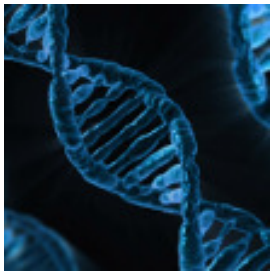

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In vivo models of Drug-Induced Interstitial Lung Disease; tools to study and improve drug safety

A number of systemically administered drugs such as Blemoycin, may cause Drug-Induce Interstitial Lung Disease (DIILD). Fibrosis progression most often occurs in the long term, although the lung injury is initiated during the early stage with leakage of inflammatory cells and proteins from the circulation, into the lungs. We aim to investigate the underlying mechanisms of cell and matrix interactions and develop imaging biomarkers for early detection and quantification of DIILD.

Methods: Rats received Bleomycin (or Saline as control) intratraceally and were longitudinally scanned at baseline, day 3, 7, 14 and 21 and 28 after Bleomycin administration. Scans were performed on a small animal 9.4T MRI system, using two different ultra-short echo (UTE) sequences (0.32ms vs 1ms echo time). MRI scans were evaluated qualitatively and quantitatively. In addition, bronchoalveolar lavage fluid (BALF) was analysed for inflammatory cells and proteins, as well as histological analysis was performed and scored for inflammation and fibrosis.

Results: MRI scans showed increased signal (oedema) at day 3-7 and again at day 21 (fibrosis) in the lungs of Bleomycin exposed rats. The total lung volume increased significantly ($p=0.001$) and dose-dependently compared to Saline control, although the functional lung volume decreased due to development of lesions (oedema or fibrotic tissue formation). Bleomycin induced plasma leakage in the lungs, showing significantly increased immune cells as well as proteins found in the lung lumen (assessed in BALF). Histology showed significant fibrotic score increase ($p<0.05$) vs. control.

Discussion: This study takes the search of DIILD imaging-biomarkers forward. We observed increased MRI signal correlating to inflammation and fibrosis as confirmed by BAL and tissue markers. The increased inflammatory cells in lung increased at various time points, demonstrating how different immune cells dominated the different stages of progressive lung injury.

Author: Dr MAHMUTOVIC PERSSON, Irma (Department of Translational Medicine, Medical Radiation Physics, Lund University, Malmö Sweden)

Co-authors: Dr ÖRBOM, Anders (Department of Clinical Sciences, Oncology and Pathology, Lund University, Lund, Sweden); Mrs FALK HÅKANSSON, Hanna (Truly Labs, Scheelevägen 2, Medicon Village, Lund, Sweden); Mr PERSSON, Janne (Truly Labs, Scheelevägen 2, Medicon Village, Lund, Sweden); Mr ÖNNERVIK, Per-Ola (Truly Labs, Scheelevägen 2, Medicon Village, Lund, Sweden); Dr VON WACHENFELDT, Karin (Truly Labs, Scheelevägen 2, Medicon Village, Lund, Sweden); Prof. OLSSON, E. Lars (Department of Translational Medicine, Medical Radiation Physics, Lund University, Malmö Sweden)

Presenter: Dr MAHMUTOVIC PERSSON, Irma (Department of Translational Medicine, Medical Radiation Physics, Lund University, Malmö Sweden)

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