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: Stacy A. Hussong

eRA COMMONS USER NAME (credential, e.g., agency login): Husse_11

POSITION TITLE: Research Health Scientist, Assistant Professor of Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of South Dakota, Vermillion, SD	B.S.	08/2005	Biology and Chemistry majors
University of Minnesota, Minneapolis, MN	Ph.D.	10/2010	Biochemistry (major) Gerontology (minor)
University of Texas Health Science Center at San Antonio, San Antonio, TX	Postdoctoral	08/2017	Physiology, Neuroscience

A. Personal Statement

The broad goal of my research is to define the molecular mechanisms involved in brain aging that contribute to the pathogenesis of Alzheimer's disease (AD). During my CDA-2 award I generated an innovative AD mouse model where mTORC1 can be inducibly attenuated specifically in neurons (hAPP/Raptor$^{fl/fl}$-Neu-Cre) during adulthood using genetic tools, that I will utilize in the studies of this proposal. I used this model to define the role of the mechanistic target of rapamycin complex 1 (mTORC1) specifically in neurons of adult mice in the pathogenesis of AD-like disease in model mice. Studies of my CDA-2 project used hAPP/Raptor$^{fl/fl}$-Neu-Cre mice in parallel with studies that used pharmacological mTORC1 inhibition to generate the preliminary data that provides a strong scientific foundation for the present Merit Award proposal.

mTOR is a major regulator of aging in mammals and across phyla. A major focus of my lab is to identify the mechanisms that link the regulation of aging to the pathogenesis of AD, and thus explain the increased vulnerability of aged brain to AD. My prior work has demonstrated that mTOR drives dysfunction in brain vascular endothelium in AD and in aging, specifically through the inhibition of nitric oxide-dependent mechanisms of vascular reactivity, critical for neurovascular coupling, a central homeostatic mechanism adjusting cerebral blood flow to the increased metabolic needs of activated neuronal networks.

Building on my graduate, postdoctoral, and CDA-2 mentored research training I acquired robust expertise in the use of biochemical, primary and continuous cell culture-based, behavioral, surgical, and electrophysiology approaches. I will utilize my acquired competences to direct and successfully complete the studies of the present proposal. Overall, my knowledge base and training have prepared me to lead the present project and ensure the successful completion of all its aims.

As Research Health Scientist at the Oklahoma City VAHCS and an Assistant Professor of Research at the Center for Geroscience and Healthy Brain Aging at the University of Oklahoma Health Sciences Center, I am in an ideal environment that ensures my access to extensive expertise and all of the resources required to complete the proposed studies. This environment will afford me access to additional expertise and resources to successfully complete all aims of the present proposal, as well as support me and my laboratory with extensive resources and expertise that will allow me to develop my independent research program and achieve my research and career goals.

Ongoing and pending projects that I would like to highlight:

Current

1 IK2 BX003798-01A1 (Hussong) 04/01/2018 - 9/30/2023
Veterans Administration Career Development Award (CDA-2)
The Role of Neuronal mTORC1 in Alzheimer's Disease
The goal of this project is to define the contribution of neuronal-driven mTOR-dependent mechanisms of Alzheimer's disease pathogenesis by measuring cognitive behaviors, synaptic function, and vascular function.

Pending

VA Medical Care Supported Mgmt. Study 10/01/2023 – 9/30/2025
Oklahoma City VA Medical Center Pilot Award
The role of mTORC1 in age-related peripheral nerve damage and dysfunction in mice
The goal of this study is to determine the mechanisms by which mTORC1 signaling drives age-associated peripheral nerve dysfunction in mice and develop an *in vitro* co-culture system to study peripheral myelination using primary motor neurons and Schwann cells.

Recent and pending publications that I would like to highlight:

