BIOGRAPHICAL SKETCH

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NAME: Merrins, Matthew

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

POSITION TITLE: Assistant 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)	END DATE MM/YYYY	FIELD OF STUDY
Oberlin College, Oberlin, OH	BA	2001	Biochemistry, Biology (Honors)
University of Michigan, Ann Arbor, MI	PHD	2008	Physiology
University of Michigan, Ann Arbor, MI	Postdoctoral Fellow	2014	Diabetes & Metabolism

A. Personal Statement

My research is focused on understanding metabolic signaling in the pancreatic islet and its deficiency in type 2 diabetes. My laboratory specializes in single-cell approaches – principally live-cell imaging and electrophysiology – with a key focus on the development of optical tools that provide new insight into diabetes pathophysiology.

B. Positions and Honors

Employment

2004 - 2005	Adjunct Professor, Washtenaw Community College
2008 - 2013	Postdoctoral Fellow, University of Michigan
2013 - 2014	Research Investigator, University of Michigan
2014 -	Research Health Scientist, WSM Memorial Veterans Hospital
2014 -	Assistant Professor of Medicine - Endocrinology, Diabetes & Metabolism, University of Wisconsin-Madison
2014 -	Assistant Professor of Biomolecular Chemistry, University of Wisconsin-Madison

Honors/Awards

2002	Systems and Integrative Biology Training Grant (NIH T32), University of Michigan
2003	Arthur J. Vander Outstanding Graduate Student Teaching Award, University of Michigan
2005	Outstanding Graduate Student Teaching Award, University of Michigan Medical School
2005	Rackham Outstanding Graduate Student Instructor Award, University of Michigan
2010	Kirschstein Postdoctoral NRSA (NIH F32), University of Michigan
2014	Research Scientist Development Award (NIH K01), University of Michigan
2016	Innovative Basic Science Award, American Diabetes Association
2017	New Investigator Award, Wisconsin Partnership Program
2017	Early Career Development Award, Central Society for Clinical and Translational Research
2018	Educational Innovation Award, University of Wisconsin-Madison

Other Professional Experience

National Grant Review Panels

2016-	American Diabetes Association (Research Grant Review Committee)
2017	NIH/NIDDK Study Section, Cellular Aspects of Diabetes and Obesity (CADO)
2018	NIH/NIDDK Study Section, Fellowships in Diabetes, Endocrinology, and Metabolic Diseases (ZDK1 GRB-2/M1)
2018	Central Society for Clinical and Translational Research (Career Development Awards)

2019 NIH/NIDDK Study Section, Human Islet Research Network/Human Pancreas Analysis Program (HIRN/HPAP-T2D U01 Clinical Trial Not Allowed)

Journal Service

2014- Ad Hoc Journal Review, *American Journal of Physiology – Endocrinology and Metabolism, Antioxidants and Redox Signaling, Biophysical Journal, British Journal of Pharmacology Diabetologia, Diabetes, Endocrinology, FASEB Journal, JCI Insight, Journal of Biological Chemistry, Journal of Neuroendocrinology, Molecular Endocrinology, Molecular Metabolism, Nature Metabolism, Physiological Reports, PLOS one, Proceedings of the National Academy of Sciences, Scientific Reports, Trends in Endocrinology and Metabolism*

2018- Editorial Board Member, *Scientific Reports*

Invited Presentations

2014 Marquette University, Department of Biology, Milwaukee, WI
2016 American Diabetes Association 76th Scientific Sessions, New Orleans, LA
2016 Yale University, Department of Cellular and Molecular Physiology, New Haven, CT
2017 UCSF Diabetes Center, San Francisco, CA
2017 Central Society for Clinical and Translational Research Annual Meeting, Chicago, IL
2017 University of Southern California Diabetes and Obesity Research Institute, Los Angeles, CA
2018 Duke Molecular Physiology Institute, Durham, NC
2018 University of Iowa Diabetes Center, Iowa City, IA
2018 Vanderbilt Islet Biology Workshop, Nashville, TN
2018 University of Southern California Diabetes and Obesity Research Institute, Los Angeles, CA
2019 University of California-Davis, Davis, CA
2019 University of Minnesota, Minneapolis, MN
2019 Medical College of Wisconsin, Milwaukee, WI [pending]
2019 University of Colorado Barbara Davis Center for Childhood Diabetes, Denver, CO
2019 American Diabetes Association 79th Scientific Sessions

