BIOGRAPHICAL SKETCH

Senior Trainer

NAME: Lamming, Dudley William

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

POSITION TITLE: Assistant Professor, University of Wisconsin-Madison
Research Health Scientist, William S. Middleton VA Memorial Hospital

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	FIELD OF STUDY
Massachusetts Institute of Technology	B.S.	06/2000	Nuclear Engineering
Harvard University	Ph.D.	03/2008	Experimental Pathology
Whitehead Institute for Biomedical Research	Postdoctoral	12/2013	

A. Personal Statement

I am an Assistant Professor in the Department of Medicine at the University of Wisconsin-Madison, with a joint appointment as a Research Health Scientist at the William S. Middleton Memorial Veterans Hospital (WSM VAH). I also serve as co-director of the UW Department of Medicine Mouse Metabolic Phenotyping Platform (M2P2), housed in the WSM VA animal facility. The primary focus of my laboratory is to understand the mechanisms by which nutrient signaling pathways regulate metabolism and age-related diseases, including diabetes and obesity, with a goal of identifying translatable interventions to promote human health. In particular, we are now investigating the physiological and molecular mechanisms by which the levels of dietary protein and specific dietary amino acids regulate health and longevity through studies in cell culture, *in vivo* in mice, and in the clinic in humans.

I have mentored 51 trainees in my research laboratory at UW-Madison. My first postdoctoral trainee, Dr. Sebastian Arriola Apelo, competed successfully for an American Diabetes Association fellowship. I currently mentor 2 Ph.D. postdoctoral associates, one VA Advanced Fellow in Women's Health, and four Ph.D. graduate students; three of these have passed their qualifying exams, and two have competed successfully for fellowships, including the T32 Biology of Aging Program (AG000213) and the American Heart Association (17PRE33410983); this later student has received approval to defend his thesis in June. Other laboratory trainees currently include one master's student, one post-bac trainee, and twelve undergraduate students. I am committed to maintaining a diverse training environment, with 3 of my 7 current graduate and postdoctoral trainees being members of underrepresented minorities.

B. Positions and Honors

Positions and Employment (since 2014)

2014- **Assistant Professor**, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI

2014- **Research Health Scientist**, William S. Middleton Memorial Veterans Hospital, Madison WI (01/2014-07/2018, WOC; 07/2018-present, GS-13)

2014- **Co-Director**, UW Department of Medicine Mouse Metabolic Phenotyping Platform (M2P2)

Other Experience and Professional Memberships

2005- American Aging Association
- 2015- Editorial Board Member, *GeroScience* (formerly *AGE*)
- 2017- Elected to the **Board of Directors** and as **Secretary**

2011- Gerontological Society of America
- 2014- Editorial Board Member and **Associate Editor** (2018-present), *The Journals of Gerontology, Series A: Biological Sciences*

2016-2018 Biological Sciences Section Representative, GSA Membership Committee
2017- Elected **Secretary** of the GSA Biological Sciences Section

2013- **Scientific Advisory Board Member**, Aeonian (formerly Delos) Pharmaceuticals
2014- Member, UW-Madison Institute on Aging and UW Carbone Cancer Center, Madison WI
2015- **Associate Editor**, Nutrition and Healthy Aging
2016- Member, International Society on Aging and Disease
2016 Early Career Reviewer, NIH Molecular and Cellular Endocrinology Study Section
2017- International Collaborator, MouseAGE (EU COST ACTION)
2017- Member, American Physiological Society
2018- Member, **American Federation for Aging Research National Scientific Advisory Council**
2018-2020 Member, American Diabetes Association Research Grant Review Committee

University of Wisconsin Graduate Program Affiliations (selected)

Biology of Aging Training Grant; Interdepartmental Graduate Program in Nutritional Sciences Training Program; Endocrinology and Reproductive Physiology; Cell and Molecular Biology; Physiology; Genetics