1. **Hussong, SA**, Burbank Roberts, R, Halloran JJ, Lin AL, Van Skike, CE, Dorigatti, AO, Hernandez, SF, DeRosa, ND, Pomilio, C, Soto, VY, Liu, Y, Walsh, ME, Pulliam, DA, Van Remmen H, Fox, PT, Austad, SA, and Galvan V. Regulation of survival, metabolism, and memory by neuronal mTOR. 2023. In revision in *iScience.*
2. Van Skike, C.E., **Hussong, S.A.**, Hernandez, S.F., Banh, A.Q., DeRosa, N., Galvan, V. 2021. mTOR attenuation with rapamycin reverses neurovascular uncoupling and memory deficits in mice modeling Alzheimer's disease *J. Neuroscience.* **41(19):** 4305-4320. PMID: 33888602. ***Featured article in 'J Neuroscience Featured Research'***
3. **Hussong, S.A.***, Banh, A.Q.*, (*authors contributed equally), Van Skike, C.E., Dorigatti, A.O., Hernandez, S.F., Hart, M.J., Ferran, B., Makhlouf, H., Gaczynska, M., Osmulski, P.A., McAllen, S.A., Dineley, K.T., Ungvari, Z., Perez, V.I., Kayed, R., and Galvan, V. 2023. Soluble pathogenic tau enters brain vascular endothelial cells and drives cellular senescence and brain microvascular dysfunction in a mouse model of tauopathy. *Nat Commun*. **14(1)**: 2367. PMCID: 37185259.
4. Van Skike, C.E., DeRosa, N., Galvan, V., and **Hussong, S.A.#** (**#senior author**) Rapamycin restores peripheral blood flow in aged mice and in mouse models of atherosclerosis and Alzheimer's disease. 2023. *Geroscience* **45(3)**: 1987-1996. PMID: 37052770.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2021-present	Research Health Scientist, Oklahoma City Veterans Health Care System, Department of Veterans Affairs
2021-present	Assistant Professor of Research, Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center
2018-2021	Research Health Scientist, South Texas Veterans Health Care System, Department of Veterans Affairs
2017-2021	Instructor/Research, Department of Cellular and Integrative Physiology and the Barshop Institute for Longevity and Aging Studies, University of Texas Health at San Antonio
2010-2017	Postdoctoral Fellow, Department of Cellular and Integrative Physiology and Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio (Mentor, Veronica Galvan, Ph.D.)
2005-2010	Graduate Research Assistant, Department of Biochemistry, Molecular Biology, & Biophysics, University of Minnesota (Mentor, Deborah Ferrington, Ph.D.)

Memberships and Other Professional Activity

2023-present	Editorial board member, *Geroscience*
2023-present	OKC VA Voting SRS Committee Member
2020-present	Editorial board member, *Frontiers in Aging: Interventions in Aging*
2019-present	Ad hoc reviewer, *Journal of Nutrition and Healthy Aging*
2018-present	Ad hoc reviewer, *Scientific Reports*
2018-present	Ad hoc reviewer, *Journal of Integrative Neuroscience*
2012-present	Ad hoc reviewer, *Journal of Gerontology*
2011-present	Ad hoc reviewer, *Journal of Alzheimer's Disease*
2011-present	Member, American Aging Association
2016-2023	Ad hoc reviewer, GeroScience-*Journal of the American Aging Association*
2006-2010	Member, Association of Research in Vision and Ophthalmology

Academic and Professional Honors

2023	Invited Speaker, 2023 Oklahoma Geroscience Symposium
2022	Invited Speaker, American Aging Association 50th Annual Meeting
2019	Junior Faculty Travel Award, American Aging Association 47th Annual Meeting
2019	Poster Presentation Award – VA Non-Clinical Research – Faculty, 22nd Annual Department of Medicine Research Day, UT Health San Antonio
2018	Junior Faculty Travel Award, American Aging Association 47th Annual Meeting
2018	Poster Presentation Award – Junior Faculty, 21st Annual Department of Medicine Research Day, UT Health San Antonio
2018	Outstanding Junior Faculty Poster Presentation, Center for Biomedical Neuroscience 16th Annual Retreat, UT Health San Antonio
2018-2023	Career Development Award (CDA-2), Department of Veterans Affairs
2016	Superior Postdoctoral Poster Award, 45th Annual Meeting of the American Aging Association
2015	Joe and Bettie Ward Award for Excellence in the Study of the Biology of Aging
2014	San Antonio Life Sciences Institute Best Poster Presentation, 2nd Annual Postdoctoral Research Forum and Distinguished Lecture
2013	Research Poster Award – 3rd Place, 1st Annual Postdoctoral Research Forum and Distinguished Lecture
2012	Third Place Best Poster Award, Center for Biomedical Neuroscience, 10th Annual Retreat, University of Texas Health Science Center at San Antonio
2010-2013	NRSA Institutional Training Grant, UTHSCSA, Biology of Aging
2010	Outstanding Poster Presentation, Midwest Eye Research Symposium
2009	Best Poster Award, Gordon Research Conference, Biology of Aging
2009	Invited Speaker, Scientists in Aging Research Fall Symposium, University of Minnesota
2009	Graduate and Professional Student Assembly Scholarly Travel Award, University of Minnesota
2008-2010	National Research Service Award (NRSA) Institutional Training Grant, University of Minnesota, Functional Proteomics in Aging
2007	Invited Speaker, San Antonio Nathan Shock Aging Center Conference on Aging
2007, 2008	Travel Fellowship Award, Department of Biochemistry, Molecular Biology, & Biophysics, University of Minnesota
2007	Best Poster Award, Biochemistry, Molecular Biology, & Biophysics Departmental Retreat, University of Minnesota
2005	Magna Cum Laude, University of South Dakota
2005	Phi Beta Kappa Society
2003-2004	Senior Merit Award in Chemistry, University of South Dakota
2002	Golden Key International Honor Society
2002	Dean Joseph H. Cash Award for Excellence in Writing, University of South Dakota
2002	Dr. Joseph R. Spies Chemistry Scholarship, University of South Dakota
1999	Alpha Lambda Delta Honor Society

