BIOGRAPHICAL SKETCH

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NAME: **Philip A. Kern, MD**

eRA COMMONS USER NAME: PAKern

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tufts University, Medford, MA	BS	06/1974	Chemistry & Biology
New York Medical College, Valhalla, NY	MD	06/1978	Medicine
Montefiore, Albert Einstein College of Medicine, Bronx, NY	Residency	06/1981	Internal Medicine
University of Colorado School of Medcine, Denver	Fellowship	06/1984	Endocrinology & Metabolism

A. Personal Statement

I am the director of the University of Kentucky (UK) Center for Clinical and Translational Science (CCTS) and Associate Provost for Clinical and Translational Science, where I report directly to the Provost and to the University Vice President for Research. The CCTS is a University of Kentucky (UK) campus-wide Center that houses the institutional Clinical and Translational Science Award (CTSA); it is supported by the CTSA grants (UL1/KL2/TL1) and institutional funds with a total yearly budget over $10 million. The mission of the CCTS is to stimulate innovative translational science on campus, promote development of the translational workforce, stimulate team science, in part through a robust pilot grant program, work with the healthcare system to develop efficiencies and improved strategies for translational research, build a clinical trials network and generally serve as a nexus at UK and in the Central Appalachian region for research that improves health in the community. That core focus on rural communities and their health needs and challenges is one of numerous vital links between the CCTS and the University of Kentucky Center for Appalachian Research in Health Sciences (UK-CARES). I have been a strong supporter of UK-CARES initiatives since the center's inception in 2017 and in particular am committed to continuing to serve on the Institutional Advisory Board. My own research interests in obesity, metabolic syndrome, and diabetes align with challenges that UK-CARES addresses in the central Appalachian region of Kentucky.

I was the inaugural Director of UK's Barnstable Brown Diabetes and Obesity Center, founded in 2009, and have a long history of studying adipose and muscle biology and I am engaged in both basic and clinical research related to obesity, metabolic syndrome, inflammation, lipid metabolism, diabetes and insulin resistance, as outlined below. As a clinician-scientist, I have become recognized as an important collaborator and advisor on many other investigators' grant-funded programs. In recognition of my research achievements, I am honored to have been selected by my peers and UK leadership as a 2019 University Research Professor, the premier research recognition at our institution. Recent collaborative publications include:

1. Nicholas DA, Proctor EA, Agrawal M, Belkina AC, Van Nostrand SC, Panneerseeian-Bharath L, Jones AR, IV, Raval F, Ip BC, Zhu M, Cacicedo J, Habib C, Sainz-Rueda N, Persky L, Sullivan PG, Corkey BE, Apovian CM, **Kern PA**, Lauffenburger DA Nikolajczyk BS. 2019. Fatty Acid Metabolites Combine with Reduced β Oxidation to Activate Th17 Inflammation in Human Type 2 Diabetes. Cell Metabolism 30:447-461. PMID:31378464.
2. Bharath LP, Agrawal M, McCambridge G, Nicholas-Alvarado DA, Hasturk H, Liu J, Jiang K, Guo Z, Deeney J, Synder-Cappione J, Hawk G, Pihl RMF, Thompson K, Belkina AC, Cui L, **Kern PA**, Nikolajczyk BS. 2020. Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. Cell Metabolism 32:44-55. PMC7217133.

3. Walton RG, Dungan CM, Long DE, Tuggle SC, Kosmac K, Peck BD, Bush HM, Villasante Tezanos AG, McGwin G, Windham ST, Ovalle F, Bamman MM, **Kern PA**, Peterson CA. 2019. Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: a randomized, double-blind, placebo-controlled, multi-center trial. Aging Cell. 26:e13039. PMC6826125
4. Schoenberg NE, Bowling B, Cardarelli K, Feltner F, Mudd-Martin G, Surratt H, **Kern PA**. 2020. The Community Leadership Institute of Kentucky (CLIK): A Collaborative Workforce and Leadership Development Program. Prog Community Health Partnership. In press.

