BIOGRAPHICAL SKETCH

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NAME: **Fredric B. Kraemer, M.D.**

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

POSITION TITLE: Staff Physician/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 |
| --- | --- | --- | --- |
| Emory University, Atlanta, GA | BA | 06/70 | Chemistry |
| New York University, New York, NY | MD | 06/74 | Medicine |
| State University of New York, Downstate, NY, NY | Resident | 06/78 | Medicine |
| Stanford University, Stanford, CA | Postdoctoral | 12/82 | Endocrinology |

A. Personal Statement

I have a broad background in endocrinology and metabolism, with specific training and expertise in key research and clinical areas, as well as administrative experience relevant to this application. Beginning as a postdoctoral fellow at Stanford, I have continuously carried out studies on a variety of aspects of cellular lipid and carbohydrate metabolism. As PI on previous VA- and NIH-funded grants over the past 30 years, I have developed substantial expertise and experimental tools involving cell biology, physiology, biochemistry and molecular biology for studying many aspects of lipid and carbohydrate metabolism, particularly adipose cell metabolism, as well as other areas of endocrinology. Indeed, it is those experiences in studying adipose lipid metabolism that have positioned me to provide expertise in lipid metabolism in my collaboration with Dr. Knowles in his current proposed studies examining *Nat1* in insulin resistance. I successfully administered these previous projects (e.g. staffing, safety, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. In addition, I have served as a member of a number of peer review committees, including the NIH, VA, AHA and ADA, experiences that provide me with important and useful perspectives on grantsmanship. Furthermore, I have extensive administrative experience that is relevant to this application, having served as Chief of Endocrinology at Stanford and ACOS for Research at the VA Palo Alto for a number of years. These experiences have provided me with a valuable perspective on avenues for mentoring junior and senior investigators and in having a deep understanding of the requirements for research compliance. In summary, I have a demonstrated record of successful and productive research in relevant scientific areas, as well as extensive administrative experiences, that position me to contribute to this application.

B. Positions and Honors

Positions and Employment

1974-78 Intern, Resident, Chief Resident, State Univ of New York, Kings County Hosp, Brooklyn, NY  
1978-82 Post-Doctoral Fellow, Div of Gerontology and Endocrinology, Stanford Univ, Stanford, CA  
1983- Asst, Assoc, Professor of Medicine, Div of Endocrinology; Stanford Univ, Stanford, CA  
1988- Staff Physician, VA Palo Alto Health Care System, Palo Alto, CA  
1988-02 Chief of Endocrinology, VA Palo Alto Health Care System, Palo Alto, CA  
2001- Chief of Endocrinology, Stanford University, Stanford, CA  
2002-07 ACOS for Research & Development, VA Palo Alto Health Care System, Palo Alto, CA

Other Experience and Professional Memberships

1978- Member, American Diabetes Association

1979- Member, American Federation for Medical Research

1979- Member, Endocrine Society

1981- Member, American Heart Association-Council on Arteriosclerosis

1983- Member, American Society for Biochemistry and Molecular Biology

1995- Member, American Society for Cell Biology

1995 NIH Peer Review Committee, Diabetes Program Projects, ad hoc reviewer

1997- Editorial Board, Metabolism, Clinical and Experimental

2006 NIH Peer Review Committee, Animal Models of Diabetes, ad hoc reviewer

2006-07 VA Merit Review Committee (Endocrinology), member

2007 NIH Peer Review Committee, Clinical Nutrition Research Centers, ad hoc reviewer

2007-15 NIH Clinical Integrative Diabetes and Obesity (CIDO) Study Section, ad hoc reviewer

