BIOGRAPHICAL SKETCH

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NAME: Lamming, Dudley William

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

POSITION TITLE: Assistant Professor, University of Wisconsin-Madison
Research Scientist (WOC), 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 MM/YYYY	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 and a Research Scientist (WOC) at the William S. Middleton Memorial Veterans Hospital; I also serve as co-director of the UW Department of Medicine Mouse Metabolic Phenotyping (M2P2) platform, housed in the WSM VA animal facility. The primary focus of my laboratory, located in the WSM VA Hospital, is to understand the mechanisms by which nutrient signaling pathways regulate metabolism and age-related diseases, including diabetes. As a result of my postdoctoral work at the Whitehead Institute in Cambridge, MA, I am very familiar with the literature on the regulation of glucose homeostasis and metabolism by the diet, as well as the practical challenges of conducting metabolic studies in mice. My prior work on metabolism and diabetes, my current location at an institute housing world-class facilities for the study of mouse physiology and metabolism such as the M2P2, and my shared laboratory space with Dr. Merrins, who possesses unique metabolic imaging capabilities, make me an ideal candidate to lead the proposed studies. As PI, I will be responsible for regulatory requirements, the data collection plan, supervision of study personnel and the overall conduct of the project. I will be actively involved in all aspect of the study design, including (i) implementation and supervision of personnel; (ii) participation in the design and execution of laboratory experiments; (iii) data interpretation; (iv) manuscript preparation; and (v) dissemination, including presentation of results at national meetings.

The following is a breakdown of my 100% effort: Research-85%, Teaching/Mentoring-10%, Administration-5%.

B. Positions and Honors

Positions and Employment

2000-2002 Associate Scientist, Enanta Pharmaceuticals, Watertown MA
Team Leader: John Benson, Ph.D.
2011 Instructor, Advanced Undergraduate Seminar Program, MIT, Cambridge, MA
Supervisor: H. Robert Horvitz
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 Scientist (WOC), William S. Middleton Memorial Veterans Hospital, Madison WI
2014- Co-Director, UW Department of Medicine Mouse Metabolic Phenotyping Platform (M2P2)

Other Experience and Professional Memberships

2005- Member, American Aging Association
2011- Member, Gerontological Society of America
2014- Editorial Board Member, The Journals of Gerontology, Series A: Biological Sciences
2014- Member, UW-Madison Institute on Aging, University of Wisconsin, Madison, WI
2014- Member, UW Carbone Cancer Center, University of Wisconsin, Madison WI

2014- Affiliate Member, Wisconsin Alzheimer's Disease Research Center, Madison, WI
2014- Faculty, UW-Madison Endocrinology and Reproductive Physiology Graduate Training Program; Interdepartmental Graduate Program in Nutritional Sciences Training Program; Graduate Program in Cell and Molecular Biology; Physiology Graduate Training Program; and Genetics Training Program, Madison, WI
2015- Editorial Board Member, AGE, the Official Journal of the American Aging Association

Teaching Experience

2003 Teaching Assistant - Molecular Biology (BCMP 200), Harvard Medical School, Boston, MA. Course Instructors: Stephen Buratowski and Johannes Walter
2011 Course Instructor - Advanced Undergraduate Seminar: The Biology of Aging: Age-Related Diseases and Interventions (7. 342), MIT, Cambridge, MA. Course Instructors: Dudley Lamming and Eric Bell, Supervisor: H. Robert Horvitz
2014 Guest Lecturer — Seminar in Nutrition (Nutritional Sciences 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); and Biology of Aging Training Grant Seminar Series. University of Wisconsin-Madison, Madison, WI.
2015 Guest Lecturer – August Krogh Seminar Series, Copenhagen, Denmark

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 Whitehead Institute Postdoctoral Association Education Award
2011 Best Oral Presentation, American Aging Association Annual Meeting, Raleigh, NC
2012 Whitehead Institute Postdoctoral Association Education Award
2012 Charles A. King Trust Postdoctoral Fellowship
2012 Aging Research Network Travel Award, Fort Worth, TX
2012- 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 Progeria Research Foundation Innovator Award

