Mechanisms of Immune Activation with Brain Death: Can This Be Modified?

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RESOLVING THE ORGAN SHORTAGE

PRACTICE | POLICY | POLITICS

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Conflict of Interest Disclosure

- I have no relevant financial relationships to disclose.
- I will discuss off-label use of:
  - Glucocorticoids
  - Anti-thymocyte globulin
  - Eculizumab

Learning Objectives

1. Discuss evidence for the contribution of brain death to outcomes after heart transplantation
2. List mechanisms of immune activation demonstrated in animal models and humans
3. Propose potential therapeutic strategies to modify the immune response to brain death

Scope of the Problem - Heart

- Internationally, survival to one year after heart transplant was 86% between 2009 to 2013 (Lund et al. JHLT 2015)
- Primary heart graft dysfunction affects about 20% of recipients; leads to death in 30% (Kobashigawa et al. JHLT 2015)

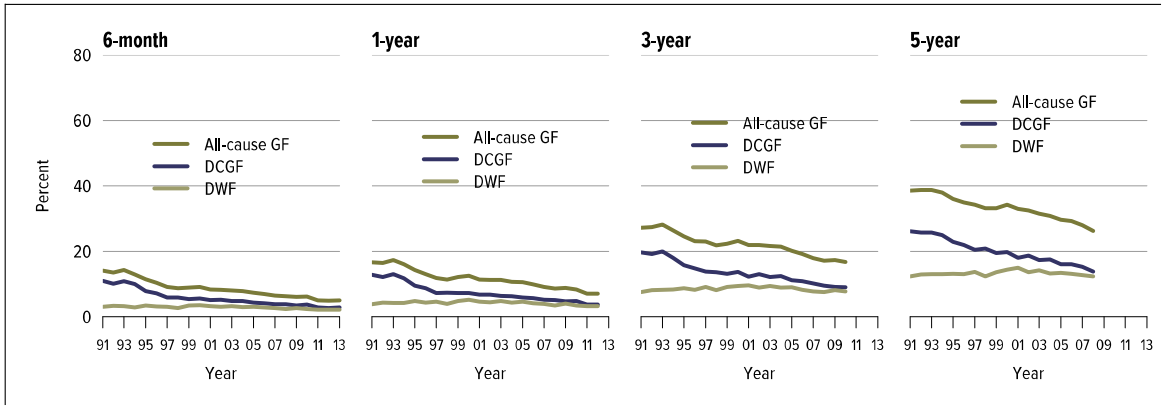
Brain Death Affects Clinical Outcomes

- Recipients of domino heart transplants have a lower incidence of cardiac allograft vasculopathy at 5 years after transplant (Anyanwu et al. JHLT 2003)
- Post-transplant survival is reduced in recipients of donor hearts with greater than 72 hours of management time (Cantin et al. Transplantation 2003)

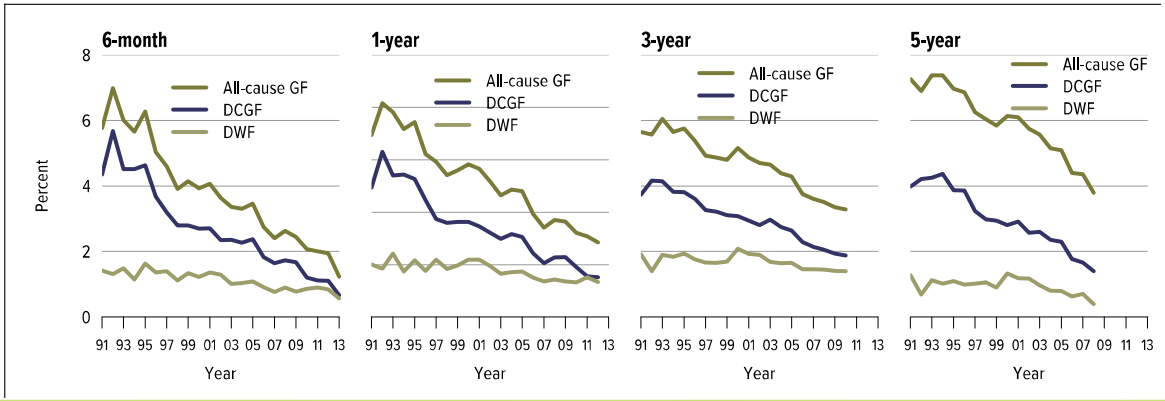
Brain Death Affects Clinical Outcomes

- Same for kidney transplantation (Matas et al. AJT 2015)

