BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

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.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin-Madsion	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 based on a recurring problem with studying and discussing the role of VEGF in pregnancy and preeclampsia. The uncertainty about how much bioavailable VEGF is present throughout gestation and what functional consequences may be linked to changes in VEGF is currently making meaningful dialogue within the field far too difficult. Therefore, innovations which may benefit many preeclamptic pregnancies by targeting circulating VEGF and VEGF signaling are slow to develop and translate to human therapy. Part of the problem is that specific functional goals are often hard to come by for lack of comprehensive data. My training in endothelial cell biology and VEGF signaling in healthy and diseased pregnancies makes me well suited to undertake the proposed studies to begin addressing some of these persistent issues. Some of the work that has come from this training has led to a more robust understanding of the myriad roles VEGF signaling plays in regulating endothelial cell function. Recently we have shown that in addition to the promotion of angiogenesis and vasodilator production responses downstream of VEGFR2 activation, VEGF165 can block vasodilator production to other agonists in certain conditions which may be occurring in preeclamptic pregnancies. This is due to inhibition of sustained Ca2+ signaling via phosphorylation of specific residues on gap junction proteins, and may result in lower vasodilator production in total. It is therefore not sufficient to only consider angiogenesis and direct vasodilator production when considering the role of VEGF in pregnancy and preeclampsia. In this proposal we look at VEGF signaling in detail and take a more inclusive approach to understanding the functional implications of changing states of VEGF bioavailability. 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 three maternal fetal medicine fellows and one resident in basic research, am currently working with a fourth fellow, and will be mentoring a neonatology fellow beginning in the fall of 2016. As a result of these activities and mentorship of graduate students and postdocs throughout the department of Ob/Gyn, I have received two teaching awards for peer mentorship. 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. From a career development perspective, my long-term goal is to develop my independent and impactful research career as a new tenure-track faculty member, specializing in regulation of endothelial cell-cell junctions, translational models for obstetric diseases, and high-throughput screening for therapeutic compounds. My 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 to dealing with obstetric disorders such as preeclampsia. 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.

Key Publications (of 12).

1. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2016 Oct 11;PubMed PMID: 27729465.
2. 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.
3. 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.
4. Boeldt DS, Yi FX, Bird IM. eNOS activation and NO function: pregnancy adaptive programming of capacitative 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-Madsion, 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

Honors

	Patent Pending, Use of 10,12 CLA isomer as an endothelial targeted therapy for preelcampsia
2008	T32 Trainee (HD041921), NIH
2009	Summer Reserach 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 - Anual 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 Socieity
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

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, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2016 Oct 11;PubMed PMID: 27729465.
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. 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.
b. 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.
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. 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.

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, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2016 Oct 11;PubMed PMID: 27729465.

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 t10,c12 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 t10,c12 CLA in both sheep and human. We have recently published a full dose response in sheep cells on the efficacy of t10,c12 CLA to rescue sustained Ca2+ bursts after VEGF pretreatment. The discovery of the potential therapeutic properties of t10,c12 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. 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. Research Support

Ongoing Research Support

R03 HD079865-01A1
Boeldt, Derek S (PI)
04/01/15-03/31/17
High Throughput Strategies for Preeclampsia Therapy
Role: PI

Completed Research Support

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 Istitute 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