B. Positions and Honors

Positions and Employment

1984-1995 Assistant / Associate Professor of Medicine, UCLA/Cedars-Sinai Med Center, Los Angeles, CA
1995-2009 Professor of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR
1995-2007 Associate Chief of Staff, Research, Central Arkansas Veterans Healthcare System, Little Rock
2007-2009 Assistant Dean Clinical Research, College of Medicine, University of Arkansas Medical Sci.
2009-2015 Director, Barnstable Brown Diabetes and Obesity Center, University of Kentucky, Lexington, KY
2009-present Professor, Department of Medicine, Division of Endocrinology, University of Kentucky
2009-present Director, Center for Clinical and Translational Science, University of Kentucky, Lexington, KY
2009-present Associate Provost for Clinical and Translational Science; University of Kentucky, Lexington, KY

Active State Medical Licensure: Kentucky and Arkansas

Board Certification: Internal Medicine, 1981, Endocrinology and metabolism, 1983

Honors and Awards

1974 Tufts University, Magna Cum Laude.
1978 New York Medical College, Alpha Omega Alpha
1983-1985 NIH National Research Service Award
1986-1989 JDF Career Development Award
1991-1996 American Heart Association Established Investigator Award
1992 American Society for Clinical Investigation
2004 Association of American Physicians
2007-2019 Best Doctors in America®
2015 Fred & Marcielle de Beer Award, Barnstable Brown Diabetes and Obesity Center
2019 University Research Professor Award, University of Kentucky

Other Experience and Professional Memberships

1996-2000 VA Merit Review Council and Appeals Committee
1996-2000 Research Grant Review Panel, American Diabetes Association
2000-2002 Associate Chair / Chair, American Diabetes Association Research Grant Review Panel
2001-2006 VA Merit Review Endocrinology and Metabolism Study Section
2005-2006 VA Merit Review Endocrinology and Metabolism Chairman
2007 NIH Review CTSA Study Section
2008 NIH Review CADO Study Section
2010-2015 NIH Review CIDO Study Section
2012-2015 NIH Review CIDO, Chairperson
2015-2019 NIH Review, Ad hoc study sections; NHLBI Mentored Patient-Oriented Research; Molecular transducers of physical activity. Sleep and diabetes; Sleep apnea and diabetes. Member conflict SEP: Obesity and diabetes
2021 NIDDK Endocrinology fellowship

C. Contributions to Science

1. **Lipoprotein lipase (over 50 publications).** Much of my career has focused on adipocyte biology and the regulation of lipoprotein lipase (LPL). Early experiments used adipocyte preparations in cell culture, and in the late 1980's, I began performing fat and muscle biopsies in humans to more directly study LPL and other genes involved in the regulation of the abnormal metabolic state that ultimately leads to type 2 diabetes. The studies on LPL examined the effects of obesity, diabetes, feeding, exercise, weight loss and other drugs and conditions on LPL. Much of LPL expression was controlled at the level of translation, and careful biochemical experiments determined that LPL translation repression in response to cAMP agonists and thyroid hormone was regulated by a trans-acting inhibitory 3'UTR RNA binding complex composed of the C

and R subunits of PKA, as well as A kinase anchor protein. This led to the examination of a known LPL variant, LPL S447X, which is a gain of function variant that confers increased LPL activity (and CHD protection) on subjects. We showed that this increase in LPL activity is likely due to improved LPL translation due to a lower binding affinity for the inhibitory RNA binding complex.

a) **Kern PA**, Ong JM, Saffari B, Carty J. 1990. The effects of weight loss on the expression of adipose tissue lipoprotein lipase in very obese humans. N. Engl. J. Med. 322:1053-1059.
b) Ranganathan G, Phan D, Pokrovskaya ID, McEwen JE, Li C, **Kern PA**. 2002. The translational regulation of lipoprotein lipase by epinephrine involves an RNA binding complex including the catalytic subunit of protein kinase A. J Biol Chem 277:43281-43287.
c) Ranganathan G, Pokrovskaya I, Ranganathan S, **Kern PA**. 2005. Role of A kinase anchor proteins in the tissue-specific regulation of lipoprotein lipase. Mol Endocrinol 19:2527-2534.
d) Ranganathan G, Unal R, Pokrovskaya ID, Tripathi P, Rotter JI, Goodarzi MO, **Kern PA**. 2012. The lipoprotein lipase (LPL) S447X gain of function variant involves increased mRNA translation. Atherosclerosis 221:143-147. PMC3288274.

