BIOGRAPHICAL SKETCH

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NAME: Juan Manuel Vazquez

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

POSITION TITLE: Postdoctoral Fellow

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
University of Rochester (Rochester, NY)	B.S.	05/2015	Biology: Molecular Genetics
University of Rochester (Rochester, NY)	B.A.	05/2015	Chemistry
University of Chicago (Chicago, IL)	M.S.	08/2020	Human Genetics
University of Chicago (Chicago, IL)	Ph.D.	08/2020	Human Genetics
University of California, Berkeley (Berkeley, CA)	Post-Doc	(Ongoing)	Biology of Aging

A. Personal Statement

My goal is to establish a comprehensive research program to study aging at all scales, from biochemical mechanisms to the evolution of longevity-associated traits. Since my first research position in 2012, I have focused on developing both a breadth and depth of knowledge and skills to become an “A-Z” biologist well-versed in chemistry, biology, computational approaches, and field work. It is this interdisciplinary background and deep knowledge of aging and evolutionary medicine that will enable me to lead and mentor a lab that can pursue any research questions wherever they lead.

Throughout my career, I have contributed to our understanding of the biology of aging by uncovering mechanisms underlying the exceptional lifespan of extraordinarily long-lived species across rodents, elephants, tortoises, rockfish, and whales. These comparative approaches excel at discovering novel pathways and genes mediating aging which can be leveraged to improve our understanding of medicine and the treatment of aging-related diseases. During this time, I saw the benefits and shortcomings of each of these clades, and realized that they lack the phylogenetic structure and experimental tractability necessary to fully leverage the power of functional genomics and evolutionary biology.

To establish a robust model system for studying the evolution of longevity and associated traits, I have generated chromosome-level reference genomes and a primary cell culture library in a clade of 10 closely-related bats, featuring over 200 individuals. This incredible resource can now be used to explore a diversity of questions in aging through various lenses, such as population genetics, evolution, and molecular cell biology. The use of primary cell lines in concert with our computational analyses allows us to further define and characterize the mechanisms underlying the evolution of longevity-associated traits, such as DNA damage response, somatic mutation rate, and metabolic regulation. Combined with my work in mouse model systems, I am well-positioned to not only identify, validate, and characterize novel pro-longevity and pro-healthspan pathways in long-lived animals; but also test their translational potential in relevant model systems and increase their value and translational potential for future development and clinical usage.

(A) JM Vazquez, M Sulak, S Chigurupati, VJ Lynch (2018). A Zombie LIF Gene in Elephants Is Upregulated by TP53 to Induce Apoptosis in Response to DNA Damage. *Cell Reports*, **24**, 1765-1776 doi:10.1016/j.celrep.2018.07.042

(B) SRR Kolora, GL Owens, **JM Vazquez**, A Stubbs, K Chatla, C Jainese, K Seeto, M McCrea, MW Sandel, JA Vianna, K Maslenikov, D Bachtrog, et al (2021). Origins and evolution of extreme life span in Pacific Ocean rockfishes. *Science*, **374**, 842-847 doi:10.1126/science.abg5332

(C) **JM Vazquez**, VJ Lynch (2021). Pervasive duplication of tumor suppressors in Afrotherians during the evolution of large bodies and reduced cancer risk. *eLife*, **10** doi:10.7554/elife.65041

(D) **JM Vazquez**, M Kraft, VJ Lynch (2022). A CDKN2C retroduplication in Bowhead whales is associated with the evolution of extremely long lifespans and alerted cell cycle dynamics. *bioRxiv* doi:10.1101/2022.09.07.506958

B. Positions, Scientific Appointments, and Honors

Positions

2017-2018	Student Representative, Department of Human Genetics, University of Chicago
2017-2018	Treasurer, University of Chicago Chapter of the Society for the Advancement of Chicanos/Hispanics and Native Americans in Science (UC SACNAS), University of Chicago
10/2017	Organizer, Molecular Biosciences Retreat, University of Chicago
04/2018	Co-chair, First Annual Midwest Regional SACNAS Conference at the University of Chicago
2018-2020	President, UCSACNAS, University of Chicago
04/2019	Corresponding Chair, Second Annual Midwest Regional SACNAS Conference at the University of Chicago
07/2019	Corresponding Chair, 2019 Gordon Research Seminar in the Biology of Aging

Professional Societies

2016-	Society for the Advancement of Chicanos/Hispanics and Native Americans in Science
2019-	North American Society for Bat Research
2020-	American Aging Association
2022-	Western Bat Working Group
2022-	Wildlife Society
2022-	International Society for Evolution, Medicine, and Public Health

