Orthotopic Lung Transplant Model in Rats

Nitin A. Das, MD

The Lung Transplant program at UTHSCSA performs nearly 40 transplants a year and helps in prolonging and improving quality of life for patients with end-stage lung diseases, many of whom are young adults. Despite progress in immunosuppression and surgical technique, the long-term survival after lung transplant is around 50% at 5 years. The problems encountered during and after lung transplants and the therapeutic interventions thereof can be evaluated in a research environment using animal models. The orthotopic rat lung transplant model is one such tool which allows teasing out the transplant related problems in-vivo so that systemic as well as local responses can be assessed in a physiological, dynamic milieu. This model utilizes the modified cuff technique to anastomose the pulmonary artery, pulmonary vein and the main bronchus of the donor lung to that of the recipient’s respective structures. Using this model, we have evaluated two common transplant related problems that of acute rejection and ischemia-reperfusion injury and their potential attenuation using a novel formulation of a commonly used immunosuppressant – tacrolimus – which was delivered directly to the lungs via inhalation. This inhalable formulation provides localized immunosuppression and can negate the adverse effects like nephrotoxicity, neurotoxicity and opportunistic infections seen in systemic immunosuppression. We would like to present results of the following studies related to inhaled tacrolimus in our rat lung transplant model.

1. Pharmacokinetic characteristics of nanoparticle tacrolimus: This study assessed the tacrolimus drug levels in the lung and compared it to the blood over period of 24 hours. It showed that appreciable levels of tacrolimus can be delivered to the transplanted lungs while the systemic drug levels remained negligible.

2. Efficacy of nanoparticle tacrolimus in attenuating Acute Rejection in Lung Transplant: With this study, it was demonstrated that the inhaled nanoparticle tacrolimus was equally effective in attenuating acute rejection as systemically administered tacrolimus. The tacrolimus drug levels in the kidney (peripheral tissue) remained low while reducing rejection in the lung allograft.

3. Role of nanoparticle tacrolimus in attenuating Ischemia-Reperfusion Injury after Lung Transplant: With this study, the effects of ischemia-reperfusion (I-R) injury seen after organ transplant was mitigated when the donor organ was pre-treated with tacrolimus. Just a single dose of inhaled tacrolimus to the donor lung prior to procurement was able to reduce the I-R injury in the isograft after transplant.

All three studies have clinical relevance and significance as they will guide future treatment protocols to improve outcomes after lung transplants.