BIOGRAPHICAL SKETCH

NAME: Conrad, Kirk P.

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

POSITION TITLE: Professor, University of Florida College of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Bowdoin College, Brunswick, ME	BA	1977	Biochemistry
Dartmouth Medical School, Hanover, NH	MD	1980	Medicine
University of Colorado Health Sciences Center, Denver, CO	Medical Intern	1980-1981	Medicine
Dartmouth Medical School, Hanover, NH	Postdoctoral Fellow (Heinz Valtin MD)	1981-1984	Renal Physiology
Case Western Reserve University, Cleveland, OH	Visiting Instructor/ Postdoctoral Fellow (Michael Dunn MD)	1985-1987	Renal/Cell Physiology

A. Personal Statement: I have longstanding research interest in several areas of Reproductive & Perinatal Biology: mechanisms underlying maternal vasodilation and increased arterial compliance during normal pregnancy with emphasis on the ovarian hormone relaxin and underlying vascular molecular mechanisms; maternal cardiovascular and renal adaptations to pregnancy in women conceiving by Assisted Reproductive Technologies (ART), as well as the perinatal outcomes of ART; the role of decidualization and trophoblast in the etiology and pathogenesis of preeclampsia and intrauterine growth restriction. I have combined preclinical and clinical research successfully throughout my career to translate our discoveries in animal models, tissues and cells to humans or vice versa. To this end, our work has provided major scientific motivation for the potential therapeutic use of relaxin in heart failure, renal disease, preeclampsia and bone fracture healing.

B. Positions and honors

Positions and Employment

1984-1990 Assistant Professor, Department of Physiology, Dartmouth Med Sch, Hanover, NH

1990-1992 Assistant Professor, Departments of Physiology and of Ob/Gyn, University of New Mexico School of Medicine, Albuquerque, NM

1992-1994 Associate Professor, Departments of Physiology and of Ob/Gyn, University of New Mexico School of Medicine, Albuquerque, NM

1994-1999 Associate Professor, Department of Ob/Gyn and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA

1996-2006 Tenure Status, Department of Ob/Gyn and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA

1996-1999 Associate Professor (Secondary Appointment), Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA

2000-2006 Professor (Primary Appointment) Department of Ob/Gyn and Reproductive Sciences, and Professor (Secondary Appointment) Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA

2000-2003 Member, NIH Human Embryology and Development Study Section-1

2004 Sabbatical Leave, Honorary Fellow Department of Zoology, University of Melbourne, Parkville, Victoria, Australia, Jan-July.

2006- Professor (with Tenure) Department of Physiology and Functional Genomics, University of Florida College of Medicine, Gainesville, FL
2007- Professor (secondary appointment) Department of Ob/Gyn, University of Florida COM
2007-2010 Council Member, Society for Gynecological Investigation
2010-2014 Secretary Treasurer, Society for Gynecological Investigation

Honors and Awards

1976 James Bowdon Honor Society
1977 Magna Cum Laude
1979 Alpha Omega Alpha Honor Society
1980 Good Physicians Award (Dartmouth Medical School)
1985-1990 Physician Scientist Award, K11 HD00662
1988-1993 8th Mallinckrodt Scholar Award
1990 Outstanding Teacher Award in the Basic Sciences
1991-1994 Flinn Newly Independent Investigator Award (American Heart Association)
1993 Basic Medical Sciences Teaching Award presented by UNM Sch. of Medicine Graduates
1995-1999 Research Career Development Award, KO4 HD01098
2010 Ernest H. Starling Distinguished Lectureship of the American Physiological Society Water & Electrolyte Homeostasis Section
2010 Senior Faculty Research Award for the University of Florida Chapter of Sigma Xi
2010 Sir William Liley Lectureship, Perinatal Research Society
2012 Dutch Heart Foundation Lecture
2013, 2014 Exemplary Teacher Award University of Florida College of Medicine
2016 J. Robert and Mary Cade Professor of Physiology