C. Contribution to Science (* indicates authors contributed equally, # indicates co-corresponding author)

1. The major focus of my laboratory at the WSM VA Hospital and UW Madison is understanding at both the physiological and molecular level how nutrient signaling pathways regulate metabolism and aging. The mTOR protein kinase is a master regulator of many metabolic processes, and the inhibition of mTORC1 significantly extends lifespan in organisms including yeast, worms, flies and mice. Treatment of mice with rapamycin (discussed below) also disrupts a second mTOR complex, mTORC2. We have determined that genetic inhibition of mTORC2 significantly impairs the lifespan of male (but not female) mice, which may explain the sexually dimorphic impact of pharmaceutical and genetic interventions in the insulin/IGF-1/mTOR signaling pathway. We are now exploring methods of specifically inhibiting mTORC1, through alternative rapamycin treatment regimens and dietary interventions, and we have determined that a low protein diet can specifically inhibit mTORC1 signaling *in vivo*.

    a. **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. doi: 10.1111/acel.12256. PubMed PMID: 25059582 PMCID: PubMed Central PMCID: PMC4172536.

    b. **Lamming DW**. Diminished mTOR signaling: a common mode of action for endocrine longevity factors. *SpringerPlus* 2014; 3:735. doi: 10.1186/2193-1801-3-735. PMID: 25674466 PMCID: PMC4320218.

c. **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, in press.

d. 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* 2015, in press.

2. Rapamycin has attracted significant attention as a robust pharmaceutical intervention that can extend mammalian lifespan. My postdoctoral studies aimed at understanding the *in vivo* physiological effects of rapamycin, specifically focusing on the mechanism by which mTOR regulates glucose homeostasis and insulin sensitivity. While rapamycin is best known as an acute inhibitor of mTORC1, we determined that chronic rapamycin treatment also inhibits mTORC2 *in vivo*, causing hepatic insulin resistance in C57BL/6 inbred mice as well as genetically heterogeneous HET3 mice. This work has significantly impacted biological research in the field of aging, as many of the effects of rapamycin, including the extension of lifespan, previously attributed solely to inhibition of mTORC1 must be reassessed to determine the role of mTORC2. We have conducted further studies to define the specific role of hepatic mTORC2 at the genomic and phosphoproteomic level. Our findings have significant translational impact, as they suggest that pharmaceutical interventions that more specifically target mTORC1 may be able to promote health and longevity while avoiding the negative impacts of rapamycin on glucose metabolism.

   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. doi: 10.1126/science.1215135. PubMed PMID: 22461615; PubMed Central PMCID: PMC3324089.

      Highlighted in: Hughes K and Kennedy B. Rapamycin Paradox Resolved. *Science.* 2012; 335:1578-9.
      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. Rapamycin impacts positively on longevity, despite glucose intolerance induction. *J Hepatol.* 2012; 57(6): 1368-9.

   b. **Lamming DW**, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest*. 2013; 123(3):980-9. Epub 2013/03/05. doi: 10.1172/JCI64099. PubMed PMID: 23454761; PubMed Central PMCID: PMC3582126.

   c. **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. doi: 10.1111/acel.12097. PubMed PMID: 23648089; PubMed Central PMCID: PMC3727050.

   d. **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. doi: 10.1096/fj.13-237743. PubMed PMID: 24072782; PubMed Central PMCID: PMC3868844.

3. The gold-standard for lifespan interventions is a calorie restricted (CR) diet, which extends healthspan and longevity in many model organisms including mice. While the precise mechanism by which mTOR signaling regulates lifespan is unknown, it has been suggested that a CR diet may act in part by regulating mTOR signaling. In this body of work, performed with several teams of collaborators, I found links between mTOR signaling and CR in yeast, mice, and humans. This work suggests that many important effects of a CR diet on health and longevity may be mediated by changes in mTOR signaling.

   a. 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. doi: 10.1371/journal.pbio.0050261. PubMed PMID: 17914901; PubMed Central PMCID: PMC1994990.

   b. Yilmaz OH, Katajisto P, **Lamming DW**, Gultekin Y, Bauer-Rowe KE, Sengupta S, Birsoy K, Dursun M, Yilmaz VO, Selig M, Nielson GP , Mino-Kenudson M, Zukerberg LR, Bhan AK, Deshpande V, Sabatini DM. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie

intake. *Nature*. 2012; 486(7404):490-5. doi: 10.1038/nature11163. PubMed PMID: 22722868; PubMed Central PMCID: PMC3387287.

