlet and operated at 60 L/min. Widely differing inspiratory flow profiles were obtained from each volunteer, with all resulting in greater than 75% of the delivered mass as particles >4.5 µm. Such ‘non-respirable’ particles may, in real use, have resulted in systemic delivery with the potential for adverse effects. Further studies are warranted with a larger number of volunteers and with other passive DPIs having different resistances.

O-057 METHOD FOR RECORDING INHALATION WAVEFORMS FROM A VALVED HOLDING CHAMBER AND COMPARISON OF POTENTIAL INHALATION TECHNIQUES ON INSPIRED VOLUME

Mark W. Nagel\textsuperscript{1}, Jason A Suggett\textsuperscript{1}, and Jolyon P. Mitchell\textsuperscript{2}

\textsuperscript{1}Trudell Medical International, London, Canada
\textsuperscript{2}Jolyon Mitchell Inhaler Consulting Services Inc., London, Canada

Instructions for a valved holding chamber (VHC) suggest that the patient should inhale slowly and deeply followed by a breath hold for 5–10 seconds. However, if they are not able to complete such an exercise, they should breath tidally for 2–3 cycles. The aim of this study was to develop a methodology by which breathing profiles can be recorded, evaluated and eventually used to generate in vitro drug delivery data. Five VHC-naïve volunteers were asked to inhale from a VHC using both types of instruction. The VHC mouthpiece was attached to a pneumotachometer flow sensor with a purpose-made adapter that replicated the mouthpiece in order to avoid any difference in the patient interface. Breathing profiles were recorded using SmartLab\textsuperscript{™} instrumentation with Insight\textsuperscript{™} recording software (Hans Rudolph Inc) and converted for use on the ASL 5000 breathing simulator (Ingmar Medical). As might have been expected, both total inspired volume and tidal volumes differed dramatically between the 2 instructions for all patients. However, even the individual single tidal breaths were larger than the internal volume of the VHC, inferring likely complete evacuation after 1 inhalation. Future studies will look to determine the potential drug delivery implications these breathing manoeuvres might have by coupling the VHC to a Next Generation Impactor equipped with a mixing inlet.

O-066 VALIDATION OF ION PAIRING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR SIMULTANEOUS QUANTIFICATION OF FORMOTEROL FUMARATE, BECLOMETHASONE AND GLYCOPYRRONIUM BROMIDE

Kazmierczak Jérôme, Ekees Myriam, Curan Edouard, and Thierry Poreé

Laboratoire OptimHal, Valognes France

Tritherapie containing fixed dose of beclometasone dipropionate (BDP), formoterol fumarate (FF) and Glycopyrronium bromide (GB) is used in the treatment of severe chronic obstructive pulmonary disease. A method based on ion pairing HPLC has been developed and validated according to ICH guidelines for the simultaneous determination of BDP, FF and GB.

The separation was achieved with a C18 175 Å (150 × 3 mm, 5µm) column, at 35°C, using a mobile phase composed of methanol: 0.02 mol/L of dodecyl sulphate sodium salt adjusted to pH 2.68 (65:35, v/v/a). Quantification was carried out within isocratic mode at 1.3 mL/min flow and UV detection at 211 nm. The linearity was 50 – 150µg/mL, 5 – 20 µg/mL and 10 – 40 µg/mL for BDP GB and FF respectively with R\textsuperscript{2} ≥ 0.999. Selectivity has been checked by comparing analytical performances between standards and commercial drugs. Accuracy test has shown an intra-day precision mean of 0.38%, 0.69% and 0.89% for BDP, GB and FF respectively. LQ and LD was found to be 0.45µg/mL and 0.13µg/mL for BDP, 0.39µg/mL and 0.12µg/mL for GB and 0.27 and 0.08µg/mL for FF. Changes on the method were made (T±5°C, Q±0.1 mL/min) in order to check the robustness of the method.

The proposed method can be used as rapid (time of experiment <7min), and sensitive (resolution factor of 10.94 between FF and BDP and 5.52 between BDP and GB) for simultaneous determination of FF, BDP and GB. Experiments on the impact of valved holding chamber on drugs deposition have begun.