C. Contribution to Science (*examples guided by more highly cited works in Web of Science as of 2016)

1. Early career work focused on validating the chronically instrumented gravid rat as a model for human systemic and renal maternal adaptations to pregnancy, which are epitomized by massive vasodilation **(1, 2)**. After demonstrating that the conscious gravid rat manifests circulatory changes during pregnancy similar to women, this animal model was used to address the major hypothesis at the time that vasodilatory prostaglandins were responsible. After 3 years of work, the hypothesis was unsupported **(3)**. These negative results set the stage to investigate a new and exciting vasodilatory substance in this context, endothelium-derived relaxin factor or nitric oxide (NO). Indeed, the metabolic production of the major second messenger of NO, cGMP, was markedly enhanced during rat gestation **(4)**. A major change in phosphoinositide metabolism was also discovered in the vasculature of gravid rats **(5).**

(1) **Conrad K.P.** Renal hemodynamics during pregnancy in chronically catheterized, conscious rats. Kidney Int. 26:24-29,1984 (*114). PMID: 6332938.

(2) Gilson G.J., Mosher M.D. and **Conrad K.P.** Systemic hemodynamics and oxygen transport during pregnancy in chronically instrumented, conscious rats. Am. J. Physiol. 263: H1911-H1918, 1992 (*79). PMID: 1481914.

(3) **Conrad K.P.** and Colpoys M.C. Evidence against the hypothesis that prostaglandins are the vasodepressor agents of pregnancy. Serial studies in conscious rats. J. Clin. Invest. 77: 236-245, 1986 (*142). PMID: 3944253.

(4) **Conrad K.P.** and Vernier K.A. Plasma level, urinary excretion and metabolic production of cGMP during gestation in rats. Am. J. Physiol. 257: R847-R853, 1989 (*135). PMID: 2552845.

(5) **Conrad K.P.,** Barrera SA, Friedman PA and Schmidt VM. Evidence for attenuation of myo-inositol uptake, phosphoinositide turnover and inositol phosphate production in aortic vasculature of rats during pregnancy. J. Clin. Invest. 87:1700-1709, 1991 (*29). PMID:1850759.

(6) ***Pertinent Review.*** **Conrad K.P.** Possible mechanisms for changes in renal hemodynamics during pregnancy: studies from animal models. Am. J. Kidney Diseases 9:253-259, 1987. (*50). PMID: 3554994.

2. Subsequently, increased NO production was discovered in rat gestation **(1)**. A functional role for NO in the gestational renal vasodilation and hyperfiltration was then demonstrated in the conscious rat **(2)**, and endothelial ET_B receptor signaling was shown to mediate the increased NO **(3)**. Interestingly, although

strong evidence for increased cGMP production was also obtained in human pregnancy, whether NO biosynthesis also increased was unclear **(4)**. However, it seems likely that circulating and urinary products of NO metabolism may not necessarily accurately reflect local production by arterioles, the latter determining blood flow.

(1) **Conrad K.P.**, Joffe G.M., Kruszyna H., Kruszyna R., Rochelle L.G., Smith R.P., Chavez J.E. and Mosher M.D. Identification of increased nitric oxide biosynthesis during pregnancy in rats. FASEB J. 7:566-571,1993 (*371). PMID: 7682524.

(2) Danielson L.A. and **Conrad K.P.** Acute blockade of nitric oxide synthase inhibits renal vasodilation and hyperfiltration during pregnancy in conscious rats. J. Clin. Invest. 96:482-490,1995 (*120). PMID: 7542284

(3) **Conrad K.P.**, Gandley R.E., Ogawa T., Nakanishi S. and Danielson L.A. Endothelin mediates renal vasodilation and hyperfiltration during pregnancy in chronically instrumented conscious rats. Am. J. Physiol. 276: F767-F776, 1999 (*60). PMID: 7542284

(4) **Conrad K.P.**, Kerchner L.J. and Mosher M.D. Plasma and 24-hour urinary NOx and cGMP in normal pregnancy and preeclampsia in women on a reduced-NOx diet. Am. J. Physiol. 277: F48-F57, 1999 (*74). PMID:10409297.

