BIOGRAPHICAL SKETCH

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NAME: Flynn, Charles Robb, Ph.D.

eRA COMMONS USER NAME (agency login): ROBBFLYNN

POSITION TITLE: Assistant Professor

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
Montana State University, Bozeman, MT	BS	05/1995	Biochemistry
Arizona State University, Tempe, AZ	PHD	05/2001	Molecular and Cellular Biology
Arizona State University, Tempe, AZ	Postdoctoral Fellow	08/2004	Department of Bioengineering

A. PERSONAL STATEMENT

The primary goal of my research program is to understand the molecular and physiologic mechanisms contributory to metabolic dysfunction upon the overprovision of fuels to insulin sensitive tissues, such as liver. My laboratory is multidisciplinary with individuals trained in human physiology, molecular biology, chemistry and cell biology. I routinely employ parallel high-throughput methodologies such as proteomics, lipidomics, transcriptomics and metabolomics to answer questions pertinent to insulin resistance, type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and cancer. I have a long standing interest in mechanisms regulating lipid metabolism ranging from protein trafficking to fatty acid mobilization to metabolic dysfunction and tissue deformation in liver disease.

B. POSITIONS AND HONORS

Positions and Employment

2004 - 2008	Research Assistant Professor, Arizona State University - Cntr of Metabolic Biology, Tempe, AZ
2008 -	Assistant Professor, Vanderbilt University Medical Center, Dept. of Surgery, Nashville, TN

Service

NIH External Reviewer, ZDK1-GRB-S – Biomarkers for T1D and Kidney Disease (2016)
Israeli Science Foundation, ad-hoc reviewer (2016)

Teaching

Integrated Science Course – Obesity, Vanderbilt University Medical School**.** Co-Director, 2015-16.

Honors

1999	ARCS Foundation Scholar, Achievement Rewards for College Scientists (ARCS)
2000	Assistantship for Research in Energy Transduction Mechanisms, National Science Foundation
2000	Outstanding Molecular and Cellular Biology Student of the Year, Arizona State University

C. Contributions to Science (45 publications total)

1. As a post-doctoral fellow, I applied my skills with molecular biology learned during my PhD training to generate designer recombinant proteins for pharmaceutical applications. Transgenic tobacco, alfalfa and other model systems were used to express designer codon-optimized cell-permeant vasorelaxant proteins, hydroxylated human collagen and vaccines. This work, under the direction of Drs. Colleen Brophy and Charles Arntzen led to the development of several molecules, including AZX100 (a phosphorylated HSP20 biomimetic), which was patented and ultimately developed by Orthologic, LLC. as a therapeutic for dermal scarring.

a. Flynn CR, Komalavilas P, Tessier D, Thresher J, Niederkofler EE, et al. Transduction of biologically active motifs of the small heat shock-related protein HSP20 leads to relaxation of vascular smooth muscle. *FASEB J.* 2003 Jul;17(10):1358-60. PMID: 12738803.

b. Flynn CR, Brophy CM, Furnish EJ, Komalavilas P, Tessier D, et al. Transduction of phosphorylated heat shock-related protein 20, HSP20, prevents vasospasm of human umbilical artery smooth muscle. *J Appl Physiol* (1985). 2005 May;98(5):1836-45. PMID: 15829720.

c. Flynn CR, Smoke CC, Furnish E, Komalavilas P, Thresher J, et al. Phosphorylation and activation of a transducible recombinant form of human HSP20 in Escherichia coli. *Protein Expr Purif.* 2007 Mar;52(1):50-8. PMID: 17084643; PMCID: PMC1839877.

d. Flynn CR, Cheung-Flynn J, Smoke CC, Lowry D, Roberson R, et al. Internalization and intracellular trafficking of a PTD-conjugated anti-fibrotic peptide, AZX100, in human dermal keloid fibroblasts. *J Pharm Sci.* 2010 Jul;99(7):3100-21. PMID: 20140957.

2. As part of the above activities, it became increasingly necessary to understand how post-translational modifications regulate protein activity. To this end I embarked on training to identify, quantify, and compare proteins and protein post-translational modifications in a high-throughput manner using mass-spectrometry-mediated profiling. This training spawned a series of studies examining the role of protein phosphorylation in the progression and amelioration of disease, particularly vasoconstriction, obesity and type 2 diabetes.

   a. Yi Z, Langlais P, De Filippis EA, Luo M, Flynn CR, et al. Global assessment of regulation of phosphorylation of insulin receptor substrate-1 by insulin in vivo in human muscle. *Diabetes.* 2007 Jun;56(6):1508-16. PMID: 17360977.

   b. Højlund K, Bowen BP, Hwang H, Flynn CR, Madireddy L, et al. In vivo phosphoproteome of human skeletal muscle revealed by phosphopeptide enrichment and HPLC-ESI-MS/MS. *J Proteome Res.* 2009 Nov;8(11):4954-65. PMID: 19764811; PMCID: PMC2783959.

   c. Hwang H, Bowen BP, Lefort N, Flynn CR, De Filippis EA, et al. Proteomics analysis of human skeletal muscle reveals novel abnormalities in obesity and type 2 diabetes. *Diabetes.* 2010 Jan;59(1):33-42. PMID: 19833877; PMCID: PMC2797941.

   d. Xie X, Yi Z, Bowen B, Wolf C, Flynn CR, et al. Characterization of the Human Adipocyte Proteome and Reproducibility of Protein Abundance by One-Dimensional Gel Electrophoresis and HPLC-ESI-MS/MS. *J Proteome Res*. 2010 Sep 3;9(9):4521-34. PMID: 20812759; PMCID: PMC2935302.