O-067 ELONGATED MUCUS-PENETRATING NANOCRYSTALS FOR LUNG DELIVERY OF A NEW ANTI-BURKHOLDERIA AGENT IN CYSTIC FIBROSIS

Gabriella Costabile\textsuperscript{1}, Silvia Buroni\textsuperscript{2}, Romina Provenzano\textsuperscript{1}, Agnese Miro\textsuperscript{1}, Alberto Azzalin\textsuperscript{2}, Viola C. Scoffone\textsuperscript{2}, Laurent R. Chiarelli\textsuperscript{2}, Vadim Makarov\textsuperscript{1}, Paola Brocca\textsuperscript{1}, Giovanna Riccardi\textsuperscript{2}, and Francesca Ungaro\textsuperscript{1}

\textsuperscript{1}Department of Pharmacy, University of Napoli “Federico II”, Napoli, Italy.
\textsuperscript{2}Department of Biology and Biotechnology “L. Spallanzani”, University of Pavia, Pavia, Italy.
\textsuperscript{3}Federal Research Centre “Fundamentals of Biotechnology” of the Russian Academy of Sciences, Moscow, Russia.

A method based on ion pairing HPLC has been developed and validated according to ICH guidelines for the simultaneous determination of BDP, FF and GB.

The separation was achieved with a C18 175 Å (150 × 3 mm, 5µm) column, at 35°C, using a mobile phase composed of methanol: 0.02 mol/L of dodecyl sulphate sodium salt adjusted to pH 2.68 (65:35, v/v/a). Quantification was carried out within isocratic mode at 1.3 mL/min flow and UV detection at 211 nm. The linearity was 50 – 150µg/mL, 5 – 20 µg/mL and 10 – 40 µg/mL for BDP GB and FF respectively with R\textsuperscript{2} ≥ 0.999. Selectivity has been checked by comparing analytical performances between standards and commercial drugs. Accuracy test has shown an intra-day precision mean of 0.38%, 0.69% and 0.89% for BDP, GB and FF respectively. LQ and LD was found to be 0.45µg/mL and 0.13µg/mL for BDP, 0.39µg/mL and 0.12µg/mL for GB and 0.27 and 0.08µg/mL for FF. Changes on the method were made (T±5°C, Q±0.1 mL/min) in order to check the robustness of the method.

The proposed method can be used as rapid (time of experiment <7min), and sensitive (resolution factor of 10.94 between FF and BDP and 5.52 between BDP and GB) for simultaneous determination of FF, BDP and GB. Experiments on the impact of valved holding chamber on drugs deposition have begun.
A poorly soluble compound, named C109, has recently shown a bactericidal effect against *Burkholderia cenocepa*, a resistant pathogen causing a severe decline in cystic fibrosis (CF) lung function. In this work, we developed inhalable nanosuspensions (NS) consisting in C109 nanocrystals stabilized with d-2-Tocopheryl polyethylene glycol 1000 succinate (TPGS). Optimised C109 formulations were achieved by evaporative precipitation into aqueous solution and subsequent freeze-drying with hydroxypropyl-β-cyclodextrin (TPGS-C109_CD). TPGS-C109_CD could be safely re-dispersed in water for *in vitro* aerosolization studies. Fine particle fractions around 40% and mass mean aerodynamic diameters lower than 3 μm were calculated. The ability of C109 to solubilize/indiffuse through mucus was suggested by release studies in simulated lung fluids and confirmed by SAXS-assisted migration studies. This behaviour could be likely ascribed to the polyethylene glycol shell and the peculiar nanocrystal shape. Based on the encouraging technological features, C109 NS underwent further *in vitro* studies, demonstrating NS safety towards human bronchial epithelial cells (wild type and CF) and efficacy against several *B. cenocepa* strains. The efficacy of the formulation in combination with piperacillin was confirmed in a *Galleria mellonella* infection model. In perspective, the developed C109 NS represent a useful therapeutic tool for resistant *B. cenocepa* lung infections in CF.