C. Contributions to Science

1. Function of the immunoproteasome in aging and disease. My graduate research focused on describing novel roles of the immunoproteasome in the retina. The immunoproteasome was previously thought to primarily function in the immune system. My graduate work demonstrated that the immunoproteasome plays an central role in the retinal stress response as well as retinal function. Immunoproteasome is upregulated with many types of stress including retinal injury, oxidative stress, age, and light damage. We showed that mice lacking immunoproteasome respond differently to stress and are more resistant to retinal injury. However, our data indicated that immunoproteasome is required for normal retinal function since immunoproteasome deficient mice have impaired retinal function as measured by electroretinogram. Overall, my research has shown that the immunoproteasome has a critical role in the retinal stress response and in retinal function.

a. Ethen, C.M., **Hussong, S.A.**, Reilly, C., Feng, X., Olsen, T.W. and Ferrington, D.A. (2007) Transformation of the proteasome with age-related macular degeneration. *FEBS Letters* 581: 885-890. PMCID: PMC1850528

b. Ferrington, D.A., **Hussong, S.A.**, Roehrich, H., Kapphahn, R.J., Kavanaugh, S., Heuss, N. and Gregerson, D.S. (2008) Immunoproteasome responds to injury in the retina and brain. *J. Neurochem.* 106: 158-169. PMCID: PMC4401486

c. **Hussong, S.A.**, Kapphahn, R.J., Phillips, S.L., Maldonado, M. and Ferrington, D.A. (2010) Immunoproteasome deficiency alters retinal proteasome's response to stress. *J. Neurochem.* 113: 1481-1490. PMCID: PMC2909641

d. **Hussong, S.A.**, Roehrich, H., Kapphahn, R.J., Maldonado, M., Pardue, M.T. and Ferrington, D.A. (2011) A novel role for immunoproteasome in retinal function. *IOVS* 52: 714-723. PMCID: PMC3053103

e. Schuld, N.J.*****, **Hussong, S.A.* (*authors contributed equally)**, Kapphahn, R.J., Lehmann, U., Roehrich, H., Rageh, A., Heuss, N., Gregerson, D.S., Ferrington, D.A. (2015) Immunoproteasome deficiency protects the retina after optic nerve crush. *PlosOne*. 10(5): e0126768. PMCID: PMC4433222

2. Molecular mechanisms of brain aging that drive Alzheimer's disease. A major focus of my research has been on the investigation of pathways that mechanistically link the regulation of the rate of brain aging by the mammalian target of rapamycin complex 1 (mTORC1) and the pathogenesis of Alzheimer's disease (AD). We identified mTOR-dependent inhibition of autophagy in neurons and the inhibition of endothelial nitric oxide (NO)-dependent release of NO in brain vasculature as two critical mechanisms that underlie the increased risk of aged brain to AD. Our work demonstrated that systemic attenuation of mTOR activity with rapamycin, an intervention that extends lifespan by delaying aging, can prevent cognitive dysfunction both during aging and in AD.

a. Halloran, J.*****, **Hussong, S.A.* (*authors contributed equally)**, Burbank, R.R., Podlutskaya, N., Fischer, K., Sloane, L., Austad, S., Strong, J.R., Richardson, A., Hart, M. and Galvan, V. (2012) Chronic inhibition of mammalian target of rapamycin by rapamycin modulates cognitive and non-cognitive components of behavior throughout lifespan in mice. *Neuroscience.* 223C:102-113. PMCID: PMC3454865. *This article was recommended by Faculty of 1000*

b. Van Skike, C.E., Lin, A-L., Burbank Roberts, R.R., Halloran, J.J., Hernandez, S.F., Cuvillier, J., Soto, V., **Hussong, S.A.**, Jahrling, J., Javors, M., Hart, M.J., Fischer, K., Austad, S.A., and Galvan, V. 2020. mTOR drives cerebrovascular, synaptic, and cognitive dysfunction in normative aging. *Aging Cell.* **19(1):** e13057. PMCID: PMC6974719.