2. **Mechanisms of insulin resistance: pioglitazone and metformin (over 20 publications).** Thiazolidinediones (TZDs) improve peripheral insulin sensitivity through the targeting of an adipocyte gene, PPARγ. Metformin has additional special properties, and we are currently conducting a NIH-funded randomized trial to examine the effects of metformin on muscle function with resistance training (see funding, below). We examined the mechanisms underlying the effectiveness of PPARγ agonists, when compared with metformin, with an eye towards better understanding mechanisms underlying insulin resistance. We performed both clinical and *in vitro* studies to characterize the effects of pioglitazone on tissue lipid distribution, adipose tissue inflammation and gene expression. These studies demonstrated an amelioration of lipotoxicity with a shift of lipid into subcutaneous adipose tissue and away from skeletal muscle. Other studies demonstrated a reduction in adipose macrophages and mast cells following pioglitazone treatment and an induction of adipose macrophage apoptosis, along with differences between African-Americans and Caucasians. We also better characterized the stimulation of adiponectin by pioglitazone, and demonstrated that this occurs mostly at the posttranscriptional level.
   a) Rasouli N, Raue U, Miles LM, Lu T, Di Gregorio GB, Elbein SC, **Kern PA**. 2005. Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. Am J Physiol Endocrinol Metab 288:E930-934.
   b) Bodles AM, Varma V, Yao-Borengasser A, Phanavanh B, Peterson CA, McGehee RE, Jr., Rasouli N, Wabitsch M, **Kern PA**. 2006. Pioglitazone induces apoptosis of macrophages in human adipose tissue. J Lipid Res 47:2080-2088.
   c) Rasouli N, **Kern PA**, Elbein SC, Sharma NK, Das SK. 2012. Improved insulin sensitivity after treatment with PPARγ and PPARα ligands is mediated by genetically modulated transcripts. Pharmacogenet Genomics 22:484-497. PMC3376224.
   d) Rasouli N, **Kern PA**, Reece EA, Elbein SC. 2007. Effects of pioglitazone and metformin on β-cell dysfunction in non-diabetic subjects at high risk for type 2 diabetes. Am. J. Physiol. Endocrinol. Metab. 292:E359-65. PMID: 169688133.

3. **Mechanisms of insulin resistance: adipose tissue inflammation and extracellular matrix (over 15 publications).** To better understand the relationship between adipose tissue inflammation and insulin resistance, many studies have examined components of the adipose tissue extracellular matrix to increase understanding of fibrosis, adipose vascularity and inflammatory cells in insulin sensitive and insulin resistant subjects. In addition to the use of careful histochemistry, these studies also used cell culture models involving human adipose stem cells and coculture experiments involving adipocytes and macrophages to examine the cell biology of adipose tissue. These studies identified thrombospondin, elastin, collagen V, and other important components of the extracelluar matrix that contribute to the adipose tissue abnormalities. In addition, these studies determined that the changes in human adipose are quite different from the changes observed in rodent models, and involve much more fibrosis and macrophage phenotypes that are more M2 than M1, with far fewer crown-like structures.
   a) Di Gregorio GB, Yao-Borengasser A, Rasouli N, Varma V, Lu T, Miles LM, Ranganathan G, Peterson CA, McGehee RE, Kern PA. 2005. The expression of CD68 and macrophage chemoattractant protein-1 genes in human adipose and muscle tissue: Association with cytokine expression, insulin resistance, and reduction by pioglitazone. Diabetes. 54:2305-13.
   b) Spencer M, Yao-Borengasser A, Unal R, Rasouli N, Gurley CM, Zhu B, Peterson CA, **Kern PA**. 2010. Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis

and demonstrate alternative activation. Am J Physiol Endocrinol Metab 299:E1016-1027. PMC3006260.

