BIOGRAPHICAL SKETCH

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NAME: John C Newman

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POSITION TITLE: Assistant Professor, Buck Institute for Research on Aging

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
Yale University, New Haven CT	BS/MS	05/2000	Molecular Biophysics and Biochemistry
University of Washington, Seattle WA	MD/PhD	06/2008	Biochemistry
UCSF, San Francisco CA	Residency	06/2010	Internal Medicine
UCSF, San Francisco CA	Fellowship	06/2014	Geriatrics

A. Personal Statement

I am an Assistant Professor at the Buck Institute for Research on Aging and in the Division of Geriatrics at the University of California, San Francisco. I am a 2014 Beeson Scholar from the National Institute on Aging. As a geriatrician and MD/PhD physician-scientist, my long-term career goal is to elucidate the molecular mechanisms of pathways that broadly regulate aging and longevity, and translate these advances into therapies targeted at elders at high risk for functional dependence.

My current scientific interest lies in investigating ketone bodies as one of the mechanisms of the health benefits of fasting and calorie restriction, based on recent work showing that major ketone body is an endogenous inhibitor of histone deacetylases. A key aim of my research is to assess phenotypes of mammalian aging that are altered by ketone bodies, including mouse models of human frailty and cognitive decline as well as longevity and healthspan. I seek to identify mechanistic pathways by which the signaling functions of ketone bodies, such as targeted modulation of chromatin structure and gene expression, broadly regulate diseases and syndromes of aging.

My studies of ketogenic diet in aging mice found amelioration of age-related memory decline as one of the phenotypes most affected. In parallel, I have been investigating how a ketogenic diet improves memory and reduces abnormal epileptiform activity in the hAPPJ20 mouse model of Alzheimer's disease. I seek to use innovate diet and chemical tools to understand the mechanism of these ketogenic diet effects, and how they are similar or different between Alzheimer's disease and normal aging. I hope this will lead the way to promising new therapies for Alzheimer's disease and related dementias in older adults.

My background has uniquely prepared me for a career in translational geroscience, spanning worm genetics and bioinformatics to mouse behavioral phenotyping and deacetylase biochemistry. After completing my MD/PhD at the University of Washington MSTP, I followed the ABIM Research Pathway through residency in Internal Medicine and fellowship in Geriatrics. As a research fellow I worked in the laboratory of Dr. Verdin, who is internationally known for his work on HIV and aging biology, in both areas focusing on the biology of protein acetylation and deacetylases. I launched my independent laboratory focused on ketone body biology at the Buck Institute in 2018. For the past several years my clinical work included geriatric primary care at the San Francisco VA Medical Center and through the UCSF Housecalls program. My clinical time now focuses on inpatient internal medicine and geriatrics at the San Francisco VA Medical Center and UCSF Medical Center.

B. Positions and Honors

Positions and employment

2000-2008 MD/PhD MSTP at University of Washington, WA
2002-2006 PhD thesis research at University of Washington, WA
2008-2010 Residency in Internal Medicine, UCSF, CA
2008-2014 Molecular Medicine Fellowship Program, UCSF, CA
2010-2011 Clinical Fellowship in Geriatrics, UCSF, CA
2011-2014 Research Fellowship in Geriatrics, UCSF, CA
2011-2017 Visiting Scientist, Gladstone Institutes, CA
2014- Assistant Professor of Medicine, Division of Geriatrics, UCSF, CA
2015- Staff Geriatrician, San Francisco VA Medical Center
2018- Assistant Professor, Buck Institute for Research on Aging, Novato CA

Honors and fellowships

2011-2013 Scholar, Hartford Center of Excellence in Geriatric Medicine
2012- Fellowship support from the Larry L. Hilllblom Foundation
2012 Gladstone Institutes "Above and Beyond" Award
2013 Gladstone Institutes "Award of Excellence in Scientific Leadership"
2013 Glenn Award for Research in Biological Mechanisms of Aging, Glenn Foundation
2014 Distinguished Research Scientist and John S. Spice Award in Aging, Larry L. Hillblom Foundation
2015 American Geriatrics Society New Investigator Award
2017 Buck Institute Impact Circle Awardee
2017 MSTAR Best Clinician Mentor Award
2018 American Geriatrics Society Outstanding Junior Investigator of the Year

Medical Licenses, Certifications, and Professional Society Memberships

2010- American Geriatrics Society
2010- Licensed Physician, Medical Board of California (A110912)
2011- Diplomate, American Board of Internal Medicine in Internal Medicine
2013- Diplomate, American Board of Internal Medicine in Geriatric Medicine

