

# Effect of Inhaled Tacrolimus on Cytokines & Other Indicators of Ischemia Reperfusion Injury in a Rat Lung Transplant Model

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**Background:** Ischemia reperfusion (I-R) injury is one of the major contributors to the development of primary graft failure, which is one of major cause for early death in first year after lung transplantation. The 5 yr survival rate is only 52%, which is significantly lower compared to other solid organ transplants. Early graft failure is a risk factor for development of acute rejection. Underlying mechanisms of ischemic injury includes production of reactive oxygen species and up-regulation of NADPH, NF $\kappa$ B, nitric oxide synthase and adhesion molecules. During reperfusion these changes induce activation of neutrophils and platelets and together with the NO signaling pathway, leading to vascular damage with increase pulmonary vascular resistance and vascular permeability. I-R injury manifests clinically as diffuse pulmonary edema, with impaired oxygenation and decreased lung compliance.

**Hypothesis:** We hypothesized that the presence of nanoparticle Tacrolimus in the donor lung prior to donor cardiac arrest and procurement will attenuate the ischemia reperfusion injury after transplantation.

**Methods:** This hypothesis will be tested using an established orthotopic left rat lung transplant model. Study design: The donor in the treatment group will be pretreated with a dose of inhaled nanoparticle Tacrolimus within one hour of lung harvest and the graft will be stored for a 3 or 6 hour period of cold ischemia at 4 C in an inflated state. After transplantation the recipient will be sacrificed after 2 or 4 hours, which will constitute the reperfusion period. At the time of sacrifice, blood, BAL, heart and lung tissue will be obtained and examined for: ABG, cytokine assay, Flow cytometry, MPO activity, wet to dry ratio and Tacrolimus drug level.

## **Results:**

In our final results we expect to see a down regulation in pro-inflammatory cytokines, decreased activation of macrophages and neutrophils in the graft, lowered MPO activity (in both heart and lungs), improved wet to dry weight ratio and ABG in the treated group when compared to a donor group not receiving the inhaled drug.