**O-068 BIODEGRADABLE NANOPARTICLES FOR PROLONGED THERAPEUTIC EFFICACY OF ANTIMICROBIAL PEPTIDES AGAINST PSEUDOMONAS AERUGINOSA LUNG INFECTIONS**

Ivana d’Angelo1, Bruno Casciaro2, Xiaoping Zhang3, Gemma Conte1,4, Maria Rosa Loffredo2, Floriana Cappiello2, Fabiana Quaglia1, Y. Peter Di3, Maria Luisa Mangoni2, and Francesca Ungaro4

1Di.S.T.A.Bi.F., University of Campania “Luigi Vanvitelli”, Caserta, Italy
2Laboratory affiliated to Pasteur Italia-Fondazione Cenci Bolognetti, Dept of Biological Sciences “A. Rossi Fanelli”, Sapienza University of Rome, Rome, Italy
3Dept of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh (PA), USA
4Dept of Pharmacy, University of Napoli “Federico II”, Napoli, Italy

Antimicrobial peptides (AMPs) hold great promise for the treatment of *Pseudomonas aeruginosa* lung infections (CF). In this work, safe and effective inhalable poly(lactide-co-glycolide) acid (PLGA) nanoparticles containing frog skin-derived Escentulin(1-21) or its diastereomer Escentulin(1-21)-1c, were successfully developed. Conceiving nanoparticles for lung delivery, poly(vinyl alcohol) was employed to tune surface properties and, in so doing, nanoparticle interactions with biological environment. An improved transport of the selected AMPs through artificial mucus and simulated bacteria extracellular matrix was achieved in *vitro*. The aerodynamic assessment of fine particles suggested that the developed formulations can be effectively delivered through a jet nebulizer available to patients. Of note, peptide-loaded nanoparticles were found to display a prolonged efficacy in inhibiting *P. aeruginosa* growth as compared to the free peptide. More importantly, a single intra-tracheal administration of peptide-loaded nanoparticles in a mouse model of *P. aeruginosa* lung infection resulted in 3-log reduction of pulmonary bacterial burden up to 36 h, with the control peptide aqueous solution causing a significant weaker effect. To the best of our knowledge, this is the first report showing a prolonged *in vivo* therapeutic efficacy of inhaled AMPs, unravelling the potential of PLGA nanoparticles as a reliable system for controlled release of peptides at lungs.

**O-069 REPURPOSING GALLIUM FOR LOCAL TREATMENT OF P. AERUGINOSA LUNG INFECTIONS THROUGH SUSTAINED-RELEASE DRY POWDERS FOR INHALATION**

Gabriella Costabile1, Romina Provenzano1, Emma Mitidieri1, Daniela Visaggio2, Ivana d’Angelo1, Roberta d’Emmanuele di Villa Bianca1, Fabiana Quaglia1, Emanuela Frangipani1, Paolo Visca1, Raffaella Sorrentino1, and Francesca Ungaro1

1Dept of Pharmacy, University of Napoli “Federico II”, Napoli, Italy
2Dept. of Sciences, Roma Tre University, Roma, Italy
3Di.S.T.A.Bi.F., University of Campania “Luigi Vanvitelli”, Caserta, Italy
4Dept. of Biomolecular Sciences, University of Urbino “Carlo Bo”, Urbino, Italy

Gallium, or Ga(III), is a drug already used for cancer-related hypercalcemia, which may function as a “Trojan horse” to substitute Fe(III) in iron-containing enzymes, ultimately repressing their essential activity for bacterial growth. The potential of intra-venous gallium to disrupt bacterial iron metabolism and to exert a therapeutic effect was recently demonstrated in a murine model of *P. aeruginosa* lung infection and in cystic fibrosis (CF) sufferers. To overcome limitations of systemic administration, we developed novel Ga(III) inhalable nano-embedded microparticles (NEM) for the treatment of *P. aeruginosa* infections in CF. Ga(III) was efficiently encapsulated into hyaluronic acid/chitosan nanoparticles (Ga_HA/CNS). To gain access to the static mucus and biofilm surrounding *P. aeruginosa*, size and surface properties of Ga_HA/CNS NPs were tuned acting on formulation conditions. Finally, to allow in vivo lung deposition, Ga_HA/CNS NPs were efficiently engineered into mannitol-based micron-scale powders (Ga_Man NEM). The powders showed high and homogeneous Ga(III) content, optimal in *vitro* aerosol performance, sustained release kinetics in lung lining fluids and good *in vitro* antimicrobial properties. Upon intratracheal insufflation of Ga_Man NEM in an *in vivo* animal model, improved Ga(III) persistence at lungs and reduction of its kidney distribution (the target organ of the adverse effect) were achieved as compared to both intravenous and intra-tracheal Ga(III) solutions.