C. Contribution to Science

1. Regulation of exocytosis. Dysregulation of vesicle transport, docking and fusion results in a number of debilitating neuronal and endocrine disorders. SNARE complexes mediate vesicle fusion and play essential roles in signal transduction. As organizational centers, SNAREs have been hypothesized to form dynamic protein docking hubs which can be directed by upstream signaling to fine tune the number of release competent vesicles. During my graduate work, I designed optical FRET reporters to identify the dynamic physical interactions between the t-SNARE syntaxin and its regulators Munc18c and tomosyn that limit vesicle fusion. I showed that the fusion rate is further defined by vesicle associated small GTPases whose effectors form a bridge to the SNAREs. Using electrophysiological measurements of insulin exocytosis, I determined that Rab27a, among five Rab GTPases, is a glucose-dependent but cAMP-independent effector of vesicle recruitment in pancreatic β-cells. In my laboratory, we continue to use both FRET and patch-clamp techniques to investigate the failure of islet hormone secretion in diabetes, and as a means of identifying potential therapeutic targets.

a. **D'Andrea-Merrins M**, Chang L, Lam AD, Ernst SA, Stuenkel EL (2007) "Munc18c interaction with syntaxin 4 monomers and SNARE complex intermediates in GLUT4 vesicle trafficking" *Journal of Biological Chemistry* 282, 16553–16566. PMID: 17412693.

b. Gladycheva SE, Lam AD, Liu J, **D'Andrea-Merrins M**, Yizhar O, Lentz SI, Ashery U, Ernst SA, Stuenkel EL (2007) "Receptor-mediated regulation of tomosyn-syntaxin 1A interactions in bovine adrenal chromaffin cells" *Journal of Biological Chemistry* 282**,** 22887–22899. PMID: 17545156.

c. **Merrins MJ** and Stuenkel EL (2008) "Kinetics of Rab27a-dependent actions on vesicle docking and priming in pancreatic β-cells" *Journal of Physiology* 586**,** 5367–5381. PMID: 18801842.

Highlighted in: Ullrich S. (2008) "Glucose-induced insulin secretion: is the small G-protein Rab27A the mediator of the K_{ATP} channel-independent effect?" *Journal of Physiology* 586**,** 5291. PMID: 19011133.

2. Metabolic control of insulin secretion. Insulin, like many other hormones, is secreted in pulses. These oscillations are lost in type 2 diabetics, although their origin is unclear. During my postdoctoral work, I used FRET imaging, biochemistry, and electrophysiology to test the hypothesis that glycolytic phosphofructokinase is the master oscillatory generator of the β-cell, producing downstream secretory oscillations which are essential for

effective insulin action at the liver. My studies indicate that phosphofructokinase works together with PFK2/FBPase2 and glucokinase to shape metabolic oscillations, while calcium feeds back to amplify them. These data support the "Dual Oscillator Model," a computational model which can uniquely account for the diversity of oscillatory patterns produced by the β-cell's metabolic and electrical subsystems. My lab is continuing to examine metabolic oscillations as a direct readout of β-cell metabolic health, and as an early marker of diabetes.

