BIOGRAPHICAL SKETCH

NAME **Kier, Ann B.**	POSITION TITLE **Professor**
eRA COMMONS USER NAME akier@cvm.tamu.edu	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Texas, Austin, TX	B.A.	05/71	Zoology
Texas A&M University, College Station, TX	B.S., D.V.M.	08/74	Veterinary Medicine
University of Missouri, Columbia, MO	Ph.D.	08/79	Comparative Pathology
University of Missouri, Columbia, MO	Postdoctoral	08/79	Experimental Pathology

A. Personal Statement

The long-term goal of my research is to understand how regulation of PPARα by fibrates, PUFA, fatty acid synthesis inhibitors, and glucose affect the pathogenesis of cardiovascular disease and diabetes through the use of cultured primary hepatocytes (human, mouse), gene-ablated and overexpression mice, and humanized mice as an animal model for understanding human conditions, and to use these discovered mechanisms to exploit new drug development. In this project, human WT or L-FABP T94A variant will be overexpressed in our L-FABP null mice—thereby avoiding potential complications due to concomitant presence of the endogenous mouse L-FABP. Our central hypothesis proposes that L-FABP mediates fibrate signaling to hepatic PPARα, an action potentiated by high glucose. Further, we propose that the human L-FABP T94A variant is impaired in its ability to function in this pathway, especially in the context of high glucose. My main focus will be on Aim 3 to examine the collective physiologic impact of fibrates and human L-FABP T94A variant on signaling to PPARα in a humanized mouse model *in vivo*. In addition, I will also contribute to studies in Aim 1 to resolve the impact of human L-FABP T94A variant and glucose on fibrate nuclear targeting for PPARα interaction and activation. I have the expertise, productivity, and interest needed to successfully carry out the proposed work. I am Director of a Transgenic Mouse Core Facility, and supervise the Injection and Morphology/Pathology Sections. I have a broad background in animal models, with specific training and expertise in key research areas in this application, including immunocytochemistry, primary hepatocyte culture, cell culture, construction of mammalian expression vectors, transfection, cloning of cells, *in vivo* lipid metabolism, and mouse phenotyping. As a Resident in Laboratory Animal Medicine and Postdoctoral Fellow in Comparative Pathology at the University of Missouri, I was trained in both human and laboratory animal pathology (comparative, experimental pathology) as well as earning Diplomate status in the American College of Laboratory Animal Medicine (ACLAM). As a faculty member the University of Missouri, I developed the first animal model of Hageman Factor (Factor XII) deficiency, RO1 funded by NIH, determining key crossover regulatory pathways between coagulation and inflammation. As PI or co-investigator on several NIH-funded grants, including a NIH SERCA KO1 faculty development award and RO1s, I worked in the laboratory of Oscar Ratnoff, an outstanding hematologist and Member of the National Academy of Medicine at Case Western Reserve University, and expanded my work into *in vivo* lipid metabolism. Relocating to the University of Cincinnati Health Sciences Center, I furthered my expertise in animal models by learning gene-ablation techniques in the laboratory of Thomas Doetschman, collaborating on several NIH PO1 project grants as well as my own RO1 grants to clone the mouse gene coding for Hageman Factor and develop a genetically deficient mouse model. As Director of Comparative Pathology while teaching human pathology, I developed collaborations with Tom Doetschman, Steve Potter, Peter Stambrook, Jeffrey Robbins and other experts in the newly expanding field of mouse gene targeting to strengthen my expertise in mouse phenotyping and pathology, having PO1 components on 3 grants as well as PI and Co-I on RO1 grants, and publishing in *Nature, Cell, J Biological Chemistry,* and other high impact journals. While at Texas A&M University, I applied this expertise to develop and phenotype new mouse models overexpressing or ablated in genes encoding fatty acid and fatty acyl CoA binding proteins in collaboration with the PI of this proposal, Fred Schroeder. Other close collaborators include NAS members James Womack in mouse genetics/genomics, and Joanne Lupton in mouse nutrition/dietary studies. I have personnel trained in the specific areas of expertise needed for this application. The highly productive integration of different disciplines with the PI is particularly unique in our ability to follow key questions from the *in vitro* isolated protein level (Schroeder), through live cell culture

imaging experiments (Schroeder and Kier), and *in vivo* into the molecular biological and physiologic environment of mouse models (Kier).

