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| **Biodistribution of inhaled AD-214 in a sheep model of lung fibrosis – a proof of concept study** |
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| **Introduction/Aim:** AD-214 is a proprietary recombinant Fc-fusion protein (i-body) that selectively binds to the drug target CXCR4, with demonstrated efficacy as an anti-fibrotic in several models of fibrosis. Our study aim was to examine the biodistribution of AD-214 following inhalation in a sheep lung fibrosis model.  **Methods:** Lung fibrosis was induced in sheep by airway delivery of bleomycin (BLM) to one region/major lung lobe, with saline delivery to a separate lobe (internal control). Soluble radiolabeled (89Zr) AD-214 i-body was delivered via nebulization (22.7mg/mL, 2mL). Blood and BAL samples were collected, and PET-MRI and CT imaging was performed under general anesthesia at several time-points. 89Zr radioactivity levels were measured in peripheral blood, BAL and post-mortem tissue samples.  **Results:** CT and MRI imaging confirmed the presence of fibrosis in the BLM-treated lung lobes. BAL cell numbers were higher in fibrotic vs healthy lungs, but no significant changes were observed following AD-214 inhalation. 89Zr radioactivity counts (kBq/mL) in whole blood and plasma increased over time, reaching maximal levels 24-72 hrs following AD-214 inhalation. There were high radioactivity counts in BAL cells and cell-free BAL fluid (BALF) at 72 hrs, indicative of significant AD-214 retention in the airways. Furthermore, radioactivity was 2-4 fold higher in BAL cells compared to cell-free BALF suggesting predominant uptake/binding with immune cells. The higher radioactivity levels in BAL cells and BALF collected from the healthy lung lobe is in agreement with the PET imaging data, suggesting delivery of inhaled AD-214 to the leading edge of fibrosis.The percentage inhaled AD-214 dose delivered to the lungs ranged from 62.9-73.4%. This remained high in post-mortem lung tissues collected at 72 hrs, indicating long retention within the lungs.  **Conclusion:** This study demonstrated effective delivery and significant lung retention of inhaled AD-214 i-body in sheep, demonstrating feasibility for the treatment of pulmonary fibrosis.    **Grant Support:** |