2008 NIH Special Emphasis Panel: Adiposity, Aging and Stem Cells, chairperson

2012 VA Middleton Award Review Committee, member

2013 NIH Special Emphasis Panel: Collaborative Interdisciplinary Team Science

2014 NIH Hepatobiliary Pathophysiology (HBPP) Study Section, ad hoc reviewer

2014 NIH Special Emphasis Panel: Members Conflict, reviewer

2014 NIH PAR Panel: NIDDK Translational Research, ad hoc reviewer

2014- Editorial Board, Journal of Lipid Research

2015- ADA Peer Review Committee

2015 Peer Review Department of Defense Congressionally Directed Medical Research Programs

2016 NIH Molecular and Cellular Endocrinology (MCE) Study Section, ad hoc reviewer

2016 NIH Cellular Aspects of Diabetes and Obesity (CADO) Study Section, ad hoc reviewer

2017 NIH Special Emphasis Panel: Members Conflict, reviewer

2018 NHLBI Program Project Review, reviewer

2018 NIH Special Emphasis Panel: Members Conflict, reviewer

2018 NHLBI Program Project Review, reviewer

Honors

1982-87 Special Emphasis Research Career Award, National Institutes of Health

1983-84 Mellon Foundation Fellow

1984-88 Hume Faculty Scholar

1998 SmithKline Beecham Junior Faculty Award in Diabetes

1999 Physician Volunteer of the Year, American Heart Association, Western States Affiliate

2005 Arteriosclerosis Special Recognition Award, Council on ATVB

C. Contribution to Science (Selected from 172 peer-reviewed publications)

My research career began with a focus on insulin resistance and glucose metabolism during which I contributed to some of the early studies utilizing insulin clamps and examining the effects of differences in the sources of carbohydrates on insulin and glucose responses in humans. Although continuing to be interested in insulin and glucose metabolism, the major focus of most of my research has been directed at understanding various aspects of cellular lipid metabolism.

Hormone Sensitive Lipase

Hormone sensitive lipase (HSL) was identified in the early 1960’s as the hormonally responsive (cAMP, PKA-mediated) enzyme expressed in adipose tissue that was responsible for hydrolyzing stored triacylglycerols. Following the initial cloning of HSL in 1988, my colleagues and I published a series of papers describing the tissue distribution of HSL, its developmental regulation, and the regulation of its expression under several physiological conditions. Using a yeast-2-hybrid screen, we were the first to discover the physical interaction of HSL with adipocyte lipid binding protein, also known as aP2 or FABP4 (1), and went on to characterize the molecular basis for this interaction and to demonstrate its importance in modulating lipolysis. Along with colleagues from Japan (2), I was the first to report the effects of knockout of HSL in mice, showing that it was not the rate-limiting enzyme for lipolysis and suggesting the existence of another rate-limiting enzyme, which was later identified by others to be ATGL. We were the first to document that HSL functions as a dimer (3) and characterized the molecular basis for dimerization. In addition, we were the first to show that a portion of the lipolytic response to hormonal stimulation and activation of HSL was mediated via ERK signaling (4).

1. Shen W-J, Sridhar K, Bernhlor DA, Kraemer FB. Interaction of hormone-sensitive lipase with adipocyte lipid binding protein. **Proc Natl Acad Sci USA** 96:5528-5532, 1999. PMCID: PMC21893
2. Osuga J-i, Ishibashi S, Oka T, Yagyu H, Tozawa R, Fujimoto A, Shionoira F, Yahagi N, Kraemer FB, Tsutsumi O, Yamada N. Targeted disruption of hormone-sensitive lipase results in male sterility and adipocyte hypertrophy, but not in obesity. **Proc Natl Acad Sci** **USA** 97:787-792, 2000. PMCID: PMC15409
3. Shen W-J, Patel S, Hong R Kraemer FB. Hormone-sensitive lipase functions as an oligomer. **Biochemistry** 39:2392-2398, 2000. PMID: 10694408
4. Greenberg AS, Shen WJ, Muliro K, Patel S, Souza SC, Roth RA, Kraemer FB. Stimulation of lipolysis and hormone-sensitive lipase via the extracellular signal-regulated kinase pathway. **J Biol Chem** 276:45456-45461, 2001. PMID: 11581251