Teaching Experience (since 2014)

2014- Guest Lecturer — Seminar in Nutrition (NS 931); Advanced Topics: Molecular Control of Metabolism and Metabolic Disease (Biochem 729); Seminar in Endocrinology-Reproductive Physiology (AN SCI 954); Molecular Pharmacology Seminar Series (PHMCOL-M 901); Biology of Aging Training Grant Seminar Series; Obesity and Diabetes, (NS 625), UW-Madison
2014- **Course Director** – Introduction to Research in the Division of Endocrinology, UW-Madison
2015- Instructor – Molecular Control of Metabolism and Metabolic Disease (Biochem 375) and Instructor – Pathogenesis of Major Human Diseases (Path 803), UW-Madison
2016- Instructor – Cell and Molecular Biology of Aging (Path 751), UW-Madison
2019- **Course Director** – Endocrinology and Metabolism (Medicine 720), UW-Madison

Honors and Awards

1996 National Finalist, Westinghouse Science Talent Search, Washington, D.C.
2002-2007 Predoctoral Trainee, NEI T32 Vision Training Grant
2005 Finalist, Best Student Presentation, American Aging Association Annual Meeting, Oakland, CA
2005 Albert J. Ryan Fellow, Albert J. Ryan Foundation
2007 AFAR Dorothy Dillon Eweson Lecture Series Travel Award, San Antonio, NM
2008-2011 NIA F32 Ruth L. Kirschstein National Research Service Award
2009, 2012 Whitehead Institute Postdoctoral Association Education Award
2011 Best Oral Presentation, American Aging Association Annual Meeting, Raleigh, NC
2012 Charles A. King Trust Postdoctoral Fellowship
2012 Aging Research Network Travel Award, Fort Worth, TX
2012 NIA Summer Training Course in Experimental Aging Research Award
2012-2017 NIA K99/R00 Pathway to Independence Award
2013 Whitehead Institute for Biomedical Research Appreciation Award
2013 Anatomical Society *Aging Cell* Best Paper Prize
2013 Best Minireview of 2013, *Cell Metabolism*
2015 American Federation for Aging Research Grant for Junior Faculty
2015 Glenn Award for Research in Biological Mechanisms of Aging
2016 Wisconsin Partnership Program New Investigator Program Award
2016 Travel Award to the Annual Meeting of the CSCTR and MWAFMR
2016 Central Society for Clinical Research – Early Career Development Award
2017 Elected Fellow of the Gerontological Society of America
2018 Elected Fellow of the American Aging Association
2018 American Physiological Society (Endocrinology & Metabolism Section) New Investigator Award
2018 Gerontological Society of America, Nathan Shock New Investigator Award

C. Contributions to Science (Selected from 51 peer-reviewed publications)
(* indicates authors contributed equally, # indicates co-corresponding author)

A major focus of my laboratory at UW-Madison is **understanding how nutrient signaling pathways regulate metabolism and health** at both the physiological and molecular level. Diets with reduced caloric intake (e.g.

calorie restriction, CR) or altered macronutrient content (e.g., protein restriction, PR) promote metabolic health, but the precise dietary components as well as the molecular mechanisms that mediate these effects have remained elusive. We have determined that both CR and PR reduce insulin/IGF-1/PI3K/mTOR signaling, and that specifically reducing consumption of the three branched chain amino acids (BCAAs) – leucine, isoleucine, and valine – recapitulates many of the metabolic benefits of a PR diet.

a. Mercken EM, Crosby SD, **Lamming DW**, *et al*. Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. *Aging Cell*. 2013; 12(4):645-51. PMID: 23601134; PMCID: PMC3714316. – Awarded *Aging Cell* 2013 Best Paper Prize by the Anatomical Society

b. **Lamming DW**[#], Cummings NE, Rastelli AL, Gao F, Cava E, Bertozzi B, Spelta F, Pili R, Fontana F[#]. Restriction of dietary protein decreases mTORC1 in tumors and somatic tissues of a tumor-bearing mouse xenograft model. *Oncotarget*, 2015; 6(31):31233-40. PMID: 26378060; PMCID: PMC4741600.

