BIOGRAPHICAL SKETCH

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NAME: **Michelle E. Kimple, PhD**

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

POSITION TITLE: **Assistant Professor of Medicine**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date 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

The goal of the proposed research is to determine the effect of a reduction in specific dietary amino acids on improved glycemic control in a pre-clinical model, as well as the molecular mechanisms mediating such improved control. I have the expertise, leadership and motivation necessary to successfully collaborate with Dr. Lamming in carrying out the proposed work. First, I have a broad background in biochemistry and pharmacology, with specific training and expertise in signal transduction, G proteins and G protein-coupled receptor signaling in the beta-cell. I have a history of peer-reviewed contributions to the general field proposed in the application, including three publications in the *Journal of Biological Chemistry* (Kimple, M.E., et al., 2005, 2008, and 2012) and *Diabetes* (Kimple, M.E., et al., 2013). I have a proven track record as PI on several university, foundation, and NIH-funded grants, and this research builds logically off of an existing collaboration between Dr. Lamming's and my groups. I am confident that with his own expertise, together with those of his chosen collaborators and consultants, Dr. Lamming will be able to make significant and impactful contributions to delineating the mechanism by which protein reduction impacts on glycemic control.

B. Positions and Honors

Professional Positions:

2010-2012 Associate Scientist, Medicine (Endocrinology), University of Wisconsin-Madison
2012- 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.

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), American Heart Association (AHA)

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 Member**, Clinical and Integrative Diabetes and Obesity (CIDO), June 4-5 2015, Bethesda MD

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 '09, 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)

C. Contributions to Science

1. Structural Studies of Proteins Regulating Heterotrimeric G protein Signaling Cascades: My Ph.D. research sparked my interest in the regulation of heterotrimeric guanine nucleotide binding protein (G protein) signaling cascades. My thesis work in the Sondek and Siderovski labs at UNC-Chapel Hill was focused on structure/function analysis of proteins involved in the *Drosophila* phototransduction cascade, a model for G_q-coupled signaling pathways. My specific project was to determine the atomic-resolution structure of the N-terminal PDZ domain of the scaffolding protein Inactivation no afterpotential D (InaD) with the C-terminal domain of the Drosophila phospholipase C-β isozyme, No receptor potential A (NorpA). This structure revealed the formation of an intermolecular disulfide bond between INAD and NorpA, a rare type of interaction for intracellular proteins and one that suggested possible regulation by the redox potential of the cell[a]. Using this unique structure, we hypothesized and confirmed that the InaD PDZ/NorpA C terminal interaction could be utilized in protein affinity tagging, with the release step catalyzed by a reducing agent such as dithiothreitol[b]. Based on this work, we submitted our idea for a novel protein affinity and purification tag for patent protection, which was granted in 2007 and licensed by Novartis[c]. Fascinatingly, other PDZ domains of InaD were later shown by other groups to also be redox-regulated, supporting our initial findings (Mishra et al., 2007, Cell 131: 80-92; Liu et al., 2011, Cell 145: 1088-101).

In addition to my primary thesis work, I also assisted in determining the atomic-resolution structure of $G\alpha_{i1}$ in complex with a peptide corresponding to the GoLoco domain of RGS14, a negative regulator of G protein signaling[d]. This structure led us to hypothesize about the nature of GoLoco/Gα interaction specificity, which we tested and confirmed *in vitro*. This work was highly impactful and has been cited over 200 times (via Google Scholar).

a. Kimple ME, Siderovski DP, and Sondek J (2001) *Functional relevance of the disulfide-linked complex of the N-terminal PDZ domain of InaD with NorpA.* EMBO Journal 20: 4414-22. PMID: 11500369
b. Kimple ME and Sondek J (2002) *Affinity tag for protein purification and detection based on the disulfide-linked complex of InaD and NorpA*. Biotechniques 33: 578, 580, 584-8 passim. PMID: 12238768
c. Kimple ME and Sondek J (2007) *Purifying target proteins using post-synaptic density 95, discs-large and zonular occludens (PDZ1) domain and a no receptor potential A (NorpA) sequence soluble matrix.* U.S. Patent No. 7,309,575; Issued Dec. 18, 2007.
d. Kimple RJ, Kimple ME, Betts L, Sondek J, and Siderovski DP (2002) *Structural determinants for GoLoco-induced inhibition of nucleotide release by Galpha subunits*. Nature. 416: 878-81. PMID: 11976690

2. Delineating the role of $G\alpha_z$ in pancreatic β-cell biology: When I began my post-doctoral training, a preliminary characterization of Ins-1 (832/13) rat insulinoma cells revealed that they expressed $G\alpha_z$, suggesting a role for $G\alpha_z$ in regulating β-cell function. I confirmed that Ins-1 (832/13) $G\alpha_z$ could be activated by endogenous receptors on the β-cell surface, and that one of the functions of β-cell $G\alpha_z$ is to inhibit glucose-stimulated insulin secretion (GSIS) by regulating cyclic AMP production[e]. This was one of the first physiological roles for endogenous $G\alpha_z$ that had ever been described.