B. Positions and Honors

POSITIONS: NIH Postdoctoral Fellow and Resident in Comparative Pathology and Laboratory Animal Medicine, Research Animal Diagnostic and Investigative Laboratory, University of Missouri, Columbia, MO (76-79); Assistant Professor, Veterinary Pathology, VMDL, University of Missouri (79-84); Associate Professor, Veterinary Pathology and Microbiology, VMDL, University of Missouri (84-87); Associate Professor, Pathology and Laboratory Medicine; University of Cincinnati College of Medicine, Cincinnati, OH (87-91); Professor and Director, Division of Comparative Pathology, Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine (91-93); Professor and Head, Department of Pathobiology, TVMC, Texas A&M University, College Station, TX (93-05); Director, Transgenic Facility Core, Texas A&M University (95-present); Professor, Department of Pathobiology, TVMC, Texas A&M University (05-present).

HONORS: NIH Postdoctoral Fellowship (76-79); Diplomate, American College of Laboratory Animal Medicine (80); ASIP, FASEB; ASBMB, FASEB; NIH Special Emphasis Research Career Development Award (SERCA, KO1) in Laboratory Animal Science (80-85); Member, NIH/NCI Immunobiology Contract Review Study Section (86-88); Member, NIH NCRR Comparative Medicine Study Section (92-96); Editorial Board, Journal of Comparative Medicine (98-present); ad hoc study sections, NIEHS, Mutant Mouse Resources, NCRR (97-present); Member, NIH NCRR Comparative Medicine Study Section (10-12).

C. Selected Peer-reviewed Publications (from 195)

Most relevant to the current application

1. Hostetler HA, Syler LR, Hall LN, Zhu G, Schroeder F, **Kier AB**: A novel high-throughput screening assay for putative anti-diabetic agents through PPARα interactions. *J Bimolecular Screening,* 13:855-861, 2008. PMCID: PMC2646813. *Based on the finding of glucose specifically binding and transactivating PPARα in vitro, we participated in a NIDDK-sponsored program to develop a screening assay for a panel of potential drugs for therapeutic development in hyperglycemia and diabetes. Three compounds in the library were identified for strong activity.*
2. Landrock D, Atshaves BP, McIntosh AL, Landrock KK, Schroeder F, **Kier AB**. Acyl CoA binding protein (ACBP) gene ablation induces pre-implantation embryonic lethality in mice. *Lipids* 45:567-580, 2010. PMCID: PMC2997683. *Ablation of L-FABP and other known members of the fatty acid binding protein family are not lethal--indicating other fatty acid/fatty acyl CoA binding proteins may compensate. Since the ubiquitous ACBP is expressed in the L-FABP null mice, the ACBP may contribute to absence of lethality in L-FABP null mice. In contrast to other FABP ablations, the loss of ACBP results in very early (<32 cell) pre-implantation embryonic lethality in mice, in which SCP-2 (also binds fatty acid/fatty acyl CoA) may partially compensate for a short period of time.*
3. McIntosh AL, Atshaves BP, Martin GG, Landrock KK, Landrock D, **Kier AB**, Schroeder F; Loss of liver fatty acid binding protein impacts mouse hepatocyte plasma membrane microdomains. *J Lipid Res* 53:467-480, 2012. PMC3276470. *While L-FABP at the plasma membrane localized to both cholesterol-rich and –poor microdomains, L-FABP directly interacted with SRB1 in the cholesterol-rich microdomains. An aim of the current application is to determine if L-FABP also interacts with FATPs present in the cholesterol-rich microdomains of cultured primary human hepatocytes.*
4. Petrescu AD, Huang H, Martin GG, McIntosh AL, Storey SM, Landrock D, **Kier AB**, Schroeder F. Impact of L-FABP and glucose on polyunsaturated fatty acid induction of PPARα regulated β-oxidative enzymes. *Am J Physiol Gastrointest and Liver Phys* 304: G241-256, 2013. PMC in progress. *VLCn-3PUFAs induce murine L-FABP translocation into the nucleoplasm, and high glucose potentiated VLCn-3PUFA-mediated PPARα transcription of proteins involved in LCFA uptake and β-oxidation, as well as LCFA β-oxidative capacity.*
5. Huang H, McIntosh AL, Martin GG, Petrescu AD, Landrock K, Landrock D, **Kier AB**, Schroeder F. Inhibitors of fatty acid synthesis induce PPARα-regulated fatty acid β-oxidative enzymes: synergistic roles of L-FABP and glucose. *PPAR Research* , in press, 2013. DOI: 10.1155/2013/865604. *High glucose*