C. Contribution to Science

1. **Ketone bodies in aging and longevity**. My current work focuses on understanding how ketone bodies regulate health and longevity, as a mechanism of the health benefits of fasting or dietary restriction. I am particularly interested in the emerging signaling functions of ketone bodies, such as how our laboratory discovered that the major ketone body is an endogenous inhibitor of histone deacetylases, and regulates genes involved in oxidative stress resistance. As one example of how ketone bodies regulate an age-related disease model, I have found that a ketogenic diet ameliorates the cognitive deficits and abnormal epileptiform activity in an Alzheimer's mouse model. I have found that a ketogenic diet can increase longevity and healthspan measures in mice, including improving age-related cognitive decline. I seek to understand the molecular mechanisms on these effects, particularly involving chromatin modification and gene regulation. I hope that the pleotropic effects of ketone bodies will suggest therapeutic targets and interventions for pleotropic syndromes of aging such as multimorbidity, frailty, and cognitive decline.
    a. **Newman JC**, Covarrubias AJ, Zhao M, Yu X, Gut P, Ng CP, Huang Y, Haldar S and E Verdin. Ketogenic diet reduces mid-life mortality and improves memory in aging mice. Cell Metab 26(3):547-57.e8 (2017). PMID: 28877458. WoS Citations: 5.
    b. Tognini P, Murakami M, Liu Y, Eckle-Mahan KL, **Newman JC**, Verdin E, Baldi P, and P Sassone-Corsi. Distinct circadian signatures in liver and gut clocks revealed by ketogenic diet. Cell Metab. 26(3):523-538.e5 (2017). PMID: 28877456. WoS Citations: 0.
    c. **Newman JC** and E Verdin. Beta-hydroxybutyrate: A Signaling Molecule. Ann Rev Nutr 37:51-76 (2017). PMID: 28826372. (review) WoS Citations: 0.

d. **Newman JC**, F Kroll, S Ulrich, JJ Palop, and E Verdin. Ketogenic diet or BHB improves epileptiform spikes, memory, survival in Alzheimer's model. *bioRxiv* 136226; doi: https://doi.org/10.1101/136226
e. **Newman JC** and E Verdin. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab.* 25(1):42-52 (2014). PMID: 24140022. (review) Wos Citations: 124.
f. Shimazu T, MD Hirschey, **J Newman**, W He, K Shirakawa, N Le Moan, CA Grueter, H Lim, LR Saunders, RD Stevens, CB Newgard, RV Farese, R de Cabo, S Ulrich, K Akassoglou, and E Verdin. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*. 339(6116):211-4 (2013) PMID: 23223453. Wos Citations: 298.

2. **Development of Translational Geroscience**. While my work on ketone bodies in the lab is intended to elucidate new therapeutics that target aging, many gaps remain in the translational pipeline that might link such advances in the laboratory study of aging to clinical trials, and eventually practice change for older adults. I have been privileged to work with devoted colleagues who seek to develop the intellectual frameworks, collaborations, and physical infrastructure that will be needed to plug the gaps in this pipeline. I co-authored two of a series of white papers, synthesizing concepts and strategies from senior investigators in the field on strategies for designing clinical trials to test drugs that target aging. I am dedicated to advancing these translational strategies, and my short-term career development goals including carrying out small-scale pilot human studies to characterize molecular phenotypes of aging and test molecular mechanisms of interventions. At my own institution I have been active in organizing educational and informational programs to promote collaboration between basic and clinical researchers.
    a. **Newman JC*,** J Justice*, JD Miller*, SK Hashmi, J Halter, SN Austad, N Barzilai, and JL Kirkland. Frameworks for Proof-of-Concept Clinical Trials of Interventions that Target Fundamental Aging Processes. *J Gerontol A Biol Sci Med Sci.* 71(11):1415-1423 (2016) PMID: 27535966 [* co-first author] WoS Citations: 4
    b. **Newman JC***, S Milman*, SK Hashmi, SN Austad, JL Kirkland, JB Halter, and N Barzilai. Strategies and Challenges in Clinical Trials Targeting Human Aging. *J Gerontol A Biol Sci Med Sci.* 71(11):1424-1434 (2016) PMID: 27535968 [* co-first author] WoS Citations: 17

