BIOGRAPHICAL SKETCH
Senior Trainer

NAME: Kling, Pamela

eRA COMMONS USER NAME (agency login): PKLING

POSITION TITLE: Professor with Tenure

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 Iowa, Iowa City, IA	BS	05/1981	Medical Technology
University of Iowa, Iowa City, IA	MD	05/1985	Medicine
University of Wisconsin, Madison, WI	Resident	06/1988	Pediatrics
University of Wisconsin, Madison, WI	Resident	06/1989	Pediatrics Chief Resident
University of Iowa, Iowa City, IA	Fellow	06/1992	Neonatology/Nutrition

A. PROJECT NARRATIVE/PERSONAL STATEMENT

I am a physician-scientist in UW's School of Medicine & Public Health (SMPH), with an independent research program since 1992. I fully support this NICHD T32 application. I have served as a research mentor for both MD and PhD postdoctoral trainees. I currently teach professional development to MD Neonatology Fellowship postdoctoral trainees. I also serve as the Director of Health Professions Student Research and Chair of the Medical Student Research Committee in the SMPH. I recently completed mentorship training sponsored by the Perinatal Research Society and two trainings sponsored by the National Research Mentoring Network (NRMN), including training in the NRMN Facilitating Entering Research Workshop and with access to expertise and curriculum developed by UW Center for the Improvement of Mentored Experiences in Research (CIMER) and Wisconsin Center for Education Research (WCER). This very exciting proposal can leverage the evidence-based, yet adaptable curriculum for postdoctoral researchers and their mentors to deal with complex, advanced concepts research ethics, scientific writing, publishing, grant writing, and mentoring relationships. As a researcher, this grant mechanism will foster clinical and research postdoctoral trainees in cross-disciplinary endocrinological developmental biology research collaboration. My participation in the Endocrinology Reproductive Physiology graduate program has exposed me to high quality research at UW-Madison. I believe that basic scientists, physician-scientists, and physicians working together will produce the highest quality science. What I bring to the table is my expertise in translational research relating to fetal erythropoiesis, nutrition, and renal development in high-pregnancies complicated by poor access to medical care, intrauterine growth restriction, diabetes, and iron deficiency. The diverse fetal exposures to maternal illness have a common thread, deficiency of iron, a key nutrient in cell division that impacts multiple organ systems, including brain and kidney development. I have expertise in collecting cord blood and followed human birth cohorts for several years, gathering ongoing data examining the developmental origins of human adult disease.

B. POSITIONS AND HONORS

Positions and Employment

1992 - 1998	Assistant Professor, University of Arizona, Pediatrics, Tucson, AZ
1998 - 2002	Associate Professor with Tenure, University of Arizona, Pediatrics, Tucson, AZ
2002 - 2007	Assistant Professor, University of Wisconsin, Pediatrics, Madison, WI
2007 - 2012	Associate Professor with Tenure, University of Wisconsin, Pediatrics, Madison, WI
2012 - ongoing	Professor with Tenure, University of Wisconsin, Pediatrics, Madison, WI
2017 - ongoing	Faculty Director, Health Professions Student Research Program and Chair, Medical Student Research Committee, UW School of Medicine and Public Health

Other Experience and Professional Memberships

2008 - ongoing	Member, Society for Pediatric Research
2008 - ongoing	Member, Perinatal Research Society
2008 - ongoing	Member, Midwest Society for Pediatric Research
2008 - 2010	Council Member, Perinatal Research Society
2008 - 2010	Council Member, Midwest Society for Pediatric Research
2011 - 2016	Secretary/Treasurer, Midwest Society for Pediatric Research

2013 - 2016	Council Member, Perinatal Research Society
2017	Trained as a Coach for National Research Mentoring Network-Big Ten Academic Alliance, Career Development and Grant Writing Conference
2018	Trained as a trainer, NRMN Facilitating Entering Research Workshop