confers on de novo fatty acid synthesis inhibitors (C75, TOFA) the ability to induce PPARα transcription of enzymes in LCFA β-oxidation in WT, but not L-FABP null, mouse hepatocytes.

Additional recent publications of importance to the field

6. Petrescu AD, Hertz R, Bar-Tana J, Schroeder F, **Kier AB**: Role of regulatory F-domain in Hepatocyte Nuclear Factor-4α (HNF4α) ligand specificity. *J Biol Chem* 280:16714-16727, 2005. *First report of the key ligand specificity of full-length HNF4α and the HNF4α ligand binding domain containing complete C-terminal F-domain for Acyl-CoAs at a separate receptor site from that for fatty acids: loss of the F-domain shifted ligand binding specificity toward fatty acids rather than fatty acyl CoAs.*
7. Atshaves B, McIntosh A, Payne H, Mackie J, **Kier AB**, Schroeder F: Effect of branched-chain fatty acid on lipid dynamics in mice lacking the L-FABP gene. *American J Physiology (Cell)* 288:C543-C558, 2005. *Clinical phenotype and pathology in L-FABP null mice: L-FABP gene ablation resulted in accumulation of hepatic lipid and hepatocyte necrosis in phytol-fed female mice. Hepatic levels of triglycerides were significantly increased, consistent with the measurements of higher levels of phytol metabolites (phytanic acid, pristanic acid) in liver and serum. These results led to the production of SCP-x, SCP-2 and SCP-2/SCP-x null mice by the Kier lab.*
8. Huang H, Atshaves BP, Frolov A, **Kier AB**, Schroeder F: Acyl-CoA binding protein expression alters liver fatty acyl CoA metabolism. *Biochemistry* 44:10282-10297, 2005. *Liver LCFA-CoA pool size increased significantly in ACBP overexpression. We showed for the first time in a physiological context that ACBP may play a role in LCFA-CoA metabolism.*
9. Atshaves BP, McIntosh AM, Landrock D, Payne HR, Mackie J, Maeda N, Ball J, Schroeder F, **Kier, AB**. Effect of SCP-x gene ablation on branched-chain fatty acid metabolism. *Am J Physiol* 292:G939-G951, 2007. *Production of the SCP-x null mouse by Kier and Maeda lab; branched-chain fatty acid liver toxicity in the SCP-x gene ablated mouse.*
10. Martin GG, Atshaves BP, McIntosh AL, Mackie JT, **Kier AB**, Schroeder F: L-FABP gene-ablated female mice exhibit increased age-dependent obesity. *J of Nutrition* 138:1859-1865, 2008. PMCID: PMC2835297. *L-FABP enhanced fatty acid uptake, activated PPARα, and enhanced fatty acid oxidation.*
11. Hostetler HA, McIntosh AL, Payne HR, Storey SM, Petrescu AD, Atshaves BP, Huang H, **Kier AB**, Schroeder F: L-FABP directly interacts with PPARα in cultured primary mouse hepatocytes. *J Lipid Research* 50:1663-1675, 2009. PMCID: PMC2724054. *L-FABP directly bound PPARα with high affinity in vitro as well as cultured primary hepatocytes, wherein L-FABP mediated VLCn-3PUFA activation of PPARα transcription of key genes in fatty acid oxidation.*
12. Mackie JT, Atshaves BP, Payne HR, McIntosh AL, Schroeder F, **Kier AB**: Phytol-induced hepatotoxicity in mice. *Tox Pathol,* 37:201-208, 2009. PMCID: PMC2838495. *Pathology of a branched-chain fatty acid showed the importance of including both sexes in all dietary studies: the toxic phenotype was more marked and earlier in control and SCP-x null female mice.*
13. Hostetler HA, Huang H, Martin GG, **Kier AB**, Schroeder F. Glucose regulates fatty acid binding protein and PPARα interactions. *J Lipid Research* 51:3103-3116, 2010. PMCID: PMC2952551. *Glucose directly interacted with L-FABP, altered L-FABP conformation, and potentiated L-FABP interaction with PPARα.*
14. Storey SM, McIntosh AL, Huang H, Martin GG, Landrock KK, Landrock D, Payne HR, **Kier AB**, Schroeder F: Loss of intracellular lipid binding proteins differentially impacts fatty acid uptake and nuclear targeting in mouse hepatocytes. *Am J Physiol Gastrointest Liver Physiol* 303:G837-G850, 2012. PMC in progress. *Upregulation of L-FABP increased, while loss of L-FABP decreased, saturated LCFA analogue uptake and nuclear targeting in living cultured primary mouse hepatocytes.*
15. Petrescu AD, McIntosh AL, Storey SM, Huang H, Martin GG, Landrock D, **Kier AB**, Schroeder F. High glucose potentiates L-FABP-mediated fibrate induction of PPARα in mouse hepatocytes. *Biochim Biophys Acta,* accepted with revision pending, 2013. *High glucose potentiated fenofibrate (PPARα specific) and bezafibrate (pan-PPAR) action in WT, but not L-FABP or PPARa null hepatocytes.*

