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P-067 SYNTHESIS AND IN VITRO EVALUATION OF POLYETHYLENE GLYCOL-PACLITAXEL CONJUGATES FOR SUSTAINED DRUG RELEASE IN THE LUNG

Tian Luo[1], Johannes Magnusson[2], Veronique Preat[3], Raphael Frederick[3], Cameron Alexander[2], Cynthia Bosquillon[2], Rita Vanbever[3]

[1]*Louvain Drug Research Institute, Addb*
[2]*School of Pharmacy, University of Nottingham*
[3]*Louvain Drug Research Institute, Université Catholique de Louvain*

Pulmonary delivery of chemotherapeutic agents is considered an attractive route of administration, with the advantages of high drug concentrations locally and low side effects systemically. However, achieving a sustained release of drugs in the lung is challenging due to the fast clearance mechanisms in the lung. In this study, we synthesized two different polyethylene glycol-paclitaxel (PEG-PTX) ester conjugates with molecular weights of 6 kDa and 20 kDa with the aim to achieve sustained release of paclitaxel in the lung. These conjugates were characterized physicochemically and showed good stability in PBS pH 6.9 and in brochoalveolar larvage, but hydrolyzed quickly in mouse serum. The conjugates showed cytotoxicity to B16-F10 melanoma cells, CT26 cells and Calu-3 cells but less than Taxol, which is the commercial paclitaxel formulated with Cremophor EL. The conjugates will be further investigated in vivo on B16-F10 lung metastasis mouse model to test the sustained drug release as well as the anti-tumor efficacy.

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P-069 NOVEL INHALED LIPOSOMAL CIPROFLOXACIN FORMULATIONS FOR PERSONALIZED THERAPY

David Cipolla[1], Huiying Wu[1], Hak-Kim Chan[2], Igor Gonda[1]

[1]*Aradigm Inc.*
[2]*Faculty of Pharmacy, Sydney University*

Introduction: Inhaled liposomal ciprofloxacin (Pulmaquin) is in development to treat lung infections.[1,2] A simple method was developed to attenuate the release rate of ciprofloxacin without changing its lipid composition.

Methods: A liposomal ciprofloxacin formulation was modified by freeze-thaw to form nanocrystals inside the liposomes to create a slower releasing formulation. These liposome formulations were characterized by cryo-TEM, dynamic light scattering, in vitro release (IVR) assay,[3] aerosol particle size distribution and the effect of mesh nebulization (PARI eFlow) on functionality.

Results and Discussion: The addition of sucrose or trehalose to the external buffer of the liposomal ciprofloxacin formulation stabilized the liposomes to freeze-thaw. After freeze-thaw, ciprofloxacin in the liposome vesicles formed nanocrystals which resulted in slower release profiles as measured by IVR. The shape and length of the nanocrystals and the release profiles of ciprofloxacin from the formulation could be adjusted by varying the amount of polysorbate 20. These formulations were robust to mesh nebulization, with retention of nanocrystals within the vesicles, and formed aerosols with a VMD of 3.8–3.9 μm and a GSD of 1.7.

Conclusions: These studies describe a simple and novel method to modify the encapsulation state and release properties of an inhaled drug in a liposome formulation. The new method has the potential to personalize therapy for patients by modulating the encapsulation and release properties of a liposomal drug product to suit an individual patient's needs.

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2. Cipolla D et al. *Ther Delivery* 4(8) 1047–1072 (2013).
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P-090 PARTICLE ENGINEERING TO DELIVER MONTELUKAST PLUS HEPARIN TOGETHER TO TREAT ASTHMA