Grants and Scholarships

2011-2015	Dean's Scholarship, University of Rochester
2012-2015	Howard Bryant Memorial Scholarship, University of Rochester
2015-2017	Initiative to Maximize Student Development (R25, NIGMS) Trainee, University of Chicago
2019-2020	Yale Ciencia Academy Fellowship
2020	(Finalist) Life Sciences Research Foundation Fellowship
2020	(Meritorious) NSF Postdoctoral Research Fellowship in Biology
2021-2023	NSF Postdoctoral Research Fellowship in Biology (NSF PRFB 2109915)

C. Contributions to Science

Aging is a fundamental rule that seemingly underlies all life, and its impacts extend to most known facets of biology. However, the large variability in lifespans – both between and within species – suggest that there are a combination of genetic and environmental factors that can control and modulate the aging process. The near-universality in mammals of aging-related diseases, such as cancer, heart disease, and sarcopenia, provides us with the opportunity to pursue a two-pronged approach to understand aging: the study the basic pathogenetics of these disorders in short-lived model organisms such as mice; and the study of mechanisms associated with extraordinary longevity in long-lived, non-model organisms. By combining these two complementary approaches, one can augment and independently verify our knowledge of the biological mechanisms underlying aging and aging-related diseases to better understand and inform treatments in humans.

1. Establishing Model Systems for Studying the Evolution and Genomics of Longevity

Mammals exhibit a wide variety of maximum lifespans; cells from exceptionally long-lived species like bats demonstrate exceptional tolerance stresses including DNA damage, oxidation, and heat shock.

Comparative studies between long- and -short-lived species link increased stress tolerance with the improved cellular homeostasis underlying their extended lifespans and exceptional health and vitality in old age. To-date, most studies have suffered from a combination of highly fragmented and erroneous genomes; enormous evolutionary breadth, with little depth; and a nearly mutual exclusivity between genomics and functional studies. These factors reduce the power of these studies to identify genetic and phenotypic differences between long- and short-lived species. In order to identify causal genes underlying longevity-associated traits, it is necessary to focus on a clade of closely-related species encompassing a dynamic range of lifespans; equipped with both high-quality genomes and the cell lines to validate hypotheses and putative genes.

In Owens and Kolora *et al* 2021, we sought to overcome the issue of evolutionary breadth and depth by sequencing over 88 species of rockfish, with lifespans ranging from 10-200 years, enabling us to use a variety of statistical approaches to link new genes to the evolution of longevity and other associated traits.

Thus far, the field of comparative biology has lacked the combination of high quality genomes and cell lines necessary for robust studies of longevity-associated traits. To combat this, I have established both reference genomes and a collection of over 200 primary cell lines from a clade of nine closely-related bats, spanning a three-fold range of lifespans. I will combine this powerful *ex vivo* system with functional genomics techniques to study the evolution of longevity and healthspan in mammals by: (1) identifying recent genetic changes associated with longevity using novel, high-quality *Myotis* genomes and population genetic data; (2) assessing thresholds and heterogeneity in the cellular stress response between 5 bat species using flow cytometry; and (3) analyzing differential changes in gene expression in response to stressors between long-and-short-lived bat species. By identifying unique genetic changes associated with long-lived bats; establishing robust measures of the cellular stress response in these species; and using transcriptomics to bridge the gap between genotypes and phenotypes, this proposal will provide a foundation to address advanced, complex questions about the biology of aging and the stress response.

By combining evolutionary and population genetics with a mutli-species, multi-individual collection of primary fibroblasts, I aim to establish a new baseline for comparative studies of aging, but also provide a model for the study of other open questions in biology. This system will allow us to address fundamental biological questions at a variety of scales ranging from population and evolutionary genomics, to cell and molecular biology and biochemistry. As such, this will be a vital tool for biologists studying development, evolution of flight and communication, conservation and ecology, immunology, and disease ecology, and other topics. Finally, the combination of ex vivo cell models, genomics, and robust phenotypic data will lay the groundwork for more advanced studies, such as identifying longevity quantitative trait loci, testing pathogen resistance and transmission between bats and other species ex vivo, and creating an induced pluripotent stem cell panel for ex vivo organ-specific studies.

(A) SRR Kolora, GL Owens, **JM Vazquez**, A Stubbs, K Chatla, C Jainese, K Seeto, M McCrea, MW Sandel, JA Vianna, K Maslenikov, D Bachtrog, et al (2021). Origins and evolution of extreme life span in Pacific Ocean rockfishes. *Science*, **374**, 842-847 doi:10.1126/science.abg5332

2. The Role of Gene Duplications in Mediating the Cancer Resistance of Long-Lived Organisms

Cancer, as a disorder of cellular organization and growth, is a condition that has been observed to affect most multicellular organisms. As neoplasms of various cell types have been described, it is thought that all cells have an intrinsic risk of malignant transformation. Thus, there is an expectation that an increased number of cells should result in an increased risk of a malignant transformation and tumor formation in an individual. Such a positive correlation has been previously described in humans and within other species, such as dogs, where differences in body size associated with differences in cell numbers and pro-growth signaling translates into a proportional risk of cancer. Similarly, the risk of developing cancer over the lifetime of an organism would be predicted to be proportional to the lifespan of the individual, as a longer life translates to more time for the organism's cells to accumulate potentially oncogenic mutations; this pattern also holds within various species such as humans, where there is a correlation between an individual's age and their propensity to be diagnosed with cancer. However, while these two life history traits correlate with cancer risk within species, the correlation does not hold when one looks between species in mammals.