Lipolysis/Lipid Droplets

My studies on HSL naturally moved me to study lipolysis and lipid droplets. In a series of studies with collaborators, we explored the functional interplay between HSL and perilipin (Plin), the major protein surrounding lipid droplets in adipose cells. We were the first to identify specific regions of Plin that were responsible for preventing the ability of HSL to access lipid droplets, thus blocking lipolysis, as well as other regions that facilitated hormone-stimulated lipolysis (1). Moreover, we discovered that a specific phosphorylation site on Plin mediated the trafficking of ATGL on the lipid droplet, allowing the initiation of lipolysis (2). In further studies of lipid droplets in adipose we were the first to demonstrate that FSP27, also known as Cidec, physically interacted with protein partners, such as NFAT5, which modulated the transcriptional activity of this transcription factor during cellular stress (3). We were the first investigators to characterize the proteome of cholesteryl ester rich lipid droplets in steroidogenic cells (4), which provided insights into the mechanisms of cholesterol movement in steroidogenesis (see below).

1. Zhang HH, Souza SC, Muliro K, Wang X, Kraemer FB, Obin M, Greenberg AS. Lipase-selective functional domains of perilipin A differentially regulate constitutive and protein kinase A-stimulated lipolysis. **J Biol Chem** 278: 51535-51542, 2003. PMID: 14527948
2. Miyoshi H, Perfield II JW, Souza SC, Shen W-J, Zhang H-H, Stancheva ZS, Kraemer FB, Obin MS, Greenberg AS. Control of ATGL action by serine 517 of perilipin A globally regulates PKA-stimulated lipolysis in adipocytes. **J Biol Chem** 282:996-1002, 2007. PMID: 17114792
3. Ueno M, Shen W-J, Patel S, Greenberg AS, Azhar S, Kraemer FB. Fat specific protein 27 modulates nuclear factor of activated-T cells 5 and the cellular response to stress. **J Lipid Res** 54:734-743, 2013. PMCID: PMC3617947
4. Khor VK, Ahrends R, Lin Y, Shen W-J, Adams CM, Roseman AN, Cortez Y, Teruel MN, Azhar S, Kraemer FB. The proteome of cholesteryl-ester-enriched versus triacylglycerol-enriched lipid droplets. **PLoS One** 9:e105047, 2014. PMCID: PMC4128735

Adipose Metabolism

In addition to lipolysis and lipid droplets, my work naturally explored more general aspects of adipose metabolism. Thus, utilizing HSL knockout mice we were the first to demonstrate that the absence of HSL made mice resistant to obesity and resulted in defects in adipogenesis and adipose differentiation (1). We were the first researchers to suggest that the defect in adipose differentiation was due to the loss of HSL-mediated generation of ligands for PPAR(2), a concept that has been extended by other investigators to other lipases. In other studies we were the first to characterize the RNA expression patterns of bone marrow adipocytes, a unique adipose depot, and the changes observed with aging (3) and with high fat diets. Along with collaborators, we developed new methodology for quantifying nuclear proteins and documented important differences in the expression of nuclear transcription factors in adipose cells from insulin resistant animals (4).

1. Harada K, Shen W-J. Patel S, Natu V, Wang J, Osuga J-i, Ishibashi S, Kraemer FB. Resistance to high fat diet-induced obesity with altered expression of adipose specific genes in hormone-sensitive lipase deficient mice. **Am J Physiol** 285:E1182-1195, 2003. PMID: 12954598
2. Shen W-J, Yu Z, Patel S, Jue D, Liu L-F, Kraemer FB. Hormone-sensitive lipase modulates adipose metabolism through PPAR. **Biochim Biophys Acta** 1811:9-16, 2011. PMCID: PMC2998198
3. Liu L-F, Shen W-J, Ueno M, Patel S, Azhar S, Kraemer FB. Age-related modulation of the effects of obesity on gene expression profiles of mouse bone marrow and epididymal adipocytes. **PLoS One** 8(8): e72367 doi:10.1371/journal.pone.0072367, 2013. PMCID: PMC3743818
4. Ota A, Kovary KM, Wu OH, Ahrends R, Shen W-J, Costa MJ, Feldman BJ, Kraemer FB, Teruel MN. Using SRM mass spectrometry to quantify nuclear protein abundance differences between adipose tissue depots of insulin-resistant mice. **J Lipid Res** 56:1068-1078, 2015. PMCID: PMC4409283

