



Effect of Inhaled Tacrolimus on Ischemia Reperfusion Injury in Rat Lung Transplant Model

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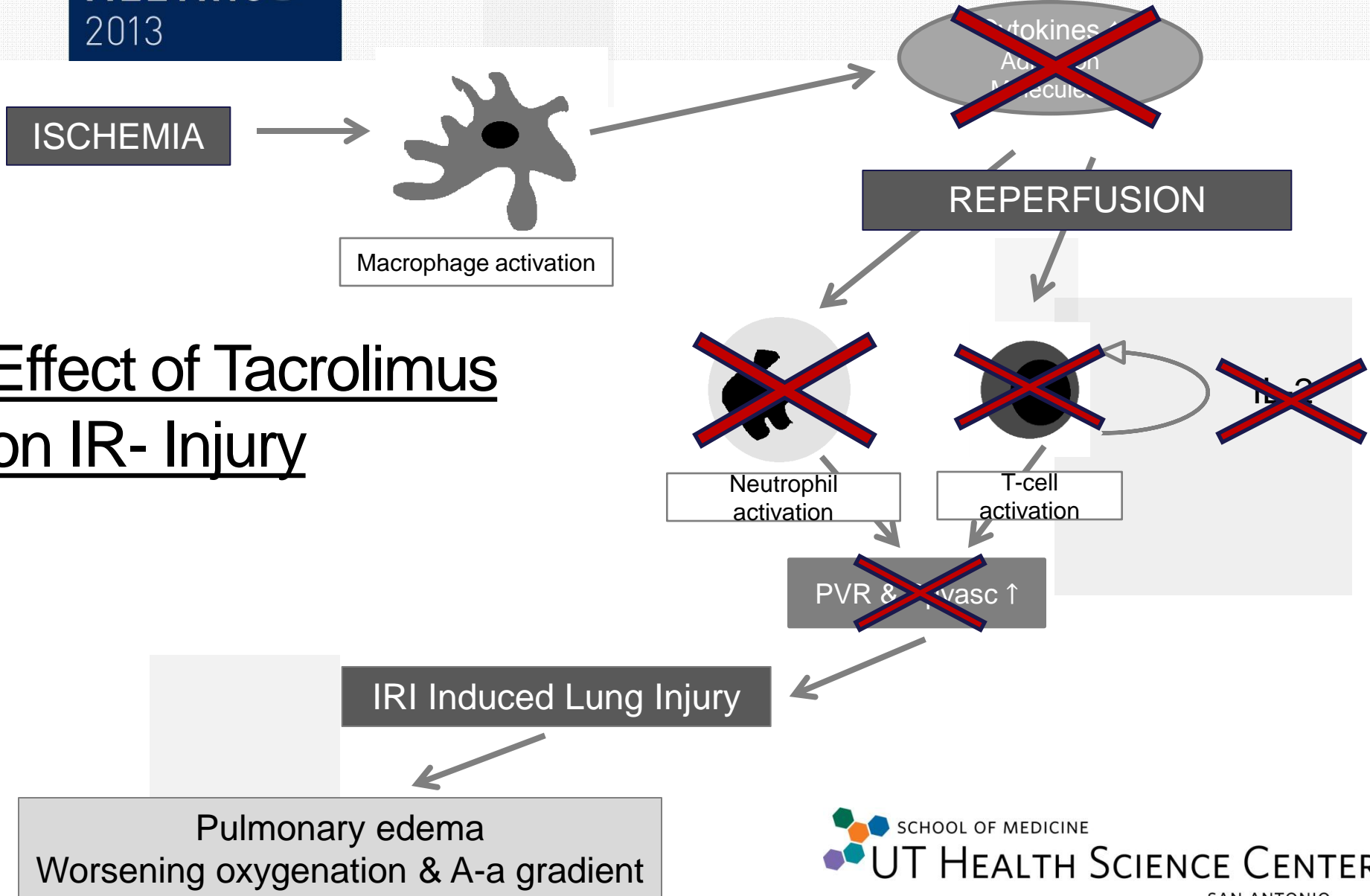
Disclosures