(5) ***Pertinent Review:*** Sladek S.M., Magness R.R. and **Conrad K.P.** Nitric oxide and pregnancy. Am. J. Physiol. 272 (Regulatory Integrative Comp. Physiol. 41): R441-R463, 1997. (*294). PMID: 9124465.

3. Next, the potential reproductive hormones that mediate the dramatic maternal circulatory changes of pregnancy including the increase in global arterial compliance were investigated in the gravid rat model. Based mainly on the coincidence in the pattern of change of both circulating relaxin and the systemic and renal hemodynamic adaptations during human pregnancy, we mainly focused on this ovarian hormone. To make a long story short, administration of relaxin to conscious, nonpregnant rats recapitulated the circulatory (and osmoregulatory) changes of pregnancy **(1)**; moreover, immunoneutralization or elimination of circulating relaxin in midterm pregnant rats inhibited the circulatory (and osmoregulatory) changes of pregnancy **(2)**. Based on studies in conscious rats and isolated renal arteries from rats and mice, as well as subcutaneous arteries from humans, the long-term (hours to days) vasodilatory responses to relaxin are mediated by arterial-derived VEGF/PlGF, MMP-2 or -9, endothelial ET_B receptor activation and NO **(3, 4)**.

(1) Danielson L.A. Sherwood O.D. and **Conrad K.P.** Relaxin is a potent renal vasodilator in conscious rats. J. Clin. Invest. 103:525-533,1999 (*161). PMID: 10021461.

(2) Novak J., Danielson L.A., Kerchner L.A., Sherwood O.D., Ramirez R.J., Moalli P.A. and **Conrad K.P.** Relaxin is essential for renal vasodilation during pregnancy in conscious rats. J. Clin. Invest. 107:1469-1475, 2001 (*123). PMID: 11390429.

(3) Jeyabalan A., Novak J., Danielson L.A., Kerchner L.J., Opett S.L. and **Conrad K.P.** Essential role for vascular gelatinase activity in relaxin-induced renal vasodilation, hyperfiltration, and reduced myogenic reactivity of small arteries. Circ. Res. 93:1249-1257, 2003 (*84). PMID: 14593002.

(4) McGuane J.T., Danielson L.A., Debrah J.E., Rubin J.P., Novak J. and **Conrad K.P.** Angiogenic growth factors are new players in the sustained relaxin vasodilatory pathway in rodents and humans. Hypertension 57:1151-60, 2011 (*35). PMID: 21536992.

(5) ***Pertinent Review:*** **Conrad K.P.** and Novak J. The emerging role of relaxin in renal and cardiovascular function. Am. J. Physiol. 287: R250-R261, 2004 (*94). PMID: 15271674.

4. Though more limited, evidence from our group and other investigators shows that the impact of relaxin on the renal and systemic circulations in humans is comparable to the rat model **(1)**, thus motivating the investigation of the hormone in heart failure **(2, 3)** and our current Program Project Grant HD065647 titled "Corpus luteal contributions to maternal circulatory physiology and outcomes in assisted reproductive technologies." Currently relaxin is in a phase IIIB trial for acute heart failure with an interim analysis expected in late 2015. Importantly, the circulatory effects of relaxin are sex independent, most likely due to the existence of a local, arterial-derived relaxin-ligand receptor system **(4)**.

(1) ***Pertinent Review:*** **Conrad K.P.** 2010 Ernest H. Starling Lectureship. Maternal vasodilation in pregnancy: the emerging role of relaxin. Am J Physiol. 301: R267-275, 2011(*47). PMID: 21613576.