c. 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, Figenshau RS, Andriole GL, Merrins MJ, Alexander CM, Kimple ME, **Lamming DW**[#]. Decreased consumption of branched chain amino acids improves glycemic control. *Cell Reports*, 2016; 16(2):520-30. Epub 2016 Jun 23. PMID: 27346343 PMCID: PMC4947548.

d. Cummings NE, Williams EM, Kasza I, Konon EN, Schaid MD, Schmidt BA, Poudel C, Sherman DS, Yu D, Sebastian I. Arriola Apelo, Cottrell SE, Geiger G, Barnes ME, Wisinski JA, Fenske RJ, Matkowskyj KA, Kimple ME, Alexander CM, Merrins MJ, **Lamming DW**. *Restoration of metabolic health by decreased consumption of branched-chain amino acids*. *J Physiology*, 2018 Feb 15; 596(4):623-645. doi: 10.1113/JP275075. Epub 2017 Dec 27. PMID: 29266268 PMCID: PMC5813603.

Rapamycin, which robustly extends the lifespan of mice, is best known as an acute inhibitor of mTORC1. We determined that **chronic rapamycin treatment inhibits mTORC2 *in vivo***, causing hepatic insulin resistance. This work has significantly impacted biological research in the field of aging, as many of the effects of rapamycin previously attributed inhibition of mTORC1 must be reassessed to determine the role of mTORC2. Our findings have significant translational impact, as they suggest that specifically targeting mTORC1 can promote healthy aging while minimizing negative side effects.

a. **Lamming DW***, Ye L*, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, Davis JG, Salmon AB, Richardson A, Ahima RS, Guertin DA, Sabatini DM, Baur JA. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science*. 2012; 335(6076):1638-43. Epub 2012/03/31. PMID: 22461615; PMCID: PMC3324089.

   Highlighted in: Hughes K and Kennedy B. Rapamycin Paradox Resolved. *Science.* 2012; 335:1578
   Ray LB. Dissecting Rapamycin Responses. *Sci. Signal.* 2012; 5(218): ec103.
   mTOR: The Master Regulator. *Cell*. 2012; 149(5): 955-7.
   Piquet AC, Martins PJ, Kozma SC. *J Hepatol.* 2012; 57(6): 1368-9.

b. **Lamming DW**, Ye L, Astle CM, Baur JA, Sabatini DM, Harrison DE. Young and old genetically heterogeneous HET3 mice on a rapamycin diet are glucose intolerant but insulin sensitive. *Aging Cell*. 2013; 12(4):712-8. PMID: 23648089; PMCID: PMC3727050.

c. **Lamming DW**, Demirkan G, Boylan JM, Mihaylova MM, Peng T, Ferreira J, Neretti N, Salomon A, Sabatini DM, Gruppuso PA. Hepatic signaling by the mechanistic target of rapamycin complex 2 (mTORC2). *FASEB J*. 2014; 28(1):300-15. PMID: 24072782; PMCID: PMC3868844.

d. **Lamming DW**[#], Mihayalova MM, Katajisto P, Baar EL, Yilmaz OH, Hutchins A, Gultekin Y, Gaither R, Sabatini DM[#]. Depletion of Rictor, an essential protein component of mTORC2, decreases male lifespan. *Aging Cell* 2014; 13(5): 911-7. PMID: 25059582 PMCID: PMC4172536.

