

BIOGRAPHICAL SKETCH

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NAME: Boeldt, Derek

eRA COMMONS USER NAME (credential, e.g., agency login): dsboeldt

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of Wisconsin-Madison	BS	12/2005	Molecular Biology
University of Wisconsin-Madison	PHD	04/2013	Endocrinology and Reproductive Physiology
University of Wisconsin-Madison	Postdoctoral Fellow	04/2015	Translational Research
University of Wisconsin-Madison	Other training	09/2016	Assistant Scientist in Translational Research

A. Personal Statement

My proposed research plan is a reflection of my overall career goal to take fundamental discoveries regarding uterine artery endothelial function in normal and dysfunctional states from an ovine model and translate them to human cell culture and tissue models. A secondary component of this goal is to develop high throughput methods that will accelerate the drug discovery process. Our limited understanding of pregnancy-specific drug targets has long been an obstacle in pregnancy-related drug discovery, and novel high-throughput methodologies paired with a specific career focus is the way forward. This work has already yielded conclusions directly relevant to developing new therapies for preeclampsia. The first critical conclusion in this process was the key observation that growth factors and cytokines elevated in preeclamptic pregnancies induce Src kinase signaling pathways to disrupt gap junctions and so impair Ca²⁺ bursting/vasodilator production to a level equivalent to the non-pregnant state. The second conclusion is the observation that PP2 rescues pregnancy adapted function in endothelial cells exposed to growth factors and cytokines and that t10,c12 CLA (a nutraceutical Src inhibitor) had a similar rescue effect. As a result of this later work I have been named a co-inventor on a pending usage patent for t10,c12 CLA as a preeclampsia therapy. These studies have yielded numerous publications, and continue to provide potentially high impact data which is in various states of manuscript preparation and submission.

In addition to my own research pursuits, I have enjoyed working with clinical fellows and faculty on a routine basis. I was highly involved in mentorship of four maternal fetal medicine fellows and one resident in basic research, and am currently mentoring a neonatology fellow and two graduate students in my lab. As a result of these activities and mentorship of other graduate students and postdocs throughout the department of Ob/Gyn, I have received two teaching awards for peer mentorship. My commitment to work collaboratively with clinician scientists has been productive, educational, and enjoyable; and most importantly, provides for an environment where ambitious translational projects can come to fruition. The result of such collaboration between basic and clinician scientists was to establish that primary HUVEC in cell culture are a viable translational model to move our ovine UAEC model to human cell type. The combination of my understanding of cell signaling in UAEC and HUVEC models, my direct validation of t10,c12 CLA as a potential therapeutic compound, and my close relationship with clinician scientists makes me ideally suited as the researcher to continue to push our translational model for disease and rescue closer to clinical trials. This proposal will push the idea of novel endothelial-targeted preeclampsia therapies forward by expanding our pool of compounds to a 75 compound library, in addition to expanding our high-throughput functional assays from just the acute Ca²⁺ assay to include long-term monolayer resistance. This recent establishment of two new high-throughput methodologies, provide an opportunity to greatly increase screening capacity over technologies employed previously. These technologies could prove beneficial in either diagnostic or, of relevance to this proposal, therapeutic approaches or targets for dealing with obstetric disorders such as preeclampsia.

1. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. *J Endocrinol.* 2017 Jan;232(1):R27-R44. PubMed PMID: [27729465](#); PubMed Central PMCID: [PMC5115955](#).
2. Boeldt DS, Krupp J, Yi FX, Khurshid N, Shah DM, Bird IM. Positive versus negative effects of VEGF165 on Ca²⁺ signaling and NO production in human endothelial cells. *Am J Physiol Heart Circ Physiol.* 2017 Jan 1;312(1):H173-H181. PubMed PMID: [27836897](#); PubMed Central PMCID: [PMC5283913](#).
3. Boeldt DS, Grummer MA, Yi F, Magness RR, Bird IM. Phosphorylation of Ser-279/282 and Tyr-265 positions on Cx43 as possible mediators of VEGF-165 inhibition of pregnancy-adapted Ca²⁺ burst function in ovine uterine artery endothelial cells. *Mol Cell Endocrinol.* 2015 Sep 5;412:73-84. PubMed PMID: [26033246](#); PubMed Central PMCID: [PMC4516676](#).
4. Boeldt DS, Yi FX, Bird IM. eNOS activation and NO function: pregnancy adaptive programming of capacitance entry responses alters nitric oxide (NO) output in vascular endothelium--new insights into eNOS regulation through adaptive cell signaling. *J Endocrinol.* 2011 Sep;210(3):243-58. PubMed PMID: [21555345](#); PubMed Central PMCID: [PMC4059042](#).