(2) 2004 U.S. Patent Application Serial No. 10/819,039 for Use of Relaxin to Treat Diseases Related to Vasoconstriction. **Primary Inventor: Conrad KP.**

(3) 2005 U.S. Patent Application No. 11/084,670 Use of Relaxin to Increase Arterial Compliance. **Co-Inventors: Conrad KP and Shroff SG.**

(4) Novak J., Parry L.J., Matthews J., Kerchner L.J., Indovina K., Hanley-Yanez K., Doty K.D., Debrah D.O., Shroff S.G. and **Conrad K.P.** Evidence for local relaxin ligand-receptor expression and function in arteries. FASEB J. 20: 2352-62, 2006 (*51). PMID: 17077312.

5. Research was expanded to include the human placenta.

a. Our studies of delivered placentas from women with preeclampsia when I realized that molecular signatures were likely to reflect as much or more consequence than cause of the disease. For example, we investigated Hypoxia Inducible transcription factors (HIFα) in the human placenta during normal development **(1)**, in preeclampsia and normotensive IUGR. HIFα and downstream genes were clearly increased in the former **(2)**, but not in the latter **(3)**. Based on these studies of delivered placentas, however, it was not possible to ascertain whether inappropriately elevated HIFα in the first trimester may have contributed to the etiology of preeclampsia, which is widely believed to begin in early gestation. Therefore, we collected early placentas (chorionic villous samples of ~11.5 gestational weeks) in women who experienced a normal pregnancy or severe preeclampsia 6 months later, and subjected the samples to DNA microarray analysis. To our surprise, rather than reflecting HIFα activation, a major molecular signature of impaired (pre-)decidualization emerged including deficient NK cell number and/or function **(4,5)**.

(1) Rajakumar A.R. and **Conrad K.P.** Expression, ontogeny and regulation of hypoxia inducible transcription factors in the human placenta. Biol. Reprod. 63:559-569, 2000 (*93). PMID: 10906065.

(2) Rajakumar A., Brandon H.M., Daftary A., Ness R. and **Conrad K.P.** Evidence for the functional activity of hypoxia inducible transcription factors overexpressed in preeclamptic placentae. Placenta 25:763-9, 2004 (*94). PMID: 15451190.

(3) Rajakumar A., Jeyabalan A., Markovic N., Ness R., Gilmore C. and **Conrad K.P.** Placental HIF-1α, HIF-2α, membrane and soluble VEGF receptor-1 proteins are not increased in normotensive pregnancies complicated by late onset intrauterine growth restriction. Am. J. Physiol. 293: R766-74, 2007 (*28). PMID: 17507435.

(4) Founds S.A., Conley Y.P., Lyons-Weiler J.F., Jeyabalan A., Hogge W.A. and **Conrad K.P.** Altered global gene expression in first trimester placentas of women destined to develop preeclampsia. Placenta 30: 15-24, 2009 (*104). PMID: 19027158.

(5) Rabaglino MB, Post Uiterweer ED, Jeyabalan A, Hogge WA, and **Conrad KP.** A bioinformatics approach reveals evidence for impaired endometrial maturation before and during early pregnancy in women who developed preeclampsia. Hypertension 65:421-429, 2015 (*7). PMID: 25421975.

b. The syncytiotrophoblast and extravillous trophoblast were shown to highly express NO synthase mRNA and protein **(1, 2)**.

c. Villous explants cultured under hypoxic conditions were demonstrated to increase production of pro-inflammatory cytokines **(3)**. Further, increased circulating levels of pro-inflammatory cytokines were observed in women with preeclampsia contributing to endothelial dysfunction **(4)**. Ironically, however, the placenta was not the major source **(5)**, and most likely, the pro-inflammatory cytokines originated from activated leukocytes and endothelium.

d. We demonstrated expression of another cytokine, erythropoietin **(6)** and its receptor by the trophoblast.