**O-071 EVALUATION OF PARTICLE INTERACTIONS IN DPI CARRIER BASED FORMULATIONS USING THERMAL ANALYSIS**

Luis Sousa1, Raquel Borda d’Água1, Maria Braga2, Eunice Costa2, and Mafalda Paiva1

1R&D Analytical Chemistry Development; 2R&D Drug Product Development; Hovione FarmaCiencia SA, Portugal

Interactions between fine and coarse lactose and drug particles are known to impact the aerodynamic performance of carrier based formulations as a result of different drug release profiles from the carrier. Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM) and Inverse Gas Chromatography (IGC) are commonly used to probe adhesion of particles, surface areas/energies which are known to impact performance. An alternative and innovative approach is proposed here for evaluating such interactions, using Differential Scanning Calorimetry (DSC). This new method detects differences in the endotherm of water evaporation from the lactose monohydrate lattice, around 135°C, for different formulations, which can be correlated to
the lactose surface energies and particle–particle interactions. A linear relationship was found between the normalized enthalpy of water evaporation and lactose particle size, which demonstrates that the method can probe differences in surface energy. A correlation between the enthalphy of water release and blending process energetics (pestle and mortar vs high shear mixing) was found for different formulations of the same drug. Finally, a preliminary assessment of the correlation between aerodynamic performance of different drug content formulations and the enthalphy of structural water release was also done. Since this method allows correlating process, product and performance, its application to formulation development has great potential.

O-075 STREPTOCOCCUS PNEUMONIAE INHIBITS PSEUDOMONAS AERUGINOSA GROWTH ON NASAL HUMAN EPITHELIUM IN VITRO

Carole Bertinetti1, Ophélie Verbeke1, Mireille Caul-Futy1, Song Huang1, Ludovic Wiszniewski1, and Samuel Constant1

Epithelix, Plan-les-Ouates, Switzerland

Pathogens colonizing the respiratory tract compete with a range of other bacteria. *Pseudomonas aeruginosa* (PA) infection are increasingly associated with acute exacerbations in chronic obstructive pulmonary disease. *Streptococcus pneumoniae* (SP), meanwhile is a main cause of pneumonia, meningitis, it can leads to infections and other respiratory diseases such as bronchitis.

We report herein the use of 3D airway epithelia reconstituted in vitro to study interactions of PA and SP on nasal mucosa. MucoAirTM, a fully differentiated human airway epithelium made of a mixture of primary nasal cells from 14 donors, was used to study the effects and behaviour of PA and SP (inoculated at 3E102 and 3E113 CFU/cm2 respectively) cultivated separately or together over 24 hours.

Apical, basolateral and intratissular PA and SP growth were quantified by Colony Forming Unit (CFU). Impairment of epithelial homeostatic barrier function was evaluated through monitoring of tissue integrity (Trans Epithelial Electrical Resistance – TEER); cytotoxicity (LDH), cilia activity, mucin and IL-8 release.

PA infection induces a loss of TEER, 20% cytotoxicity and an increase of IL-8 (+100 ng/ml). On the contrary, SP strongly increases the mucin production. While inoculated together, a lower apical PA growth is observed (-3E10 CFU/cm2) suggesting an inhibition due to the presence of SP.

These results suggest that in vitro human airway epithelia is a useful model to study bacterial interaction on the human nasal mucosa.