a. **Merrins MJ**, Fendler B, Zhang M, Sherman A, Bertram R, Satin LS (2010) "Metabolic oscillations in pancreatic islets depend on the intracellular Ca^{2+} level but not Ca^{2+} oscillations" *Biophysical Journal* 99, 76–84. PMID: 20655835.
b. **Merrins MJ**, Bertram R, Sherman A, Satin LS (2012) "Phosphofructo-2-kinase/fructose-2,6-bisphosphatase modulates oscillations of pancreatic islet metabolism" *PLOS one* 7, e34036. PMID: 22532827.
c. **Merrins MJ**, Van Dyke AR, Mapp AK, Rizzo MA, Satin LS (2013) "Direct measurements of oscillatory glycolysis in pancreatic islet β-cells using novel FRET biosensors for pyruvate kinase M2 activity" *Journal of Biological Chemistry* 288, 33312–33322. PMID: 24100037.
d. **Merrins MJ**, Poudel C, McKenna JP, Ha J, Sherman A, Bertram R, and Satin LS. (2016) "Phase Analysis of Metabolic Oscillations and Membrane Potential in Pancreatic β-cells" *Biophysical Journal* 110, 691–699. PMID: 27129239.

3. Crosstalk between β-cell metabolism and the cell cycle machinery in aging and diabetes. My independent laboratory has begun a research program to understand the effects of age on islet function. Aged β-cells from mice, but not humans, compensate for insulin resistance with the loss of inhibitory K_{ATP} channels. The mechanism of compensation in mice appears to involve cyclin-dependent kinases (CDKs), which in addition to their proliferative roles, control metabolic and secretory function in pancreatic β-cells. Both CDK1 and CDK2, which are inhibited by senescence, stimulate metabolism while inhibiting insulin secretion.

a. Gregg T, Poudel C, Schmidt BA, Dhillon RS, Sdao SM, Truchan NA, Baar EL, Fernandez LA, Denu JM, Eliceiri KW, Rogers JD, Kimple ME, Lamming DW, and **Merrins MJ** (2016) "Pancreatic β-cells from Mice Offset Age-Associated Mitochondrial Deficiency with Reduced K_{ATP} Channel Activity" *Diabetes* 65, 2700-10. PMID: 27284112.
b. De Leon ER, Gregg TA, Brinkman J, Fenske RJ, Schmidt BA, Kimple ME, Lamming DW, and **Merrins MJ** (2018) "Age-Dependent Protection of Insulin Secretion in Diet Induced Obese Mice" *Scientific Reports* 8(1), 17814. PMID: 30546031.
c. Kim SY, Lee JH, **Merrins MJ**, Gavrilova O, Bisteau X, Kaldis P, Satin LS, and Rane SG (2017) "Loss of Cyclin-Dependent Kinase 2 in the Pancreas Links Primary β-cell Dysfunction to Progressive Depletion of β-cell Mass and Diabetes" *Journal of Biological Chemistry* 292(9), 3841-3853. PMID: 28100774.
d. Gregg T, Sdao SM, Dhillon RS, Rensvold JW, Lewandowski SL, Pagliarini DJ, Denu JM, and **Merrins MJ** (2019) "Obesity-Dependent CDK1 Signaling Stimulates Mitochondrial Respiration at Complex I in Pancreatic β-cells" *Journal of Biological Chemistry* 22;294(12). PMID: 30700550.

4. Ca^{2+} and cAMP-dependent regulation of insulin secretion. Insulin secretion is modulated by intrinsic, organellar signaling, as well as by paracrine signals from neighboring islet cells. Collaborators have leveraged my laboratory's expertise with high-sensitivity measurements of β-cell mitochondrial and ER calcium. We have been instrumental in uncovering a novel link between mitochondrial fission-fusion dynamics and the metabolic amplification of insulin secretion. In addition, we developed live-cell imaging tools to quantitatively describe α-cell glucagon/GLP1 feedback on β-cell cAMP.