Honors

1988	Pediatric Resident Research Award, University of Wisconsin-Madison
1999	Faculty Award for Service to Pediatric Residents, University of Arizona
1999	Faculty Award for Service to Family Medicine Residents, University of Arizona
2003	Faculty Odell Award for Research Excellence, University of Wisconsin-Madison Department of Pediatrics
2008, 2010, 2012	Madison "Top Docs" Biannual Award, Madison Magazine
2012	Dean's Award for Excellence in Medical Student Research Mentorship, University of Wisconsin-Madison
2015	President, Perinatal Research Society

C. CONTRIBUTION TO SCIENCE (From 55 peer-reviewed manuscripts)

Intrauterine Growth Restriction/IUGR: Work in our lab has used animal models of intrauterine growth restriction (IUGR) to investigate the impact of iron and other nutritional restriction on renal development. Inadequate iron status during fetal life may have long-term implications, including impairing renal development. Kidneys undergo substantial development of branching morphogenesis both intrauterine and after birth in IUGR newborns. We examined IUGR in sheep fetuses (*Meyer-Gesch*, 2013), finding that morphological and functional defects in renal development. We found that iron-deficiency altered normal renal development in young rats. Furthermore, we found that iron metabolism and fetal iron status in IUGR was impeded, especially in premature infants.

a. Meyer-Gesch KM, Sun MY, Koch JM, Ramadoss J, Blohowiak SE, Magness RR, **Kling PJ**. Ovine fetal renal development impacted by multiple fetuses and uterine space restriction. J Dev Orig Health Dis. 2013 Oct;4(5):411-20. PMID: 24159370; PMCID: PMC3805357.
b. *Drake KA*, Sauerbry MJ, Blohowiak SE, Repyak KS, **Kling PJ**. Iron deficiency and renal development in the newborn rat. Pediatr Res. 2009 Dec;66(6):619-24. PubMed PMID: 19730160.
c. Sun MY, *Habeck JM*, Meyer KM, Koch JM, Ramadoss J, Blohowiak SE, Magness RR, **Kling PJ**. Ovine uterine space restriction alters placental transferrin receptor and fetal iron status during late pregnancy. Pediatr Res. 2013 Mar;73(3):277-85. PubMed PMID: 23202722; PubMed Central PMCID: PMC3678369.
d. McCarthy PJ, Zundel HR, *Johnson KR*, Blohowiak SE, **Kling PJ**. Impact of growth restriction and other prenatal risk factors on cord blood iron status in prematurity. J Pediatr Hematol Oncol 2016 Apr;38(3):210-5. doi: 10.1097/MPH.0000000000000536.

Iron Endowment at Birth: To better understand fetal iron acquisition, our translational work led to the exploring a biomarker to identify babies with risk factors at birth to facilitate preventative treatment. This led to exploration of iron status in with sociodemographic and medical risk factors placing them at-risk for iron deficiency in infancy. We tallied these identified risk factors showed that the more the risk factors, the poorer the iron endowment (McLimore, et al. 2013). We identified a novel risk factor, maternal obesity and weight gain during pregnancy (Phillips, et al. 2014). Although obesity impairs Iron absorption in adults it had not previously been shown to impact newborn iron endowment. Based on a report describing mineral deficiency may predispose to allergy, we investigated the linkage between iron status at birth and the development of an allergic phenotype (*Weigert, et al*. *J Perinatol* 2015:35:621-6). Our most recent manuscript (Dosch, et al., 2016) supported that iron and obesity program immune pathways, especially in morbid obesity. Another manuscript found that a best practice alert in the electronic health record can markedly improve screening for iron deficiency in clinical practice. We recently submitted a manuscript describing that iron deficiency was common in obese and overweight adolescents.