O-077 ENABLING PULMONARY DELIVERY OF SirNA IN CYSTIC FIBROSIS LUNG INFILTRATION THROUGH HYBRID LIPID/POLYMER NANOPARTICLES

Ivana d’Angelo1, Gemma Conte1,2, Gabriella Costabile3, Domizia Baldassi3, Fabiana Quaglia1, Raffaella Sorrentino1, Olivia. M. Merkel1, and Francesca Ungaro2

1Di.S.T.A.Bi.F., University of Campania “Luigi Vanvitelli”, Caserta, Italy
2Dept. of Pharmacy, University of Napoli “Federico II”, Napoli, Italy
3Dept. of Pharmacy, Pharmaceutical Technology and Biopharmacy, Ludwig-Maximilians-Universität München, München, Germany

The down-regulation of genes directly involved in the pathogenesis of severe lung diseases through pulmonary delivery of short RNA fragments, also known as siRNA, has gained recently remarkable research interest, especially in cystic fibrosis (CF). In this context, the general aim of this work is the development of inhalable hybrid nanoparticles (hNPs) for siRNA delivery made up of a combination of lipids and polymers. To this purpose, the therapeutic potential of hNPs delivering a siRNA pool against one of the most critical signals in evoking the inflammatory response in CF, the nuclear factor-kB (NF-kB), is under investigation. hNPs loaded with siRNA against NF-kB were prepared from poly(lactic-co-glycolic acid) and endogenous phospholipids. The most adequate formulation conditions to produce non-PEGylated and PEGylated siRNA-loaded hNPs with optimal aerosolization and mucus-penetrating properties have been identified. In vitro data suggest that siRNA-loaded hNPs are not cytotoxic and may penetrate lung extracellular barriers, allowing siRNA uptake inside human bronchial epithelial cells. Furthermore, a rat model of lung inflammation has been set up and validated to start with in vivo efficacy studies. In perspective, the development of a siRNA delivery system already engineered for in vivo inhalation and transfection might shorten the time to translation to patients, providing a therapeutic platform to address multiple targets that are still considered “undruggable” in CF.

O-080 DOES CAPSULE ROUGHNESS IMPACT DPI AERODYNAMIC PERFORMANCE?

Ruben Chaves1, Luis Sousa1, and Maria Paisana1

1Analytical Chemistry Development, R&D, Hovione FarmaCiencia SA Lisboa, Portugal

The moisture content of hard capsules used in dry powder inhalers (DPI) depends on the environmental relative humidity (RH) in which they equilibrate. Different moisture contents often affect formulation performance. Herein a relationship between capsule water absorption and the roughness of its inner surface is studied. Two HPMC capsules with different colors (clear and orange) were stored at different conditions (1%RH/22°C, 75%RH/22°C, 75%RH/45°C) with and without a powder formulation. Empty and filled capsules were tested by atomic force microscopy (AFM) and water content (coulometric Karl-Fisher). The water content was about 1%, 11% and 9% w/w in empty capsules after being stored for 1 week at 1%RH/22°C, 75%RH/22°C and 75%RH/45°C conditions, respectively. For the same time period, and for any of the storage conditions, no modification in water was found for the powder formulations kept inside the capsules. AFM showed smaller roughness values for clear capsules stored at 75%/22°C (55 nm) and 75%/45°C (31 nm) when compared to the ones stored at 1% RH (138 nm), probably due to the plasticization of the HPMC by water and temperature. The same was not observed in orange capsules: The rationale is that the presence of the color pigment reduces the ability of water to interact directly with the capsule polymer. The impact of these findings will be determined in aerodynamic performance tests.

O-081 KEY CONSIDERATIONS WHEN REPOSITIONING A KNOWN DRUG FOR INHALATION THERAPY

Geraldine Venthoyle1

1Skyepharma AG, a member of the Vectura Group of companies, Muttenz, Switzerland

Repositioning or repurposing known “old drugs” via inhalation for respiratory or systemic indications can present attractive assets to
organisations looking to manage risk and maximise value. With the escalating cost, risk and time associated with developing NCEs, these products bестore a more palatable risk profile to portfolios. Opportunities which ideally leverage established capability are analysed against threshold criteria for key considerations including: unmet therapeutic need, market potential, competitive landscape, and development complexity. Many poorly treated niche respiratory diseases are benefiting from such developments.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib	\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

Repositioned products include drug reformulations to treat new or established indications via change of delivery route, e.g., antimuscarinics for COPD, antibiotics in CF, and insulin for diabetes. Repositioned products include those with improved product profile for better lung dosing, deposition, or administration. Smart nebulisers can enable improved lung delivery and treatment times, with the monitoring of compliance through connectivity. Two repositioned product case studies target this differentiation, Breelib\textsuperscript{\textregistered}, (Fox\textsuperscript{\textregistered}) for PAH and VR647 Inhalation System (budesonide) for asthma in children.

