BIOGRAPHICAL SKETCH

Steering Committee, Senior Trainer

NAME: Michelle E. Kimple, PhD

eRA COMMONS USER NAME: PLISKEMI

POSITION TITLE: Associate Professor of Medicine-Endocrinology and Director of the Basic Science Selective, University of Wisconsin-Madison School of Medicine and Public Health; Research Health Scientist, William S. Middleton Memorial VA Hospital

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YYYY	FIELD OF STUDY
Michigan State University	B.S.	05/1998	Biology (honors)
University of North Carolina-Chapel Hill	Ph.D.	05/2003	Biochemistry & Biophysics
Duke University	Postdoctoral	06/2010	Pharmacology & Islet Biology

A. Personal Statement

During my PhD work at UNC-Chapel Hill, I received extensive training in GPCR pharmacology and mechanisms of G protein signaling. I put this technical expertise to bear in my post-doc, where I initiated a collaborative project spanning the research programs of my co-mentors, Drs. Pat Casey and Chris Newgard, to determine the role of the alpha-subunit of the unique inhibitory G protein, G_z, in the pancreatic beta-cell. My key finding that $G\alpha_z$ acts as a tonic brake on beta-cell cAMP production and glucose-stimulated insulin secretion (GSIS) [**1,2**] led to a K01 proposal to determine whether loss of $G\alpha_z$ would protect mice from developing glucose intolerance when subject to high-fat diet-induced obesity [**3**]. I continue to study the role of G_z and its associated receptor, EP3, in the regulation of beta-cell function and mass, but have also expanded on this work to develop a new overarching model that specific G protein-mediated signaling pathway "hubs," both those mediated by heterotrimeric and monomeric G proteins (including Rap1) are absolutely crucial to the ability of the beta-cell to mount a compensatory increase in functional beta-cell mass in response to insulin resistance or the immune insult of type 1 diabetes. My interest in studying the interplay among intracelluar beta-cell signaling networks began during my post-doctoral training [**4**], and has continued throughout my independent research career. I have trained a number of basic science and clinical pre-doctoral and post-doctoral trainees in translational diabetes research, and as an iPEND T32 trainer, my trainees will study the roles of these critical intra-islet cell signaling mechanisms in mouse and human beta-cells and tissues, translating basic science findings into identifying novel therapeutic targets for improving beta-cell function and maintaining or augmenting functional beta-cell mass in type 1 and type 2 diabetes.

1. **Kimple ME,** Nixon AB, Kelly P, Bailey CL, Young KH, Fields TA, and Casey PJ. (2005) *A role for $G\alpha_z$ in beta-cell biology*. J Biol Chem. 280: 31708-13.
2. **Kimple ME**, Joseph JW, Bailey CL, Fueger PT, Hendry IA, Newgard CB, and Casey PJ (2008) *$G\alpha_z$ negatively regulates insulin secretion and glucose clearance.* J Biol Chem. 283: 4560-7.
3. **Kimple ME**[#], Moss JB, Brar HK, Rosa TC, Truchan NA, Pasker RL, Newgard CB, Casey PJ (2012) *Deletion of $G\alpha_z$ protein protects against diet-induced glucose intolerance via expansion of β-cell mass.* J Biol Chem. 287: 20344-55. PMCID: PMC3370216. [#]corresponding author.
4. Pagliarini DJ, Wiley SE, **Kimple ME**, Dixon JR, Kelly P, Worby CA, Casey PJ, and Dixon JE. (2005) *Involvement of a mitochondrial phosphatase in the regulation of ATP production and insulin secretion in pancreatic beta cells*. Molecular Cell 22: 197-207.

B. Positions and Honors

Professional Positions:

2010-2012 Associate Scientist, Medicine (Endocrinology), University of Wisconsin-Madison
2012-2017 Assistant Professor, Medicine (Endocrinology), University of Wisconsin-Madison
2012- Endocrinology Researcher, William S. Middleton Memorial Veterans Hospital (Madison VA), Madison, Wisconsin.
2014- Co-Director, UW Department of Medicine Mouse Metabolic Phenotyping Platform (M2P2) at the Madison VA.
2016- Faculty Affiliate, Department of Cell and Regenerative Biology, University of Wisconsin-Madison

2018- Associate Professor, Medicine (Endocrinology), University of Wisconsin-Madison
2018- Director of the UW SMPH Basic Science Selective, Department of Academic Affairs, University of Wisconsin-Madison School of Medicine and Public Health
2018- Research Health Scientist, William S. Middleton Memorial VA Hospital

Editorial Boards:

2014- *Nutrition and Diabetes* (Nature Publishing Group)
2019- *Diabetes* (American Diabetes Association)