We hypothesized that the side effects of rapamycin could be reduced through dosing regimens that more specifically target mTORC1. Our work has demonstrated that **intermittent administration of rapamycin reduces side effects while still promoting longevity**.

a. Arriola Apelo SI, Neuman JC, Baar EL, Syed FA, Cummings NE, Brar HK, Pumper CP, Kimple ME, **Lamming DW**. Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. *Aging Cell.* 2016; 15(1):28-38. doi: 10.1111/acel.12405. Epub 2015 Oct 13. PMID: 26463117; PMCID: PMC4717280.

b. Arriola Apelo SI, Pumper CP, Baar EL, Cummings NE, **Lamming DW**. Intermittent administration of rapamycin extends the lifespan of female C57BL/6J mice. *J Geron Biol Sci,* 2016, Apr 18. pii: glw064. PMID: 27091134 PMCID: PMC4906329.

c. Arriola Apelo SI, **Lamming DW**. Rapamycin: An InhibiTOR of Aging Emerges From The Soil of Easter Island. *J Geron Biol Sci,* 2016, May 21. pii: glw090. PMID: 27208895; PMCID: PMC4906330.

d. Kennedy BK and **Lamming DW**. The mechanistic Target of Rapamycin: The grand conducTOR of metabolism and aging. *Cell Metabolism,* 2016; 23(6):990-1003. PMCID: PMC4910876.

We have collaborated broadly to understand **how nutrient-responsive signaling pathways including mTOR are affected by aging and disease** in diverse tissues.

a. Yilmaz OH, Katajisto P, **Lamming DW**, *et al*. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie intake. *Nature*. 2012; 486(7404):490-5. PMID: 22722868; PMCID: PMC3387287.

b. Baar EL, Carbajal KA, Ong IO, **Lamming DW**. Sex- and tissue-specific changes in mTOR signaling with age in C57BL/6J mice. *Aging Cell.* 2016; 15(1):155-66. Epub 2015 Nov 24. PMCID: PMC4717274.

c. Tran CM, Mukherjee S, Ye L, Frederick DW, Kissig M, Davis JG, **Lamming DW**, Seale P, Baur JA. Rapamycin blocks induction of the thermogenic program in white adipose tissue. *Diabetes*, 2016; 65(4):927-41. PMID: 26858361. PMCID: PMC4806661.

d. Gregg T, Poudel C, Schmidt, BA, Dhillon RS, Sdao SM, Truchan N, Baar EL, Fernandez, LA, Denu JM, Eliceiri KW, Rogers JD, Kimple ME, **Lamming DW**[#], Merrins MJ[#]. Pancreatic β cells from Mice Offset Age-Associated Mitochondrial Deficiency with Reduced KATP Channel Activity. *Diabetes*. 2016; 65(9):2700-10. PMID: 27284112; PMCID: PMC5001174.

Yeast Sir2 is a NAD^+-dependent histone deacetylase that regulates lifespan. As a graduate student, **I explored the regulation of the Sir2 family of genes (sirtuins) by nutrients and resveratrol**.

a. Howitz KT, Bitterman KJ, Cohen HY, **Lamming DW**, ***et al.*** Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature*. 2003; 425(6954):191-6. PMID: 12939617.

Highlighted in: Finkel T. Ageing: a toast to long life. *Nature*. 2003; 425(6954): 132-3.

b. **Lamming DW***, Latorre-Esteves M*, Medvedik O*, Wong SN*, Tsang FA, Wang C, Lin SJ, Sinclair DA. HST2 mediates SIR2-independent life-span extension by calorie restriction. *Science*. 2005; 309(5742):1861-4. PMID: 16051752.