(1) Conrad K.P., Vill M., McGuire P.G., Dail W.G. and Davis A.K. Expression of nitric oxide synthase by syncytiotrophoblast in human placental villi. FASEB J. 7:1269-1276,1993 (*138). PMID: 7691671.

(2) Martin D. and **Conrad K.P.** Expression of endothelial nitric oxide synthase by extravillous trophoblast cell in the human placenta. Placenta 21:23-3, 2000 (*43). PMID: 10692247.

(3) Benyo D.F., Miles T.M. and **Conrad K.P.** Hypoxia stimulates cytokine production by villous explants from the human placenta. J. Clin. Endocrinol. Metab. 82:1582-1588,1997 (*190). PMID: 9141553.

(4) Conrad K.P., Miles T.M. and Benyo D.F. Circulating levels of cytokines in women with preeclampsia. Am. J. Reprod. Immunol. 40:102-111,1998 (*271). PMID: 9764352.

(5) Benyo D.F., Smarason A., Redman C.W.G., Sims C. and **Conrad K.P.** Expression of inflammatory cytokines in placentas from women with preeclampsia. J. Clin. Endocrinol. Metab. 86:2505-2512, 2001 (*220). PMID: 11397847

(6) Conrad K.P., Benyo D.F., Westerhausen-Larson A. and Miles T.M. Expression of erythropoietin by the human placenta. FASEB J. 10:760-768,1996 (*91). PMID: 8635693.
(7*) Pertinent Review:* Conrad K.P. and Benyo D.F. Placental cytokines and the pathogenesis of preeclampsia. Am. J. Reprod. Immunol. 37:240-249, 1997 (*294). PMID: 9127646

Click for a full list of publications in:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1TUh93lYilukr/bibliography/43109883/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

• **5P01HD065647** 09/27/2011-02/28/2017 with mid-project extension
NIH/NICHD
Corpus Luteal Contribution to Maternal Pregnancy Physiology and Outcomes in ART
Role: PD/PI
The Program Project will investigate the corpus luteal contribution to maternal pregnancy physiology and outcomes in ART using fundamental, clinical, and epidemiological approaches. Its successful completion will provide novel and groundbreaking insights into the maternal physiology of ART and spontaneously conceived pregnancies, as well as the adverse pregnancy outcomes of ART. We expect that it will also facilitate the translation of this newly gained knowledge to improving clinical practice.

• **CRLX030AUSNC06T** 05/15/2014-12/31/2016
Novartis Pharmaceuticals Corp
Unveiling Novel Signaling mechanisms of Serelaxin in Vasculature
Role: PI
The purpose of this project is to elucidate: the cellular localization of the relaxin receptor, RXFP1, in the vascular wall that s relevant to “sustained” arterial vasodilation by Serelaxin; the cellular basis for attenuation of angiotensin II contraction by Serelaxin; the mechanism underlying the unexpected preserved vasodilation of Serelaxin in the setting of endothelial dysfunction or denudation.

• **USAMRMC PR140949** 04/01/15-09/30/17 (NCE)
Discovery Award Proposal
Role: PI
Potential Therapeutic Use of Relaxin in Healing Cranial Bone Defects
The purpose of this project is to test whether the many salutary actions of relaxin to improve blood flow will accelerate bone fracture healing in a preclinical mouse model.

• **UF COM Matching Funds** 09/27/11-02/28/17
5P01HD065647
Role: PD/PI

• **UF COM Matching Bridge Funds** 07/01/14-06/30/17
Endometrial Antecedents or Preeclampsia
Role: PD/PI

Recently Completed Research Support

• R21 HL093605 07/01/09-06/30/13 (NCE)
Mechanisms of vasodilation by relaxin
Role: PI

• RO1 HL067937-09 09/01/06-03/31/12 (NCE)
Endogenous Relaxin Regulates Vascular Function in Nonpregnant Females and Males
Role: PI