Brijeshkumar Patel, Nilesh Gupta, Fakhrul Ahsan

Texas Tech University Health Sciences Center

This study seeks to develop a steroid-free inhalable combination therapy to alleviate the broad spectrum of inflammatory reactions in asthma. Montelukast, a cysteinyl-leukotriene type 1 receptor antagonist, possesses a series of secondary anti-inflammatory property at a relatively higher concentration. Low molecular weight heparin (LMWH) also exhibits anti-inflammatory effect by interfering leukocyte adhesion and migration. Thus, we hypothesize that inhalable particles containing montelukast and LMWH is a viable combination therapy for asthma. To test this hypothesis, we prepared and characterized dual drug containing microparticles, and optimized formulations were evaluated for efficacy in asthmatic rats. The infiltration of inflammatory cells in BAL fluid was quantified; the influence of the formulations on bronchoconstriction was evaluated in plethysmograph after methacholine challenge. Large porous particles (size: 10.3 ± 0.7 μm) showed $66.8 \pm 0.4\%$ entrapment for montelukast and $91.7 \pm 0.8\%$ adsorption efficiency for LMWH. Dual-drug particles produced $\geq 4\%$ reduction in the number of infiltrating cells compared with untreated asthmatic animals; dual-drug treated rats showed significantly reduced airway wall-thickness (17.96 ± 4.11 μm) compare with that observed in untreated asthmatic animals ($p < 0.001$). Untreated asthmatic animals showed a $>50\%$ reduction in mid-tidal-end-expiratory-flow (EF_{50}), optimized formulation reduced the EF_{50} to $\sim 20\%$, indicating a significant improvement in lung functions. Thus, this study demonstrates the feasibility of a novel steroid-free dual-drug approach to enhance drug concentrations in the lungs and amplify anti-inflammatory effect in asthmatic condition.

P-102 COMPARISON OF THREE MODALITIES OF CORTICOSTEROIDS ADMINISTRATION IN CHRONIC RHINOSINUSITIS

Gregory Reychler, Colbrant Coralie, Huart Caroline, Leguellec Sandrine, Laurent Vecellio, Giuseppe Liistro, Rombaux Philippe

Cliniques Universitaires Saint-Luc

Background: Olfactory dysfunction is deemed to be a significant contributor to poor quality of life in chronic rhinosinusitis (CRS).

Objective: To compare the effectiveness of three modalities of corticosteroids administration in patients with CRS.

Methods: 30 patients with CRS were randomized in three groups depending on the route of corticosteroids administration. Corticosteroids were administrated during 16 days by oral (Medrol®, 32 mg/8d - 16 mg/4d - 8 mg/4d), nasal spray (Rhinocort®, $2 \times 2 \times 64$ μg/nostril) or nebulized (Pulmicort®, 2×1 mg/4 mL) (Sonic nebulizer, AOHBOX NL11SN, DTF Medical) route. Olfactory function was assessed

using orthonasal (Sniffing stick test) (TDI) and retronasal psychophysical olfactory (odors identification) (RETRO) tests at inclusion and after the treatment.

Results: TDI and RETRO were similar between three groups at baseline. TDI improved by 5.5, 5.8 and −1.1 for sonic nebulization, oral and nasal spray groups respectively. This improvement was similar between oral and nebulized administration but significantly higher than nasal spray administration ($p=0.010$) and only clinically relevant for oral and nebulized administration. RETRO improved by 1.1, 4.2 and 0.7 for sonic nebulization, oral and nasal spray groups respectively ($p=0.231$)

Conclusion: Effectiveness of nebulized and oral administration is demonstrated on orthonasal olfactory. The benefit is better than with nasal spray.

P-103 INFLUENCE OF TRACHEOSTOMY ON LUNG DEPOSITION IN SPONTANEOUSLY BREATHING PATIENTS

Pitance Laurent, Gregory Reychler, Laurent Vecellio, Leal Teresinha, Reychler Hervé, Giuseppe Liistro

Cliniques Universitaires Saint-Luc

Rationale: Nebulized drugs are frequently administrated through tracheostomy in clinical routine. So far, the amount of drug deposited to the lung in these patients remains unknown.

Objectives: To compare lung deposition of amikacin in 2 conditions: in spontaneously breathing through a tracheostomy and through the mouth.

Methods: Lung delivery was measured by amikacin urinary drug concentration in nine patients who were transitory tracheostomized for the need of a head and neck oncologic surgery. Patients performed two nebulization sessions: with and without tracheostomy using an adapted jet nebulizer (Sidestream®).