Professional Memberships:

American Society for Biochemistry and Molecular Biology (ASBMB), American Society for Pharmacology and Experimental Therapeutics (ASPET), The Endocrine Society, Women in Endocrinology, American Diabetes Association (ADA), American Physiological Society (APS)

Other Professional Experience:

2015 **NIH Early Career Study Section Member,** Cellular Aspects of Diabetes and Obesity (CADO), Feb 19-20 2015, Bethesda, MD
2015 **Ad-Hoc NIH Study Section(s) Member**, Clinical and Integrative Diabetes and Obesity (CIDO), June **&** CADO/Molecular and Cellular Endocrinology (MCE) Special Emphasis Panel, Nov.
2015 **Ad-Hoc NIH Study Section Member**, CADO/Molecular and Cellular Endocrinology (MCE) Special Emphasis Panel, Nov.
2016 **Ad-Hoc NIH Study Section(s) Member**, Endocrinology, Metabolism, Nutrition and Reproductive Sciences IRG (EMNR) Special Emphasis Panel, July **&** MCE, October.
2017 **Ad-Hoc NIH Study Section Member**, MCE, June 2017
2018 **Ad-Hoc NIH Study Section Member**, CADO, Feb 2018
2019 **Ad-Hoc NIH Study Section(s) Member**, Diabetes Endocrinology and Metabolism (DEM) Fellowship Review Panel, June **&** "Human Islet Research Network - Consortium on Targeting and Regeneration (HIRN-CTAR) (U01 Clinical Trial Not Allowed), June
2016-present **Standing Member**, American Diabetes Association Research Grant Review Committee

Honors (PhD training-present):

1998-1999 J. Logan Irvin Fellowship, UNC-Chapel Hill (Merit award to one incoming Biochemistry & Biophysics graduate student per year)
1998-2000 UNC-Chapel Hill Molecular and Cellular Biophysics Training Program (T32), Fellow
2001 ASBMB Graduate Travel Award to Experimental Biology 2001, Orlando, FL
2003-2004 Duke Comprehensive Cancer Center Fellowship, Duke University
2003-2004 Duke Training Grant in Digestive Diseases (T32), Fellow
2004-2006 Ruth L. Kirschstein National Research Service Award (F32), NIH/NIDDK
2005 Travel Award to Gordon Research Conference on Phosphorylation & G-Protein Mediated Signaling Networks, Biddeford, ME
2006-2007 Preparing Future Faculty Fellowship, Duke University Postdoctoral Association
2007 Postdoctoral Travel Award to Keystone Symposium on Diabetes: Molecular Genetics, Signaling Pathways and Integrated Physiology, Keystone, CO
2008 ASBMB Postdoc Travel Award to Experimental Biology 2008, San Diego, CA
2008-2011 Mentored Research Scientist Development Award (K01), NIH/NIDDK
2009 ASPET Postdoc Travel Award to Experimental Biology 2009, New Orleans, LA
2012 ASBMB/JBC Drug Development Theme Poster Award, Experimental Biology 2012
2013 Hilldale Undergraduate/Faculty Research Fellowship, Mentor (with Harpreet Brar, B.S.)
2013 ASPET Zannoni Summer Undergraduate Research Fellowship, Mentor (with Allison Brill, B.S.)
2015 ADA Minority Undergraduate Internship Award, Mentor (Mark T. Cadena, trainee)
2016 ASPET Translational and Clinical Pharmacology Division Early Career Faculty Showcase, Experimental Biology 2016, San Diego, CA.
2016 UW Madison Department of Medicine Puestow Research Award (awarded to junior Medicine faculty making a significant research contribution towards advancing the field of medicine)
2018 Vilas Life Cycle Professorship, UW-Madison Women in Science & Engineering Leadership Institute (WISELI) & Office of the Provost

C. Contributions to Science

PGE_2, EP3, and $G\alpha_z$ signaling and the regulation of beta-cell function, proliferation, survival and mass
My work from my post-doctoral training to the present day identified a key role for signaling mediated by $G\alpha_z$, and its associated receptor, EP3, in the loss of functional beta-cell mass in type 1 and type 2 diabetes. Functional beta-cell mass is dramatically upregulated in high-fat-diet-fed $G\alpha_z$-null mice (reference **[3]** in Personal Statement). $G\alpha_z$ loss synergizes with a sub-therapeutic dose a GLP-1 receptor agonist, exendin-4, to preserve beta-cell function and increase survival and replication in a multiple-low-dose streptozotocin induction model of diabetes in mice (MLD-STZ) **[5]**. The manuscript reporting the results of this study was the May 2016 *Molecular Endocrinology* "Featured Article," and first author, Allison Brill, was awarded the Endocrine Society's 2016 "*Molecular Endocrinology* Trainee Author Award." $G\alpha_z$-null non-obese diabetic (NOD) mice are completely protected from developing diabetes in a beta-cell centric manner **[6]**.