D. Research Support

Ongoing Research Support

T32 RR031229 Kier (PD) 07/01/2010-06/30/2015

The goal of this training grant is to allow DVM postdoctoral residents to obtain PhD degrees in biomedical research and to encourage them to be retained within the biomedical research environment in comparative medicine, comparative pathology, and related fields.
Role: Project Director

Pending Research Support

R25 OD016574 Kier (PD) 04/01/2013-03/30/2018
The goal of this training grant is to allow veterinarians to be trained in laboratory animal medicine, have an in-depth exposure to research, and to be retained within the biomedical research environment in comparative medicine, comparative pathology, and related fields that contribute to translational research in human disease. Priority score 23 (no percentile assigned).

Research Support Completed During the Last Three Years

RO1 DK41402 Schroeder (PI) 07/1/2006-6/30/2012
The goals were to determine the impact of L-FABP gene ablation on mouse phenotype.
Role: Co-Investigator

R01 GM31651 Schroeder (PI) 08/31/2004-07/31/2012
The goals were to define functions of sterol carrier protein-2 (SCP-2) in cholesterol transfer and in regulating membrane cholesterol microdomains.
Role: Co-Investigator

K99 DK077573 Hostetler (PI) 04/1/2007-03/31/2012
The training portion of this grant examined the effect of long chain fatty acyl CoAs on nuclear receptor regulation, and ended on April 1, 2009. In August 2010, Dr. Hostetler accepted a faculty position at another university where she has activated the R01 portion of the grant.
Role: Co-mentor with F. Schroeder