Stabilization of Gap and Tight Junctions Ameliorates Ischemia-Reperfusion Injury in a Porcine Model of Renal Transplantation

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BACKGROUND

- The field of transplantation continues to exhibit a significant disparity between suitable allografts and those in need of life saving organs.

- aCT1 is a novel Cx43-based peptide that has been shown to stabilize gap junctions

- Hypothesis:
Pre-treatment of a donor organ with aCT1 will stabilize gap and tight junctions during cold storage, resulting in reduced organ damage and improved quality of marginal organs.

METHODS

- Ex vivo model:
    - Procured pig kidneys as part of donor after
    cardiac/circulatory death simulated model
    - Kidneys flushed with either standard preservation
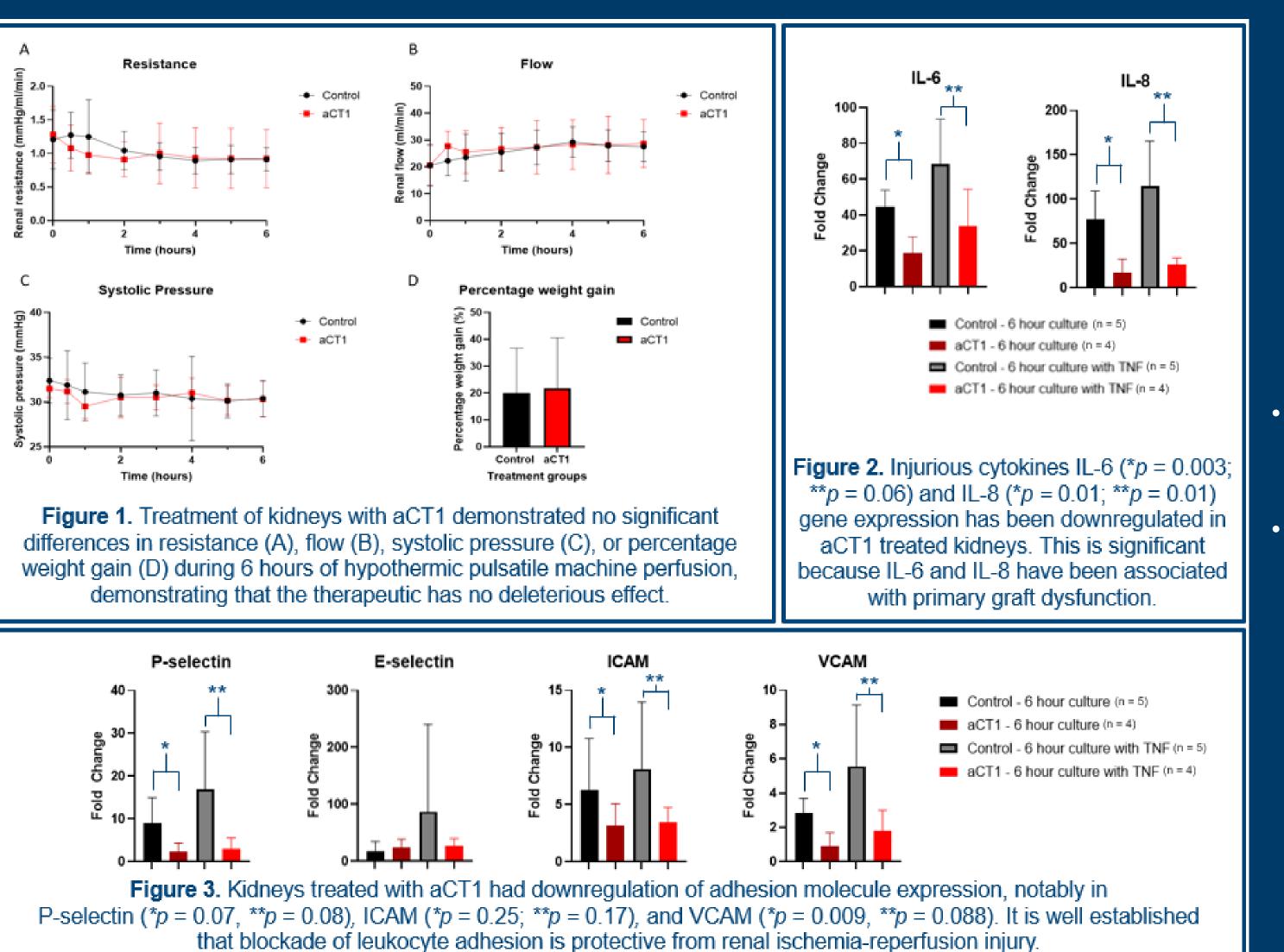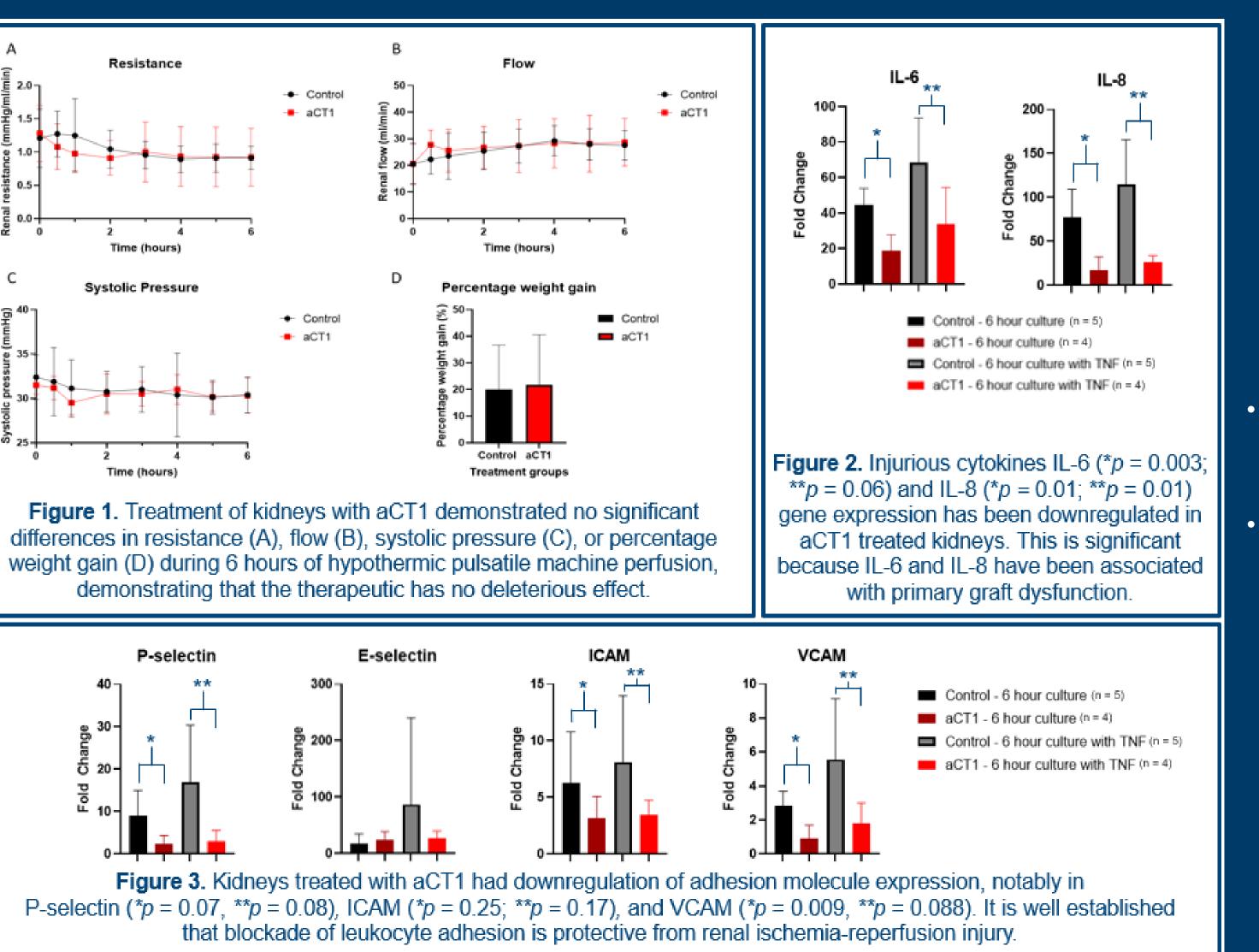   solution (Htk n=6) or Htk+aCT1 (n=4)
    - Subjected to 36 hours cold static storage
    - Hypothermic pulsatile perfusion for 6 hours
    - Biopsies taken and *ex-vivo* organ culture performed