This observation, known as Peto's Paradox, suggests that the evolution of large body sizes and lifespan must also be coupled with an evolution of mechanisms to suppress the cancer risk in members of the species. Of special interest are clades of closely-related species that have a wide variation in size, longevity, or both, such as in elephants and their closest relatives, the hyrax and the manatee (Paenungulata). We explored the

landscape of gene duplications in a range of mammals (Vazquez and Lynch 2021; Vazquez *et al* 2022a), and explored the functional consequences of many of these duplicates, including the resurrected pseudogene *LIF6* in elephants (Vazquez *et al* 2018) and the retroduplicated *CDKN2C* gene in the Bowhead whale (Vazquez *et al* 2022b).

(A) **JM Vazquez**, M Sulak, S Chigurupati, VJ Lynch (2018). A Zombie LIF Gene in Elephants Is Upregulated by TP53 to Induce Apoptosis in Response to DNA Damage. *Cell Reports*, **24**, 1765-1776 doi:10.1016/j.celrep.2018.07.042

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(C) **JM Vazquez**, M Kraft, VJ Lynch (2022). A CDKN2C retroduplication in Bowhead whales is associated with the evolution of extremely long lifespans and alerted cell cycle dynamics. *bioRxiv* doi:10.1101/2022.09.07.506958

(D) **JM Vazquez**, MT Pena, B Muhammad, M Kraft, LB Adams, VJ Lynch (2022). Parallel evolution of reduced cancer risk and tumor suppressor duplications in Xenarthra. *bioRxiv* doi:10.1101/2022.08.04.502824

3. **Probing the Link between Genetics, Epigenetics, and Gene Expression in Aging at the Tissue and Single Cell Levels**

Since the dawn of the modern era, the extension of human lifespan that arose from advances in medicine has brought a new and unprecedented challenge to prosperous nations like the United States. Over the next decade, for the first time in history, the population of older Americans is projected to surpass that of children, and by 2030 it is estimated that 20% of the population will be made up of individuals older than 65. This tide will bring with it a significant public health challenge, since age is the primary risk factor for many of the most common human pathologies including neurodegenerative conditions, heart disease, cancer, and general decline of biological processes.

The decline of various physiological processes, such as in sarcopenia and dementia, are strongly associated with old age; however, many studies have also demonstrated a strong genetic component to these declines. For example, a review of large-scale genetic association and family studies suggest a heritability of 30-80% for muscle strength and lean muscle mass, suggesting that there is a strong relationship between genetics, age, and gender in sarcopenia. Furthermore, studies by George Brooks *et al* have demonstrated a decline in the human body's ability to metabolize a diversity of energy sources as a function of age, and that this impacts muscular output via mitochondrial function. How genetics and aging-related metabolic inflexibility influence each other and sarcopenia, however, remains unclear.

We are tackling the question of how genetics, epigenetics, and aging interplay using a combination of computational and experimental approaches. To understand how genetics and aging affects both chromatin structure and gene expression across tissues, we have leveraged available datasets such as GTEx and the UK BioBank to explore the relative contributions of genetics and environment to gene expression across tissues throughout human lifespans, showing that the effects of genetics on aging vary by tissue type. (Yamamoto *et al* 2022)

In order to functionally ascertain the role of chromatin status and genetics on aging-related changes in physiology, we are linking fitness and other physiological measurements alongside multiplexed single-cell ATAC-seq and nucleic RNA-seq of donor muscle tissues collected from young and old individuals in both a trio of mice strains as well as in humans. In mice, intra-strain comparisons will allow us to see chromatin changes associated with aging, and its effect on gene expression, while inter-strain comparisons using allele-specific chromatin changes paired will show the effects of genetics and sex-specific inheritance on aging-related chromatin changes. Our studies in mice will inform our studies in humans, allowing us to explore the underlying biology of Yamamoto *et al* 2022.

(A) R Yamamoto, R Chung, **JM Vazquez**, H Sheng, PL Steinberg, NM Ioannidis, PH Sudmant (2022). Tissue-specific impacts of aging and genetics on gene expression patterns in humans. *Nature Communications*, **13** doi:10.1038/s41467-022-33509-0

Complete list of my published work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/juan.vazquez.1/bibliography/public/