BIOGRAPHICAL SKETCH

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NAME: Lauren R. Miller (maiden name: Bellcock)

eRA COMMONS USER NAME (credential, e.g., agency login): LAUREN-MILLER

POSITION TITLE: Post-Doctoral Research Fellow (University of Oklahoma Health Sciences Center)

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Oklahoma Christian University, Edmond, OK	B.S.	08/2013	04/2017	Cellular and Molecular Biology
University of Oklahoma Health Sciences Center, Oklahoma City, OK	Ph.D.	07/2017	08/2022	Cell Biology
Oklahoma Medical Research Foundation, Oklahoma City, OK	Post-Doctoral Fellowship	09/2022	05/2024	Cardiovascular Biology
University of Oklahoma Health Sciences Center, Oklahoma City, OK	Post-Doctoral Fellowship	07/2024	Present	Geroscience

A. Personal Statement

My long-term career goal is to obtain a faculty position at an institution where I can both conduct cerebrovascular aging research and train the next generation of scientists. During my undergraduate studies, I was thoroughly trained in molecular, biochemical, and cellular biology techniques. Oklahoma Christian University's (OC) curriculum emphasized courses with a heavy laboratory component which allowed me to learn a wide range of techniques common to the research laboratory.

While an undergraduate student, I had the opportunity to work on two different research projects which allowed me to expand my repertoire of lab skills and research knowledge. During the summer of 2015, I participated in OC's undergraduate research program in Dr. Landon Moore's lab. We studied centromere resolution in *Caenorhabditis elegans*. During this project, I became skilled at doing fine manipulations and dissections using a dissecting microscope, along with various molecular techniques. In the summer of 2016, I participated in the Summer Undergraduate Research Experience at the University of Oklahoma Health Sciences Center with my eventual Ph.D. mentor, Dr. Shannon Conley. During this program and my summer research project in her lab the following summer, I was introduced to the field of vascular smooth muscle cell (VSMC) biology. My first project focused on studying the roles of small G proteins in regulating growth factor-induced phenotypic switching in VSMCs. From this project, I learned how to perform many techniques used in this field and about the functions and relevance of VSMCs to vascular health. Through these initial studies and my subsequent work, I have become excited about the critical role the vasculature plays in aging pathologies, particularly in the brain where vascular cognitive impairment can significantly limit healthspan. In spite of these clear associations, we suffer from a great lack of understanding of the cellular mechanisms of age-related vascular fragility.

In 2017, I joined the interdisciplinary GPiBS program at OUHSC, and officially joined Dr. Conley's lab to further pursue these vascular aging studies. During my time in Dr. Conley's lab I focused on developing and

executing my dissertation research. My project involved understanding changes in vascular smooth muscle cells (VSMCs) in the aging cerebral vasculature. I was particularly interested in the role of VSMCs in the development of cerebral microhemorrhages (CMHs), microvascular fragility, and associated cognitive decline. My dissertation project was an offshoot of Dr. Conley's Geroscience COBRE and R01 projects, and is a key research focus of her lab. Over my five years in the Conley lab, I conducted numerous aged mouse cohort studies, optimized multiple cell isolation techniques for RNA expression studies, become proficient in basic animal surgical technique, and vastly improved my presentation abilities.

After completing my PhD studies, I joined Dr. Audrey Cleuren's lab at Oklahoma Medical Research Foundation as a Post-Doctoral Research Fellow. Dr. Cleuren's lab studies endothelial cell (EC) translatomic changes in response to states of acute and chronic inflammation. My main project in Dr. Cleuren's lab focused on using the RiboTrap mouse model crossed with the 5XFAD transgenic Alzheimer's disease (AD) mouse model. Other projects that I worked on included a high fat diet-induced obesity model to look at EC transcriptional changes and acute inflammation induced by LPS and IL-6 injections. During my time in Dr. Cleuren's lab, I learned about how to conduct transcriptomics experiments in a careful and robust manner to ensure quality data. I also discovered that my research passion is actually for brain aging research and not vascular inflammation, and thus decided to transition to a different postdoctoral position.