a. Capozzi ME, Svendsen B, Encisco SE, Lewandowski SL, Martin MD, Lin H, Coch RW, Haldeman JM, MacDonald PE, **Merrins MJ**, D'Alessio DA, and Campbell JE (2019) "β-cell tone is defined by proglucagon peptides through cyclic AMP signaling" *JCI Insight* 7;4(5). PMID: 30720465.
b. Hennings TG, Chopra DG, De Leon ER, VanDeusen HR, Choe JJ, Sesaki HS, **Merrins MJ**, and Ku GM (2018) "*In vivo* Deletion of β-cell Drp1 Impairs Insulin Secretion without Affecting Islet Oxygen Consumption" *Endocrinology* 159(9), 3245-3256. PMID: 30052866.
c. Hernandez R*, Graves SA*, Gregg T, VanDeusen HR, England CG, Valdovinos HF, Jeffery JJ, Barnhart TE, Severin GW, Nickles RJ, Kimple ME, **Merrins MJ**#, and Cai W# (2017) "Assessing Functional β-cell Mass with Radiomanganese PET" *Diabetes* 66(8), 2163. PMID: 28515126. #Co-corresponding authors

d. Johnson JS, Kono T, Tong X, Yamamoto WR, Zarain-Herzberg A, **Merrins MJ**, Satin LS, Gilon P, and Evans-Molina C (2014) "Pancreatic and duodenal homeobox protein 1 (Pdx-1) maintains endoplasmic reticulum calcium levels through transcriptional regulation of sarco-endoplasmic reticulum calcium ATPase 2b (SERCA2b) in the islet β-cell" *Journal of Biological Chemistry* 289, 32798–32810. PMID: 25271154.

5. Dietary and surgical interventions affecting glucose metabolism. My laboratory routinely lends islet biology expertise for dietary intervention studies targeted to improve glucose homeostasis. These include studies of amino acid restriction and prostaglandin signaling, which enhance glucose tolerance, health, and longevity, and bariatric surgery, currently the most effective therapy for diabetes.

a. Douros J, Niu J, Sdao SM, Gregg T, Fisher-Wellman K, Bharadwaj M, Molina A, Arumugam R, Martin M, Petretto E, **Merrins MJ**, Herman MA, Tong J, Campbell JE, and D'Alessio DD (2019) "Sleeve gastrectomy rapidly enhances islet function independent of body weight" *JCI Insight* 21;4(6). PMID: 30777938.

b. Fontana L, Cummings NE, Arriola Apelo SI, Neuman JC, Kasza I, Schmidt BA, Cava E, Spelta F, Tosti V, Syed FA, Baar EL, Veronese N, Cottrell SE, Fenske RJ, Bertozzi B, Brar HK, Pietka T, Bullock AD, Fiigenshau RS, Andriole GL, **Merrins MJ**, Alexander CM, Kimple ME, and Lamming DW (2016) "Decreased Consumption of Branched Chain Amino Acids Improves Metabolic Health" *Cell Reports* 16(2), 520-30. PMID: 27346343.

c. Neuman JC, Schaid MD, Brill AL, Fenske RJ, Kibbe CR, Fontaine DA, Sdao SM, Brar HK, Connors KM, Wienkes HN, Eliceiri KW, **Merrins MJ**, Davis DB, and Kimple ME (2017) "Enriching Islet Phospholipids with Eicosapentaenoic Acid Reduces Prostaglandin E_2 Signaling and Enhances Diabetic β-cell Function" *Diabetes* 66(6), 1572-1585. PMID: 28193789.

d. Alejandro EU, Gregg B, Wallen, T, Kumusoglu D, Meister D, Chen A, **Merrins MJ**, Satin LS, Liu M, Arvan P, and Bernal-Mizrachi E. (2014) "Maternal diet-induced microRNAs and mTOR underlie β cell dysfunction in offspring" *Journal of Clinical Investigation* 124, 4395-4410.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/matthew.merrins.1/bibliography/public/

D. Research Support

Ongoing Research Support:

NIH/NIDDK R01DK113103 (PI: Merrins) 4/1/17-3/31/22
"Metabolic functions of pyruvate kinase M2 (PKM2) in pancreatic β-cells"
Goals: Identify the requirement for PKM2 in insulin secretion using β-cell specific PKM2 knockout mice and a combination of proteomics, live cell imaging and electrophysiological approaches.