For treating infectious diseases, pulmonary drug delivery is advantageous non-invasive and moreover reduces systemic exposure and first-pass metabolism. Our lab has worked on innovative in vitro approaches to mimic the human air-blood barrier. Some 20 years ago, we were first to publish a primary culture of human alveolar type 1-like cells (hAEpC) with tight intercellular junctions, allowing meaningful transport studies across the human air-blood barrier, and since this protocol has continuously been refined. Recently, a new human alveolar epithelial cell line (hAELVi) with similar barrier properties could be created via mild lentiviral immortalization and is meanwhile commercially available.

This approach has been expanded to cocultures of epithelial cells and macrophages, the two main players of the air-blood barrier, as well as on devices allowing metered deposition of pharmaceutical aerosols. In order to make the model better reproducible human primary cells were replaced by the cell lines hAELVi and THP-1. To model the lung not only in healthy state, the focus has shifted towards mimicking the state of disease, e.g., inflammation and/or infection. Recent work includes the implementation of bacterial biofilms as well as mucus in such models for testing the penetration, antimicrobial and immunological effects of novel anti-infective drugs and nanocarriers.

Conclusion: Non-invasive ventilation (NIV) is a commonly utilised method of ventilatory support, for patients with acute and chronic respiratory conditions, using a mask interface. The addition of aerosol therapy would benefit the clinical outcome of patients. Here we assessed aerosol delivery during NIV in both adult and paediatric patient populations.

Method: A vibrating mesh nebuliser (Aerogen Solo, Aerogen, Ireland) was positioned between the mask and circuit of a single limb (IMT Medical, Switzerland) or dual limb patient circuit (Fisher & Paykel, NZ) with a non-vented face mask (Adult: Respironics, US or Paediatric: Fisher & Paykel, NZ). The mask was attached to a breathing simulator (IngMar Medical, US) set to simulate adult (Vt 500mL, 15BPM, IE 1:1) or paediatric (Vt 200mL, 25BPM, IE 1:2) breathing and to a ventilator (Bellavista, IMT Medical, Switzerland). 1ml of 2mg/ml albuterol sulphate (GSK, Ireland) was nebulised and delivered dose captured on a filter was determined using UV spectroscopy at 276nm.

Results: Results obtained gave a delivered dose of 24.30% ± 0.17% for adults and 24.15% ± 0.34% for paediatrics with a single limb circuit. For a dual limb circuit, a result of 22.71% ± 0.47% for adults and 21.04% ± 0.74% for paediatrics was observed.

Conclusion: Patients would benefit from simultaneous delivery of aerosol and oxygen therapy. This study indicates that efficient aerosol delivery is feasible during NIV.
O-111 DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL FOR THE INHALATIONAL ROUTE

N Nowak1, DS Winkler1, SE Escher1, T Hansen1, K Blümlein1, and K Schwarz1

Fraunhofer Institute for Toxicology and Experimental Medicine, HANNOVER, Germany

For the pre-clinical development of new drugs and for safety assessment of chemicals PBPK-modeling is an attractive tool. A general Physiologically-Based Pharmacokinetic (PBPK) model for airborne substances with special focus on inhalation as portal of entry has been developed. It simulates substance transport through the lung into the systemic circulation and considers further relevant processes for removal of inhaled substances from the lung. To simulate internal doses in the human plasma and tissues, the PBPK-model uses in-silico and in-vitro parameter. Permeation values under air-liquid-conditions are derived from human cell or tissue models using e.g. the P.R.I.T air-liquid exposure system, or ex vivo models like the Isolated Perfused Rat Lung (IPL).

For a small molecule substance with many ADME-parameter available, an effective transfer velocity has been determined using the IPL. Comparison of temporal substance concentration profile calculated by the PBPK-model to human data shows good agreement. The principal applicability of the PBPK-model to simulate nanoparticle (NP) uptake and bio-distribution after inhalation has been successfully shown for one NP substance.

