The effects of inhaled Rapamycin solid lipid particle size on transport across lung epithelial cells

Emelie Land, Lyn M. Moir, Daniela Traini, Paul M. Young and **Hui Xin Ong**
The University of Sydney, Australia

Background: Lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by the uncontrolled growth of smooth like muscle cells (LAM cells) in the lungs that can spread to other body parts via the lymphatic system Current treatment for LAM is oral Rapamycin, which is limited by its low bioavailability (~15%) and side effects [1, 2]. It's been shown that particles of approximately <1000nm with a negative surface charge are able to enter the lymphatic system [3].

Aim: The current study aimed to determine the optimum size of Rapamycin solid lipid nanoparticles (SLN) that will facilitate drug entry into the lymphatic system through the inhaled route in order to increase lung bioavailability, reduce systemic side effects and potentially have increased efficacy.

Methods: Three different sized (1-3) of Rapamycin-SLN: 200, 500 and 800nm, were produced by dissolving Rapamycin and glyceryl behenate in methanol and dichloromethane. The organic solvents were evaporated prior to mixing with hot Tween80 (1.5 %w/v) solution. The solution was either homogenized (1700rpm) or passed through a membrane with specified pore sizes mini-extruder before being freeze-dried overnight. Size and charge were determined using a Zetasizer. Transepithelial drug transport of the formulations was evaluated *in-vitro* using a Calu-3 air-liquid interface bronchial epithelial cell model.

Results: All Rapamycin-SLNs formulations had negative surface charge (table 1) and average particle sizes: 237 ± 1.8nm, 583 ± 1.3nm and 790 ± 2.3nm, respectively. The formulations showed varying encapsulation efficiencies ranging from 65.8 to 97.32%. The transport studies showed that 83 ± 4.2% and 68 ± 2.5 % of SLN200 and SLN500 formulations were transported, respectively, across the epithelium after 4hrs compared to 22 ± 2.15% of the SLN800 formulation.

Conclusion & Discussion: The current study showed that Rapamycin-SLN with negative surface charge and size of approximately 200nm is able to cross the lung epithelium faster than larger particles. Future studies will be expanded to evaluate the entry of these SLN particles

Recent Publications:

1. Smolarek, T.A., et al., Evidence that lymphangiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangiomyomatosis. Am J Hum Genet, 1998. 62(4): p. 810-5.
2. Kumasaka, T., et al., Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangioleiomyomatosis. Am J Surg Pathol, 2005. 29(10): p. 1356-66.
3. Videira, M.A., et al., Lymphatic uptake of pulmonary delivered radiolabelled solid lipid nanoparticles. J Drug Target, 2002. 10(8): p. 607-13.

Biography

Emelie Landh completed her Bachelor in Medical Sciences, majoring in Pharmacology at the University of Sydney in 2013. She went on to complete a Graduate Diploma in Pharmacology with the Respiratory Technology Group at the Woolcock Institute of Medical research at the University of Sydney in 2014. She is currently at the end of the second year of her PhD under the supervision of Dr. Hui Xin Ong with the Respiratory Technology Group. Her PhD project involves developing an inhaled combination treatment using Solid-Lipid Nanoparticles for treating Lymphangioleiomyomatosis (LAM).