I joined Dr. Veronica Galvan's lab because she is a leader in the aging field. She has the expertise in brain aging and knowledge of the field to give me the training I desire to become a geroscience researcher focusing on brain aging. My project with Dr. Galvan studying the role of mTOR in regulating brain microvascular dysfunction in a mouse model of Alzheimer's disease will allow me to follow my passion in brain aging and cognitive function research while finding my niche to establish an independent career.

B. Positions, Scientific Appointments and Honors

Positions

2024-Present	Post-doctoral Research Fellow, Lab of Dr. Veronica Galvan, Department of Bioch
2022-2024	Post-doctoral Research Fellow, Lab of Dr. Audrey Cleuren, Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation,
2021-2022	Adjunct Instructor of Biology, New College, Oklahoma Christian University
2021	Adjunct Instructor of Chemistry, Department of Natural Sciences, Oklahoma Christian University
2018-2022	Graduate Research Assistant, Lab of Dr. Shannon Conley, Department of Cell Biology, University of Oklahoma Health Sciences Center
2017-2018	Graduate Research Assistant, Graduate Program in Biomedical Sciences, University of Oklahoma Health Sciences Center,
2017	Summer Research Student, Lab of Dr. Shannon Conley, Department of Cell Biology, University of Oklahoma Health Sciences Center
2016	Summer Research Student, SURE Program, Lab of Dr. Shannon Conley, Department of Cell Biology, University of Oklahoma Health Sciences Center
2015-2016	Undergraduate Research Assistant, Lab of Dr. Landon Moore, Department of Biology, Oklahoma Christian University
2014-2017	Teaching Assistant, Department of Chemistry and Physics, Oklahoma Christian University

Honors, Memberships, and Service

Ad hoc Journal Review for Scientific Reports, 2024.
Brain and Brain PET Imaging Symposium 2022 Travel Bursary, $1100, 2022
American Age Association Nathan Shock Center Travel Award, $1000, 2022
Vice President of Research Scientific Achievement Award, OUHSC GREAT Symposium, 2021
Social Chair, Graduate Student Association, University of Oklahoma Health Sciences Center, 2020-2021
Pre-GREAT Symposium Workshop Chair, Graduate Student Association, University of Oklahoma Health Sciences Center, 2019-2020
Member, Crimson Club, University of Oklahoma Health Sciences Center, 2018-2022
Member, Leadership HSC, University of Oklahoma Health Sciences Center, Class of 2018
Member, Graduate Student Association, University of Oklahoma Health Sciences Center, 2017-present
Outstanding Senior Award, Oklahoma Christian University Department of Biology, 2017

Fellowships and Training Grants

Institutional National Research Service Award (T32) (Role: Post-Doctoral Fellow) **08/01/2024-07/31/2025.** *Geroscience Training Program in Oklahoma, Fellowship* (Direct $61,428). This training grant provides me with stipend support for my postdoctoral research. This program also provides valuable training in grant writing, presentation

American Heart Association Pre-Doctoral Fellowship Award (Role: PI) **04/01/2021-03/31/2022**
The role of vascular smooth muscle cell IGF-1 signaling in the pathogenesis of vascular fragility and cognitive decline. (Direct: $31,520.) This grant was a predoctoral fellowship that provided stipend support for my dissertation research. The goal of this grant was to evaluate the effects of deficient IGF-1 signaling on vascular smooth muscle cells in the development vascular fragility pathologies and cognitive decline.

Institutional National Research Service Award (T32) (Role: Predoctoral Trainee) **11/08/2020-03/31/2021**
Geroscience Training Program in Oklahoma. (Direct: $25,320.) This is a group training grant that provided stipend support for my dissertation research. In addition, it provided valuable training opportunities to assist me in my career advancement as a geroscience researcher.