In future, it is envisaged to improve the model by a more detailed inclusion of mucociliary and macrophage-mediated clearance and dissolution. The applicability of dissolution rates and further biological parameters determined in vitro, such as metabolism rates for lung and liver, will also be investigated.

O-112 COMPARATIVE ANALYSIS OF NEBULIZER AND “LINE OF SIGHT” SPRAY DRUG DELIVERY TO CHRONIC RHINOSINUSITIS TARGET SITES

Zainab Farzal1, Saikat Basu2, Mohammed Mamdani1, Brian D. Thorp2, Adam M. Zanation1, Adam J. Kimple1, Brent A. Senior1, Charles S. Ebert Jr.1, and Julia S. Kimbell1

1Department of Otolaryngology/Head & Neck Surgery, University of North Carolina at Chapel Hill, North Carolina, USA
2Department of Mechanical Engineering, South Dakota State University, Brookings, South Dakota, USA

Nasal sprays are the most common means of targeting chronic rhinosinusitis (CRS) disease sites, the sinuses and ostiomeatal complex (SOMC). Nebulizers may improve drug deposition, but are prescribed less commonly. Optimizing particle size in both delivery methods and developing a “line of sight” (LOS) aiming technique for sprays may improve SOMC delivery. Using computational fluid dynamics (CFD), nebulized and LOS spray particle deposition in the SOMC were compared in 3 patients with CRS (2 males, 1 female). 3-D sinonasal CFD models were created from pre-surgical CT scans. Using Fluent® (ANSYS, Inc.), steady-state inspiratory airflow and the transport of monodispersed nebulized particles (NP, 1–30 μm) and sprayed particles (SP, 1–120 μm) were simulated. NP were passively released from the nostril. SP were released from a point 10 mm inside the nasal vestibule, aimed in the LOS direction toward the SOMC in the 5 sinonasal sides that had a LOS view, using properties of fluticasone propionate spray. Greater maximal SOMC deposition (MSDF) was achieved by SP in 3 of 5 cases compared to NP (range: 6.8–61.5% vs. 3.7–24.8%). Particle size ranges achieving at least 50% MSDF were similar: 9–12 μm for SP in 4 of 5 cases and 11–16 μm for NP in 5 of 6 cases. Nasal valve penetration depended more on particle size (less with larger sizes) than on delivery method. Once validated, these preliminary results suggest novel LOS spray techniques may be competitive with nebulizers for CRS targeting.

O-119 EFFICIENT REPLICATION OF RESPIRATORY Syncytial Virus INDUCES A DECREASE OF MUCOCILIARY CLEARANCE IN HUMAN SMALL AIRWAY 3D CULTURE

Bernadett Boda1, Rosy Bonfante1, Jimmy Vernaz1, Song Huang1, Ludovic Wiszniewski1, and Samuel Constant1

1Epithelix, 18 chemin des aulx, Plan-les-Ouates, Switzerland

Respiratory syncytial virus (RSV) infection causes upper and lower respiratory tract infections and is the most common cause of bronchiolitis and pneumonia in young children. To understand RSV pathogenesis in humans and to test new molecules for alleviating the diseases, an in vitro RSV infection platform based on three dimensional (3D) fully differentiated human airway epithelia cultured at air-liquid interface was developed. One such model, SmallAirTM, representing the small airway epithelia with characteristic cell types (basal, ciliated and Club cells) was successfully infected with clinical isolate of RSV B. Virus genome was quantified using Taqman PCR on the N gene of the RSV. With an initial inoculum of 106 viruses, the genome copy number reached 1010 gc/ml 4 days post-inoculation in the apical washes. The RSV B infection did not impair the tissue integrity nor cause cytotoxicity. Solely the mucociliary clearance showed a dramatic decrease at 4 days post-inoculation of RSV B (22% of the non-infected control), however cilia beating frequency was not altered (95% of the control). Ribavirin, as reference antiviral against RSV, applied either apically (1-10-100 mM) or basally (10-100-1000 mM), inhibited viral replication in a dose-dependent manner and partially prevented the decrease of the mucociliary clearance. These results demonstrate that SmallAirTM is a pertinent tool to perform anti-RSV drug screening.