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## **Regulatory dendritic cell treatment prevents the development of vasopressin-induced preeclampsia**

Sabrina M. Scroggins, PhD,<sup>1</sup> Donna A. Santillan, PhD,<sup>1</sup> Jeremy A. Sandgren, PhD,<sup>2</sup> Gary L. Pierce, PhD,<sup>3</sup> Curt D. Sigmund, PhD,<sup>2</sup> Justin L. Grobe, PhD,<sup>2</sup> Mark K. Santillan, MD, PhD,<sup>1</sup>

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The concept that persistent fetoplacental intolerance is important in the pathogenesis of preeclampsia (PE) has been demonstrated by our lab and others. Arginine vasopressin (AVP) infusion during pregnancy induces cardiovascular, renal, and immune alterations in mice consistent with human PE. These findings identify AVP as a potential contributor to poor fetal tolerance and the development of PE. In addition to their conventional immunostimulatory role, dendritic cells (DCs) also play a vital role in immune tolerance. In contrast to conventional DCs, regulatory DCs (DCregs) express

low levels of co-stimulatory markers, produce anti-inflammatory cytokines, induce T regulatory cells, and promote tolerance. In mice, DCregs are able to prevent pro-inflammatory responses and induce antigen-specific tolerance. Given these known functions of DCregs, we hypothesize that DCregs will prevent the development of AVP-induced PE.

C57BL/6J dams were infused with AVP (24 ng/hour) or saline throughout gestation via osmotic minipump. To generate DCregs, bone marrow derived cells from C57BL/6J mice were cultured with human TGF- $\beta$ 1, and murine GM-

<sup>1</sup>Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, IA

<sup>2</sup>Department of Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA

<sup>3</sup>Department of Health and Human Physiology, University of Iowa, Iowa City, IA

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Corresponding author: Mark K. Santillan, PhD, Department of Obstetrics and Gynecology, 200 Hawkins Drive, Iowa City, IA 52242. Email: [mark-santillan@uiowa.edu](mailto:mark-santillan@uiowa.edu)

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CSF and IL-10 and phenotype confirmed via flow cytometry. At the time of pump implantation or early post-placentation on gestational day (GD) 7, AVP dams received a single intravenous injection of DCregs. Blood pressure was taken throughout pregnancy and total urine protein was measured on GD 17. Maternal tissues were collected on GD 18. Cytokine concentrations were determined via commercially available ELISAs and normalized to total protein.

Treatment of AVP-infused dams with DCregs before mating (GD -3) and on GD 7 prevented AVP-induced hypertension (AVP:  $120 \pm 1.8$ , n=27 vs GD -3:  $108 \pm 3.3$ , n=7 vs GD 7:  $110 \pm 4.4$ , n=5 p<0.05) and elevations in urine protein (AVP:  $37.4 \pm 2.3$ , n=24 vs GD -3:

$25.6 \pm 2.9$ , n=7 vs GD 7:  $24.1 \pm 3.1$ , n=5 p<0.05). Treatment with DCregs also reversed AVP-induced suppression of anti-inflammatory TGF $\beta$  (AVP: 1.3, n=9 vs GD -3: 3.2, n=7 vs GD 7: 2.9, n=5 ug/g, p<0.05) in the plasma.

These data support the hypothesis that DCreg treatment prevents AVP-induced PE. It further provides evidence for the use of personalized, cellular therapy in the prevention of cardiovascular, renal, and immune alterations induced in PE.

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