Measurements and main results: Lung deposition was similar with the two conditions of nebulization (6.5 ± 2.5 vs. $6.3 \pm 2.0\%$ of the nominal mass of amikacin respectively for MB and TB; $p=0.87$). Duration of nebulization was also comparable (19.7 ± 1.6 vs. 20.1 ± 1.8 min respectively for mouth and tracheostomy breathing; $p=0.92$). The half-life and elimination rate constant were not different between the two settings.

Conclusions: The nebulized therapy can be administered in spontaneously breathing tracheostomized patients with a similar amount of drug deposited in the lung compared with untracheostomized spontaneously breathing patients.

P-108 CATIONIC LIPOSOMES AS CARRIERS FOR LOCAL IMMUNOTHERAPY OF LUNG CANCER

Cristina Loira Pastoriza, Caroline Herin, Rita Vanbever

Université Catholique de Louvain

Lung cancer is the leading cause of cancer-related death worldwide with more than 1.2 million of new cases per year. Local immunotherapy may be an effective approach for the treatment of lung cancer. Liposome-based vaccines have the advantage that they can be prepared with lipids endogenous to the lungs. The goal of our work was to develop liposomes containing both tumor antigens (Melan A and Gp 100) and adjuvants (CpG or Poly IC) able to target lung dendritic cells and to produce a specific immune response against cancer cells. For this purpose, different lipid compositions have been studied, including cationic lipids (DOTAP and DC-Cholesterol) which are reported to present immunostimulatory capacities.

We have obtained two liposome formulations which remain stable for at least three weeks. These formulations can successfully co-encapsulate both peptides and adjuvants. For instance, peptide loading efficiency is comprised between 50 to 80% depending on liposome composition and peptide sequence and more than 80% of adjuvant is also encapsulated. Sizes are comprised between 150 and 180 nm which is suitable for lung dendritic cells targeting. Moreover, a sustained release from liposomes has been observed: 20 to 40% of peptide is released during the first 30 h.

In a next step, liposomes fate will be studied after intratracheal delivery in mice. Different techniques as confocal microscopy and HPLC-MS will be used in order to study peptide disposition within the lungs.

P-111 THE INFLUENCE OF ENVIRONMENTAL FACTORS ON PRESSURIZED METERED DOSE INHALER PERFORMANCE

James Ivey, Chelsea Morin, Farzin Shemirani, Jonathan Suderman, Jordan Titosky, Susan Hoe, Warren Finlay, Reinhard Vehring

University of Alberta, Department of Mechanical Engineering

Recent experimental work evaluating the influence of environmental factors on pressurized metered dose inhaler (pMDI) performance is presented. The effects of ambient temperature, ambient humidity, device temperature, and altitude on the *in vitro* lung dose of five commercial and two research pMDIs was explored. The Alberta Idealized Throat was utilized to assess the *in vitro* lung dose. An environmental chamber allowed experiments with variable temperature and humidity, while a mobile testing station was developed to enable the high altitude tests. It was found that increasing altitude and thus reducing ambient pressure had a negligible effect in the tested range. However, reducing ambient or device temperature or increasing ambient humidity reduced the *in vitro* lung dose. The magnitude of the temperature and humidity effects was found to depend on formulation and device variables, indicating that further experimental and theoretical work is required to better understand the interactions. The results of this work illustrate the challenges inherent in utilizing pMDIs outside of ideal laboratory conditions, and highlight opportunities for developing more environmentally robust pMDI therapies.

P-112 MONITORING OF ADHERENCE WITH AN EFLOW NEBULIZER IN CLINICAL TRIALS FOR INHALATION THERAPIES

Carola Fuchs, Matthias Finke, Gerhard Boerner, Stephanie Prante, Philipp Kroneberg, Stefan Seemann, Martin Knoch

Pari Pharma GmbH

A telemonitoring feature was implemented in an eFlow nebulizer system (PARI Pharma, Germany) for monitoring adherence to inhalation therapies. The system fulfils requirements for clinical trials and potentially subsequent transfer to commercial products. The eFlow device is equipped with a Bluetooth chip and automatically transfers data on each nebulization via a hub and a cloud to a server for evaluation by the physician.