- Robert Williams and Jay Peters: Patent rights for inhaled tacrolimus have been sold to the UT Board of Regents.
- None of the other authors have anything to disclose



Problems

- Ischemia Reperfusion Injury (IR Injury) is inevitable in transplantation
- Contributes to primary graft dysfunction (PGD)
- Negatively affects overall survival after lung transplantation



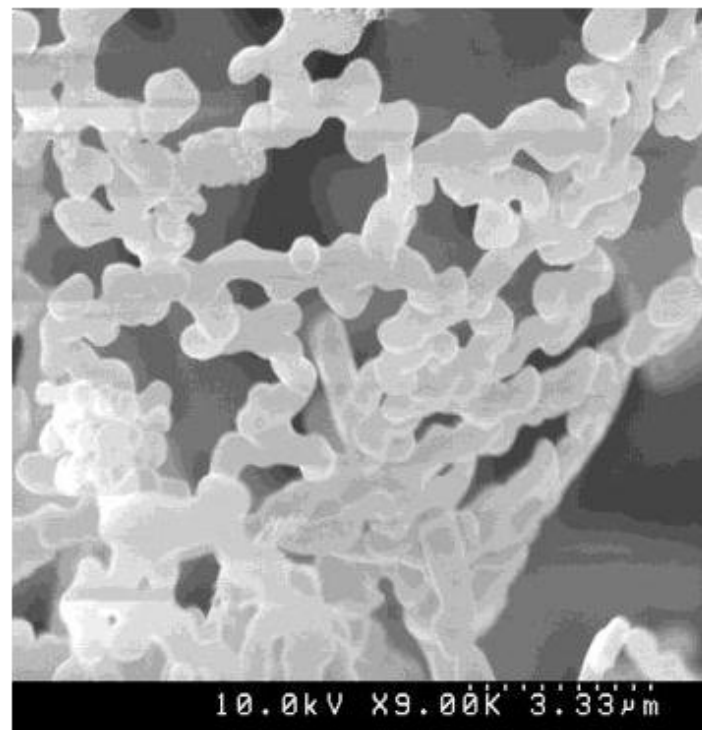