NIH/NIA R01AG062328 (**PI: Merrins**; PI: Lamming) 9/30/18-5/31/23
"*Comparative analysis of geroprotective interventions in novel mouse models of Alzheimer's disease"*
Goals: Evaluate geroprotectors for the treatment of Alzheimer's disease at the *in vivo* and cellular levels.

NIH/NIA R01AG056771 (PI: Lamming; **Co-I: Merrins**) 1/1/18-12/31/22
"The regulation of health and longevity by branched-chain amino acids"
Goals: Examine how aging and longevity is regulated by dietary branched chain amino acids.

NIH/NIDDK R01DK123075 (PI: Campbell; **Co-I: Merrins**) 1/1/23-12/31/25
"Mechanisms of insulin secretion mediated by alpha cells"
Goals: Understand whether the β-cell response to α-cells is critical for normal glucose homeostasis.

VA BLR&D 1I01 BX003700 (PI: Kimple; **Co-I: Merrins**) 10/1/17-09/30/21
"G protein-mediated mechanisms of β-cell death, dysfunction, and decompensation in diabetes"
Goals: Examine how β-cell health is regulated by prostaglandin E2 signaling via Gaz.

VA BLR&D 1I01 BX004921 (PI: Setaluri; **Co-I: Merrins**) 10/1/19-09/30/23
"Role of EPAC Signaling in Melanoma Progression"
Goals: Examine how EPAC signaling regulates melanoma growth and progression.

UW-Madison 2020 Award (PI: Audhya; **Co-I: Merrins**) 5/1/18-4/30/20
"Advancing CRISPR-mediated genome editing technology at UW-Madison to model human disease"
Goals: Achieve large sequence insertions into the mouse genome using CRISPR.

UW-Madison 2020 Award (PI: Audhya; **Co-I: Merrins**) 5/1/19-4/30/21
"Lightsheet fluorescence microscopy: shared instrumentation to visualize biology in four dimensions"
Goals: Achieve large sequence insertions into the mouse genome using CRISPR.

HRSA Postdoctoral T32 (PI: Foster; **Mentor: Merrins**) 6/1/18-5/30/20
"Effects of amino acids on metabolic health"
Goals: Understand the effects of amino acids on nutrient-stimulated insulin secretion.

Completed Research Support:

NIH/NIDDK K01DK101683 (PI: Merrins) 4/1/14-3/31/17
"Cyclin-dependent kinase 2 (Cdk2) function in pancreatic β-cells"
Goals: Identify the targets of Cdk2 in the β-cell secretory pathway.

NIH/NIA R21AG050135 (**PI: Merrins**; PI: Lamming) 5/1/16-4/30/18
"Analysis of age-associated changes in β-cell function and metabolism through single-cell imaging"
Goals: Identify age-related defects in the metabolic and secretory pathways of pancreatic β-cells.

NIH/NIA R21AG050135 (**PI: Merrins**; PI: Lamming) 9/1/17-4/30/18
"Administrative Supplement to Existing Award AG050135 to Develop Research on Alzheimer's Disease"
Goals: Identify the metabolic processes altered in Alzheimer's disease using cellular and animal models.

American Diabetes Association 1-16-IBS-212 (PI: Merrins) 1/1/16-12/31/18
Innovative Basic Science Award
"Cyclin-dependent kinase 1 (Cdk1) effector pathways as novel targets for type 2 diabetes"
Goals: Identify the specific steps in the β-cell secretory pathways that are altered by Cdk1 signaling.

Central Society for Clinical and Translational Research (PI: Merrins) 5/1/17-4/30/18
Early Career Development Award
"Rewiring islet metabolism to prevent and rescue type 2 diabetes"
Goals: Manipulate β-cell glycolytic enzymes to enhance insulin secretion in diabetic islets.

Wisconsin Partnership Program New Investigator Award (PI: Merrins) 2/1/17-1/31/18 (NCE)
"Reprogramming β-cell metabolism to prevent and rescue type 2 diabetes"
Goals: Test the efficacy of manipulating β-cell metabolism to enhance secretory function.