In a lean $G\alpha_z$ knockout mouse, I demonstrated that, other than $G\alpha_z$ expression, there were no significant differences between the gross islet morphology; islet protein, DNA, or insulin content; or insulin sensitivity of wild-type and $G\alpha_z$-null mice. $G\alpha_z$-null mice did, however, have significantly increased plasma insulin concentrations and a corresponding increase in glucose clearance following glucose challenge. Islets isolated from $G\alpha_z$-null mice had significantly increased glucose-stimulated insulin secretion, supporting the phenotype of the $G\alpha_z$-null mouse being specific for loss of β-cell $G\alpha_z$[f]. This work further distinguished $G\alpha_z$ signaling from that of the other $G\alpha_i$ subfamily members, which are all inhibitory towards adenylate cyclase, and suggested a tonic inhibition of $G\alpha_z$ on adenylate cyclase. Interestingly, our suggestion of non-redundant roles for $G\alpha_{i/o}$-subfamily members in pancreatic islets was supported by the Birnbaumer and Jang groups in 2010 with their phenotyping of $G\alpha_{o2}$ knockout mice (Wang Y et al., 2010, PNAS 108: 1693-8) [14].

Finally, to explore the role of $G\alpha_z$ in the development of diabetes, I subjected wild-type and $G\alpha_z$-null mice to an extended high-fat diet. $G\alpha_z$-null mice were completely protected from developing glucose intolerance, apparently due to a significant increase in β-cell replication and mass[g]. This work, which marked the start of my independent research program, garnered me invitations for six local, one regional, and thirteen national/international seminars. Furthermore, these findings suggested that $G\alpha_z$ might also be a therapeutic target for type 1 diabetes (T1D), where stimulation and maintenance of increases in β-cell mass might be curative. Leveraging my preliminary data from the T2D model, I successfully applied for funding from the JDRF to confirm the relevance of the $G\alpha_z$ pathway in T1D using chemical and genetic mouse models. Our first study is soon to be published[h], and after extensive backcrossing, we have now duplicated in these results in the Non-Obese Diabetic (NOD) mouse model (manuscript in preparation).

e. Kimple ME, Nixon AB, Kelly P, Bailey CL, Young KH, Fields TA, and Casey PJ (2005) *A role for G(z) in pancreatic islet beta-cell biology.* J Biol Chem. 280: 31708-13. PMID: 16157560

f. 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. PMID: 18096703

g. Kimple ME, Moss JB, Brar HK, Rosa TC, Truchan NA, Pasker RL, Newgard CB, Casey PJ (2012) *Deletion of GαZ protein protects against diet-induced glucose intolerance via expansion of β-cell mass.* J Biol Chem. 287: 20344-55. PMID: 22457354

h. Brill, AL, Wisinski, JA, Cadena, MT, Thompson, MR, Brar, HK, Pasker, RL, Fenske, RL, and Kimple, ME (2015) *Synergy between Gαz deficiency and a GLP-1 receptor agonist in preserving functional beta-cell mass.* Reviewed at and in revision for Mol Endocrinol.

3. Other Intracellular Players in the Regulation of Pancreatic Beta-cell Function and Mass: I began my study of Rap1 in β-cell biology due to the ability of activated $G\alpha_z$ to bind to its negative regulator, Rap1GAP, and recruit it to the plasma membrane. I showed that active Rap1 leads to increased islet glucose-stimulated insulin secretion, beta-cell size, and beta-cell proliferation: three downstream processes that can become dysfunctional in T2D[i]. Using constitutively-active variants of Rap1 and other related monomeric G proteins, we showed that only Rap1 led to activating phosphorylation of ribosomal protein S6 (RPS6), one of the terminal targets in the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) signaling pathway. mTORC1 had already been shown to be important for regulation of growth and proliferation pathways in islets, but we demonstrated that cAMP-mediated activation of mTORC1 through Rap1 was independent of PI3K and Akt, the canonical upstream regulators of the mTORC1 pathway. Rap1 activation of mTORC1 was also dependent on Rheb, suggesting a mechanism whereby Rap1 recruits the inhibitory Tsc1/2 complex away from Rheb, allowing Rheb to activate mTORC1.

My expertise with the mTORC1 pathway in the beta-cell has led to a new collaboration with Dudley Lamming, PhD, an assistant professor in my division and a nascent leader in the field of aging research. Rapamycin is a commonly-used immunosuppressive that has been proposed to ameliorate aging pathologies, but it has the undesirable side effect of blocking beta-cell function and replication. Our laboratories have shown that intermittent rapamycin dosing can provide the positive effects of rapamycin on whole-body metabolism, while preserving beta-cell function and mass. This work is in preparation and is likely to be of high impact[j].