Inhaled nanoparticle Tacrolimus

Standard



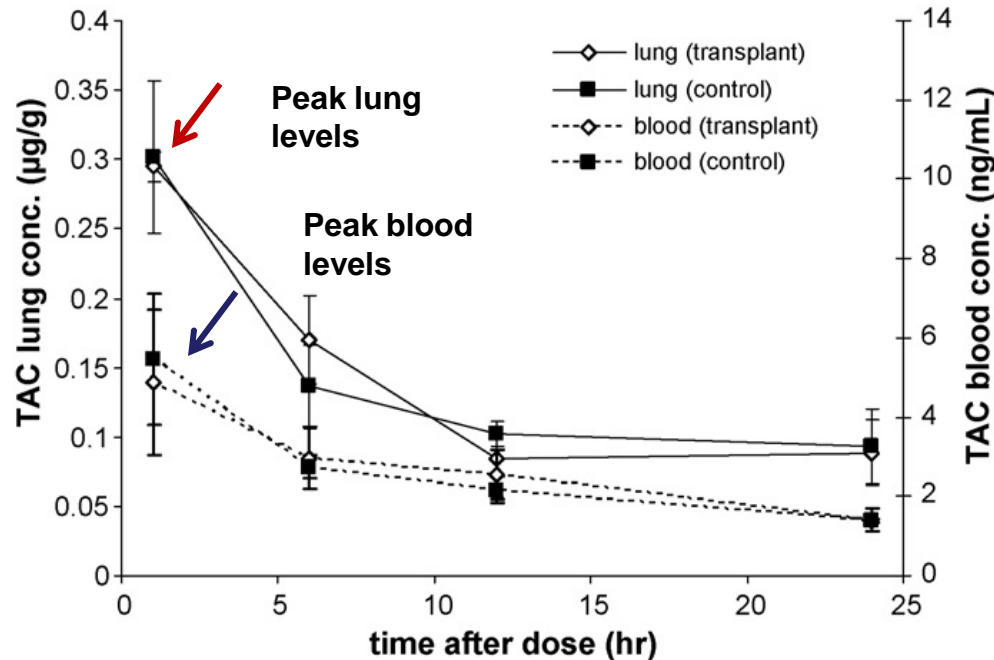
Diameter: 10 000 nm

Nanoparticle



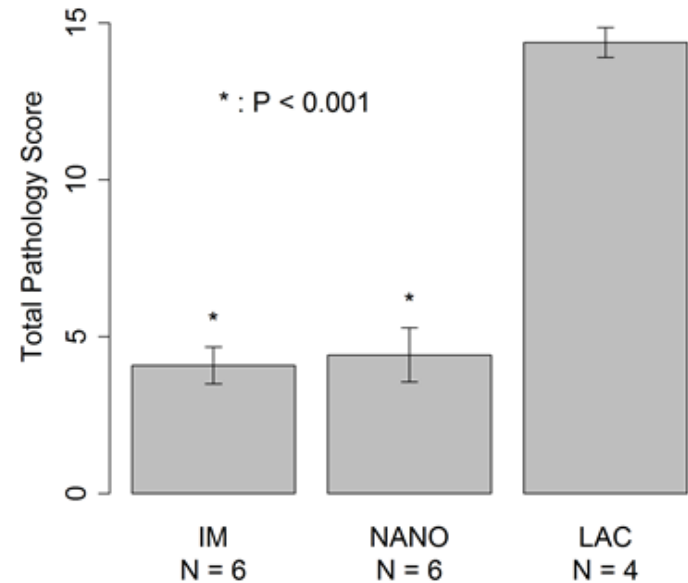
Diameter: 200 nm

Pharmacokinetics



Watts AB, Saad AR, Johnson SB et al, Characterization and pharmacokinetic analysis of tacrolimus dispersion for nebulization in a lung transplant rodent model, International Journal of Pharmaceutics, 2010

