BIOGRAPHICAL SKETCH

NAME: Headley, Colwyn Ansel

eRA COMMONS USERNAME: CAHEADLEY

POSITION TITLE: Post-Doctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	COMPLETION	FIELD OF STUDY
The Ohio State University, OH	B. S	05/2014	Microbiology
The Ohio State University, OH	Ph.D.	05/2020	Biomedical Sci. - Immunology
Texas Biomedical Research Institute, TX	-	5/2021	Host-Pathogen Interactions
Stanford University, CA	-	-	Cardiovascular Medicine

A. Personal Statement

My passion lies in investigating the complex interplay between aging-associated mitochondrial dysfunction and immune dysregulation, which are both causes and consequences of various chronic pathologies in the elderly, including cardiovascular disease (CVD). As an independent interdisciplinary researcher, my primary goal is to shed light on the contributions of mitochondrial dysfunction to immune dysregulation during aging, and to explore the therapeutic potential of mitochondrial transplantation for improving health outcomes in the elderly. Under the mentorship of Dr. Philip Tsao, a renowned cardiovascular scientist, I am currently investigating whether preserving mitochondrial health through transplantation can mitigate immuno-cardiovascular dysfunctions associated with abdominal aortic aneurysm (AAA), a CVD that is strongly associated with aging.

The research I am proposing is partially informed by my extensive experiences in mitochondrial biology, immunology, which were gained through rigorous training and mentorship under Dr. Frederick Villamena and Dr. Joanne Turner [1-3]. For example, during my time in Dr. Villamena' s laboratory, I investigated the impact of nitrones, a class of synthetic antioxidants, on hyperglycemia-induced endothelial dysfunction. My work generated new insights into how cellular and mitochondrial dysregulation affects the redox signaling in endothelial cells and demonstrated that nitrones have the potential to ameliorate endothelial dysfunction [1]. In Dr. Turner's laboratory, I studied the adaptive immune response to Mycobacterium avium and the impact of M. avium on the cardiac function of aged mice [3]. My findings suggested that pre-existing inflammation, a common consequence of aging, may predispose older individuals to cardiac dysfunction when infected with M. avium, highlighting the significance of studying the interactions between immune cells and cardiovascular health in the context of aging.

This research project represents a unique opportunity to deepen my understanding of how mitochondrial dysfunction influences maladaptations in the immuno-cardiovascular axis [4]. The completion of my proposed specific aims and career development activities will give me the necessary foundation for a productive, independent career as a scientific innovator, and pursue a research direction that is both novel and distinctly different from my previous mentors. The K99 phase will support my targeted immuno-cardio-metabolic postdoctoral research and training plan, with a specific emphasis on improving my deficiencies in transcriptional analysis and Bioinformatics. A greater understanding of how mitochondrial health influences the immuno-cardiovascular axis during biological aging will contribute toward novel immune-vascular cell interaction assays, immune or metabolic phenotyping parameters, or even therapeutic strategies, that may be applicable across the spectrum of aging-associated cardiovascular pathologies. The R00 phase will provide essential guidance and partial monetary resources to collect data of high quality and reproducibility for smaller exploratory R03 and R21 grants, as well as my R01 submissions.

Ongoing or recently completed projects:

Burroughs' Wellcome Fund Post-Doctoral Enrichment Program
Headley (PI)
09/01/2023 – 08/31/2026
Mitochondrial Dysfunction and Transplantation in the Cardiovascular System
Stanford's Propel Post-Doctoral Scholar Award

Headley (Awardee)
01/01/2023 – 01/01/2025
Mitochondrial Dysfunction and Transplantation in the Cardiovascular System

Stanford University, Cardiovascular Institute Seed Grant
Ikeda (PI), Role: Co-Investigator
01/01/2023 – 12/31/2023
Mitochondrial Transplantation Therapy for Mitochondrial Disease

Stanford's Jump Start Award for Excellence in Research
Headley (PI)
09/20/2021 – 07/21/2022
Mitochondrial Dysfunction in Abdominal Aortic Aneurysm (AAA) Pathology

NIH-NHBLI T-32 Mechanisms and Innovations in Cardiovascular Disease (1T32HL098049)
Tsao (PI), Role: Co-Investigator
05/01/2021 – 04/30/2023
Mitochondrial Phoenix: The dysfunction, transplantation, and rejuvenation of mitochondria in CVD.

