BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: John C Newman

eRA COMMONS USER NAME (credential, e.g., agency login): NEWMANJ00

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 School of Medicine. As a geriatrician MD/PhD physician-scientist, and a Beeson Scholar from the National Institute on Aging, 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 conditions that put older adults at risk for disability and functional dependence.

My core scientific interest lies in investigating ketone bodies as signaling metabolites that link nutrition to aging and age-related disease. My work in this area was inspired by the hypothesis of ketone bodies as a mechanism for the effects of fasting and dietary restriction on aging phenotypes, and by my role in identifying the ketone body beta-hydroxybutyrate (BHB) as an endogenous inhibitor of histone deacetylases. I have shown that a non-obese ketogenic diet improves survival and functional phenotypes in aging mice, including visuospatial memory and cardiac function. My laboratory currently takes a mechanistic approach to the study of ketone body effects on the brain, using models of normal aging and Alzheimer's disease. In the course of creating new experimental tools, I helped develop a set of novel ketone esters that either combine medium chain fatty acids with ketone bodies to improve the kinetics of ketone body delivery, or permit delivery of specific stereoisomers of ketone bodies to differentiate energy and signaling activities. We have since co-founded a company, BHB Therapeutics, to develop these molecules for potential human use.

My background is ideally suited to carry out interdisciplinary, translational work spanning bench to bedside. I completed an MD/PhD in Biochemistry at the University of Washington MSTP, focusing on computational analysis of gene expression patterns and fusion-protein transposon genomic evolution in the progeroid Cockayne syndrome. I then followed the ABIM Research Pathway through residency in Internal Medicine and clinical fellowship in Geriatrics at UCSF. I began studying ketone bodies during my research fellowship with Eric Verdin, and continued as I started an independent laboratory at the Buck Institute. In addition, I have contributed to proteomic bioinformatics analyses of large data sets from mouse studies of post-translational acylation. My research work has been published in *Cell Metabolism*, *Science*, *PNAS*, *PLoS Genetics*, and other journals. I have written reviews and opinion pieces for *NEJM*, *JAMA Internal Medicine*, *Annual Reviews*, *Trends*, and others. I have been invited to speak on ketone body biology and on translational approaches to geroscience at national and international meetings. My clinical work now focuses on inpatient Internal Medicine and Geriatrics services 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. Hillblom 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 one of the molecular mechanisms of the health effects of fasting or dietary restriction. I am particularly interested in the emerging signaling functions of ketone bodies, such as how I helped discover that the major ketone body is an endogenous inhibitor of histone deacetylases, and regulates genes involved in oxidative stress resistance. I have found that a ketogenic diet can increase longevity and healthspan measures in mice, including improving age-related memory decline. In a related, ongoing project, I have found that a ketogenic diet ameliorates the memory deficits and abnormal epileptiform activity in an Alzheimer's mouse model. I seek to understand the molecular mechanisms on these effects, particularly involving epigenetic regulation and inflammatory modulation. I have collaborated widely with investigators studying ketone body mechanisms in specific systems, including inflammatory disease, the gut microbiome, neurodegenerative diseases, and circadian gene regulation.
    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; PMCID: PMC5605815.
    b. **Newman JC**, Kroll F, Ulrich S, Palop JJ, and Verdin E. Ketogenic diet or BHB improves epileptiform spikes, memory, survival in Alzheimer's model. *bioRxiv* 136226; doi: https://doi.org/10.1101/136226. (preprint)
    c. Shimazu T, Hirschey MD, **Newman J**, He W, Shirakawa K, Le Moan N, Grueter CA, Lim H, Saunders LR, Stevens RD, Newgard CB, Farese RV Jr, de Cabo R, Ulrich S, Akassoglou K, Verdin E. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase

inhibitor. *Science*. 2013 Jan 11;339(6116):211-4. doi: 10.1126/science.1227166. Epub 2012 Dec 6. PMID: 23223453; PMCID: PMC3735349.

d. Tognini P, Murakami M, Liu Y, Eckel-Mahan KL, **Newman JC**, Verdin E, Baldi P, Sassone-Corsi P. Distinct Circadian Signatures in Liver and Gut Clocks Revealed by Ketogenic Diet. *Cell Metab*. 2017 Sep 5;26(3):523-538.e5. doi: 10.1016/j.cmet.2017.08.015. PubMed PMID: 28877456.