c) Unal R, Yao-Borengasser A, Varma V, Rasouli N, Labbate C, **Kern PA**, Ranganathan G. 2010. Matrix metalloproteinase-9 is increased in obese subjects and decreases in response to pioglitazone. J. Clin. Endocrinol. Metab. 95:2993-3001. PMC2902064.

d) Spencer M, Unal R, Zhu B, Rasouli N, McGehee RE, Jr., Peterson CA, **Kern PA**. 2011. Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. J Clin Endocrinol Metab 96:E1990-1998. PMC3232606.

4. **The role of circadian rhythms in human metabolism.** It has been clear that there is a striking association between disordered circadian rhythms and obesity, diabetes and heart disease, but the mechanisms and solutions for this problem are complex. Many studies have been performed in mice and there have been a number of excellent human studies, often performed on a CRC setting, which allows for precise control of the environment, but which may not be reflective of the free-living environment. Recent studies in collaboration with Dr. Julie Pendergast have been focused on better understanding of circadian markers in humans and how they related to metabolic disorders.

   a) Arble DM, Bass J, Behn CD, Butler MP, Challet E, Czeisler C, Depner CM, Elmquist J, Franken P, Grandner MA, Hanlon EC, Keene AC, Joyner MJ, Karatsoreos I, **Kern PA**, Klein S, Morris CJ, Pack AI, Panda S, Ptacek LJ, Punjabi NM, Sassone-Corsi P, Scheer FA, Saxena R, Seaquest ER, Thimgan MS, Van Cauter E, Wright KP. 2015. Impact of Sleep and Circadian Disruption on Energy Balance and Diabetes: A Summary of Workshop Discussions. Sleep. 38:1849-60. PMC4667373.

   b) Harfmann BD, Schroder EA, England JH, Senn NJ, Westgate PM, Esser KA, **Kern PA**. 2017. Temperature as a circadian marker in older human subjects: relationship to metabolic syndrome and diabetes. J. Endocr. Soc. 1:843-51. PMC5686633.

   c) Thomas JM, **Kern PA**, Bush HM, McQuerry KJ, Black WS, Clasey JL, Pendergast JS. 2020. Circadian rhythm phase shifts caused by timed exercise vary with chronotype. J. Clin Invest Insight In Press. PMID: 31895695.

5. **Novel physiologic and mechanistic studies to improve insulin resistance: adipose beiging and mast cells.** For my entire career, I have tried to translate basic findings into clinical research, and have taken clinical observations on human obesity/metabolic syndrome back to the lab for mechanistic studies. In recent studies, we have, for the first time, demonstrated that human white adipose tissue can undergo beiging in response to seasons, cold exposure and the β3 adrenergic receptor agonist mirabegron, with an increase in UCP1 mRNA and protein; this process is inhibited by obesity and inflammation. Recent studies have identified a role of adipose tissue mast cells, which increase in response to cold and degranulate, releasing histamine to active beige adipose tissue.

   a) Finlin BS, Zhu B, Confides AL, Westgate PM, Harfmann BD, Dupont-Versteegden EE, **Kern PA**. 2017. Mast Cells Promote Seasonal White Adipose Beiging in Humans. Diabetes 66:1237-46. PMC5399616.

   b) Finlin BS, Memetimin H, Confides AL, Kasza I, Zhu B, Vekaria HJ, Harfmann B, Jones KA, Johnson ZR, Westgate PM, Alexander CM, Sullivan PG, Dupont-Versteegden EE, **Kern PA**. 2018. Human Adipose Beiging in Response to Cold and Mirabegron. J. Clin Invest Insight 3(15):e121510. PMC6129119.