Efficacy



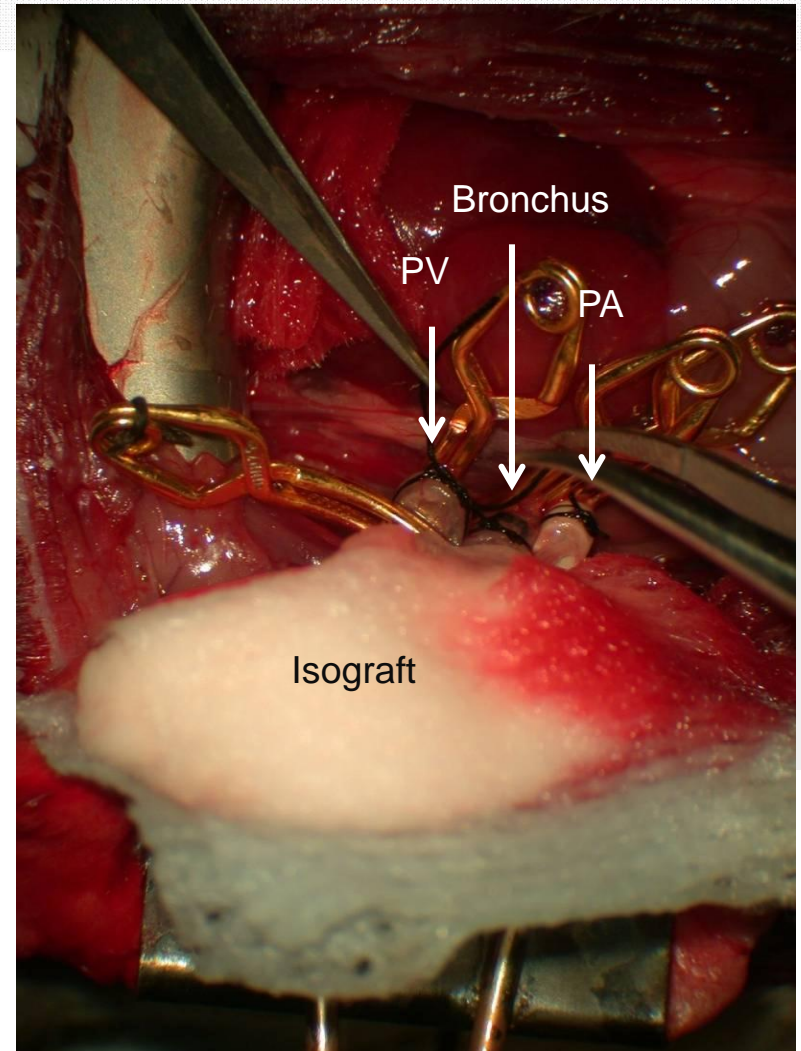
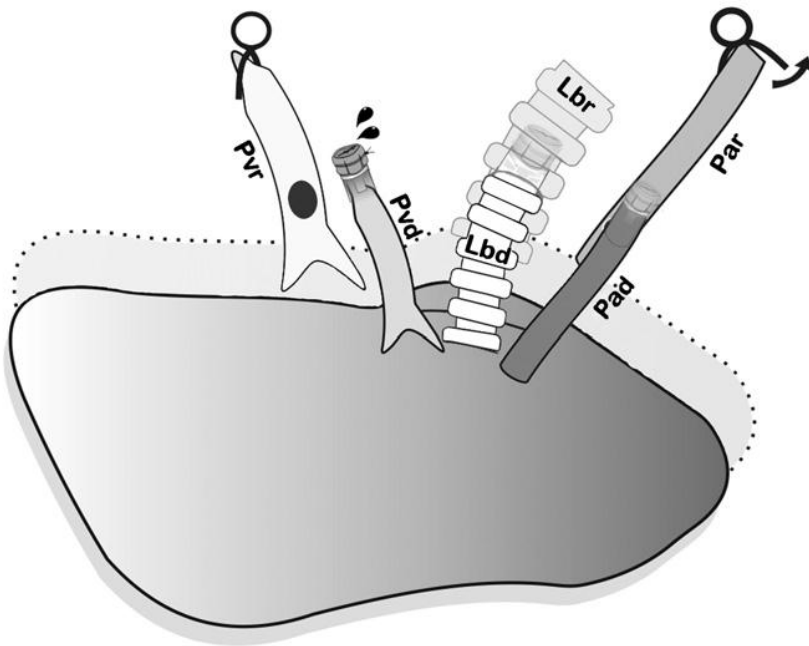
Simmons JD, Johnson SB et al, The Efficacy of Inhaled Nanoparticle Tacrolimus in Preventing Rejection in an Orthotopic Rat Lung Transplant Model, Aust society presentation June 2011



Hypothesis

Administration of inhaled nanoparticle
Tacrolimus to the **donor** prior to procurement
will attenuate ischemia reperfusion injury after
lung transplantation

Orthotopic Rat Lung Transplant



Study design

Control Group:
(n=6)

Treatment Group:
(n=6)

