Intratracheal Delivery of a Hydrogel Containing iPSC derived Pneumocytes and Endothelial Cells Improves Lung Function in a Rat Emphysema Model

Objective: To determine if human induced pluripotent stem cells (iPSC) derived pneumocytes and endothelial cells could be delivered intratracheally, could engraft, and could contribute to lung repair in a rodent emphysema model.

Method: To induce emphysema, fifteen nude rats were injected with 32-units/100g of elastase intratracheally; five rats were age matched as the healthy control (figure,1A). After 21days, development of emphysema was confirmed by chest CT. Animals were divided into three groups: untreated (Control), intratracheally injected with 3mg/ml collagen and Matrigel only (Vehicle), or injected with iPSC derived endothelial (80 million) and pneumocytes (20 million) cells (Cell treated). At day 49, blood gas, rat body weight, lung weight and volumes, and lung compliance were measured, and lungs were removed for histology.

Results: At day 21 post elastase injections, CT scans confirmed the formation of emphysema by decreased means of Hounsfield units (-836±63 in emphysema vs. -679±35 in healthy controls, p=3x10-3). Oxygen diffusion capacity in rats breathing 100% oxygen followed by atmospheric oxygen did not show a significant difference among conditions: PO2 at 100% oxygen was 487.75±146.7, 592±79.01, 451.25±49.7, and 574.75±90.42 and at atmospheric air was 97.5±27.8, 110.5±25.5, 88.75±5.68, and 104.75±13.42 for cell-treated, healthy controls, emphysema controls, and vehicle conditions, respectively. Neither body weight nor lung weight were different amongst the treatment groups. Cell engraftment was confirmed by confocal imaging of cell-treated lungs stained with human-specific CD31 antibodies for endothelial cells, anti-GFP for GFP-NKX2.1 pneumocytes, and anti-human major histocompatibility class I for both cell types. Using mean linear intersect (MLI), morphometric parameters of lung unit size showed MLI of cell-treated condition was 14±1.34 (vs healthy control18±1, p=0.31); the intersect decreased in emphysema (9±1.5, p=0.02) and Vehicle (9.6±0.1, p=0.02) in mean± standard error. Dynamic lung compliance analysis showed improved compliance in the cell-treated condition (figure,1B), where mean ±standard error was -1.70x ±0.65 (vs. healthy control 0.03±0.26, p=0.009); compliance decreased in emphysema (-4.8x±0.20, p=3x10-5) and Vehicle (-4.5x±0.28, p=0.0003).Saline displacement of recruited then deflated lungs showed that the cell-treated condition's residual volume is 1.868±0.11 (vs. healthy lungs 1.620±0.27, p=0.47), compared to emphysema (2.99±0.0.27, p=0.03) and Vehicle (3±0.0.20, p=0.017) in mean± standard error (figure,1C), suggesting improved elastance in the cell-treated condition.