a. *McLimore HM*, Phillips AK, Blohowiak SE, Pham DQ, Coe CL, Fischer BA, **Kling PJ**. Impact of multiple prenatal risk factors on newborn iron status at delivery. J Pediatr Hematol Oncol. 2013 Aug;35(6):473-7. PMID: 23042017; PMCID: PMC3562554.

b. Phillips AK, *Roy SC*, Lundberg R, Guilbert TW, Auger AP, Blohowiak SE, Coe CL, **Kling PJ**. Neonatal iron status is impaired by maternal obesity and excessive weight gain during pregnancy. J Perinatol. 2014 Jul;34(7):513-8. PMID: 24651737; PMCID: PMC4074453.
c. Dosch NC, *Guslits EF, Weber MB, Murray SE, Ha B*, Coe CL, Auger AP, **Kling PJ.** Maternal obesity affects inflammatory and iron indices in umbilical cord blood. J Pediat 2016: 172;20-8.
d. *Ha B*, *O'Sullivan DL*, Diamond CA, Plumb AJ, Sleeth JS, Greer FR, Kling PJ. Improving rates of screening for anemia in infancy. Clin Pediatr (Phila). 2017 Nov 1:9922817744608. doi: 10.1177/0009922817744608.

Indices of Iron Status at Birth: Because of the critical role of iron status in development, we investigated indices, or biomarkers of iron status. Half of the iron needed for infant growth is acquired before birth, so fetal iron allotment impacts short- and long-term iron status in infants. An MD student *David Lott* found infants of mothers with diabetes or IUGR (*Lott*, et al, 2005) suffer from decreased iron endowment, while and infants large for gestation, but without diabetes have normal endowment (Kleven, et al, 2007). An MD student *Olamide Zaka* worked with a Pediatric resident Nichole Baumann-Blackmore to find that infants at-risk for iron deficiency as toddlers, minority status and/or of lower socioeconomic status, start out life iron-deficient, with decreased iron endowment (Baumann-Blackmore, et al.). An MD student *Melinda Chen* work with others in our lab to find that reticulocyte enrichment of ZnPP/H was more sensitive to early and subtle changes in iron status (Blohowiak, 2008). An MD student *Ryan Baxter* worked with our research nurse team to describe the specific concerns of Latina women when recruited for a clinical study examining iron deficiency in their offspring.

a. *Lott DG*, Zimmerman MB, Labbé RF, **Kling PJ**, Widness JA. Erythrocyte zinc protoporphyrin is elevated with prematurity and fetal hypoxemia. Pediatrics. 2005 Aug;116(2):414-22. PubMed PMID: 16061597.
b. Baumann-Blackmore NL, Goetz E, Blohowiak SE, *Zaka O*, **Kling PJ**. Cord zinc protoporphyrin/heme ratio in minority neonates at-risk for iron deficiency. *J Pediatr* 2008:153;133-136.
c. Blohowiak SE, *Chen ME*, Repyak KS, Baumann-Blackmore NL, Carlton DP, Georgieff MK, Crenshaw TD, **Kling PJ**. Reticulocyte enrichment of zinc protoporphyrin/heme discriminates impaired iron supply during early development. Pediatr Res. 2008 Jul;64(1):63-7. PMID: 18360311; PMCID: PMC3071474.
d. Phillips AK, Shafranski SA, *Baxter RJ,* Fischer BA, Coe CL, **Kling PJ**. Enrollment and participation of Latina women in a birthing center clinical research study in Wisconsin: barriers and suggestions for future research, *Wisconsin Med J* 2011:110;26-31. PMCID: PMC3148080.