Finally, I have contributed to two studies elucidating novel roles for the incretin hormones GLP-1 and bombesin in regulating pancreatic beta-cell function and mass. My laboratory helped to delineate that one of the mechanisms by which GLP-1 protects beta-cells from death is by up-regulating islet production of another peptide hormone, cholecystokinin[k]. Finally, our work with bombesin in a total parenteral nutrition model revealed that its effects on the beta-cell were mediated by an indirect pathway, though the promotion of GLP-1 secretion from the gut, resolving a significant controversy in the literature[l].

i. 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. PMID: 20339002

j. Arriola Apelo, SI, Neuman, JC, Baar, EL, Syed, F, Cummings, NE, Brar, HK, Pumper, C, Kimple, ME, and Lamming, DW (2015) *An intermittent treatment regimen mitigates deleterious consequences of rapamycin treatment*. Accepted for publication in Aging Cell.

k. 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. PMID: 26153246

l. 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. in press. PMID: 26185331

4. Delineating the role of the EP3 receptor in diabetic beta-cell dysfunction: In my initial publication on $G\alpha_z$ in the beta-cell (Kimple, JBC, 2005), I found that prostaglandin E1 (PGE1) reduced insulin secretion in a pertussis-toxin sensitive manner, suggesting that PGE1 was acting through G_z and not any other G_i proteins. When I moved to the UW-Madison in 2010, Mark Keller in Alan Attie's lab searched their microarray database for "G protein," and I immediately saw that EP3, a receptor for E prostanoids such as PGE1, was specifically up-regulated in islets from diabetic BTBR-Ob mice as compared to lean or non-diabetic mice. Upon confirming that EP3 was specifically up-regulated in diabetic islets by qRT-PCR, I found the primary endogenous ligand for EP3, prostaglandin E2 (PGE2), was also specifically up-regulated in diabetic islets. Ultimately, I confirmed that the PGE2/EP3 interaction could be targeted by a specific receptor antagonist to improve diabetic beta-cell function in both mouse and human islets[m]. The findings from this publication, for which I served as corresponding author, were used as the basis of a patent application on EP3 as a novel diabetes drug target[n]. This work has been very well-received; I or my trainees have been asked to present this work orally at three local, three regional, and ten national/international venues. Dr. Attie has continued to pursue the drug development aspects of this project, while my laboratory has continued pursue the mechanistic characterization upstream and downstream of the EP3 receptor (forming the basis for the currently-funded R01), as well as the translational aspects of targeting this receptor.

Besides targeting the EP3 receptor with a specific antagonist, I proposed that individuals with higher PGE2 production might be preferentially resistant to the effects of beta-cell diabetes drugs that work through the stimulatory G protein-coupled receptor, GLP-1. I was awarded a PhRMA Foundation Translational Medicine and Therapeutics Starter Grant to study this hypothesis in a human population. An interim analysis of or results confirms our initial hypotheses, and will be presented at the 2015 Endocrine Society Meeting by my Endocrine Fellow, Alicia Weeks, MD[o]. Due to the excellence of her abstract and career development aspirations, Alicia was awarded one of only two Women in Endocrinology/Endocrine Society Early Career Travel Awards to present her work. Furthermore, her abstract was pulled out for special presentation at the 15th Annual Rachmiel Levine Diabetes and Obesity Symposium, which will be held at City of Hope prior to ENDO 2015.

m. 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. PMID: 23349487

n. Keller M, Attie A and Kimple ME (2013) E-*prostanoid receptor, ptger3, as a novel anti-diabetic therapeutic target*, US patent application 20130244932 A1.

o. Weeks, AC, Dart M, Li X, Davis DB, and Kimple ME (2015) *The Impact of Prostaglandin E2 levels on glycemic control and therapeutic response in human subjects with type 2 diabetes mellitus*, Presented at ENDO 2015, San Diego, CA, March 2015.

Please find my full bibliography at: http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/41160290/

D. Research Support

Ongoing Research Support

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 determine the molecular mechanisms regulating EP3 coupling to its upstream and downstream effectors in the non-diabetic and type 2 diabetic beta-cell, and how these pathways become dysfunctional in the diabetic state.
Role: PI

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 are to identify the key differences in the arachidonic acid metabolome in non-diabetic and type 2 diabetic beta-cell models.
Role: PI

Translational Medicine Starter Grant, PhRMA Foundation Kimple (PI) 10/01/13-9/30/15
Using Plasma Prostaglandin E2 Levels to Customize Type 2 Diabetes Therapy
The goal of this project is to conduct a clinical study, enrolling type 2 diabetes patients to determine whether their initial plasma PGE2 metabolite levels correlate with their degree of diabetes control or any other clinical or demographic parameters. For any patients who have not begun therapy with an incretin-based therapeutic, we will follow them at 6 months to determine their response to the therapy.
Role: PI

Completed Research Support

JDRF grant 17-2011-608 Kimple (PI) 09/01/11-02/27/14
Mechanisms for augmenting residual beta-cell mass
The goal of this study is to determine whether Gαz-null mice are protected from loss of beta-cell mass and resulting hyperglycemia in classical mouse models of type 1 diabetes, and to explore the mechanisms conferring said protection.
Role: PI

Translational Research Pilot Grant, UW-ICTR Kimple (PI) 09/01/12-02/27/14
Plasma PGE2 as biomarker for human beta-cell function
The goal of this project is to determine whether the plasma PGE2 metabolite levels in human organ donors correlates with their diabetic status and/or response of their isolated islets to GPCR agonists and antagonists that act through the EP3 receptor.
Role: PI