## BIOGRAPHICAL SKETCH

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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 |
| Yale University, New Haven CT | BS/MS | 05/2000 | Molecular Biophysics and Biochemistry |

### A. Personal Statement

I am delighted to work as a co-investigator with Dr. Kapahi on this innovative investigation of the roles and regulation of advanced glycation end-products in Alzheimer's disease. I bring to our collaboration deep expertise in metabolism, ketone bodies, and Alzheimer's disease through a geriatrics and geroscience lens. I am a geriatrician and geroscientist, 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. 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. I am a Beeson Scholar from the National Institute on Aging, and established my independent laboratory in 2018 to study ketone bodies as a geroscience mechanism in the aging brain.

My laboratory investigates mechanisms of ketone bodies, metabolites related to fasting and dietary restriction, in Alzheimer's Disease and delirium. The ketone body β-hydroxybutyrate (BHB) provides readily metabolized energy to cells, bypassing defects in glucose metabolism, and also has variety of protein-binding signaling activities relevant to aging through regulation of epigenetics, inflammation, metabolism, and senescence. I found that a ketogenic diet fed to aging mice ameliorates age-related memory decline as well as having broader effects on survival and functional phenotypes of aging. In parallel, I have investigated how a ketogenic diet improves memory and reduces abnormal epileptiform activity in the hAPPJ20 mouse model of Alzheimer's disease. I have developed an innovative diet and chemical toolkit to parse ketogenic diet effects in fine mechanistic detail, and I seek to use these tools to identify relevant mechanisms of ketogenic diet and ketone bodies in both Alzheimer's disease and normal aging. I hope that by identifying mechanisms common to aging and AD as well as mechanisms specific to AD pathophysiology, this work will point the way to new precision therapies for Alzheimer's disease and related dementias in older adults.

My background is ideally suited to carry out interdisciplinary, translationally relevant work spanning Alzheimer's disease and geroscience. 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 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 in my independent laboratory at the Buck Institute. I have helped conceptualize how to use aging biology mechanisms to understand and treat geriatric problems. 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 more. My clinical work now focuses on the inpatient Internal Medicine and Geriatrics services at the San Francisco VA Medical Center.

## B. Positions and Honors

**Positions and employment**

2000-2008 MD/PhD MSTP at University of Washington, WA
2008-2010 Residency in Internal Medicine, 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
2012-2015 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
2018- American Aging Association
2019- American Delirium Society

## C. Contributions 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, how BHB regulates protein function through covalent and non-covalent interactions. I found that a ketogenic diet can improve mortality and functional measures in aging 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 of these effects, particularly involving epigenetic regulation and metabolic 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. PMCID: pending (NIHMSID 903274). [Preprint].

2. **Signaling activities of ketone bodies and novel exogenous ketogenic compounds**. I am a thought leader on conceptualizing ketone bodies as signaling metabolites. These are 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. Ketone body signaling activities, including deacetylase inhibition, protein beta-hydroxybutyrylation, NLRP3 inflammasome inhibition, hnRNPA1 binding, 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 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. (PMC Exempt - invited 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 01/24/2019. (patent application)

3. **Mitochondrial protein acylation in diseases of aging**. BHB is only one example of an ecosystem of metabolite signaling molecules. 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, including analyses of pathway enrichments, sequence targets, and evolutionary conservation.

   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.

4. **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 three 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, and on training geroscience investigators. 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.
c. **Newman JC**, Sokoloski JL, Robbins PD, Niedernhofer LJ, Reed MJ, Wei J, Austad SN, Barzilai SN, Cohen SJ, Kuchel GA, Kirkland JL, and Pignolo RJ. Creating the Next Generation of Translational Geroscientists. *J Am Geriatr Soc*. 67(9):1934-1939 (2019). PMID: 31287934; PMCID: PMC6771814.
d. Campisi J, Kapahi, P, Lithgow GJ, Melov S, **Newman JC**, and Verdin E. From discoveries in ageing research to therapeutics for healthy aging. *Nature*. 571 (7764):183-192 [Preprint] (2019). PMID: 31292558.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/john.newman.2/bibliography/public/

**D. Additional Information: Research Support**

**Ongoing Research Support**

K08AG048354-05 (Newman) 06/01/18 - 05/31/20
NIH/NIA
Epigenetic regulation of healthspan and longevity by ketone bodies
The goals of this project is to seek new treatments for ameliorating the geriatric syndromes, and preserving elder independence, based on molecular mechanisms that regulate longevity and diseases of aging. The project will explore one such molecular mechanism, ketone bodies, in deep detail, and attempt to understand how ketone bodies affect specific geriatric syndromes and diseases of aging.
Role: PI

K08AG048354-05S1 (Newman) 06/01/18 - 05/31/20
NIH/NIA
Epigenetic regulation of healthspan and longevity by ketone bodies
Nutrition-based therapies such as ketogenic diet show promise in the laboratory for treating Alzheimer's disease both by improving brain resilience and by directly targeting the disease process. This project will uncover how a ketogenic diet works at a molecular level in mouse models of Alzheimer's disease, compare this to how it improves the overall health of an aging brain, and thereby guide the intelligent design and testing of new therapies for Alzheimer's disease.
Role: PI

U01AG060906-02 (Schilling) 09/30/18 – 04/30/23
NIA/NIH
Quantitative Proteomics to Develop Robust Senescence-Related Biomarkers for Aging
The goals of this project are: 1) Verify the feasibility of using a panel of protein candidates, secreted by senescent cells as biomarkers of aging in human plasma, by applying modern quantitative proteomics technologies. 2) Assay panels of biomarkers in human plasma/exosomes from patients with different aging phenotypes and correlate to clinical metrics. 3) Determine Biomarkers for Aging that successfully extend applications to mouse models to advance the understanding of Mechanisms of Aging.
Role: Co-Investigator

BhB Therapeutics Research Agreement (Verdin, PI) 01/10/19 – 01/09/21
Proprietary
Role: Co-Investigator

**Completed Research Support** 09/01/14 – 05/31/19

No Grant # (Newman)
American Federation for Aging Research (AFAR)
Paul Beeson Career Development Award (BCDA)
*"Epigenetic regulation of healthspan and longevity by ketone bodies"*
The goals of this project is to seek new treatments for ameliorating the geriatric syndromes, and preserving elder independence, based on molecular mechanisms that regulate longevity and diseases of aging. The project will explore one such molecular mechanism, ketone bodies, in deep detail, and attempt to understand how ketone bodies affect specific geriatric syndromes and diseases of aging.
Role: PI