Impaired Regulation of Erythropoietin (Epo): It was important to understand the regulation Epo in infants due to a need for multiple transfusions in prematurity accompanying a relative Epo deficiency. I was a co-investigator at the University of Iowa site in the first US multicenter trial in prematurity. Because it was ultimately shown that the drug, Epo, although efficacious, was insufficient to eliminate transfusion in babies, I studied the regulation of Epo production *in vitro*, finding that iron depletion upregulated Epo expression. Collaborating with adult hematologists, I found that depletion of cellular iron delivery in healthy adults and in cancer patients also upregulated Epo (*Kling, et al. 1996*); also cited as important in Oncology Digest in 1997. We found that immunosuppressive medications inhibited Epo production in pediatric renal transplant recipients (*Al-Uzri, et al, 2003*). Recently, a graduate student also found that plasma Epo levels were relatively blunted in intrauterine growth restriction (IUGR) sheep fetuses despite evidence for substantial hypoxemia and polycythemia (*Meyer, et al. 2010*). This work continued, leading us to further examine plasma volume regulation in the IUGR fetus, leading us to conclude that higher fetal polycythemia in IUGR may not all be due to hypoxemia-stimulated Epo production, but altered regulation of plasma volume (Meyer-Gesch, et al. 2013), findings allowing for funding, R01 HL117341.

a. **Kling PJ**, Dragsten PR, Roberts RA, Dos Santos B, Brooks DJ, et al. Iron deprivation increases erythropoietin production in vitro, in normal subjects and patients with malignancy. Br J Haematol. 1996 Nov;95(2):241-8. PMID: 8904876.
b. Al-Uzri A, Yorgin PD, **Kling PJ**. Anemia in children after transplantation: etiology and the effect of immunosuppressive therapy on erythropoiesis. Pediatr Transplant. 2003 Aug;7(4):253-64. PMID: 12890002.

c. Meyer KM, Koch JM, Ramadoss J, **Kling PJ**, Magness RR. Ovine surgical model of uterine space restriction: interactive effects of uterine anomalies and multifetal gestations on fetal and placental growth. Biol Reprod. 2010 Nov;83(5):799-806. PMID: 20574052; PubMed Central PMCID: PMC2959109.
d. Meyer-Gesch KM, Sun MY, Koch JM, Ramadoss J, Blohowiak SE, Magness RR, **Kling PJ**. Ovine fetal renal development impacted by multiple fetuses and uterine space restriction. J Dev Orig Health Dis. 2013 Oct;4(5):411-20. PMID: 24159370; PMCID: PMC3805357.

Nonerythropoietic Roles of Epo: One theory why the drug Epo was not efficacious in prematurity, was that Epo played important, novel, nonerythropoietic roles in early development. Because Epo exerts local paracrine effects, we examined the effects of Epo on other nonerythropoietic tissues. This was important because Epo was in high concentrations in human milk. We investigated the role of milk-borne Epo (Kling, *Sullivan*, et al, 1998). In rat work, an undergraduate student working in the lab found that Epo played a role in intestinal development (Miller-Gilbert, 2001). These nonerythropoietic roles of Epo may protect organ development from insults such as hypoxia. We found that enteral Epo played a role in vasculogenesis (*Ashley, et al, 2002*). In addition, when given enterally, Epo impacts intestinal iron absorption (Kling, et al. 2008). We showed that Epo in the presence of iron deficiency improves neurogenesis, myelination patterns and potentially brain growth in suckling rats. This is an important finding relating the potential neuroprotective mechanisms behind Epo.

a. **Kling PJ**, *Sullivan TM*, Roberts RA, Philipps AF, Koldovsky' O. Human milk as a potential enteral source of erythropoietin. *Pediatr Res* 1998:43; 216-221
b. Miller-Gilbert AL, Dubuque SH, Dvorak B, Williams CS, Grille JG, Woodward SS, Koldovsky O, **Kling PJ**. Enteral absorption of erythropoietin in the suckling rat. Pediatr Res. 2001 Aug;50(2):261-7. PMID: 11477213.
c. *Ashley RA*, Dubuque SH, Dvorak B, Woodward SS, Williams SK, **Kling PJ**. Erythropoietin stimulates vasculogenesis in neonatal rat mesenteric microvascular endothelial cells. Pediatr Res. 2002 Apr;51(4):472-8. PMID: 11919332.
d. *Flores KP,* Blohowiak SE, Winzerling JJ, Georgieff MK, **Kling PJ**. The impact of erythropoietin and iron status on brain growth in the newborn rats. *J Neurosci Res, 2018*; Mar;30(2):238-244. DOI: 10.1177/1040638717752217. Epub 2018 Jan 2. PMID: 29291683.