3. I have a strong interest in the molecular and cellular basis for metabolic dysfunction with obesity and its amelioration after bariatric surgery.

   a. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, Kin HS, Flynn CR, Hill S, Hayes McDonald W, Olivier AK, Spitz DR, Gius D. Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. *Mol Cell.* 2010 40(6):893-904. PMID: 21172655; PMCID: PMC3266626.

   b. Albaugh VL, Flynn CR, Cai S, Xiao Y, Tamboli RA, Abumrad NN. Early increases in plasma bile acids post Roux-en-Y gastric bypass are driven by insulin sensitizing, secondary bile acids. *J Clin Endocrinol Metab*. 2015 100(9):E1225-33. PMID: 26196952.

   c. Flynn CR, Albaugh VL, Cai S, Cheung-Flynn J, Williams PE, Brucker RM, Bordenstein SR, Guo Y, Wasserman DH, Abumrad NN. Bile diversion to the distal small intestine has comparable metabolic benefits to bariatric surgery. *Nat Commun*. 2015 Jul 21;6:7715. PMID: 26197299; PMCID: PMC4518285.

4. The over-provisioning of lipid to insulin sensitive tissues including muscle and liver is central to obesity and the associated metabolic dysfunction commensurate with this disease. In this setting we have worked extensively to characterize nonalcoholic fatty liver disease (NAFLD) of varying severity ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis (CIRR) to hepatocellular carcinoma. We have made considerable progress in defining the derangements underpinning this disorder at the molecular level.

a. Sharifnia T, Antoun J, Verriere TG, Suarez G, Wattacheril J, Wilson KT, Peek RM Jr, Abumrad NN, Flynn CR. Hepatic TLR4 signaling in obese NAFLD. *Am J Physiol Gastrointest Liver Physiol*. 2015 Aug 15;309(4):G270-8. PMID: 26113297; PMCID: PMC4537925.

b. Garcia AE, Kasim N, Tamboli RA, Gonzalez R, Antoun J, Eckert EA, Marks-Shulman PA, Dunn JP, Wattacheril J, Wallen T, Abumrad NN, Flynn CR. Lipoprotein Profiles in Class III Obese Caucasian and African American Women with Nonalcoholic Fatty Liver Disease. *PLoS One*. 2015 10(11):e0142676. PMID: 26599819.

c. Wattacheril J, Rose KL, Hill S, Lanciault C, Murray CR, Washington K, Williams B, English W, Spann M, Clements R, Abumrad N, Flynn CR. NAFLD Phosphoproteomics: A Functional Piece of the Precision Puzzle. *Hepatol Res.* 16:30118-22. PMID: 28390813.

d. Guo Y, Xiong Y, Flynn CR. (2016) A Micro-RNA Expression Signature of Human NAFLD Progression. Journal of Gastroenterology. 51(10): 1022-30. PMID: 26874844.

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Complete List of Published Work in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/charles.flynn.1/bibliography/40150796/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing Research Support

2015/04/01-2020/03/31
1R01DK105847-01, NIH/NIDDK
Charles Flynn, Jim Goldenring and Abumrad, Naji (contact)
Bile Diversion: A Simple and Effective Method of Treating Obesity
In this proposal we will determine how bile acids contribute to improved lipid and glucose homeostasis, insulin sensitivity and energy expenditure after bariatric surgery.
Role: co-PI

01/01/2017 – 12/31/2019
1R44 AG055184-01, Metabolic Technologies Inc. (MTI)/NIH/NIA
Rathmacher, John (PI)
2-Hydroxybenzylamine for the Prevention of Alzheimer's Disease: Initial Evaluation in Humans
We will determine in human subjects the safety and tolerability of a novel lipid peroxide scavenger termed 2-HOBA with potential therapeutic utility in preventing Alzheimer's Disease.
Role: Consultant

2013/12/19-2017/12/18
5R01HL070715-10, NIH/NHLBI
Brophy, Colleen (PI)
Prevention of Vein Graft Failure
The aims of this project are to: 1) Determine the effect of oxidative injury during surgical preparation on the post-translational modification of proteins in the human saphenous vein (HSV); and 2) Determine if reducing apoptosis and senescence, and enhancing eNOS activity during graft preparation will decrease intimal hyperplasia.
Role: KP

2001/09/21-2016/06/30
5R01DK091748-04, NIH/NIDDK
Abumrad, Naji (PI)
RYGB Improves Metabolism by Interrupting the Gastric Adipose Tissue Axis

This study addresses the mechanisms associated with these metabolic improvements immediately following bariatric surgery.
Role: Co-Investigator

Completed Research Support

2014/09/01-2015/09/31
1R43AA023715-01, Metabolic Technologies Inc. / NIAAA
Rathmacher, John (PI)
Gamma-ketoaldehyde Scavengers for Alcoholic Liver Disease
The scope of work essentially involves testing the efficacy of a novel, proprietary compound for minimizing hepatocellular injury in mouse models of alcoholic liver disease. The compound, 2-hydroxybenzylamine, if proven safe and effective, would eventually be developed into a commercial dietary supplement supporting liver health.
Role: Co-Investigator/sub-contract

2012/02/01-2016/01/31
5R01HL105731-03, NIH/NHLBI
Cheung-Flynn, Joyce (PI)
Methods to reduce vein harvest injury
The aims of this proposal are to 1) Determine the mechanism(s) by which P2X7R antagonism restores viability and functional responses after stretch injury in porcine saphenous veins and 2) Determine if stretch injury accelerates intimal hyperplasia and whether P2X7R blockade will reduce intimal hyperplasia in a porcine vein graft model.
Role: Co-Investigator