B. Positions and Honors

Positions and Employment

2013 - 2014	Postdoctoral Research Fellow, University of Wisconsin-Madison, Dept Ob/Gyn
2014 - 2015	Research Associate, University of Wisconsin-Madison, Dept Ob/Gyn
2015 - 2016	Assistant Scientist, University of Wisconsin-Madison, Dept Ob/Gyn
2016 -	Assistant Professor, University of Wisconsin-Madison, Dept Ob/Gyn

Other Experience and Professional Memberships

2013 - 2016	Associate Member, Perinatal Research Society
2016 -	Member, Perinatal Research Society
2016 -	Junior Trainer, Endocrinology and Reproductive Physiology Graduate Training Program
2016 -	Member, University of Wisconsin Integrated Program in Endocrinology (IPEnd)
2016 -	Member, Integrated Program in Endocrinology (IPEnd)
2017 -	Member, Society for Reproductive Investigation

Honors

2008	Patent Pending, Use of 10,12 CLA isomer as an endothelial targeted therapy for preeclampsia T32 Trainee (HD041921), NIH
2009	Summer Research Conference Travel Award, FASEB Ion Channel Regulation Meeting
2010	Herman I Shapiro Distinguished Graduate Fellowship, University of Wisconsin School of Medicine and Public Health
2010	Graduate Student Peer Mentor Award, University of Wisconsin Graduate Student Collaborative
2012	Abbott Nutrition Sponsored Young Investigator - Annual Meeting, Perinatal Research Society
2012	10yr Graduate Program (ERP) Review Student Panel Member, University of Wisconsin School of Medicine and Public Health
2013	Douglas W Laube Best Trainee Paper Award, University of Wisconsin-Madison Dept Ob/Gyn
2013	Invited Trainee - Grant Writing Workshop, Perinatal Research Society
2016	Associate Member Best Paper Award (Basic Science Track), Perinatal Research Society
2016	Chester B Martin Graduate Training Program Mentorship Award, University of Wisconsin-Madison Dept Ob/Gyn
2016	Douglas W Laube Best Trainee Paper Award, University of Wisconsin-Madison Dept Ob/Gyn
2017	Top Downloaded Authors "Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia", <i>Journal of Endocrinology</i>
2018	Most Cited Papers "Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia", <i>Journal of Endocrinology</i>