Inhaled
Lactose

Donor
pretreatment

Inhaled
Lactose + NP
Tacrolimus

within 1
hr

Donor lung harvest

3 hrs
ischemia

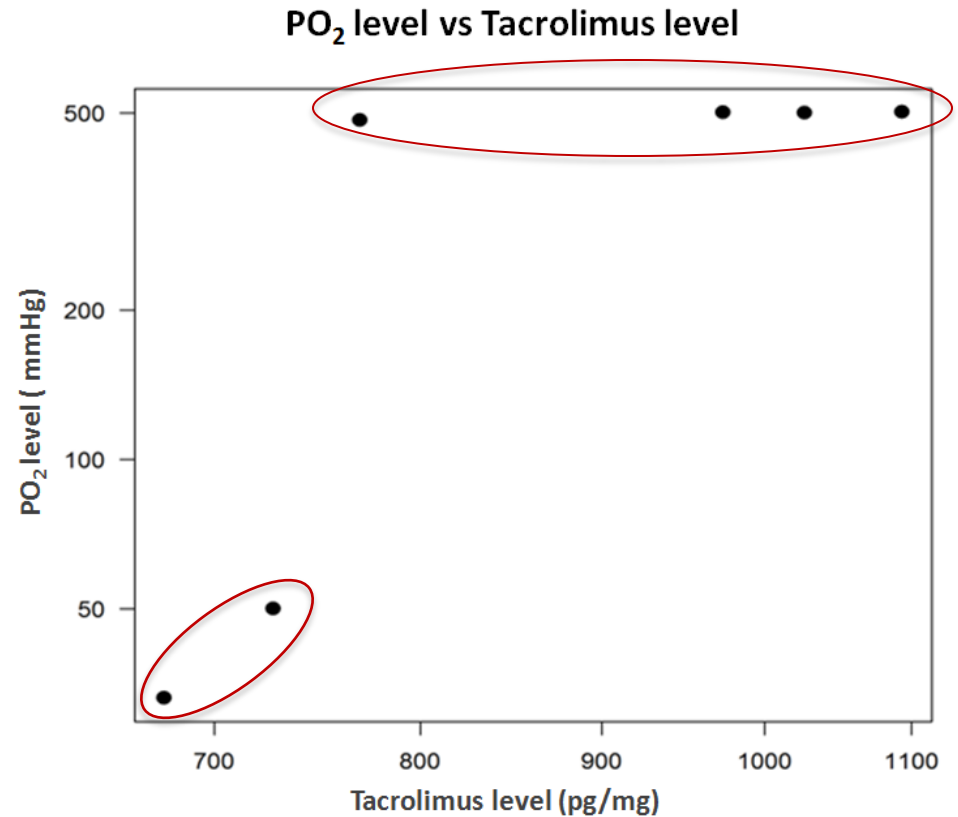
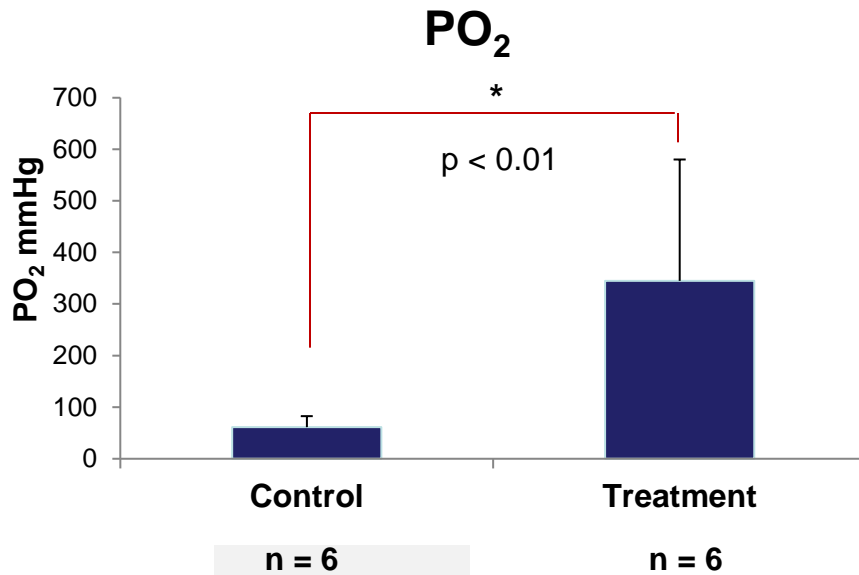
Orthotopic left lung transplant