Highlighted in: Harris TE, Thorner MO. Caloric restriction in mTORC1 control of intestinal homeostasis. *Cell Metab*. 2012; 16(1): 6-8.
Ramos FJ and Kaeberlein M. Ageing: A healthy diet for stem cells. *Nature*. 2012; 486: 477-8.

c. Mercken EM, Crosby SD, **Lamming DW**, JeBailey L, Krzysik-Walker S, Villareal DT, Capri M, Franceschi C, Zhang Y, Becker K, Sabatini DM, de Cabo R, Fontana L. Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. *Aging Cell*. 2013; 12(4):645-51. doi: 10.1111/acel.12088. PubMed PMID: 23601134; PubMed Central PMCID: PMC3714316.

Awarded *Aging Cell* 2013 Best Paper Prize by the Anatomical Society

d. **Lamming DW**, Anderson RM. Metabolic effects of caloric restriction. In *eLS.* 2014. John Wiley & Sons, Ltd. doi: 10.1002/9780470015902.a0021316.pub2.

4. After the initial discovery that rapamycin disrupted mTORC2 *in vivo*, I realized that many of the biological effects of long-term rapamycin treatment could potential stem from inhibition of mTORC2. With many collaborators, I investigated the role of mTORC2 in muscle and the immune system, and determined the persistence of the effects of rapamycin *in vivo*.

a. Ye L, Varamini B, **Lamming DW**, Sabatini DM, Baur JA. Rapamycin has a biphasic effect on insulin sensitivity in C2C12 myotubes due to sequential disruption of mTORC1 and mTORC2. *Front Genet*. 2012; 3:177. doi: 10.3389/fgene.2012.00177. PubMed PMID: 22973301; PubMed Central PMCID: PMC3438685.

b. Byles V, Covarrubias AJ, Ben-Sahra I, **Lamming DW**, Sabatini DM, Manning BD, Horng T. The TSC-mTOR pathway regulates macrophage polarization. *Nature Communications*. 2013; 4:2834. doi: 10.1038/ncomms3834. PubMed PMID: 24280772; PubMed Central PMCID: PMC3876736.

c. Ye L, Widlund AL, Sims CA, **Lamming DW**, Guan Y, Davis JG, Sabatini DM, Harrison DE, Vang O, Baur JA. Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance. *Aging*. 2013; 5(7):539-50. PubMed PMID: 23929887; PubMed Central PMCID: PMC3765582.

d. Liu Y, Diaz V, Fernandez E, Strong R, Ye L, Baur JA, **Lamming DW**, Richardson A, Salmon AB. Rapamycin-induced metabolic defects are reversible in both lean and obese mice. *Aging.* 2014; 6(9):742-54. PubMed PMID: 25324470; PubMed Central PMCID: PMC4221917.

5. The yeast protein Sir2 is a NAD^+-dependent histone deacetylase that regulates lifespan. In this body of work, to which I contributed as a graduate student, I explored the role of the Sir2 family of genes (sirtuins) in the response to nutrient restriction. With collaborators both inside and outside my graduate laboratory, I also examined how mammalian sirtuins are activated in response to nutrient depravation, and determined a potential mechanism by which resveratrol can directly activate sirtuins.

a. Howitz KT, Bitterman KJ, Cohen HY, **Lamming DW**, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, Sinclair DA. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature*. 2003; 425(6954):191-6. doi: 10.1038/nature01960. PubMed 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. doi: 10.1126/science.1113611. PubMed PMID: 16051752.