- Evaluated:
    - Machine perfusion parameters
    - Gene expression

RESULTS

Figure 1. Treatment of kidneys with aCT1 demonstrated no significant differences in resistance (A), flow (B), systolic pressure (C), or percentage weight gain (D) during 6 hours of hypothermic pulsatile machine perfusion, demonstrating that the therapeutic has no deleterious effect.

Figure 2. Injurious cytokines IL-6 ($*p = 0.003$; $**p = 0.06$) and IL-8 ($*p = 0.01$; $**p = 0.01$) gene expression has been downregulated in aCT1 treated kidneys. This is significant because IL-6 and IL-8 have been associated with primary graft dysfunction.

Figure 3. Kidneys treated with aCT1 had downregulation of adhesion molecule expression, notably in P-selectin ($*p = 0.07$, $**p = 0.08$), ICAM ($*p = 0.25$; $**p = 0.17$), and VCAM ($*p = 0.009$, $**p = 0.088$). It is well established that blockade of leukocyte adhesion is protective from renal ischemia-reperfusion injury.

CONCLUSIONS

- Treatment with aCT1 during cold storage does not have a deleterious impact on renal grafts during pulsatile perfusion.

- Gene expression profiling of aCT1 therapy:
    - Downregulates injurious cytokine expression
    - Downregulates adhesion molecule expression

SUMMARY

- Successfully developed marginal allograft DCD porcine model

- Early results of aCT1 therapy in this model demonstrate promise. Next steps include performing porcine allograft renal transplantation using aCT1 treated kidneys.

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