Presbyterian Health Foundation Research Support Grant, Fellowship (Role: PI) **07/2019-06/2021**
IGF-1, smooth muscle plasticity, and pathogenesis of cerebral microhemorrhages in aging. (Direct: $30,000) This grant was a predoctoral fellowship that provided stipend support for my dissertation research. The goal of the project was to evaluate vascular smooth muscle cell changes in aging and IGF-1 deficiency in the brain. **I received a second year of funding from this competitive renewal grant.**

C. Contributions to Science

1. **mTOR-driven mechanisms of brain microvascular dysfunction in Alzheimer's disease.** Alzheimer's disease is the most prevalent form of age-related dementia. The Galvan lab has demonstrated that the mammalian target of rapamycin (mTOR) is a driver of cerebrovascular dysfunction and cognitive impairment in animal models of aging and AD. mTOR impairs interneuron-derived nNOS causing impaired neurovascular coupling (NVC) responses, which we hypothesize may lead to the cognitive decline seen in AD models. This project aims to identify the molecular mechanisms that underlie mTOR-driven regulation of NVC and downstream cognitive impairment in models of AD.
2. **Endothelial cell translatomics and vascular phenotypes in chronic hypertension and Alzheimer's disease.** Alzheimer's disease (AD) is increasingly recognized as a disease with significant vascular contributions. Dr. Cleuren's lab is particularly interested in the endothelial translatome (total population of actively translating mRNAs) and how it changes in response to inflammatory disease states. The goal of this project is to model the course of human disease by inducing chronic, low-grade hypertension in young adult mice with familial AD. We have conducted studies examining neurovascular coupling, amyloid distribution, and cognition to complement transcriptomic analyses. We discovered transcriptional changes in ECs from 5XFAD brains indicating cellular stress, inflammation, and senescence. My time in Dr. Cleuren's lab has allowed me to learn about transcriptomics, present at national meetings, and discover my interest in Alzheimer's research.
    a. **Miller LR,** Saunders D, Negri S, Beckstead M, Tarantini S, Cleuren ACA. (2024) The cerebrovasculature in a mouse model of Alzheimer's disease. *North American Vascular Biology Organization Meeting 2023 Poster Presentation Session.*
    b. **Miller LR,** Saunders D, Beckstead M, Cleuren ACA. (2023) Alzheimer's disease and chronic hypertension are associated with endothelial changes in the brain. *Annual AGE meeting 2023 Poster Presentation Session.*
3. **IGF-1 signaling, mural cell plasticity, and vascular pathologies of aging**. Levels of Insulin-like growth factor-1 (IGF-1) decrease with age and are associated with vascular aging pathologies such as microvascular rarefraction, impaired neurovascular coupling, and cerebral microhemorrhages. Vascular smooth muscle cells (VSMCs) are critical for maintaining vascular stability and function. The Conley lab, in collaboration with Dr. Csiszar's lab, is studying cellular mechanisms of cerebrovascular aging and cognitive decline, with particular interest in the role of IGF-1 and VSMCs. As part of this collaboration, I conducted *in vivo* studies on hypertensive mice and documented the presence of microbleeds in cases of IGF-1 deficiency and evaluated the role of VSMCs in this process. I also contributed to writing a review about vascular changes in the eye during aging and their role in in age-related macular degeneration. Dr. Conley's expertise in studying VSMCs and aging eye pathologies in combination with Dr. Csiszar's

expertise in studying cerebral vascular pathologies me provided a considerable opportunity to become proficient in variety of fields and techniques.