4 hrs
reperfusion

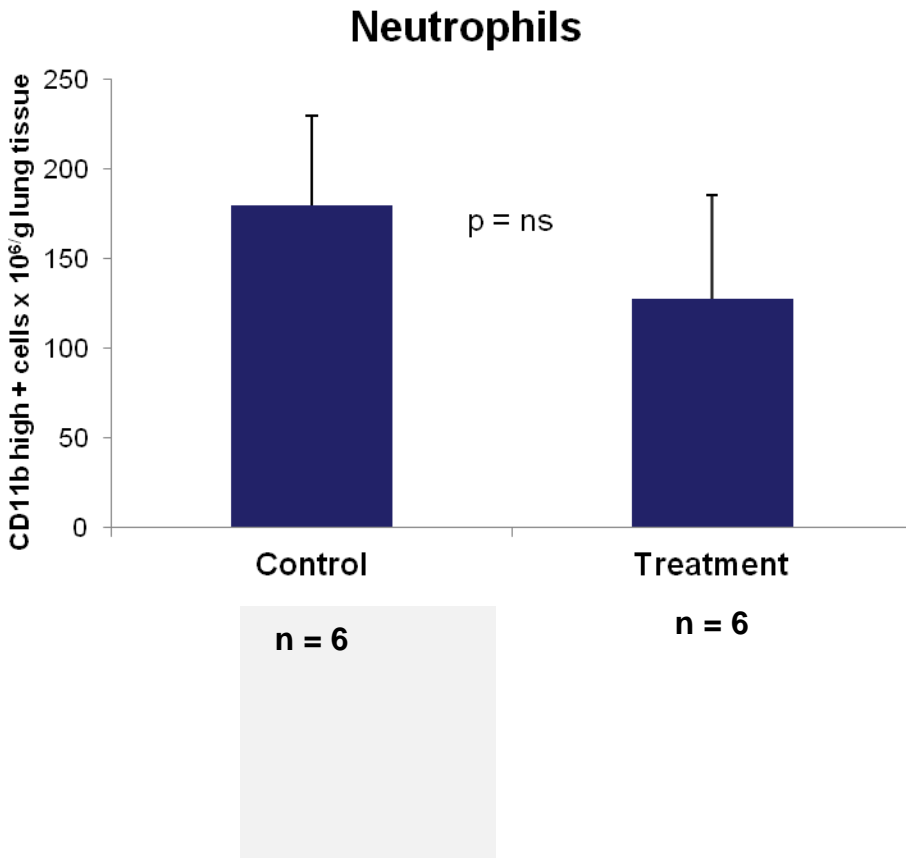
Recipient euthanized

- **Functional assessment**
 - Arterial Blood Gas
- **Cellular changes**
 - Flow cytometry
- **Cytokines**
 - Luminex Assay
- **Tacrolimus levels**
 - Liquid chromatography/mass spectrometry