My post-doctoral research identified E prostanoid receptor 3 (EP3) as specifically coupled to G_z in the beta-cell (references **[1]** and **[3]** in personal statement). EP3 expression and production of its endogenous ligand, PGE_2, are significantly increased in primary islets isolated from T2D mice and humans **[7].** An EP3 antagonist restores beta-cell function **[7].** A published patent establishes EP3 as a therapeutic target for the beta-cell dysfunction and loss of functional beta-cell mass in T2D humans resistant to therapy with GLP-1 receptor agonists(Keller, Attie, and Kimple, 2016). A 2017 *Diabetes* article confirmed EPA enrichment, thus reducing production of PGE_2 in favor of PGE_3, improves diabetic beta-cell function and reduces inflammatory markers and immune cell infiltration in both T2D (BTBR-Ob) and T1D (NOD) mouse models **[8]**. This comprehensive work was impactful: a commentary accompanied our work, by Dr. R. Paul Robertson, an undisputed leader in the field (Robertson RP: The COX-2/PGE_2/EP3/$G_{i/o}$/cAMP/GSIS Pathway in the Islet: The Beat Goes On. Diabetes. 2017: 1464-1466; PMCID: PMC5440014).

1. Brill, AL, Wisinski, JA, Cadena, MT, Thompson, MR, Fenske, RJ, Brar, HK, Schaid, MD, Pasker, RL, and **Kimple, ME** (2016) *Synergy between $G\alpha_z$ deficiency and a GLP-1 receptor agonist in preserving functional beta-cell mass in experimental diabetes.* Molecular Endocrinology 30: 543-56. PMCID: PMC4853566.
2. Fenske, RJ†, Cadena, MT†, Harenda, QE, Wienkes, HN, Carbajal, K, Schaid, MD, Laundre, E, Brill, AL. Truchan, NA, Brar, H, Wisinski, JA, Cai, J, Graham, TE, Engin, F, and **Kimple, ME** (2017) The inhibitory G-protein α-subunit, $G\alpha_z$, promotes Type 1 diabetes-like pathophysiology in NOD mice. Endocrinology 158: 1645-58. †co-first authors. PMCID: PMC5460933
3. **Kimple ME**#, Keller MP, Rabaglia MR, Pasker RL, Neuman JC, Truchan NA, Brar HK, and Attie AD (2013) *Prostaglandin E2 receptor, EP3, is induced in diabetic islets and negatively regulates glucose- and hormone-stimulated insulin secretion.* Diabetes 62: 1904-12. PMCID: PMC3661627. #corresponding author.
4. 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: 1572-85. PMCID: PMC5440023

Delineating the role of Rap1/mTORC1 in cellular function, proliferation, and survival. Rap1 has long-been known as an important player in the amplification pathway of insulin secretion. We replicated this work in both mouse and human islets in a 2010 JBC publication **[9]**. Our work was the first to show cAMP-activated Rap1 acts through non-canonical activation of mechanistic target of rapamycin complex 1 (mTORC1) to promote beta-cell replication. Rap1 also augmented beta-cell size through an mTORC1-independent pathway, possibly through direct interaction with mTORC2. These results identify Rap1 as an ideal target to augment functional beta-cell mass, particularly in individuals taking immunosuppressive therapies. A direct link to upstream EP3:$G\alpha_z$ signaling was confirmed in collaborative work among our group and those Richard Breyer and Maureen Gannon, finding an EP3 antagonist synergizes with prolactin to promote human and mouse beta-cell proliferation in a rapamycin-sensitive manner **[10]**. We extended our studies of the requirement for mTORC1 signaling in the beta-cell and glucose homeostasis through collaborative work with the lab of Dudley Lamming. The mTORC1 inhibitor, rapamycin, has been proposed as an anti-aging therapy; yet, chronic administration leads to detriments in functional beta-cell mass, even in lean animals. Together with the Lamming group, we identified three intermittent rapamycin dosing protocols that preserved functional beta-cell mass while promoting changes in mTORC1 signaling pathways that improved healthy lifespan in mice **[11]**.