C. Contribution to Science

1. **Role of Gap Junctions in Pregnancy Adaptation.** My studies in the essential role gap junctions play in uterine artery adaptation to pregnancy have paved the way for new insights into disease and avenues for treatment in the pregnant patient. These studies show that increased Connexin 43 gap junction coupling between neighboring uterine artery endothelial cells allows for increased capacity to produce vasodilators, and thus drop local vascular resistance in the uterus to shunt blood to the developing fetus.
 - a. Boeldt DS, Krupp J, Yi FX, Khurshid N, Shah DM, Bird IM. Positive versus negative effects of VEGF165 on Ca²⁺ signaling and NO production in human endothelial cells. *Am J Physiol Heart Circ Physiol.* 2017 Jan 1;312(1):H173-H181. PubMed PMID: [27836897](#); PubMed Central PMCID: [PMC5283913](#).
 - b. Boeldt DS, Grummer MA, Yi F, Magness RR, Bird IM. Phosphorylation of Ser-279/282 and Tyr-265 positions on Cx43 as possible mediators of VEGF-165 inhibition of pregnancy-adapted Ca²⁺ burst function in ovine uterine artery endothelial cells. *Mol Cell Endocrinol.* 2015 Sep 5;412:73-84. PubMed PMID: [26033246](#); PubMed Central PMCID: [PMC4516676](#).
 - c. Bird IM, Boeldt DS, Krupp J, Grummer MA, Yi FX, Magness RR. Pregnancy, programming and preeclampsia: gap junctions at the nexus of pregnancy-induced adaptation of endothelial function and endothelial adaptive failure in PE. *Curr Vasc Pharmacol.* 2013 Sep;11(5):712-29. PubMed PMID: [24063383](#).
 - d. Yi FX, Boeldt DS, Gifford SM, Sullivan JA, Grummer MA, Magness RR, Bird IM. Pregnancy enhances sustained Ca²⁺ bursts and endothelial nitric oxide synthase activation in ovine uterine artery endothelial cells through increased connexin 43 function. *Biol Reprod.* 2010 Jan;82(1):66-75. PubMed PMID: [19741206](#); PubMed Central PMCID: [PMC2802114](#).
2. **Understanding the Complex Relationship between VEGF and Ca²⁺.** I have worked extensively in characterizing VEGF signaling characteristics in uterine artery endothelial cells. The goal of this was to better understand both the essential role VEGF plays in maintaining vascular function through angiogenic and vasodilatory signaling. In certain situations, elevated levels could promote pathological vascular function. VEGF is essential in both Ca²⁺ dependent vasodilator production, but also induces signals which inhibit the ability of other Ca²⁺ mobilizing agonists to do the same. In particular, these studies examined VEGF-stimulated kinase signaling pathways (Src and ERK) which result in phosphorylations on Connexin 43 that are inhibitory to maximal function. Connexin 43 function is crucial for endothelial production of Ca²⁺ dependent vasodilators, and any reduction in function is paralleled by a reduction in vasodilator production. Further detailed studies show that doses of VEGF in the normal physiological range may promote vasodilatory signals in the endothelium, while any increase out of this range may have the opposite effect.
 - a. Boeldt DS, Krupp J, Yi FX, Khurshid N, Shah DM, Bird IM. Positive versus negative effects of VEGF165 on Ca²⁺ signaling and NO production in human endothelial cells. *Am J Physiol Heart Circ Physiol.* 2017 Jan 1;312(1):H173-H181. PubMed PMID: [27836897](#); PubMed Central PMCID: [PMC5283913](#).
 - b. Boeldt DS, Grummer MA, Yi F, Magness RR, Bird IM. Phosphorylation of Ser-279/282 and Tyr-265 positions on Cx43 as possible mediators of VEGF-165 inhibition of pregnancy-adapted Ca²⁺ burst function in ovine uterine artery endothelial cells. *Mol Cell Endocrinol.* 2015 Sep 5;412:73-84. PubMed PMID: [26033246](#); PubMed Central PMCID: [PMC4516676](#).
 - c. Boeldt DS, Grummer MA, Magness RR, Bird IM. Altered VEGF-stimulated Ca²⁺ signaling in part underlies pregnancy-adapted eNOS activity in UAEC. *J Endocrinol.* 2014 Oct;223(1):1-11. PubMed PMID: [25063757](#); PubMed Central PMCID: [PMC4161637](#).
 - d. Yi FX, Boeldt DS, Magness RR, Bird IM. [Ca²⁺]_i signaling vs. eNOS expression as determinants of NO output in uterine artery endothelium: relative roles in pregnancy adaptation and reversal by VEGF165. *Am J Physiol Heart Circ Physiol.* 2011 Apr;300(4):H1182-93. PubMed PMID: [21239633](#); PubMed Central PMCID: [PMC3075018](#).