2. **Signaling activities of ketone bodies and novel exogenous ketogenic compounds**. I am a thought leader on the concept of ketone bodies as signaling metabolites, molecules with core roles in basic energy metabolism but which also act as sensors for the metabolic state of the cell or organism and effectors to activate regulatory pathways based on that metabolic state. These signaling activities, including deacetylase inhibition, protein beta-hydroxybutyrylation, NLRP3 inflammasome inhibition, and FFAR3 and HCAR2 receptor binding, may be responsible for many of the health effects of ketone bodies and ketogenesis. I also co-created novel molecules that can deliver beta-hydroxybutyrate exogenously as a drug, and co-founded a company to develop these for potential human use. Such compounds may be useful both as experimental tools and as human therapeutics.
    a. **Newman JC** and Verdin E. Beta-hydroxybutyrate: A Signaling Molecule. *Ann Rev Nutr* 37:51-76 (2017). PMID: 28826372. (review)
    b. **Newman JC** and Verdin E. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab*. 2014 Jan;25(1):42-52. doi: 10.1016/j.tem.2013.09.002. Epub 2013 Oct 18. Review. PMID: 24140022; PMCID: PMC4176946. (review)
    c. **Newman JC,** Ulrich S, and Verdin E.; Medium chain fatty acid esters of beta-hydroxybutyrate and butanediol and compositions and methods for using same. Patent application US2017035826, WO2017213999, published 12/14/2017. (patent application)
    d. **Newman JC** and Verdin E.; S-enantiomers of beta-hydroxybutyrate and butanediol and method for using same. Patent application US2018042948, WO2019018683, published 1/24/2019. (patent application)

3. **Development of Translational Geroscience**. Many gaps remain in the translational pipeline linking 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. At my own institution I have been active in organizing educational and informational programs to promote collaboration between basic and clinical researchers.
    a. J Justice, JD Miller, **Newman JC** [Co-first authors]**,** Hashmi SK, Halter J, Austad SN, Barzilai N, and Kirkland JL. 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; PMCID: PMC5055651.
    b. **Newman JC**, Milman S [Co-first authors], Hashmi SK, Austad SN, Kirkland JL, Halter JB, and Barzilai N. Strategies and Challenges in Clinical Trials Targeting Human Aging. *J Gerontol A Biol Sci Med Sci.* 71(11):1424-1434 (2016) PMID: 27535968; PMCID: PMC5055653.

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; PMCID: PMC4105152.

b. Rardin MJ, **Newman JC**, Held JM, Cusack MP, Sorenson DJ, Li B, Schilling B, Mooney SD, Kahn CR, Verdin E, and Gibson BW. 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.

c. **Newman JC**, He W [Co-first authors], and Verdin E. Mitochondrial protein acylation and intermediary metabolism: regulation by sirtuins and implications for metabolic disease. *J Biol Chem*. 287(51):42436-43 (2012) PMID: 23086951: PMCID: PMC3522244.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/john.newman.2/bibliograpahy/47605651/public/?sort=date&direction=descending
Peer-reviewed publications: 20 (4 first-author primary research)
Total publications: 27
1942 total Web of Science citations from 27 publications (mean 72)
274 citations from 4 first-author primary research publications (mean 68)
Overall h-index: 18
(Updated 04/11/2019)

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

K08 AG048354-05S1 Newman (PI) 09/13/18 - 05/31/19
Administrative supplement to K08 award to study effects of ketone bodies on memory in normal aging and Alzheimer's mouse models.
Role: PI

Completed Research Support

Postdoctoral fellowship, Larry L. Hillblom Foundation 07/01/12 - 06/30/15
Health and lifespan effects of histone deacetylase inhibition by ketone bodies
The goal of this project was to develop ketogenic diets as an 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 - 04/30/15
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