Deceased Donor

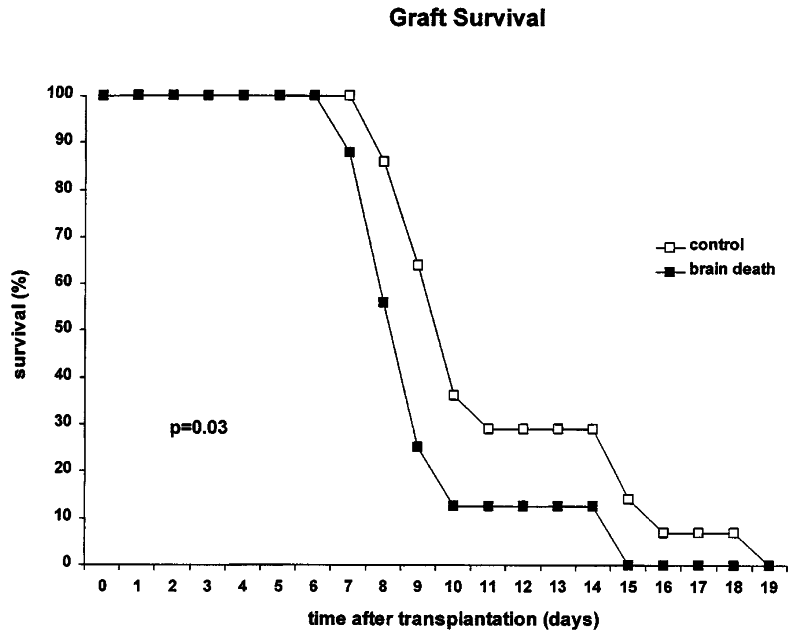


Living Donor



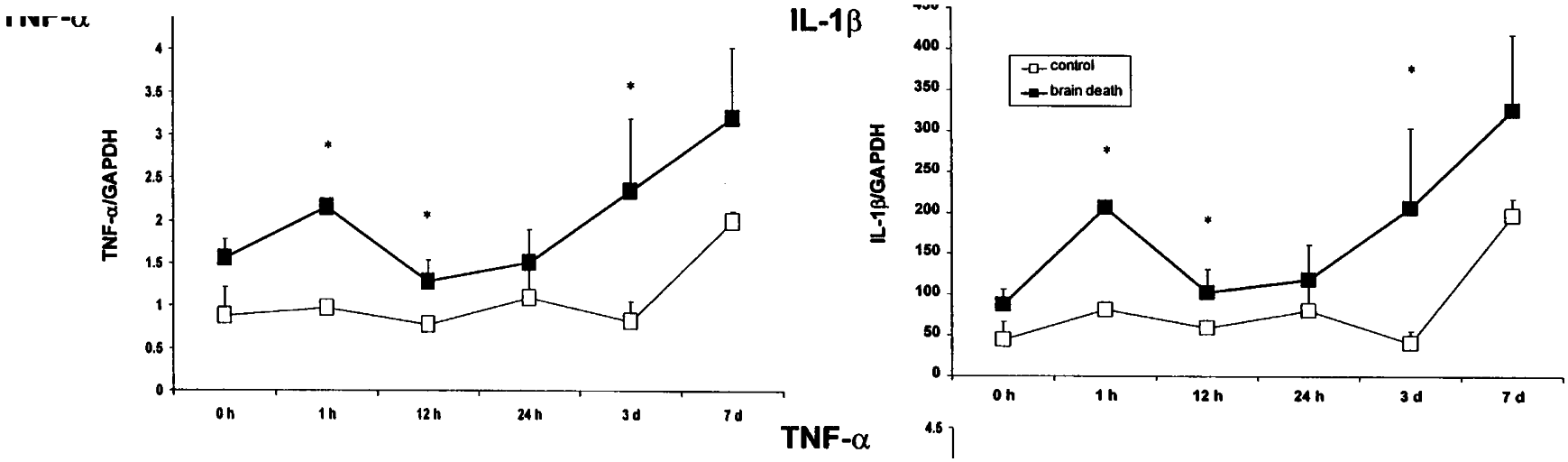
Evidence of Immune Activation: Animal Models