3. **Translation of Ovine Cell Culture Model of Preeclampsia to Human.** My post-doctoral work focused in large part on translation of the ovine UAEC model to human by utilizing a primary HUVEC culture model. This key translational step allows us to study the concepts worked up in detail in an ovine model, but now in a human context. This step was critical for us to go from basic science to novel drug discovery, setting the stage for future clinical trials.
 - a. Boeldt DS, Krupp J, Yi FX, Khurshid N, Shah DM, Bird IM. Positive versus negative effects of VEGF165 on Ca²⁺ signaling and NO production in human endothelial cells. *Am J Physiol Heart Circ Physiol.* 2017 Jan 1;312(1):H173-H181. PubMed PMID: [27836897](#); PubMed Central PMCID: [PMC5283913](#).
 - b. Anaya HA, Yi FX, Boeldt DS, Krupp J, Grummer MA, Shah DM, Bird IM. Changes in Ca²⁺ Signaling and Nitric Oxide Output by Human Umbilical Vein Endothelium in Diabetic and Gestational Diabetic Pregnancies. *Biol Reprod.* 2015 Sep;93(3):60. PubMed PMID: [26203178](#); PubMed Central PMCID: [PMC4710185](#).
 - c. Boeldt DS, Hankes AC, Alvarez RE, Khurshid N, Balistreri M, Grummer MA, Yi F, Bird IM. Pregnancy programming and preeclampsia: identifying a human endothelial model to study pregnancy-adapted endothelial function and endothelial adaptive failure in preeclamptic subjects. *Adv Exp Med Biol.* 2014;814:27-47. PubMed PMID: [25015799](#).
 - d. Krupp J, Boeldt DS, Yi FX, Grummer MA, Bankowski Anaya HA, Shah DM, Bird IM. The loss of sustained Ca(2+) signaling underlies suppressed endothelial nitric oxide production in preeclamptic pregnancies: implications for new therapy. *Am J Physiol Heart Circ Physiol.* 2013 Oct 1;305(7):H969-79. PubMed PMID: [23893163](#); PubMed Central PMCID: [PMC3798749](#).
4. **High Throughput Assay Development for Endothelial-Targeted Therapy Discovery.** While high throughput assays are commonly used on endothelium, few are useful for high-confluence, extended kinetic studies. Thus, the development of high throughput techniques to study sustained Ca²⁺ signaling and endothelial cell monolayer integrity in high-density primary endothelial cell cultures allows us to now more rapidly screen an endothelial cell model of preeclampsia for potential therapies. It also allows a platform for understanding the effect of complex interactions between multiple circulating factors associated with preeclampsia such that we can continue to refine our models of the disease.
5. **t10,c12 CLA as a Potentially Novel Endothelial-Targeted Therapy for Preeclampsia.** The first experiments on 10,12 CLA as a potential novel endothelial-targeted therapeutic for preeclampsia were done in the ovine model. We have since applied for a usage patent and furthered our basic understanding of function of 10,12 CLA in both sheep and human. We have recently published a full dose response in sheep cells on the efficacy of 10,12 CLA to rescue sustained Ca²⁺ bursts after VEGF pretreatment. The discovery of the potential therapeutic properties of 10,12 CLA in preeclampsia is even more impactful due to the fact that therapeutic doses can be achieved through diet modification alone, reducing the chances of unforeseen side effects on mother or fetus.
 - a. Ampey AC, Boeldt DS, Clemente L, Grummer MA, Yi F, Magness RR, Bird IM. TNF-alpha inhibits pregnancy-adapted Ca²⁺ signaling in uterine artery endothelial cells. *Mol Cell Endocrinol.* 2019 May 15;488:14-24. PubMed PMID: [30779937](#); PubMed Central PMCID: [PMC6475486](#).
 - b. Boeldt DS, Grummer MA, Yi F, Magness RR, Bird IM. Phosphorylation of Ser-279/282 and Tyr-265 positions on Cx43 as possible mediators of VEGF-165 inhibition of pregnancy-adapted Ca²⁺ burst function in ovine uterine artery endothelial cells. *Mol Cell Endocrinol.* 2015 Sep 5;412:73-84. PubMed PMID: [26033246](#); PubMed Central PMCID: [PMC4516676](#).

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Fall Competition, WARF

Boeldt, Derek (PI)

07/01/19-06/30/20

Mapping Immune Cell-Endothelial Cell Interactions in Preeclamptic Pregnancies

Wisconsin Alumni Research Foundation funding for 1 calendar year supporting the studies of Aishwarya Rengarajan including support for Research Assistant stipend, tuition, fringe benefits, and supplies. Total award \$46,637.

Role: PI

Completed Research Support

R03 HD079865-01A1, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Boeldt, Derek S (PI)

04/01/15-03/31/17

High Throughput Strategies for Preeclampsia Therapy

Role: PI

PRJ79VW, UW-Madison Environmental Health Center

Boeldt, Derek (PI)

01/01/14-06/30/14

Screening Toxins Impacting on Ca²⁺ Signaling in Endothelial Cells

UW-Madison Toxicology Center project development for studies in environmental toxicology award made to Faculty and Postdoc CoPI Teams.

Role: CPI

UL1TR000427, UW-Madison Institute for Clinical and Translational Research

Boeldt, Derek (PI)

08/07/13-01/07/14

High Throughput Screening of CLA Isoforms as a Novel Therapy for Preeclampsia

UW-Madison Institute of Clinical and Translational Research support for use of equipment and supplies to be used in highly clinically relevant basic research aimed at translating discovery into therapy.

Role: PI

2010, UW-Madison School of Medicine and Public Health

Boeldt, Derek (PI)

09/01/10-08/31/11

Herman I. Shapiro Distinguished Graduate Fellowship

Stipend support for graduate training in the field of hypertension with an emphasis on translational research.

Role: PI