D. RESEARCH SUPPORT

Ongoing Research Support

R01 AA022999, NIH/NIAAA
Smith, Susan (PI)
06/01/2014 – 05/31/2019
Prenatal alcohol exposure disrupts maternal-fetal iron metabolism in FASD.
We are studying the cellular interaction between fetal alcohol spectrum disorders (FASD), a leading cause of neurodevelopmental disability, and maternal and fetal iron deficiency. Ethanol-exposure can alter fetal iron metabolism and iron needs compared to normal pregnancy. We are studying this in rodent models.
Role: PI of Madison site

670, UnityPoint Meriter Foundation
Kling, Pamela (PI)
01/01/2019-12/31/2019
Impact of Prenatal Depression and Anxiety on Iron-Mediated Inflammatory Pathways in Infants.
The purpose of this grant is to examine iron-mediated pathways in cord blood in a birth cohort in order to understand these data within the context of maternal depressive and anxiety symptoms, infant behavior, and infant brain MRI imaging. These data should guide our understanding of the diverse health implications of psychosocial stressors during pregnancy.
Role: PI

R01HD089989 (Coe, PI of the Wisconsin site) 09/22/17-06/30/18
University of Minnesota, Raghavendra Rao, PI

Detection and Correction of Iron Deficiency Induced Abnormal Brain Metabolism
This project will refine methods and discover new biomarkers of iron deficiency in the central nervous system by applying metabolomics approaches.
Role: Kling is Co-Investigator, Wisconsin sub award.

Completed Research Support

1508-3828, Gerber Foundation
Kling, Pamela (PI)
07/01/2014-7/31/2017
Impact of Obesity During Pregnancy on Neonatal Iron Status and Programming of Inflammatory Response Patterns.
This study examined whether obesity and excessive weight gain during pregnancy directly disturbed fetal iron metabolism and altered allergic inflammatory responses. We studied the physiological links between obesity and life-long programming of pro-inflammatory pathways that lead to allergic disease.
Role: PI

575, UnityPoint Meriter Foundation
Kling, Pamela (PI)
01/01/2016-12/31/2016
Multifetal Gestation Pregnancies, Fetal Kidney Dysfunction, and Programming of Life-Long Blood Pressure.
This purpose of this project was to study the interactions between growth-restricted multifetal gestation fetuses, the developing renin-angiotensin system, and iron status in controlling renal development and blood pressure.
Role: PI

R01 HL117341, NIH/NHLBI
Magness, Ronald (PI)
12/15/2013-11/30/2018
Endothelial Function in a Model of IUGR Induced by Uterine Space Restriction
We studied programming of adult health (hypertension) and disease especially conditions of angiogenic growth restriction appear to be dependent upon fetal exposure to various in utero stresses using a model of uterine space restriction, examining both uterine and placental vasculature adaptations and fetal renal tissues.
Role: Co-I

604, UnityPoint Meriter Foundation
Kling, Pamela (PI)
01/01/2017-12/31/2017
Recombinant erythropoietin as a renal protective agent in prematurity.
This grant investigated the impact of erythropoietin and iron protecting renal development and structure in a rat model of severe anemia and Acute Kidney Injury.
Role: PI

UW Graduate School Competition
Kling Pamela (PI)
7/1/17-7/1/18
Cellular signaling and disordered nephrogenesis during intrauterine growth restriction.
The grant investigated the iron-regulated mechanisms controlling the renin-angiotensin system in a sheep model of intrauterine growth restriction.
Role: PI