Steroidogenesis

In studies of lipid metabolism that extend beyond adipose cells, we were the first to discover that HSL physically interacts with steroidogenic acute regulatory protein (StAR) and that this interaction was important in the movement of cholesterol for adrenal steroid hormone production. In other studies we showed that HSL was responsible for mediating the hydrolysis of cholesteryl esters in the adrenal and was critical for the utilization of HDL cholesterol for steroidogenesis. Furthermore, we were the first to demonstrate that vimentin was important in steroidogenesis, as it participates in the trafficking of cholesterol to mitochondria (1). In other studies our collaborators and we demonstrated that HSL hydrolysis of cholesteryl esters increased oxysterol production and stimulated the transcription of StAR via LXR in a feed-forward manner (2). Using a mitochondrial reconstitution assay and knockdown studies, we were the first to demonstrate the involvement of specific SNAREs in the trafficking of cholesterol for steroidogenesis (3). More recently, we described the effects of miR-132 on steroidogenesis (4).

1. Shen W-J, Zaidi SK, Patel S, Cortez Y, Ueno M, Azhar R, Azhar S, Kraemer FB. Ablation of vimentin results in defective steroidogenesis. **Endocrinology** 153:3249-3257, 2012. PMCID: PMC3380307
2. Manna PR, Cohen-Tannoudji J, Counis R, Gamer CW, Huhtaniemi I, Kraemer FB, Stocco DM. Mechanisms of action of hormone-sensitive in mouse Leydig cells: its role in the regulation of the steroidogenic acute regulatory protein. **J Biol Chem** 288:8505-8518, 2013. PMCID: PMC3605665
3. Lin Y, Hou X, Shen W-J, Hanssen R, Khor VK, Cortez Y, Roseman AN, Azhar S, Kraemer FB. SNARE-mediated cholesterol movement to mitochondria supports steroidogenesis in rodent cells. **Mol Endocrinol** 30:234-247, 2016.PMCID: PMC4792230
4. Hu Z, Shen W-J, Kraemer FB, Azhar S. Regulation of adrenal and ovarian steroidogenesis by miR-132. **J Mol Endocrinol** 59:269-283, 2017. PMID: 28729436

Scavenger Receptor Class B, Type 1

Since HDL cholesterol is the major source of cholesterol for adrenal and ovarian steroid hormone production in rodents and scavenger receptor class B, type 1 (SR-B1) is the receptor for HDL, we have undertaken a number of studies on the function and regulation of SR-B1. Along with collaborators, we demonstrated that the absence of HSL resulted in an upregulation of SR-B1 expression in the testis. We were the first to identify microRNAs that regulate the expression of SR-B1 in steroidogenic cells (2) and thus modulate steroid production. Additionally, we were the first to identify the post-transcriptional regulation of SR-B1 expression in steroidogenic cells through interaction with accessory proteins (3), as well as through its phosphorylation by salt-inducible kinase 1 (4). Thus, our work in this area has substantially contributed to the understanding of how cholesterol is delivered for steroidogenesis.