Texas Biomedical Post-Doctoral Fellowship
Headley (PI)
01/01/2021 – 12/31/2021
Ameliorating Aging-Associated T Cell Dysfunction Through Mitochondrial Transplantation

Citations:

1. **Headley CA,** DiSilvestro D, Bryant KE, Hemann C, Chen CA, Das A, Ziouzenkova O, Durand G, Villamena FA. (2016), Nitrones Reverse Hyperglycemia-Induced Endothelial Dysfunction in Bovine Aortic Endothelial Cells*. Biochemical Pharmacology,* 104, 108-117. PMCID: PMC5248535
2. **Headley CA,** Hoffman CM, Freisen JM, Han Y, Macklin JM, Zweier JL, Kuret J, Rockenbauerc A, VillamenaFA. Membrane-specific spin trap, 5-dodecylcarbamoyl-5-N- dodecylacetamide-1-pyroline-N-oxide (diC_{12}PO): Theoretical, bioorthogonal fluorescence imaging and EPR studies. Organic and Biomolecular Chemistry. (17): 7694-7705. 2019. PMCID: PMC6703941
3. **Headley CA,** Gerberick A, Mehta S, Ganesan LP, Wu Q, Yu L, Fadd P, Kha M, Turner J, Rajaram M. N Nontuberculous Mycobacterium M. avium infection predisposes aged mice to cardiac abnormalities and inflammation. *Aging Cell 2019;18(3):e12926.* PMCID: PMC6516181
4. **Headley, CA**., & Tsao, P. Building the Case for Mitochondrial Transplantation as an Anti-aging Cardiovascular Therapy. *Frontiers in Cardiovascular Medicine, 10, 707*. PMCID: PMC10203246

B. Positions, Scientific Appointments, and Honors

Positions

2021 – Post-Doctoral Fellow, Stanford University, Stanford, California
2020 – 2021 Post-Doctoral Scientist I, Texas Biomedical Research Institute, San Antonio, Texas
2015 – 2020 Graduate Student, Immunology, The Ohio State University/ Texas Biomed
2014 – 2015 Lab Technician, Biological Chemistry and Pharmacology, Cardiox Corporation
2014 – 2015 Research Assistant, Dept. Biomedical Engineering, The Ohio State University, College of Dentistry, Div. of Orthodontics**,** Columbus, Ohio
2011 – 2015 Research Assistant, Dept. Biological Chemistry and Pharmacology, The Ohio State University, College of Medicine**,** Columbus, Ohio
2010 – 2011 Research Assistant, Dept. Plant Pathology, The Ohio State University/ USDA-ARS/ OARDC, Wooster, Ohio

Scientific Appointments

2022 – Grant Coach/Teaching Assistant, The Grant Writing Academy, Stanford University, CA
2022 – Trainee/Member, Endocrine Society
2022 – Trainee/Member, American Heart Association (AHA)
2022 – Trainee/Member, American Aging Association (AGE)
2022 Mentor, Metascience Analyses and Explorations of Reproducibility in Cardiovascular Science, Stanford University, Palo Alto, California

2022 – VP of Diversity, Equity & Inclusion, Biotech Connection Bay Area, San Francisco, California,
2021 – Co-Organizer, Social Media Coordinator, Black-In-Immuno, Houston, Texas
2020 – 2021 Mentor, Post-Baccalaureate Research Education Program (PREP), UT Health San Antonio, San Antonio, Texas, Texas
2020 – 2021 Team Lead, Diversity, Equity & Inclusion Committee, Texas Biomedical Research Institute, San Antonio, Texas
2019 – 2021 Committee Member, Community Outreach, Texas Biomedical Research Institute
2019 – 2020 Co-founder and Deputy Director, Enventure San Antonio (Non-profit), San Antonio, Texas
2018 – 2020 Co-founder and Executive Committee member, Texas Biomedical Research Institute Student Association (TBAT), Texas Biomedical Research Institute
2018 – 2020 Associate, The Initiative on Maximizing Student Development (IMSD), UT Health San Antonio
2016 – 2020 Mentor, Discovery Post-Baccalaureate Research Education Program, The Ohio State University, Columbus, Ohio
2016 – 2020 Graduate Student Ambassador, Biomedical Sciences Graduate Program, College of Medicine The Ohio State University, Columbus, Ohio
2011 – 2015 Student Trainer, Department of Pharmacology, College of Medicine, The Ohio State University, Columbus, Ohio

