News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Press conference time: May 17, 4:30 p.m. in the ATS Press Room (E-1)

Mini-Symposium session time: 1:30-4:00pm. May 17
Location: CC-Room 238-239 (Second Level), Morial Convention Center

Stem Cells Restore Tissue Affected By ALI

ATS 2010, NEW ORLEANS— Human stem cells administered intravenously can restore alveolar epithelial tissue to a normal function in a novel *ex vivo* perfused human lung after *E. coli* endotoxin-induced acute lung injury (ALI), according to research from the University of California San Francisco.

The findings will be reported at the ATS 2010 International Conference in New Orleans.

ALI is a common cause of respiratory failure in the intensive care units, often leading to death. It can be caused by both direct injury such as aspiration and pneumonia, and indirect injury such as sepsis and from trauma. ALI is characterized by diffuse bilateral infiltrates on chest x-ray, hypoxemia and both lung endothelial and epithelial injury. Because ALI causes injury to the alveolar epithelium, it impairs its ability to reabsorb pulmonary edema fluid from the airspaces of the lung. Yearly, ALI affects approximately 200,000 patients in the US and has a 40 percent mortality rate despite extensive investigations into its causes and pathophysiology. Innovative therapies are desperately needed.

To determine whether stem cell therapy given intravenously would be able to repair the damaged alveolar epithelium, researchers used right human lungs that had been declined for transplantation by the Northern California Transplant Donor Network. The lungs were perfused with whole blood and ventilated with continuous positive airway pressure. The researchers then infused the right middle lung with endotoxin, which induces acute lung injury. One hour following injury, clinical grade human mesenchymal stem cells (hMSC)—those that are derived from bone marrow of healthy adults— were given intravenously.

"We found that intravenous infusion of clinical grade cryo-preserved allogeneic hMSC were effective in restoring the capacity of the alveolar epithelium to resolve pulmonary edema when given after the establishment of *E. coli* endotoxin-induced acute lung injury in an *ex vivo* perfused human lung preparation," explained Jae-Woo Lee, M.D., who led the study in the laboratory of Michael A. Matthay, M.D. "In addition, we found that intravenous infusion of hMSC preferentially homed to the injured areas of the lung, which means that the cells find their way from the bloodstream to the sites in the lung of injury."

Prior research from the group focused on delivering stem cells intrabronchially. Importantly, in this study, the group found that intravenous delivery of hMSC worked as well as intrabronchial administration. Intravenous administration would be preferred in critically ill mechanically ventilated patients with ALI because bronchoscopy may lead to transient problems with oxygenation and ventilation.

In addition to having restored function of alveolar epithelial cells, lungs treated with hMSC showed a reduction in inflammatory cytokine, IL-1β and IL-8, levels suggesting a favorable shift away from a proinflammatory environment in the injured alveolus.

"These results suggest that the intravenous route would be ideal for potential clinical trials of hMSC for severe acute lung injury, a syndrome of acute respiratory failure in critically ill patients that is associated with 40 percent mortality," said Dr. Lee.

"These results extend our recent publication, which demonstrated that hMSC may have therapeutic potential clinically in patients with severe acute lung injury. We need to do more experiments with testing the effect of hMSC against live bacterial induced lung injury in the perfused human lung and now advance to doing Phase I and II safety and efficacy studies in patients."

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"Intravenous Allogeneic Human Mesenchymal Stem Cells Home to The Site of Injury and Restore Alveolar Fluid Clearance to a Normal Level in an Ex Vivo Perfused Human Lung Injured by E.Coli Endotoxin" (Session B98 and B81, Monday, May 17, 1:30 to 4 p.m., CC-Room 238-239 (Second Level) and CC Room 243-245 (Second Level), Morial Convention Center; Abstract 2736)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Intravenous Allogeneic Human Mesenchymal Stem Cells Home to the Site of Injury and Restore Alveolar Fluid Clearance to a Normal Level in an Ex Vivo Perfused Human Lung Injured by E.Coli Endotoxin