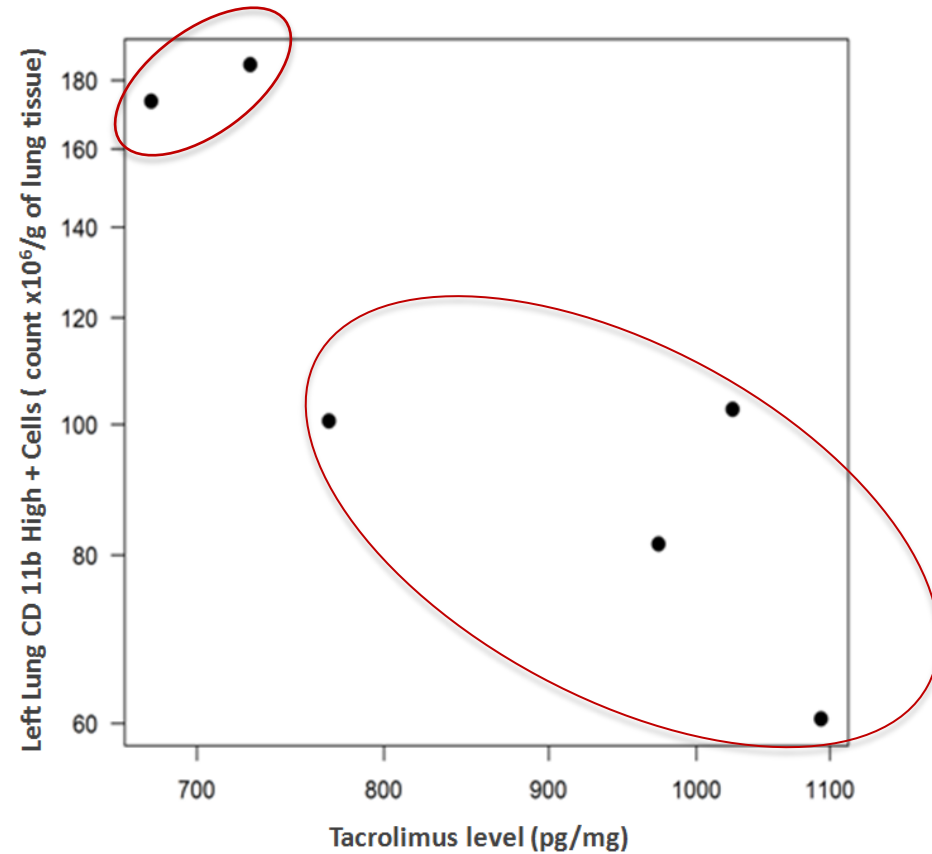
Results: Oxygenation



Results: Neutrophils

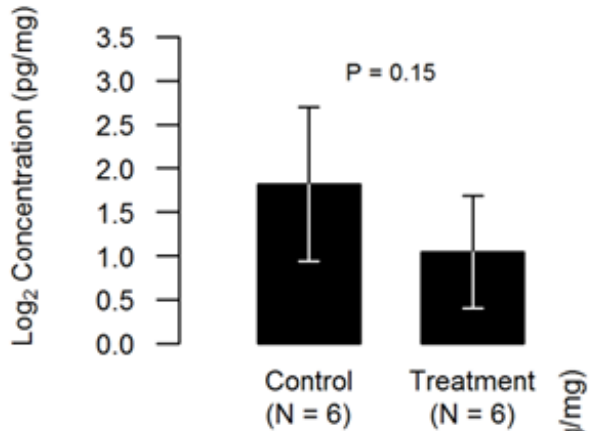


Left Lung CD 11b High + Cells vs Tacrolimus level

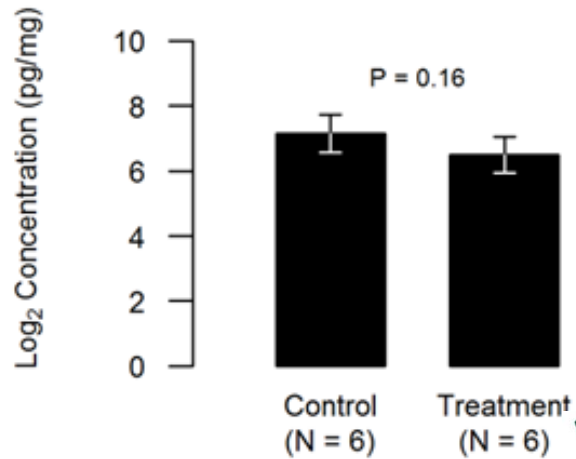


Results: Cytokines

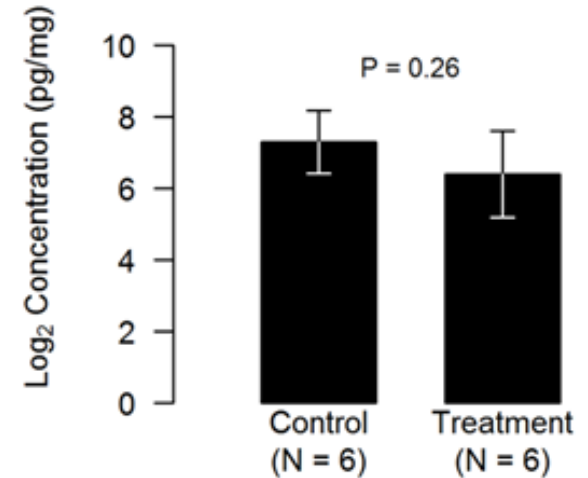
TNF



IL-1b



IL-6



Conclusion

Inhaled nanoparticle Tacrolimus treatment of lung donors is associated with attenuation of ischemia-reperfusion injury on a functional level in lung transplantation

Thank you

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