Conclusion: Human iPSC derived endothelial and epithelial cells can be delivered intratracheally in a hydrogel, engraft in emphysematous lungs, and improve lung mechanics in a rodent emphysema model.
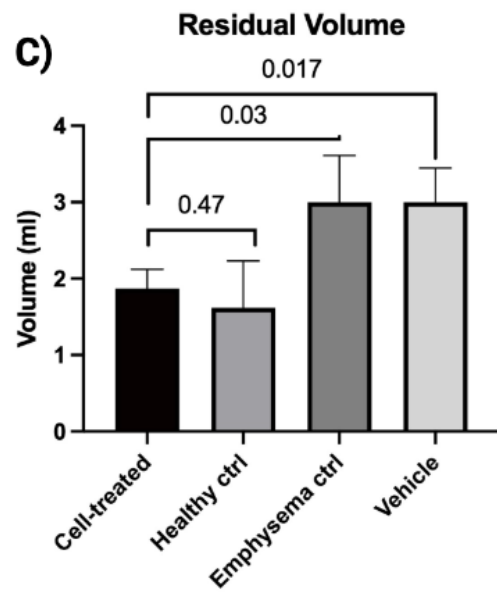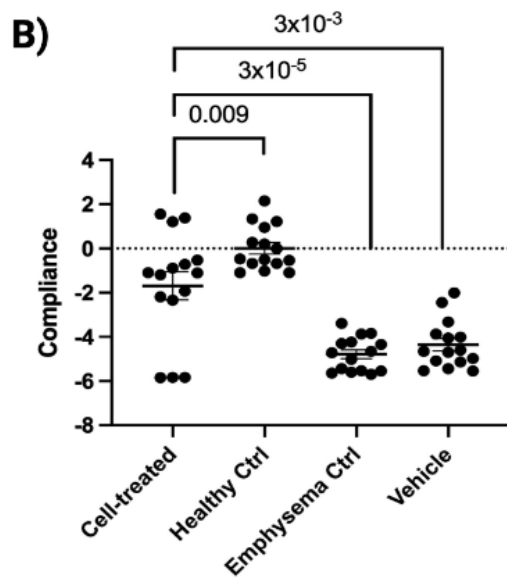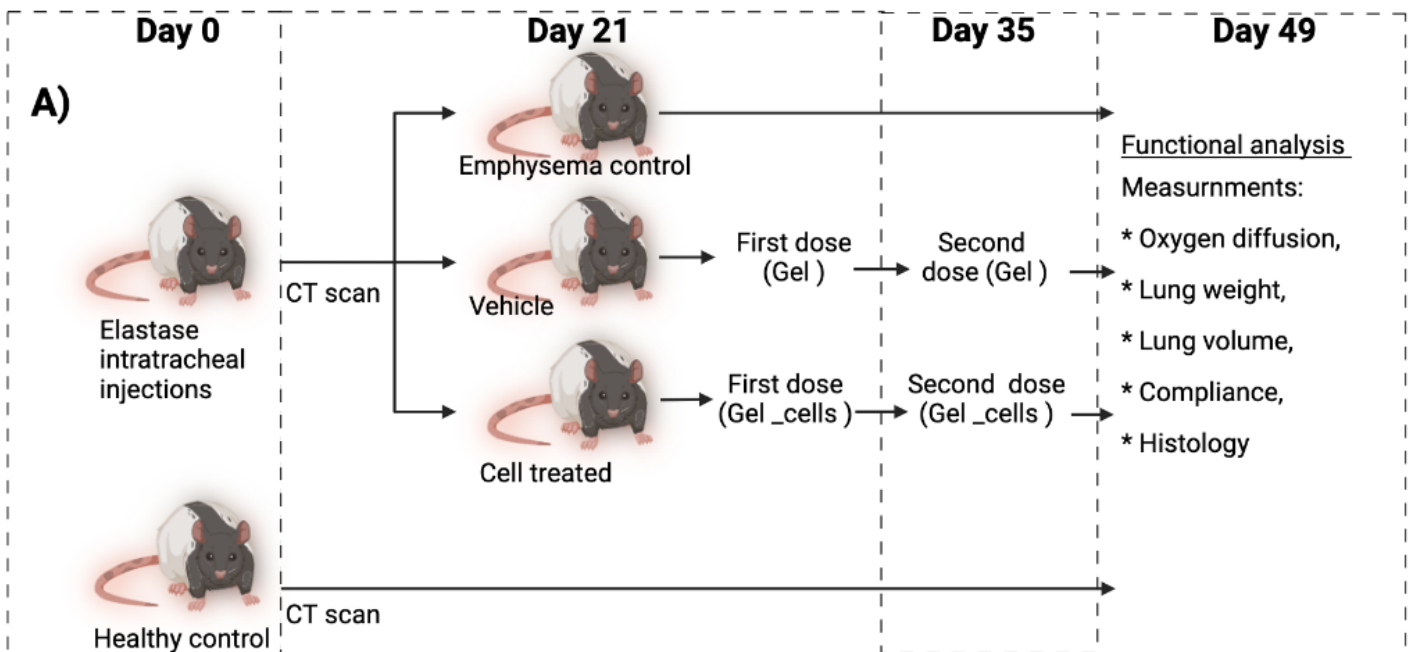
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Figure 1: Overall experimental plan and main outcomes: A) experimental scheme; B and C) cell-treated lungs exhibite improved lung comliance and reduced pulmonary residual volume compared to emphysema control and vehicle conditions, data are presented in mean ± strandered error.