Honors

2023 – 2026 Burroughs' Wellcome Fund Post-Doctoral Enrichment Program Awardee
2023 Sanford Burnham Prebys Rising Star
2023 – 2025 Stanford University, Propel Post-Doctoral Award
2023 Future Leaders Advancing Research in Endocrinology (FLARE) 2023 Fellowship
2022 Best Post-Doctoral Poster, Stanford-Cornell Cardiovascular Research Symposium
2022 Vasculata Scholarship/Travel Award
2022 Rockefeller University Exceptional Scholar Award
2021 – 2022 Jump Start Award for Excellence in Research
2021 – 2023 Mechanisms & Innovations in Vascular Disease NIH T-32 – Stanford University
2020 – 2021 Texas Biomedical Post-Doctoral Forum Fellowship
2020 Stanford PRISM Scholar (Cohort 5)
2017 – 2019 Douglass Foundation Forum Scholarship
2017 Hodges Family Legacy Trainee Travel Award for Infectious Diseases
2014 The Ohio State University, College of Arts and Sciences Dean's list
2014 The Davis Heart and Lung Institute Research Day (Undergraduate Div. – 2nd Place
2012 – 2014 The Ohio State University Arts and Sciences Undergraduate Research Scholar
2011 The Ohio State University Scarlet and Gray-Grant

C. Contributions to Science

1. Research in Cellular Oxidative Stress & Antioxidants

I have conducted several projects focused on the role of reactive oxygen species (ROS) in biological systems and the cytoprotective effects of antioxidants. ROS are generated due to the univalent transfer of electrons, which can result from exposure to environmental toxins, radiation, and homeostatic cellular processes such as oxidative phosphorylation (Ox-Phos).

ROS Scavenging: In one collaborative project, I investigated the antioxidant properties of 7 novel hydroxycoumarin compounds and determined their ability to protect endothelial cells from ROS-induced cell death. Our findings indicated that 2 of the 7 tested compounds were effective in scavenging ROS and protecting endothelial cells. This work led to my first peer-reviewed publication.

a. Pérez-Cruz F, Villamena FA, Zapata-Torres G, Das A, **Headley CA**, Quezada E, Lopez-Alarcon C and Olea-Azar C. (2013), Selected hydroxycoumarins as antioxidants in cells: physicochemical and reactive oxygen species scavenging studies, *Journal of Physical Organic Chemistry.* 26:773-783.

Endothelial Dysfunction In another project, I investigated the impact of nitrones on hyperglycemia-induced endothelial dysfunction in endothelial cells. Reduced vasodilation and a shift of the endothelium towards a pro-inflammatory phenotype are associated with cardiovascular abnormalities, including atherosclerosis, coronary heart disease, diabetes, and AAA. My work demonstrated that the nitrones alpha-phenyl-n-tert-butylnitrone

(PBN) and 5,5-dimethyl-1-pyrroline N-oxide (DMPO) can reverse hyperglycemia-induced endothelial dysfunction in bovine aortic endothelial cells.

b. **Headley CA,** DiSilvestro D, Bryant KE, Hemann C, Chen CA, Das A, Ziouzenkova O, Durand G, Villamena FA. (2016), Nitrones Reverse Hyperglycemia-Induced Endothelial Dysfunction in Bovine Aortic Endothelial Cells*. Biochemical Pharmacology,* 104, 108-117. PMCID: PMC5248535

In Situ Visualization of Nitrones: Finally, I developed a technique for in situ conjugation of nitrones to a fluorescently labeled alkyne, which provided a simple and cost-effective alternative for determining their intracellular compartmentalization. This method allowed for the visualization of nitrones in living cells and expanded our understanding of their intracellular localization and therapeutic potential.

c. **Headley CA,** Hoffman CM, Freisen JM, Han Y, Macklin JM, Zweier JL, Kuret J, Rockenbauerc A, VillamenaFA. Membrane-specific spin trap, 5-dodecylcarbamoyl-5-N- dodecylacetamide-1-pyroline-N-oxide (diC_{12}PO): Theoretical, bioorthogonal fluorescence imaging and EPR studies. Organic and Biomolecular Chemistry. (17): 7694-7705. 2019. PMCID: PMC6703941

Overall, my contributions to these projects have advanced our knowledge of the role of ROS and antioxidants in cellular processes and have potential implications for the treatment of cardiovascular diseases.