3. **Copyright barriers to bedside cognitive testing**. A health policy issue inspired by my clinical work in geriatrics, I saw how aggressive enforcement of copyright on widely used bedside cognitive tests like the Mini Mental State Examination was disrupting patient care and harming research. I have collaborated with a legal expert in biomedical intellectual property issues to argue that copyright law may be misapplied to clinical tools like bedside cognitive tests, depression screens, and functional assessments; and to advocate for an open-access model for these vital clinical tools.
    a. **Newman JC**. Copyright and bedside cognitive testing: Why we need alternatives to the Mini-Mental State Examination. *JAMA Intern Med*. 175(9):1459-60 (2015). PMID: 26053392. WoS Citations: 10.
    b. Feldman R and **J Newman**. Copyright at the Bedside: Should We Stop the Spread? *Stan Tech L Rev*. 16:623 (2013).
    c. **Newman JC** and R Feldman. Copyright and Open Access at the Bedside. *New Eng J Med*. 365(26):2447-9 (2011). PMID: 22204721. WoS Citations: 27.

4. **Mitochondrial protein acylation in diseases of aging**. Deacetylase inhibition by ketone bodies (above) is just one specific example of how post-translational protein modifications, cellular metabolism, and aging are intertwined. I have participated in collaborative work to understand how various metabolite-derived modifications like acetylation, succinylation and malonylation – and the sirtuin deacylase enzymes that remove these modifications – control cellular metabolism and affect diseases of aging. My contributions to these works were primarily in the interpretation and bioinformatical analysis of large “acyl-ome” datasets generated by mass spectrometry.
    a. Rardin MJ, He W, Nishida Y, **Newman JC**, Carrico C, Danielson SR, Guo A, Gut P, Sahu AK, Li B, Uppala R, Fitch M, Riiff T, Zhu L, Zhou J, Mulhern D, Stevens RD, Ilkayeva OR, Newgard CB, Jacobson MP, Hellerstein M, Goetzman ES, Gibson BW, Verdin E. SIRT5 Regulates the Mitochondrial Lysine Succinylome and Metabolic Networks. *Cell Metab*. 18(6):920-33 (2013). PMID: 24315375. Wos Citations: 156.
    b. Rardin MJ, **JC Newman**, JM Held, MP Cusack, DJ Sorenson, B Li, B Schilling, SD Mooney, CR Kahn, E Verdin, and BW Gibson. Label-free quantitative proteomics of the lysine acetylome in

mitochondria identifies substrates of SIRT3 in metabolic pathways. *Proc Natl Acad Sci USA*. 110(16):6601-6 (2013). PMCID: PMC3631688. WoS Citations: 159.

c. **Newman JC***, W He*, and E Verdin. Mitochondrial protein acylation and intermediary metabolism: regulation by sirtuins and implications for metabolic disease. *J Biol Chem*. 287(51):42436-43 (2012) PMID: 23086951 [* co-first author] (review) WoS Citations: 108.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/john.newman.2/bibliograpahy/47605651/public/?sort=date&direction=descending
Peer-reviewed publications: 18 (4 first-author primary research)
Total publications: 25
Web of Science (WoS) citations as of 2/1/2018
1397 Total WoS citations from 25 publications (mean 56)
224 citations from 4 first-author primary research publications (mean 56)
Overall h-index: 14

D. Research Support

Ongoing Research Support

K08 AG048354 Newman (PI) 09/01/14-05/31/19
Epigenetic regulation of healthspan and longevity by ketone bodies
Paul B. Beeson Clinical Scientist Development Award in Aging (NIA, AFAR)
The goals of this study are career development in translational geroscience, and determining pathways through which healthspan, longevity, and diseases of aging are regulated by ketone bodies via deacetylase inhibition.
Role: PI

Completed Research Support

Postdoctoral fellowship, Larry L. Hillblom Foundation 07/01/12-6/30/15
Health and lifespan effects of histone deacetylase inhibition by ketone bodies
The goal of this project was to develop ketogenic diets as a experimental tool to assess aspects of healthspan and longevity that are regulated by ketone bodies.
Role: PI

Glenn Award, Glenn Foundation for Medical Research 05/01/13-4/30/15
Health and lifespan effects of histone deacetylase inhibition by ketone bodies
This unsolicited award was provided to advance work on how endogenous histone deacetylase inhibition by ketone bodies regulates cellular pathways relevant to aging and longevity.
Role: PI

Geriatric Medicine Scholar, John A. Hartford Foundation 07/01/11-06/30/13
Hartford Center of Excellence
The Hartford Centers of Excellence supported promising advanced academic trainees and junior faculty in Geriatric Medicine who seek to pursue new models of research, training, and clinical care.
Role: Scholar/Trainee