   c) Finlin BS, Memetimin H, Zhu B, Confides AL, Vekaria HJ, El Khouli RH , Johnson ZR, Westgate PM, Chen J, Morris AJ, Sullivan PG, Dupont-Versteegden EE, **Kern PA**. 2020. The β3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. J. Clin Invest. 130:2319-2331. PMC7190997.

   d) Finlin BS, Memetimin H, Zhu B, Confides AL, Vekaria HJ, El Khouli RH, Johnson ZR, Westgate PM, Chen J, Morris AJ, Sullivan PG, Dupont-Versteegden EE, **Kern PA**. 2021. Pioglitazone does not synergize with mirabegron to increase beige fat or further improve glucose metabolism. J. Clin Invest Insight. In press. PMID 33571166.

Complete bibliography: http://www.ncbi.nlm.nih.gov/pubmed/?term=kern+pa

D. Additional Information: Research Support

Ongoing Research Support

UL1 TR001998 Kern, P (PI) 08/15/16-05/31/21
"Kentucky Center for Clinical and Translational Science (NCATS)"

Goals: This CTSA award to UK involves numerous Cores, including the clinical research center, a trial innovation network, team science, a pilot grant program, informatics, workforce development and community engagement. A TL1 Training Program (PI: S. Smyth) and KL2 Career Development Program (PI: T. Kelly) are part of this effort.

R01 DK124626 Kern, P (PI) 12/01/20-11/30/25
"Mechanisms for activation of beige adipose tissue in humans"
Goals: This grant aims to better understand the mechanism of action of the β3AR drug mirabegron on glucose homeostasis.

R01 DK112282 Kern, P (PI) 09/15/16-08/31/21 NCE
"The activation of brown and beige fat and role in insulin sensitivity"
Goals: This study will evaluate the activation of beige fat in obese humans through biopsies, and brown fat through PET-CT scans, in response to β3 agonist and PPARγ agonist drugs.

P30 DK020579 Schaffer, J (PI) 12/01/18-11/30/22
"Diabetes Research Center" at Washington University, St. Louis
Goals: This subcontract involves pilot grants and other interactions between Washington University and UK.
Role: UK Site PI

R01 DK108056 Nikolajczyk, B (PI) 04/01/18-03/31/21 NCE
"Inflammation in Human Obesity and Type 2 Diabetes"
This project tests the hypothesis that a T cell signature distinguishes T2D from non-T2D subjects and is a predictive biomarker for T2D. Dr. Kern is involved in the clinical recruitment and characterization.
Role: Co-I

R01 DK119619 McCarthy, Peterson (MPIs) 09/01/18 – 08/31/23
"Exercise-induced Skeletal Muscle Exosomes Promote Adipocyte Lipolysis"
This proposal hypothesizes that resistance exercise promotes the release of miR-1 containing exosomes from muscle which are taken up by fat to increase lipolysis and βAR activity, in both mice and humans.
Role: Co-I

R01 AG062550 Johnson, LA (PI) 04/01/19-03/31/24
"Changing the energy substrate balance: Does APOE2 promote glucose usage to protect from Alzheimer's Disease?"
This proposal hypothesizes that apoE2 affords neuroprotection of Alzheimer's disease by virtue of shifting metabolism from fatty acid oxidation to glucose utilization. Studies are in both mice and humans.
Role: Co-I

VAC31518COV3001 Greenberg, R (PI) 09/25/20-08/18/21
Janssen Vaccines and Prevention BV.
"A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adults Aged 18 Years and Older"
This study is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein.
Role: Co-I

Completed Support

R01 AG046920 Bamman, M; Kern P; Peterson C MPIs) 09/30/14-05/31/20
NIH/NIA
"Novel actions of metformin to augment resistance training adaptation in older adults"
Goals: To assess potential benefits of metformin on muscle function in elderly subjects in resistance training.
Role: MPI

R01 DK107646 Kern, P (PI) 09/21/15-07/31/20
"Cold induced changes in human subcutaneous white adipose"
Goals: To examine the extent to which subcutaneous white adipose can become brownish or beige and whether this process is inhibited by inflammation and characterize the effects of cold on adipose triglyceride turnover.