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

c. Yang H, Yang T, Baur JA, Perez E, Matsui T, Carmona JJ, **Lamming DW**, Souza-Pinto NC, Bohr VA, Rosenzweig A, de Cabo R, Sauve AA, Sinclair DA. Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. *Cell*. 2007; 130(6):1095-107. doi: 10.1016/j.cell.2007.07.035. PubMed PMID: 17889652; PubMed Central PMCID: PMC3366687.

d. Hubbard BP, Gomes AP, Dai H, Li J, Case AW, Considine T, Riera TV, Lee JE, E SY, **Lamming DW**, Pentelute BL, Schuman ER, Stevens LA, Ling AJ, Armour SM, Michan S, Zhao H, Jiang Y,

Sweitzer SM, Blum CA, Disch JS, Ng PY, Howitz KT, Rolo AP, Hamuro Y, Moss J, Perni RB, Ellis JL, Vlasuk GP, Sinclair DA. Evidence for a common mechanism of SIRT1 regulation by allosteric activators. *Science*. 2013; 339(6124):1216-9. doi: 10.1126/science.1231097. PubMed PMID: 23471411; PubMed Central PMCID: PMC3799917.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/dudley.lamming.1/bibliography/43848875/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support:

NIH/NIA R00AG041765 Dudley Lamming (PI) 01/01/14-12/31/16
Pathway to Independence Award $158,485 (current year direct costs)
"The in vivo regulation of glucose homeostasis and lifespan by mTORC2"
This NIH Pathway to Independence K99/R00 Award provides both salary and research support for Dr. Lamming's transition to an independent faculty position. The R00 (independent) phase of this award will focus on 1) understanding the role of mTORC2 in normal aging, 2) assessing the role of mTORC2 in the response to a CR diet, and 3) exploring the effects of increased mTORC2 activity on health and longevity.

UW-Carbone Cancer Center Dudley Lamming (PI) and David Pagliarini (PI) 10/01/14-3/31/16
Cell Signaling Pilot Grant $10,000 (total direct costs)
"Identifying metabolic vulnerabilities of cancer: exploring a role for mTOR in controlling mitochondrial function"
This grant will examine the role of mTOR in regulating the mitochondrial phosphoproteome and identifying metabolic vulnerabilities of cancer.

American Federation for Aging Research Dudley Lamming (PI) 07/01/15-06/30/17
AFAR Research Grant for Junior Faculty $45,000 (current year direct costs)
"Sexual dimorphism in response to longevity interventions"
This grant will examine the mechanistic basis for the sexually dimorphic impact of longevity interventions in the insulin/IGF-1/mTOR signaling pathway.

Progeria Research Foundation 2015-61 Dudley Lamming (PI) 09/01/15-08/31/17
Innovator Award $75,000 (current year direct costs)
"Intervention in Progeria by Restriction of Specific Dietary Amino Acids"
This grant will determine if reduced dietary intake of specific amino acids can promote longevity in a mouse model of Hutchinson-Gilford Progeria Syndrome.

Completed Research Support (past 3 years):

NIH/NIA K99AG041765 Dudley Lamming (PI) 09/30/12-09/29/14
Pathway to Independence Award (terminated 12/13 to accept Assistant Professor position)
"The in vivo regulation of glucose homeostasis and lifespan by mTORC2"
This NIH Pathway to Independence K99/R00 Award provided both salary and research support for Dr. Lamming's transition to an independent faculty position. The K99 (mentored) phase of this award focused on understating the role of mTORC2 in mammalian longevity and metabolism using mouse models.

The Medical Foundation Dudley Lamming (PI) 07/01/12-06/30/14
Charles A. King Trust Postdoctoral Research Fellowship (terminated 9/12 to accept NIH K99/R00 fellowship)
"Mammalian Target of Rapamycin Complex 2 signaling in aging and the response to calorie restriction"
This postdoctoral fellowship focused on understanding the role of mTORC2 in the regulation of mammalian longevity, and determining if mTORC2 plays a role in the response to a calorie-restricted diet.

American Federation for Aging Research David Sabatini (PI) 07/01/09-06/30/13
Julie Martin Mid-Career Award in Aging
"Mammalian Target of Rapamycin (mTOR) Signaling in Health and Longevity"
Role: Authored proposal, supported postdoctoral research
This grant, which focused on determining the effects of decreased mTOR signaling on mammalian health and aging, provided the majority of the research funds for Dr. Lamming's postdoctoral studies.