The critical role of Rap1 in cell proliferation was further confirmed in a collaborative work with the lab of Vijay Setaluri, identifying Rap1 as a molecular switch controlling primary melanoma cell growth vs. metastatic melanoma cell proliferation and metastasis **[12]**. One of the most intriguing conclusions from this work is that Epac/Rap1 controls melanoma proliferation and metastatic potential, regardless of the underlying mutational status of the carcinoma, suggesting precision medicine therapies targeted towards activated Braf or Ras will be completely ineffective in patients with metastatic disease and that the Epac/Rap1 axis might be a much better therapeutic target. In addition, the links between the effects of Rap1 in the beta-cell and in carcinoma cells provide a potential model for the poorer outcomes of individuals with metastatic melanoma who are co-morbid for type 2 diabetes.

1. Kelly P, Bailey CL, Fueger PT, Newgard CB, Casey PJ, and **Kimple ME** (2010) *Rap1 promotes multiple pancreatic islet cell functions and signals through mammalian target of rapamycin complex 1 to enhance proliferation.* J Biol Chem 285:15777-85. PMCID: PMC2871445
2. Carboneau, BA, Allan, JA, Townsend, SE, **Kimple, ME**, Breyer, RM, and Gannon, M (2017) Opposing effects of Prostaglandin E_2 Receptors EP3 and EP4 on Mouse and Human β-Cell Survival and Proliferation. Molecular Metabolism 6(6): 548-59. PMCID: PMC5444094
3. Arriola Apelo, SI, Neuman, JC, Baar, EL, Syed, F, Cummings, NE, Brar, HK, Pumper, C, **Kimple, ME**, and Lamming, DW. (2015) Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. Aging Cell 15: 28-38. PMCID: PMC4717280
4. Rodriguez, CI, Castro-Perez, E, Wisinski, JA, Block, L, Prabhakar, K, Longley, JB, **Kimple, ME**, and Setaluri, V. (2017) EPAC-RAP1 axis-mediated switch in the response of melanoma cells to cyclic AMP signaling during melanoma progression. Molecular Cancer Research 15(12): 1792-1802. PMCID—PMC Journal in Process

Dietary interventions to improve glucose metabolism and diabetic/insulin resistant phenotypes. Diet is well-known to impact beta-cell function and metabolic health. A collaborative *AJP-GLP* work between my group and the Kudsk group revealed the gastrin releasing peptide-like analog, bombesin, preserved both exocrine and endocrine pancreas cell function and mass in a mouse model of total parenteral nutrition (TPN) **[13]**. As TPN is often used in critical care situations, sometimes for extended periods, this therapeutic approach has the potential to relieve the re-feeding syndrome often associated with the return of individuals to enteral feeding.
A series of papers with our close collaborator, Dr. Dudley Lamming, explored the impact of diets deficient in BCAAs or methionine—essential amino acids—on longevity and metabolic health **[14,15,16]**. In all cases, my group defined the impact of these diets on beta-cell function and mass; a critical phenotype to characterize when reporting on whole-body glucose homeostasis. I anticipate this collaboration between our groups to continue and to be long and fruitful.

1. Pierre JF, Neuman JC, Brill AL, Brar HK, Thompson MF, Cadena MT, Connors KM, Busch RA, Heneghan AF, Cham CM, Jones EK, Kibbe CR, Davis DB, Groblewski GE, Kudsk KA, **Kimple ME** (2015) *The Gastrin Releasing Peptide Analog, Bombesin, Preserves Exocrine and Endocrine Pancreas Morphology and Function during Parenteral Nutrition.* Am J Physiol Gastrointest Liver Physiol. 309: G431-42. PMCID: PMC4572409
2. 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, A.D., Figenshau, R.S., Andriole, G.L., Merrins, M.J., Alexander, C.M., **Kimple, ME**, and Lamming, DW. (2016) Decreased Consumption of Branched Chain Amino Acids Improves Metabolic Health. Cell Reports 15: 520-30. PMCID: PMC4947548
3. Cummings, NE, Williams, EM, Kasaza, I, Nonon, EN, Schaid, MD, Schmidt, BA, Poudel, C, Sherman, DS, Yu, D, Arriola Apeulo, SI, Cotrell, SE, Geiger, G, Barnes, ME, Wisinski, JA, Fenske, RJ, Matkowskyj, KA, **Kimple, ME**, Alexander, CM, Merrins, MJ, and Lamming, DW. (2018) Restoration of metabolic health by decreased consumption of branched-chain amino acids. The Journal of Physiology. 596(4): 623-645. PMCID—PMC Journal in Process
4. Yu**,** D, Yang, S, Miller, B, Wisinski, JA, Sherman, D, Brinkman, J, Tomasiewicz, J, Cummings, NE, **Kimple, ME**, Cryns, V, and Lamming, DW. Short-term methionine deprivation improves metabolic health independently of mTORC1 and induces sexually dimorphic response. The FASEB Journal. 32(6): 3471-3482. PMCID—PMC Journal in Process