- Survival of heart transplant recipients of brain dead donor organs inferior to recipients of living donor organs (Wilhelm et al. Circ 2000)



Evidence of Immune Activation: Animal Models

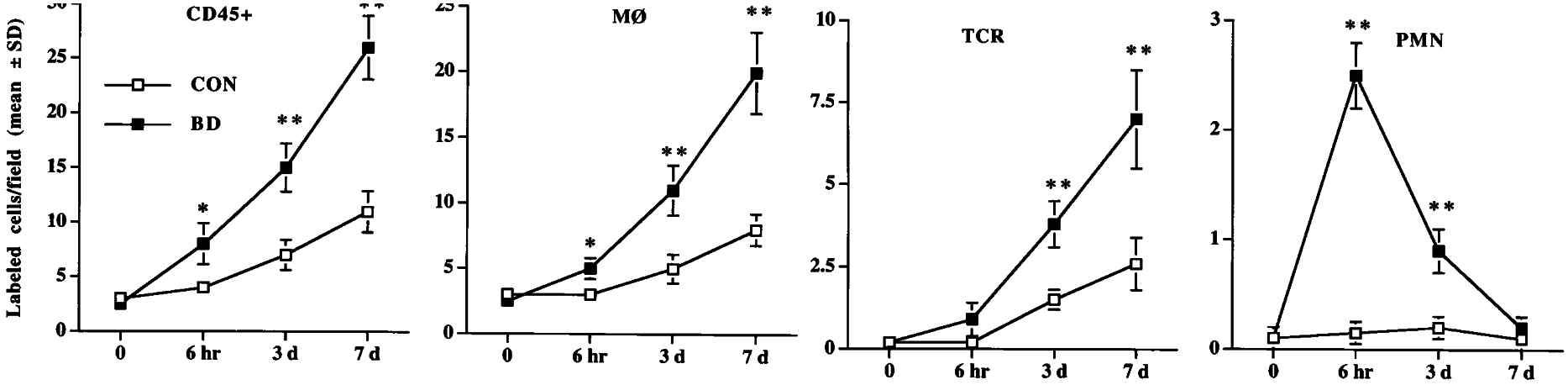
- Increased expression of inflammatory cytokines IL-1 and TNF-α



Wilhelm et al. Circ 2000

Evidence of Immune Activation: Animal Models

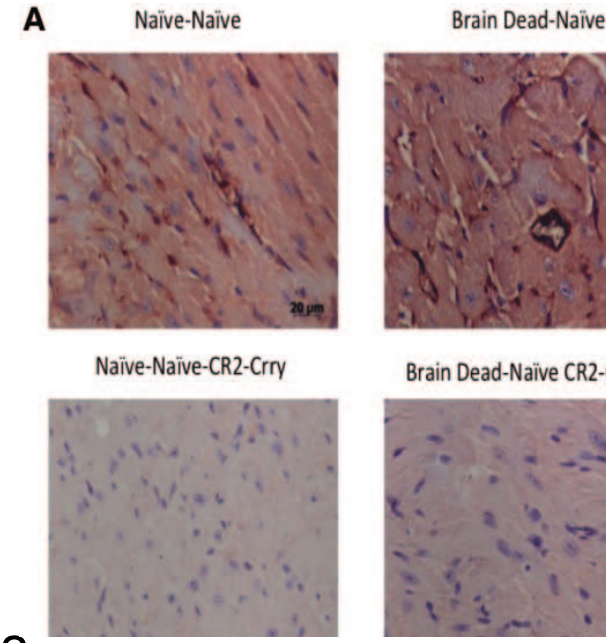
- Increased leukocyte, macrophage, T cell, PMN infiltration



