Name: Rachel (Lane) Dahn

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Major Professor: Ian Bird

Degree Objective: PhD, Endocrinology and Reproductive Physiology

Background: BS Biology and Animal Science, University of Findlay

Current Research Project: Pregnancy specific adaptations of vascular endothelial function occur during normal pregnancy, and the associated increase in vasodilation supports increased blood flow to the utero-placental unit. How this happens and the consequences when these adaptations fail has been documented and studied over the last 20 years by the Bird lab. Preeclampsia (PE) is one such disease state in pregnant women marked by hypertension, proteinuria, and edema. While in normal pregnancy, the body is in a state of inflammation, this normal increase in the growth factors and cytokines in circulation promotes angiogenesis, the other aspect of increased blood flow to the uterus. In PE, the growth factors and cytokines become so elevated that the endocrine profile in the utero-placental unit appears to be more like that of a wound. There are also two different types of wounding endocrinology; healing wounding and non-healing wounding. Preeclamptic patients exhibit growth factor and cytokine profiles more like non-healing wounding. PE is also particularly associated local uteroplacental production of VEGF, TNF and a variety of interleukins. Acutely, this promotes endothelial dysfunction initially by kinase mediated Cx43 closure between cells and reducing sustained phase Ca^{2+} signaling in uterine artery endothelial cells (UAEC). This reduction in Ca^{2+} bursting potential results in a decrease in the activation of endothelial nitric oxide synthase (eNOS), and a fall in circulating NO in pregnancy is known to associate with hypertension. Longer term, the endothelial monolayer is a barrier that is essential to maintain in healthy pregnancy. The longer term effect of elevated TNF in particular results in monolayer breakdown, and it can lead to a cascade of events leading to increased vascular permeability, consistent with increased edema commonly seen in PE subjects. The goal of my project is to build upon recent data implication of both Src and ERK kinases as mediators of these negative effects of growth factors and particularly cytokines on endothelial Cx43 gap junction function and also longer term on cell-cell connectivity. While Src and Erk are clearly implicated, the exact nature of the response still needs to be determined. Inhibition of Src and ERK in part restore endothelial function, but they do not fully restore endothelial monolayer integrity. There are clearly other signaling pathways yet to be identified. My initial work has involved fleshing out the role of p38MAPK in combination with both Src and ERK kinases on endothelial monolayer function. As I complete identifying the missing players, we propose now to expand our focus on the actions of TNF in combination with IL6, because it predicts IUGR in more severe PE subjects and we know it can interact at the level of signaling with TNF effects. Our hope is that we will then better understand this diseased state, and the specific endocrine factors and cell signaling mechanisms involved in causing endothelial damage. Long term we hope to identify the specific growth factors and cytokines involved and how they converge their cell signaling events so we can then identify drugs that may block their destructive effects.

Grants Received:

2019-20. Award to R Dahn. T32. Ruth L. Kirschstein National Research Service Award training grant (T32 HD041921-17). PI Ian Bird.

Ruth L. Kirschstein National Research Service Award training grant awarded to the Endocrine & Reproductive Physiology (ERP) Program by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), a pre-doctoral traineeship through the Endocrinology-Reproductive Physiology Training Grant. Training grant has the opportunity of a one year renewal.

2017-19. Award to R Lane. R25. Training and Education to Advance Minorities in Science (TEAM-Science). PI Molly Carnes.

The overall goal of the TEAM-Science Program is to develop a diverse biomedical and behavioral research workforce. In addition to increasing the numbers of URM and SWD students awarded doctorates in biomedical or behavioral disciplines, the TEAM-Science program aims to initiate enduring changes in the approach to recruitment, retention, and academic career development of graduate students at UW.

National Presentations:

Poster Presentation: Dahn RL, Clemente L, Ampey AC, Austin JL, Bird IM. (2019) Src and ERK are not the only Mediators of Endothelial Dysfunction; p38MAPK also Regulates Pregnancy-Derived Uterine Artery Endothelial Monolayers. Society Reproductive Investigation - Annual Meeting, Paris, France. Abstract LB-049.

Other Presentations:

Oral Presentation: Dahn RL, Clemente L, Ampey AC, Austin JL, Bird IM. (2019) Src and ERK are not the only Mediators of Endothelial Dysfunction; p38MAPK also Regulates Pregnancy-Derived Uterine Artery Endothelial Monolayers. Madison Scholars Symposium May 8, 2019

Poster Presentation: Dahn RL, Clemente L, Ampey AC, Austin JL, Bird IM. (2019) Src and ERK are not the only Mediators of Endothelial Dysfunction; p38MAPK also Regulates Pregnancy-Derived Uterine Artery Endothelial Monolayers. Endocrinology Reproductive Physiology Symposium April 18, 2019.

Oral Presentation: Dahn RL, Clemente L, Ampey AC, Austin JL, Bird IM. (2018) Investigating Endothelial Dysfunction in Preeclampsia. Endocrinology Reproductive Physiology Seminar Dec 6, 2018.

ERP Service:

Acted as an ERP ambassador for the very first Madison Scholars Science of Aging Symposium. I assisted at the event, and volunteered as one of the speakers for this new symposium representing programs blessed with T32 funding. This will hopefully turn into an annual event and serve as a symbol of gratitude and progress marker to show NIH how UW-Madison T32 programs are thriving.