Highlighted in: Rine J. Twists in the tale of the aging yeast. *Science.* 2005; 310(5751): 1124-5.

c. Medvedik O*, **Lamming DW***, Kim KD, Sinclair DA. MSN2 and MSN4 link calorie restriction and TOR to sirtuin-mediated lifespan extension in Saccharomyces cerevisiae. *PLoS Biol*. 2007; 5(10):e261. PMID: 17914901; PMCID: PMC1994990.

d. Hubbard BP, Gomes AP, Dai H, Li J, Case AW, Considine T, Riera TV, Lee JE, E SY, **Lamming DW**, *et al*. Evidence for a common mechanism of SIRT1 regulation by allosteric activators. *Science*. 2013; 339(6124):1216-9. PMID: 23471411; PMCID: PMC3799917.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43848875/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

NIH/NIA R21AG050135 Lamming (PI) and Merrins (PI) 05/01/16-04/30/19 (no cost extension)
Exploratory/Developmental Research Grant Award
Analysis of age-associated changes in beta cell function and metabolism through live single-cell imaging
This grant will identify age-related changes in beta cell function and metabolism using *ex vivo* islet imaging.

UW-Madison Department of Medicine Dudley Lamming (PI) and Dawn Davis (PI) 06/01/2016-05/30/2019
Research Pilot Award
The metabolic response to reduced branched chain amino acids in humans
This pilot grant will determine if reducing dietary BCAAs using BCAA-free medical food is feasible in humans.

Delos Pharmaceuticals Dudley Lamming (PI) 08/03/2017-05/31/2019
Sponsored Research Agreement

Metabolic effects of rapamycin analogs
The goal of this project is to examine the effect of novel rapamycin analogs on mTOR signaling in cell culture.

NIH/NIA R21AG051974 Dudley Lamming (PI) 09/15/2017-03/31/2019
Exploratory/Developmental Research Grant Award
Intervention in Progeria by Alterations in dietary macronutrient Composition
This grant will identify diets with low mTORC1 activity and test the effect of these diets on the longevity, healthspan and cardiac function of a new mouse model of Hutchinson-Gilford Progeria Syndrome.

NIH/NIA R01AG056771 Dudley Lamming (PI) 01/01/2018-12/31/2022
Research Project Grant
The regulation of health and longevity by branched-chain amino acids
The goal of this project is to determine if reducing dietary BCAAs promotes healthspan and longevity, if BCAAs are involved in the response to dietary interventions, and to examine the effect of BCAAs on hepatocyte glucose metabolism using novel biosensors

VA/BLR&D BX004031 Dudley Lamming (PI) 07/01/2018-06/30/2022
Merit Review Award
Promoting metabolic health through the reduction of dietary branched chain amino acids
To determine the specific metabolic effects of each (BCAA) in the context of obesity and pre-diabetes, and in genetically heterogeneous mice, and to examine the role of GCN2 in the metabolic response to BCAAs.

NIH/NIA R01AG062328 Lamming (PI) and Merrins (PI) 09/30/2018–05/31/2023
Research Project Grant
Comparative analysis of geroprotective interventions in established and novel mouse models of Alzheimer's disease
This project will test several geroprotective interventions in established early-onset and novel late-onset mouse models of AD, and determine if geroprotectors can rescue the cellular metabolic defects of AD neurons.

Completed Research Support (selected, past 3 years):

Wisconsin Partnership Program Dudley Lamming (PI) 03/01/16-02/28/19 (no cost extension)
WPP New Investigator Program Grant
Improved glycemic control through reduction of specific dietary amino acids
This grant will investigate if altering dietary essential amino acids can protect mice fed a diabetogenic diet.

American Federation for Aging Research Dudley Lamming (PI) 07/01/15-06/30/18
AFAR Research Grant for Junior Faculty *Sexual dimorphism in response to longevity interventions*
This grant examines the mechanistic basis for the sexually dimorphic impact of pro-longevity interventions

NIA R00AG041765 Dudley Lamming (PI) 01/01/14-12/31/17
Pathway to Independence Award *The in vivo regulation of glucose homeostasis and lifespan by mTORC2*
This Pathway to Independence Award focused on the role of mTORC2 during aging and a CR diet.

Glenn Foundation for Medical Research Dudley Lamming (PI) 09/15/15-09/14/17
Glenn Award for Research in Biological Mechanisms of Aging
This research award was used to augment research into the biological mechanisms of aging