3. mTOR-dependent molecular mechanisms of Alzheimer's disease. A major focus of my research has been on the mTOR-dependent mechanisms of Alzheimer's disease pathogenesis, including the inhibition of autophagy, increased production of Aβ, and decreased brain microvascular integrity. We found that decreased vascular integrity impairs Aβ clearance from brain in manner dependent on eNOS-mediated NO release and vasodilation. Our studies demonstrated, for the first time, that attenuation of mTOR with rapamycin blocks progression and treats established cognitive deficits in AD mouse models by increasing autophagy and improving brain microvascular integrity. Because mTOR inhibitors such as rapamycin are FDA-approved, our studies have significant immediate translational implications for the treatment of AD and potentially other neurological diseases of aging including AD-related dementias. I was contributing author in four publications and senior author in a recently published article resulting from this research.

a. Lin, A.-L., Zheng, W., Halloran, J.J., Burbank, R.R., **Hussong, S.A.**, Hart, M.J., Javors, M., Shih, Y.-Y., Muir, E., Solano Fonseca, R., Strong, R., Richardson, A.G., Lechleiter, J.D., Fox, P.T., and Galvan, V. (2013) Chronic rapamycin restores brain vascular integrity and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. *J. Cereb. Blood Flow Metab.* 33: 1412-1421. PMCID: PMC3764385 *This article was recommended by Faculty of 1000*

b. Pierce, A., Podlutskaya, N., **Hussong, S.A.**, Halloran, J.J., Burbank, R.R., Strong, J.R., Richardson, A., Hart M.J. and Galvan, V. (2013) Upregulation of heat shock proteins by chronic rapamycin treatment lowers Aβ and prevents cognitive impairment in mice modeling Alzheimer's disease. *J. Neurochem.* 124: 880-893.

c. Van Skike, C.E.,Jahrling, J.B., Olson, A.B., Sayre, N.L., **Hussong, S.A.**, Ungvari, Z., Lechleiter, J.D., Galvan, V. (2018) Inhibition of mTOR protects the blood-brain barrier in models of Alzheimer's disease and vascular cognitive impairment. *Am J. Physiol. Heart Circ. Physiol.* 314(4): 58-74. PMCID: PMC5966773

d. Van Skike, C.E., **Hussong, S.A.**, Hernandez, S.F., Banh, A.Q., DeRosa, N., and Galvan, V. 2021. mTOR attenuation with rapamycin reverses neurovascular uncoupling and memory deficits in mice modeling Alzheimer's disease. *J. Neurosci* **41(19)**: 4305-4320. PMCID: PMC8143195.

e. Van Skike, C.E., DeRosa, N., Galvan, V., and **Hussong, S.A.[#] ([#]senior author)** (2023) Rapamycin restores peripheral blood flow in aged mice and in mouse models of atherosclerosis and Alzheimer's disease. *Geroscience* **45(3)**: 1987-1996. PMID: 37052770.

4. Pathogenic tau-induced brain microvascular dysfunction and senescence in AD. Pathogenic forms of tau have a causative role in Alzheimer's disease (AD). Previous studies have shown that tau is transmitted transneuronally in a prion-like fashion. We recently showed that, in addition to tau transmission to neurons, pathogenic forms of tau enter brain vascular endothelial cells *in vitro* and *in vivo* in tauopathy models, triggering endothelial cell dysfunction including microtubule cytoskeleton destabilization, endogenous native tau phosphorylation, reduced endothelial nitric oxide synthase activity and potent induction of cellular senescence, that lead to profound brain microvascular deficits. Brain microvascular dysfunction in mice modeling tauopathy was rescued by specific removal of pathogenic forms of tau using immunotherapy, demonstrating causality of pathogenic tau in brain vascular dysfunction of tauopathy. Our data opened up a new avenue in AD research by identifying brain microvascular endothelial cells as a novel target of pathogenic tau and indicates that immunotherapies directed at pathogenic forms of tau may have promise for treating AD. I was lead author on this publication and helped design and perform experiments as well as prepare the manuscript for publication.

Hussong, SA*, Banh, AQ*, (*authors contributed equally), Van Skike, CE, Dorigatti, AO, Hernandez, SF, Hart, MJ, Ferran, B, Makhlouf, H, Gaczynska, M, Osmulski, PA, McAllen, SA, Dineley, KT, Ungvari, Z, Perez, VI, Kayed, R, and Galvan, V. (2023) Soluble pathogenic tau enters brain vascular endothelial cells and drives cellular senescence and brain microvascular dysfunction in a mouse model of tauopathy. *Nat Commun.* **14(1)**: 2367. PMCID: PMC10126555

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/stacy.hussong.2/bibliography/public/