Other intracellular players in beta-cell function, proliferation, and survival. In a collaboration with Dr. Dawn Davis, we showed the putative transcription factor, Tcf19, is necessary for a full proliferation and survival effect

in a well-accepted rat beta-cell model line, INS-1 **[17]**. A second collaborative work with the Davis group identified beta-cell cholecystokinin as a paracrine regulator of alpha cell GLP-1 production and downstream effects on beta-cell function **[18]**. A collaborative work among the Kimple, Lamming, and Merrins' groups identified the role of the K_{ATP} channel in the beta-cell dysfunction of aging, revealing mice with enhanced beta-cell function in aging actually had down-regulated K_{ATP}-channel function and/or activity **[19]**. Finally, my expertise in G protein signaling was tapped by collaborator and former UW-Madison colleague, Sushant Bhatnagar, in his characterization of a G protein ligand/receptor pair, C1ql3 and BAI3, and the role this pathway plays in diabetic beta-cell dysfunction **[20]**. This work was recently accepted for publication in *JBC*.

1. Krautkramer KA, Linnemann AK, Fontaine DA, Whillock AL, Harris TW, Schleis GJ, Truchan NA, Marty-Santos L, Lavine JA, Cleaver O, **Kimple ME**, and Davis DB. (2013) *Tcf19 is a novel islet factor necessary for proliferation and survival in the INS-1 β-cell line.* Am J Physiol Endocrinol Metab 305: E600-10. PMCID: PMC3761170
2. Linnemann AK, Neuman JC, Battiola TJ, Wisinski JA, **Kimple ME** and Davis DB (2015) *Glucagon-Like Peptide-1 Regulates Cholecystokinin Production in β-Cells to Protect From Apoptosis*. Mol Endocrinol 29: 978-87. PMCID: PMC4484781
3. 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. PMCID: PMC5001174
4. Koltes, JE, Gupta, R, Schaid, MD, Appakalai, B, Kim, J, **Kimple, ME**, and Bhatnagar, S. The Complement 1q-like 3 secreted protein acts as an inhibitor of insulin secretion from pancreatic β-cells. J Biol Chem. 293: 18066-98. PMCID—PMC Journal in Process

Please find my full bibliography at:

http://www.ncbi.nlm.nih.gov/sites/myncbi/michelle.kimple.1/bibliography/41160290/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

I01 BX003700-01A1, VA BLR&D — Kimple (PI) — 04/01/18-03/31/22
G-protein-mediated mechanisms of beta-cell death, dysfunction, and decompensation in diabetes
The goals of this project are (1) determine the differential effects of $G\alpha_z$ signaling stimulated by specific EP3 receptor splice variants and transmitted through different downstream effectors on mechanisms mediating the K_{ATP}-channel dependent and -independent glucose-stimulated insulin secretion process, and (2) validate a potential new role for $G\alpha_z$ in the α-cell.

R01 DK102598, NIH/NIDDK — Kimple (PI) — 09/10/14-06/30/19
Molecular mechanisms of dysfunctional prostaglandin signaling in the beta-cell
The goals of this project are to (1) Identify the role of arachidonic acid membrane incorporation and release in diabetic β-cell dysfunction; (2) Determine the role of C-terminal splice variants of the EP3 isoform of the PGE_2 receptor in coupling to G protein signaling partners; and (3) Elucidate the signaling mechanisms downstream of EP3 in regulating β cell function, replication, and survival.

UW2020 Initiative — Kimple, Davis, and Cox (Co-PIs) — 06/01/18-05/30/20
Building a Translational Research Pipeline to Personalize Diabetes Prevention and Treatment
The goals of this project are to standardize and coordinate patient biosample collection and preservation at the UW, creating a biobank resource associated with de-identified clinical and demographic data to serve as a resource for diabetes and obesity researchers across campus. In Year 2, unbiased genomic and metabolomic studies will be performed, the results of which will similarly be available for campus researchers to mine.

Completed Research Support

Innovative Basic Science Award, American Diabetes Association — Kimple (PI) — 01/01/14-12/31/16
Arachidonic Acid Metabolism and Beta-Cell Dysfunction: Beyond COX-2
The goals of this project were to identify key differences in the arachidonic acid (AA) metabolome in non-diabetic and type 2 diabetic beta-cell models, as well as identify different steps in the AA metabolism process beyond the rate-limiting COX-2 enzyme that might serve as therapeutic targets for T2D beta-cell dysfunction.