a. **Miller LR,** Bickel MA, Vance ML, Vaden H, Nagykaldi D, Nyul-Toth A, Bullen EC, Gautam T, Tarantini S, Yabluchanskiy A, Kiss T, Ungvari Z, Conley SM. (2024). Vascular smooth muscle cell-specific Igf1r deficiency exacerbates the development of hypertension-induced cerebral microhemorrhages and gait defects. *GeroScience 2024 Feb 23.*
b. **Miller LR*,** Bickel MA*, Tarantini S, Runion ME, Matacchiera Z, Vance ML, Hibbs C, Vaden H, Nagykaldi D, Martin T, Bullen EC, Pinckard J, Kiss T, Howard EW, Yabluchanskiy A, Conley SM. (2024) IGF1R deficiency in vascular smooth muscle cells impairs myogenic autoregulation and cognition in mice. *Frontiers in Aging Neuroscience 2024 Feb 15;16:1320808.* **(*Co-first authors.)**
c. **Miller LR**, Tarantini S, Nyúl-Tóth A, Johnston MP, Martin T, Bullen EC, Bickel MA, Sonntag WE, Yabluchanskiy A, Csiszar A, Ungvari ZI, Elliot MH, Conley SM. (2021) Increased susceptibility to cerebral microhemorrhages is associated with imaging signs of microvascular degeneration in the retina in an IGF-1 deficient mouse model of accelerated aging. *Frontiers in Aging Neuroscience. 2022 Mar 9;14:788296.*
d. Lipecz A*, **Miller LR*,** Kovacs I, Czakó C, Csipo T, Baffi J, Csiszar A, Ungvari ZI, Yabluchanskiy A, Conley SM. (2019) Microvascular contributions to age-related macular degeneration (AMD): from mechanisms of choriocapillaris aging to novel interventions. *GeroScience,* Dec;41(6):813-845. **(*Co-first authors.)**

4. **Regulation of PDGF-induced phenotypic switching in vascular smooth muscle cells.** VSMCs can dedifferentiate from a contractile phenotype to a proliferative, migratory phenotype in response to growth factor signals such as platelet-derived growth factor (PDGF). While the ability of differentiated VSMCs to switch phenotypes is established, the mechanisms that regulate this switch are not as well understood. During the summers of 2016-2017, I was a summer research student in Dr. Conley's lab and my project focused on studying the role of the small G proteins Rnd3 and Rap1B in regulating the PDGF-induced phenotypic switch of vascular smooth muscle cells (VSMCs). We collaborated with Dr. Eric Howard's lab to use a lentivirus mediated approach. I found that Rnd3 knockdown inhibits gene expression changes associated with the phenotypic switch, but does not prevent cell migration or changes in morphology. I also found that Rap1B activation exacerbates PDGF-induced morphological change in VSMCs, but inhibits migration via decreased cell adhesion. We concluded that these small G proteins regulate distinct aspects of the phenotypic switch. I presented a poster of my findings at undergraduate research days at both the OUHSC and Oklahoma Christian University.
    a. **Bellcock LR,** Bullen EC, Howard EW, Sherry DM, Watson JN, Conley SM. (2016) Regulation of PDGF-induced phenotypic switching in vascular smooth muscle cells and fibroblasts. *OUHSC SURP poster presentation competition*; Oklahoma City, Oklahoma.
    b. **Bellcock LR,** Bullen EC, Howard EW, Sherry DM, Watson JN, Conley SM. (2016) Regulation of PDGF-induced phenotypic switching in vascular smooth muscle cells and fibroblasts. *Oklahoma Christian University Summer Undergraduate Experience and Research Poster Presentation session*; Edmond, Oklahoma.
5. **Conservation of a partial gene duplication of the *Top-2* like protein, *cin-4,* in *Caenorhabditis elegans.*** *Caenorhabditis elegans* is a model organism often used for genetic studies because of its hermaphroditic reproduction, large number of progeny, and easily scorable phenotypes. During my undergraduate research in Dr. Landon Moore's laboratory, I studied a partial gene duplication of *Topoisomerase II (Top-2), cin-4*, that is conserved in *C. elegans*, but is not present in other organisms. Preliminary studies using an RNAi knockdown strategy suggested that *cin-4* was essential for centromere resolution. My work involved helping generate a CRISPR-Cas9 knock out-knock in line of *C. elegans* with a phenotypic marker gene in the place of *cin-4* and genotyping and phenotyping potential knock out animals. During my project, we established and characterized a stable line of *C. elegans* that had a heterozygous deletion of *cin-4*. I presented my results at the Oklahoma Academy of Sciences Technical Meeting in 2015. This work provided a new model for studying the function of *cin-4* and centromere resolution.
    a. **Bellcock LR**, Miller, JM, Moore, LL. (2015) Conservation of a Partial Gene Duplication of the Top-2 Like Protein, cin-4, in *Caenorhabditis elegans*. *Oklahoma Academy of Sciences Technical Meeting;* Oklahoma City, Oklahoma.