2. Research in Immunology & Host-Pathogen Interactions

During my doctoral training with Dr. Joanne Turner, we investigated how aging affects the immune response to mycobacteria and the underlying mechanisms contributing to increased susceptibility to tuberculosis in the elderly. The overaching hypothesis was that inflammaging, or age-related changes in inflammatory pathways, lead to suboptimal reprogramming of pulmonary and systemic immunity and worsen infection outcomes in older individuals.

Mycobacterial Infections and Cardiac Dysregulations: I led a groundbreaking study examining how mycobacteria affects cardiac function in aged mice, finding that pre-existing inflammation from aging may lead to cardiac dysfunction in *M. avium*-infected old mice. Our findings showed dysrhythmia, increased recruitment of CD45+ leukocytes, cardiac fibrosis, and increased expression of inflammatory genes in isolated heart tissue.

a. **Headley CA,** Gerberick A, Mehta S, Ganesan LP, Wu Q, Yu L, Fadd P, Kha M, Turner J, Rajaram M. N Nontuberculous Mycobacterium M. avium infection predisposes aged mice to cardiac abnormalities and inflammation. *Aging Cell 2019;18(3):e12926.* PMCID: PMC6516181

b. **Headley, C.,** Turner, J., & Rajaram, M. V. (2019). Aging heart and infection. *Aging,* 11(14), 4781-4782. PMCID: PMC6682520

Immunological Correlates of TB Exposure: I assisted Dr. Russell Ault in studying a gene signature (250 genes) in blood samples that correlates with recent *M.tb* exposure and is reproducible across different species. Our findings showed that this signature could predict recent tuberculosis exposure in mice, macaques, and humans. This research has significant implications for developing non-invasive diagnostic tools for tuberculosis and understanding host-pathogen interactions.

c. Ault, R. C., **Headley, C. A.**, Hare, A. E., Carruthers, B. J., Mejias, A., & Turner, J. (2020). Blood RNA signatures predict recent tuberculosis exposure in mice, macaques and humans. Scientific reports, 10(1), 16873. https://doi.org/10.1038/s41598-020-73942-z. PMCID: PMC7547102

COVID-19: I assisted in validating the K18-hACE2 transgenic rodent model for studying SARS-CoV-2 and evaluating the therapeutic efficacy of human monoclonal antibodies against SARS-CoV-2 infections in these animals. These highly collaborative projects were sponsored by the Bill & Melinda Gates Foundation and publications (2+) are still pending. One publication that resulted from this work reported on the lethality of SARS-CoV-2 infection in K18-hACE2 transgenic mice.

d. Oladunni, F. S., Park, J. G., Pino, P. A., Gonzalez, O., Akhter, A., Allué-Guardia, A., Olmo-Fontánez, A., Gautam, S., Garcia-Vilanova, A., Ye, C., Chiem, K., **Headley, C.,** Dwivedi, V., Parodi, L. M., Alfson, K. J., Staples, H. M., Schami, A., Garcia, J. I., Whigham, A., Platt, R. N., 2nd, … Torrelles, J. B. (2020). Lethality of SARS-CoV-2 infection in K18 human angiotensin-converting enzyme 2 transgenic mice. Nature communications, 11(1), 6122. https://doi.org/10.1038/s41467-020-19891-7. PMCID: PMC7705712

Overall, my contributions to these projects have advanced our knowledge of host-pathogen interactions.