1. Casado A, Huerta L, Ortiz AI, Pérez-Crespo M, Gutiérrez-Adán A, Kraemer FB, Lasunción MA, Busto R, Martin-Hidalgo A. HSL-knockout mouse testis exhibits class B scavenger receptor up-regulation and disrupted lipid raft microdomains. **J Lipid Res** 53:2586-2597, 2012. PMCID: PMC3494238
2. Hu Z, Shen W-J, Kraemer FB, Azhar S. MicroRNAs-125a and 455 repress lipoprotein-supported steroidogenesis by targeting scavenger receptor class B, type I (SR-BI) in steroidogenic cells. **Mol Cell Biol** 32:5035-5045, 2012. PMCID: PMC3510537
3. Hu Z, Hu J, Shen W-J, Yun CC, Berlot CH, Kraemer FB, Azhar S. Regulation of expression and function of scavenger receptor class B, type 1 (SR-BI) by Na+/H+ exchanger regulatory factors (NHERFs). **J Biol Chem** 288:11416-11435, 2013. PMCID: PMC3630890
4. Hu Z, Hu J, Shen W-J, Kraemer FB, Azhar S. A novel role of salt-inducible kinase 1 (SIK1) in the post-translational regulation of scavenger receptor class B type 1 activity. **Biochemistry** 54:6917-6930, 2015. PMID: 26567857

Link to complete list of publications:

http://www.ncbi.nlm.nih.gov/sites/myncbi/fredric.kraemer.1/bibliograpahy/40495262/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

I01 BX000398 (Kraemer) 04/1/17 – 03/31/21

VA

Lipid Trafficking for Steroidogenesis

The overall goal of this proposal is to elucidate the mechanisms underlying the trafficking of cholesterol for steroidogenesis.

Role: PI

P30 DK116074 (Kim) 09/15/2017 – 06/30/22 0.6 calendar

NIH $999,020

Stanford Diabetes Research Center

The mission of the Stanford Diabetes Research Center (SDRC) is to foster knowledge, support training, and promote innovative basic and translational research in biomedical, epidemiological, and behavioral research in diabetes.

Role: Project Leader of Pilot and Feasibility Program

Completed Research Support

1-12-BS-103 Kraemer (PI) 01/15/13 – 07/14/16

American Diabetes Association

Modulation of Inflammation by a Droplet-Associated Protein

The goal of this proposal is to test the hypothesis that FSP27 directly interacts with and sequesters NFAT5 on the droplet, preventing its normal trafficking and dampening the transcriptional activation of NFAT5 target genes, such as MCP1 and TNF.

Role: PI

Merit Review Kraemer (PI) 04/1/13 – 03/31/17

VA

Lipid Droplet Metabolism

The objective of this proposal is to advance our understanding of the cell biology of lipid droplets. We will test 2 hypotheses: 1) The physical properties of lipid droplets are distinctively altered in quantifiably defined ways by specific droplet-associated proteins and these physical properties contribute to lipid droplet size (growth and fusion) and metabolism. 2) The formation of cholesteryl ester-rich lipid droplets differs in important and identifiable ways from triacylglycerol-rich lipid droplets and that cholesteryl ester-rich lipid droplets have a complement of droplet-associated proteins that specifically facilitates their utilization for steroidogenesis.

Role: PI

I21 RX002175 SPiRE Kraemer (PI) 04/01/2016 – 03/31/18

VA

Manipulating Adipose Genes to Improve Bone Healing

The overall goal of this proposal is to take advantage of the known interplay between adipose cells and osteoblasts by manipulating specific genes involved in adipose metabolism to favor the differentiation of mesenchymal stem cells into bone and, thus, accelerate bone healing following injury.

Role: PI

R01 NS070308 (Kraemer, Zhou) 04/01/11 – 03/31/18

NIH

Long-Term Cognitive Effects of Microembolization Associated with Carotid Stenting

This is an intensive five-year longitudinal study of side-effects within a population that receives carotid artery stenting for treatment of carotid artery stenosis.

Role: administrative PI (Dr. Kraemer assumed administrative PI responsibilities on this project. The original PI (Dr. Zhou) moved to another institution (University of Arizona).