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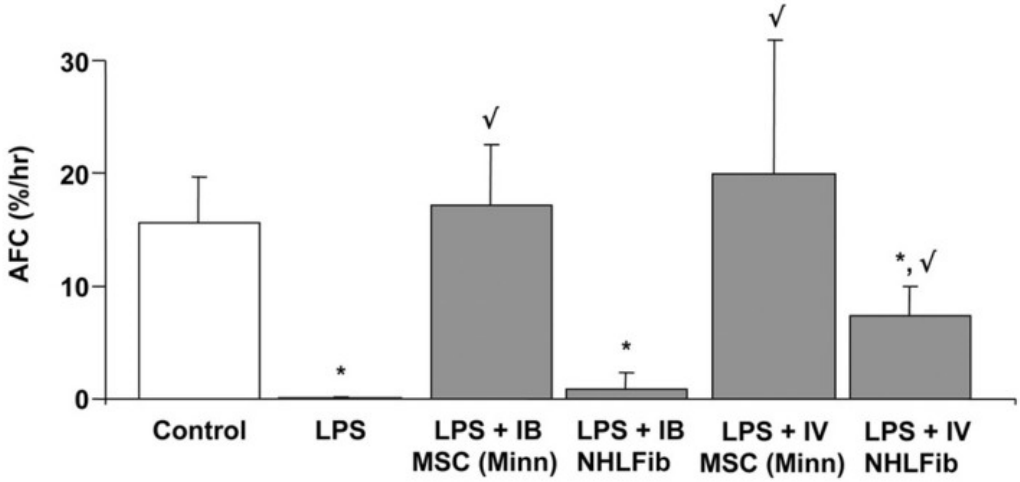
Introduction: We previously found that intra-bronchial (IB) instillation of allogeneic human mesenchymal stem cells (hMSC) restored alveolar fluid clearance (AFC) following *E.Coli* endotoxin ALI in the *ex vivo* perfused human lung (*PNAS* 2009). The current studies were designed to determine if clinical grade cryopreserved allogeneic hMSC obtained from an NHLBI Production Assistance for Cellular Therapy (PACT, U of Minn) Program are effective when given intravenously (IV) in restoring AFC in an *ex vivo* perfused human lung injured by endotoxin. In addition, we carried out localization studies to detect homing of the MSC to the injured areas of the lung.

Methods: Right human lungs declined for transplantation were perfused with fresh whole blood and ventilated with continuous positive airway pressure (*AJP:Lung*, 2007). Endotoxin (0.1 mg/kg) was instilled into the right middle lobe (RML). The right upper lobe (RUL) was used as an internal control. One hour following endotoxin exposure, hMSC (5 x10^6 cells) were given intravenously. In separate experiments, hMSC were given intra-bronchially to duplicate previous published results (*PNAS* 2009). AFC was measured in both the control and injured lung lobes at 4 h. Normal human lung (NHL) fibroblasts were used as controls for the MSC. Tracking of the injected hMSC was accomplished by labeling MSC with the fluorescent probe, PHK26.

Results: Intravenous delivery of hMSC following endotoxin induced lung injury restored AFC in the injured RML to a normal level (**Figure**) and was also associated with a reduction in both IL-1β and IL-8 levels in the injured air spaces of the RML. This beneficial effect was comparable to the effect with intra-bronchial administration of hMSC for endotoxin lung injury. In addition, histological studies indicated that the intravenously delivered hMSC homed primarily to the injured areas of the RML.

Conclusions: Intravenous allogeneic human MSC are as effective as intra-bronchial MSC for restoring the capacity of the alveolar epithelium to remove alveolar fluid normally when given following *E. Coli* endotoxin-induced ALI in the *ex vivo* perfused human lung. Furthermore, intravenous hMSC preferentially home to the injured areas of the lung, suggesting that the intravenous route would be logical for clinical trials of hMSC for severe acute lung injury.



* P<0.05 vs. Control
√ P<0.05 vs. LPS