3. Research in Immuno-Metabolism

Mitochondrial Transplantation**:** I investigated the role of mitochondrial dysfunction in T cells and its contribution to inflammaging, which is associated with increased tissue oxidative stress and dysregulated signaling and function of CD4+ T lymphocytes in the elderly. In a proof of principle study, I examined whether the transfer of functional mitochondria into aged CD4+ T cells from mice and elderly humans could abrogate aging-associated mitochondrial dysfunction and improve their functionality. The delivery of exogenous mitochondria led to significant improvements in mitochondrial aerobic metabolism and decreased cellular mitochondrial ROS. Additionally, mito-transferred aged CD4+ T cells displayed improved activation-induced TCR-signaling kinetics, increased IL-2 production, enhanced proliferation *ex vivo*, and decreased expression of surface markers associated with T cell exhaustion and T cell senescence. Notably, adoptive transfer of mito-transferred aged CD4+ T cells protected immune-deficient mice from influenza A and *Mycobacterium tuberculosis* infections. These findings highlight the potential for mitochondria as targets for therapeutic interventions in aging-related diseases. (Under review at eLife)

a. **Headley CA,** …Ault R, TorrelesJ, Gelfond J, Turner J. Extracellular Delivery of Functional Mitochondria Reverses the Dysfunction of CD4+ T Cells in Aging. bioRxiv doi:10.1101/2021.02.21.432151

Mitochondrial Dysfunction in Aging-Associated Cardiovascular Diseases: As a T32 fellow at the National Heart, Lung, and Blood Institute (1T32HL098049), I am focusing on the impact of aging-associated mitochondrial dysfunction on immune and vascular dysregulation that is associated with the acceleration of abdominal aortic aneurysm growth and rupture. Specifically, my research aims to investigate the role of mitochondrial dysfunction in aging-associated cardiovascular diseases, and to identify potential therapeutic interventions that target mitochondria to slow or prevent disease progression.

b. **Headley, CA**., & Tsao, P. Building the Case for Mitochondrial Transplantation as an Anti-aging Cardiovascular Therapy. Frontiers in Cardiovascular Medicine, 10, 707. PMCID:NA

Provisional Patent: I've identified previously unexplored aspects of mitochondrial dysfunction. This work accentuates the potential of a novel therapeutic approach I've developed, known as mitochondrial therapy. Significantly, this innovative therapy shows promise in addressing a range of complex health conditions, offering a promising new direction in the treatment landscape.

c. Mitochondrial Transfer for Treatment of Disease - Patent Application No. 63/502,036

4. STEM-related advocacy

Mentorship: Mentorship is a crucial part of my academic journey, and I place a high value on representation. I have been fortunate to have mentors and colleagues who have nurtured my curiosity, and I aim to pay it forward by mentoring underrepresented minority (URM) students interested in research. I also co-authored a “best practices” guide, which included both perspectives and strategies that graduate school interviewees can use when preparing for interviews.

a. Mentor in the Discovery Post-Baccalaureate Research Education Program, The Ohio State University, Columbus, Ohio (2016-2021)
b. Mentor in the Metascience Analyses and Explorations of Reproducibility in Cardiovascular Science (MAVERICS), Stanford University, Palo Alto, California (2022)
c. Ransey, E., Brookens, S., Beasley, H. K., Marshall, A., Marlin, B. J., Rodriguez-Aliaga, P., **Headley, C. A.**, Wanjalla, C., Vazquez, A. D., Murray, S., Damo, S., Taabazuing, C. Y., & Hinton, A., Jr (2023). A Practical Guide to Graduate School Interviewing for Historically Excluded Individuals. American journal of physiology. Heart and circulatory physiology,10.1152/ajpheart.00123.2023.https://doi.org/10.1152/ajpheart.00123.2023. PMCID: PMC10191121

Advocacy: In addition to mentorship, I am committed to trainee advocacy. At the Texas Biomedical Institute, I advocated for graduate and post-doctoral trainees and co-founded the Texas Biomedical Research Institute Student Association, serving on its Executive Committee from 2018 to 2020. I have also been involved in entrepreneurship and non-academic career exposure, co-founding Enventure San Antonio to connect advanced degree graduate students with entrepreneurial opportunities in the health sciences sectors and provide exposure to non-traditional careers in science and innovation. As Vice President of DEI at the non-profit Biotech Connection Bay Area (BCBA), I help with the recruitment and retention of qualified URM in the science consulting landscape in San Francisco. As an Endocrine Society Future Leaders Advancing Research in Endocrinology (FLARE) Fellow, I will also travel to Washington, D.C., to lobby for research funding.