Wilhelm et al. Circ 2000

Evidence of Immune Activation: Animal Models

- Increased complement deposition in grafts from brain dead donors



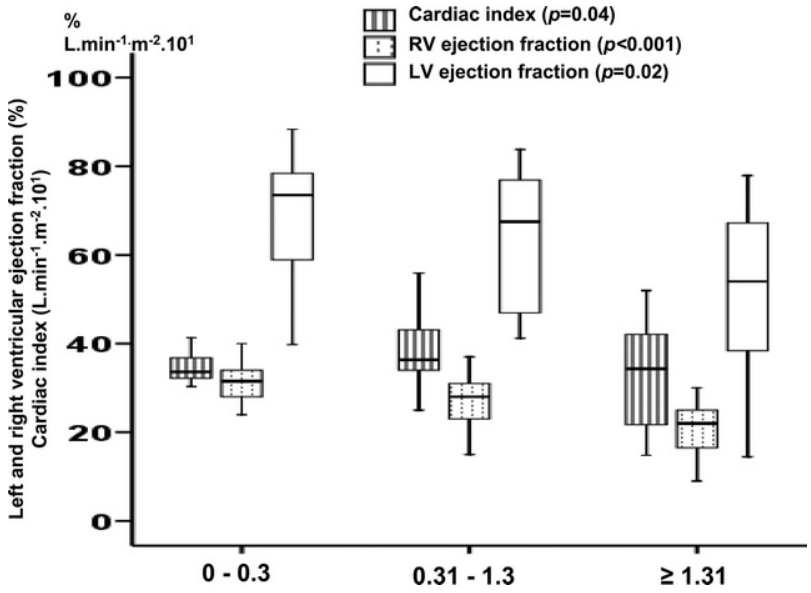
Atkinson et al. Circ 2013

Evidence of Immune Activation: Humans

- Elevated inflammatory cytokine levels in brain dead donors (Venkateswaran et al. Transplantation 2009)
  - IL-1 elevated in 16%
  - IL-6 elevated in 100%
  - TNF-α elevated in 28%
  - Procalcitonin elevated in 87%

Evidence of Immune Activation: Humans

- Procalcitonin levels were associated with graft function



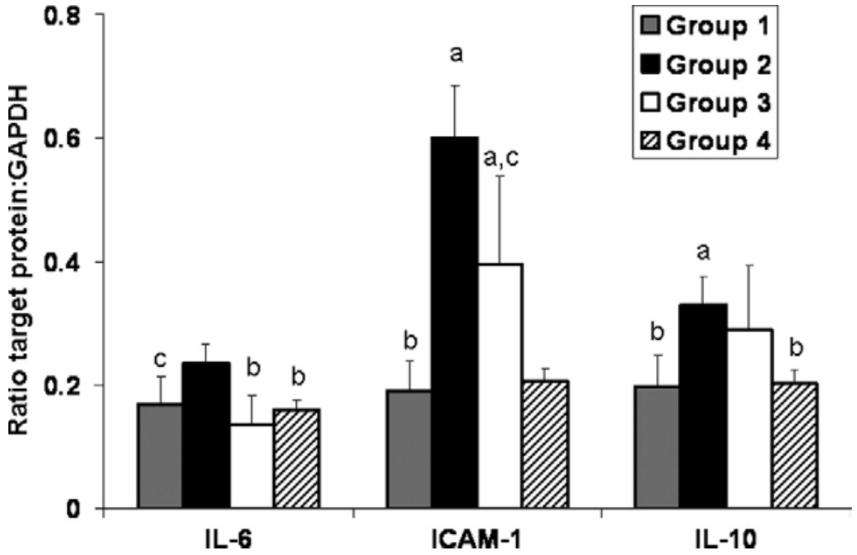
Venkateswaran et al. Transplantation 2009

Evidence of Immune Activation: Humans

- Increased complement deposition in human allografts from brain dead donors (Atkinson et al. Circ 2013)
  - Pre-transplant:
    - Living donor: 0 of 4 positive for C4d
    - Brain dead donor: 5 of 8 positive for C4d
  - Post-transplant:
    - Living donor: 0 of 4 positive for C4d
    - Brain dead donor: 5 of 8 positive for C4d

Potential Therapeutic Strategies: Animal Models

- Glucocorticoid treatment reduces inflammatory cytokine levels after brain death

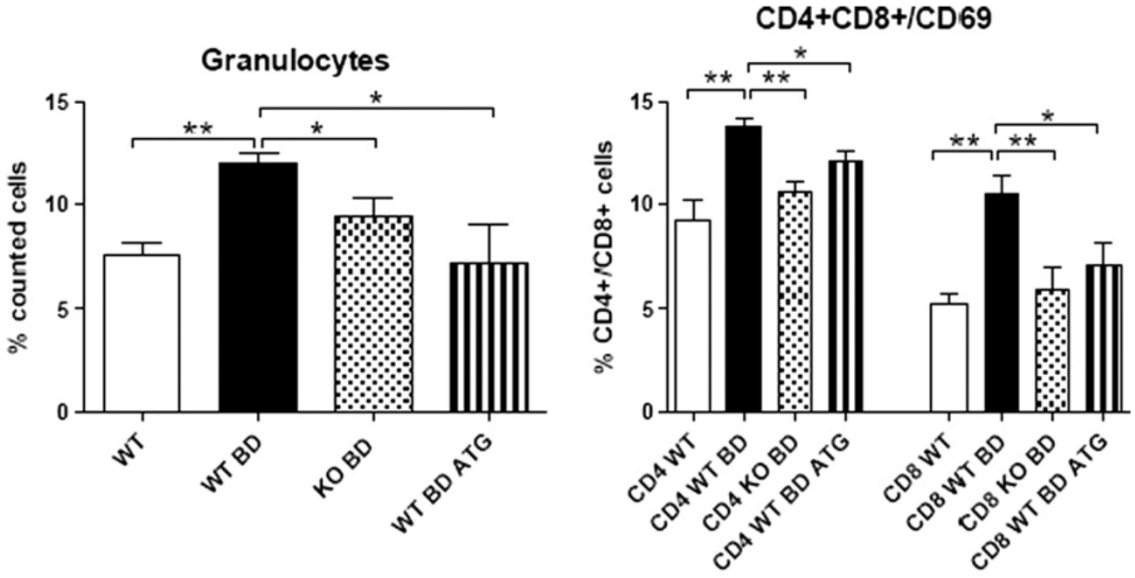


G1: sham
G2: brain death
G3: steroid + BD
G4: BD + steroid

McLean et al. JHLT 2007

Potential Therapeutic Strategies: Animal Models

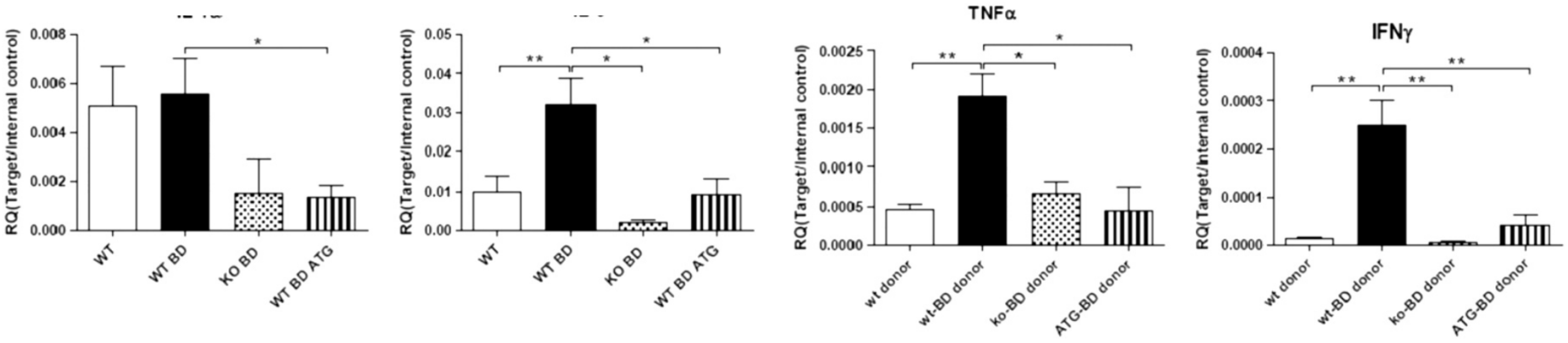
- Anti-thymocyte globulin treatment of brain dead donors reduces inflammatory cell infiltration



Floerchinger et al. JHLT 2012

Potential Therapeutic Strategies: Animal Models

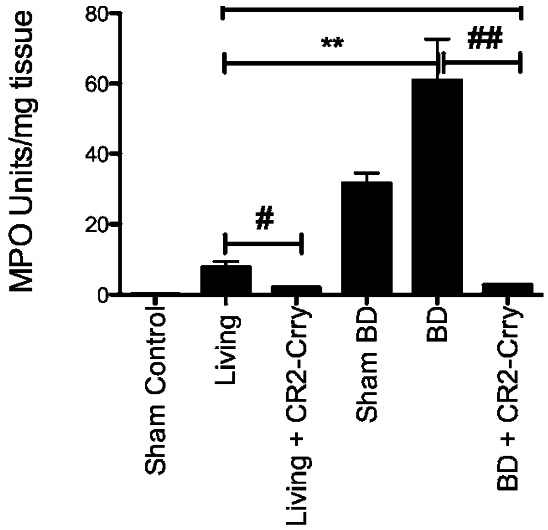
- Anti-thymocyte globulin treatment of brain dead donors reduces graft inflammatory cytokine expression

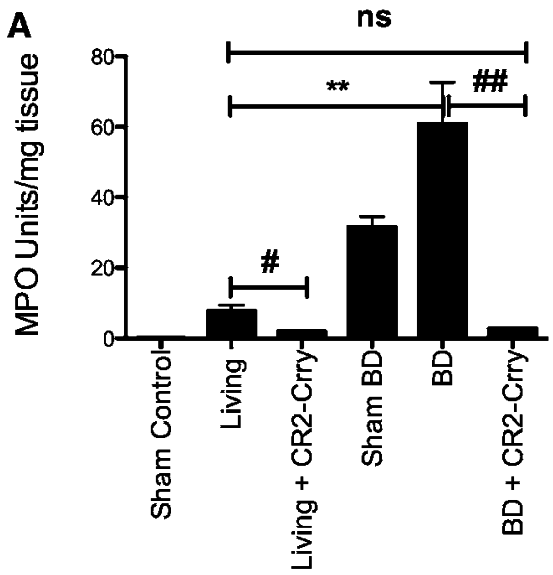


Floerchinger et al. JHLT 2012

Potential Therapeutic Strategies: Animal Models

- Treatment of recipients with a complement inhibitor reduced inflammatory cell infiltration





Atkinson et al. Circ 2013

Summary

- Brain death contributes to the recipient alloimmune response
- Specific mechanisms include:
  - Cellular infiltration
  - Inflammatory cytokine expression
  - Complement activation

Summary

- Potential therapeutic strategies investigated in animal models include:
  - Donor glucocorticoid treatment
  - Donor anti-thymocyte globulin treatment
  - Donor complement inhibitor treatment
- Additional translational and clinical investigations are needed