BIOGRAPHICAL SKETCH

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NAME: Risher, William Christopher

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

POSITION TITLE: Assistant Professor of Biomedical Sciences

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
Clemson University, Clemson, SC	B.Sc.	05/2003	Biological Sciences
Medical College of Georgia, Augusta, GA	Ph.D.	12/2010	Neuroscience
Duke University Medical Center, Durham, NC	Postdoc	03/2018	Cell Biology

A. Personal Statement

I am an Early Stage Investigator who recently established my own research program in the Department of Biomedical Sciences at the Joan C. Edwards School of Medicine at Marshall University. As a graduate student at the Medical College of Georgia (MCG), I began my training with Dr. Kristen Harris, a foremost expert on serial section electron microscopy. Under Dr. Harris's tutelage, I became adept at using this technically challenging method to study the complex structural relationships between astrocytes and synapses. I then joined the lab of Dr. Sergei Kirov to investigate how synaptic connectivity is disrupted after acute brain injury. With Dr. Kirov's guidance, I completed an NINDS-sponsored F31 NRSA fellowship using in vivo two-photon laser scanning microscopy to allow me to image post-stroke structural changes in astrocytes and neurons in real time in the brains of live mice. After graduating, I joined the Duke University Department of Cell Biology in the lab of Dr. Cagla Eroglu, a leading expert on topics such as glial biology and synaptic development. In the Eroglu lab, I completed a Postdoctoral Training Fellowship in Fundamental and Translational Neuroscience (T32) as well as an NINDS-sponsored F32 NRSA, both of which investigated the role of astrocyte-secreted proteins in synapse formation and maturation. I was able to add a wide variety of techniques to my repertoire, including purified neuronal and glial cultures, fluorescence immunohistochemistry, molecular cloning, DNA transfection, and mouse genetics. I was also fortunate enough to be able to train a number of undergraduates, rotating graduate students, and research volunteers, many of whom have continued their training in the academic research career track.

My long-term goal as an independent investigator is to understand the complex relationships between astrocytes and synapses during development and in disease that will be key to forging new therapies for brain disorders characterized by aberrant synaptic connectivity, including substance use disorders. Just in my short time in West Virginia so far, I have witnessed firsthand the extent to which the opioid epidemic has impacted the lives of so many in the community. I have attended meetings of Marshall University's Substance Use Recovery Coalition, which is made up of individuals from varied backgrounds including educators, nurses, psychologists, journalists, and social workers; all of whom have come together to address ways to ameliorate the burden of substance use in Huntington and beyond. Of the many critical issues raised at these meetings, it is clear there is still a strong need for basic science research to understand the biology of addiction and especially neonatal abstinence syndrome (NAS), which occurs at a rate at least 5-fold higher than the national average in our state and county and at an alarming rate up to 10% of all live births in neighboring counties. Little is known about how opioid exposure affects early life brain development, or whether there are serious long-term complications for the children born with NAS. My hope is that our work will inform future studies on

NAS aimed at developing therapeutics to improve long-term outcomes for these children who, through no fault of their own, must live with the devastating consequences of the opioid epidemic.

1. **Risher WC**, Eroglu C. 2012. Thrombospondins as key regulators of synaptogenesis in the central nervous system. Matrix Biology 31(3): 170-7. PMCID: PMC3961754.
2. **Risher WC** et al. 2018. Thrombospondin receptor α2δ-1 promotes synaptogenesis and spinogenesis via postsynaptic Rac1. J. Cell Bio 217(10): 3747-65. PMCID: PMC6168259.
3. Boggess T, **Risher WC**. 2020. Clinical and basic research investigations into the long-term effects of prenatal opioid exposure on brain development. *J Neurosci Res*: Opioids Special Issue. Early View. PMID: 32459039
4. Boggess T, Sexton H, Mazur A, Egleton RD, Grover LM, **Risher WC**. 2020. Alterations in excitatory and inhibitory synaptic development within the mesolimbic dopamine pathway in a mouse model of prenatal drug exposure. *Biorxiv*. DOI: 10.1101/2020.12.18.423503

B. Positions and Honors

2004-2010	Graduate Research Assistant, PhD Program in Neuroscience, Medical College of Georgia, Augusta, GA
2011-2018	Postdoctoral Associate, Department of Cell Biology, Duke University Medical Center, Durham, NC
2018-Present	Assistant Professor, Department of Biomedical Sciences, Joan C. Edwards School of Medicine at Marshall University, Huntington, WV

Other Experience and Professional Memberships

2005-Present	Member, Society for Neuroscience
2016-2018	Member, Triangle Chapter of the Society for Neuroscience
2018-Present	Member, Neurobiology and Developmental Biology Research Cluster (Marshall University)
2020-Present	Member, Marshall University Faculty Senate, School of Medicine Representative

Honors

2003 Magna cum Laude, Calhoun Honors College, Clemson University, Clemson, SC
2009 Award of Excellence in Research, Graduate Research Day, Medical College of Georgia, Augusta, GA
2012 Honorable Mention, Best Postdoc Poster, Duke University Cell Biology Retreat
2013 Best Postdoc Poster, Duke University Neurobiology Retreat
2013 International Journal of Biochemistry and Cell Biology Poster Prize, FASEB Science Research Conference on Matricellular Proteins in Development, Health and Disease
2013 Best Postdoc Talk, Duke University Neurobiology Retreat
2014 Best Postdoc Talk, Duke University Cell Biology Retreat
2016 Best Postdoc Poster, Neuroimmunology and Glia Group Spring Symposium
2017 Best Postdoc Poster (Runner-up), Neuroimmunology and Glia Group Spring Symposium
2018 NARSAD Young Investigator, Brain and Behavior Research Foundation
2019 "Hot Topic" Poster Presentation, Society for Neuroscience Annual Meeting (Student: Taylor Boggess)
2019 Faculty Mentor, Marshall Undergraduate Creative Discovery and Research Award (Student: Ean Bills)
2020 John and Polly Sparks Foundation Investigator
2020 Faculty Mentor, WV-INBRE Research Internship for HSTA Scholars (Student: Ethan Niebergall)

C. Contributions to Science

Link to Pubmed listings: http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=risher+wc

1. Aberrant synaptogenesis in neonatal abstinence syndrome. Marshall University is located in the Central Appalachian region of the United States which has been particularly hard hit by the opioid epidemic. Our region has seen a troubling increase in the number of babies being born to mothers who abused drugs including opioids during pregnancy, resulting in a dramatic rise in the incidence of neonatal abstinence syndrome (NAS). NAS manifests as a set of withdrawal-like symptoms in newborns that often requires pharmacological treatment. Though much research in this area has focused on the acute signs and symptoms of NAS, there are still few long-term studies on the effects of prenatal opioid exposure on brain development. From my background in the realm of astrocytes and synaptogenesis, I was able to determine an important mechanistic

link between developmental synapse formation and gabapentin, a drug that is commonly co-abused with opioids that leads to a particularly severe form of NAS. This line of research is currently being funded through the Brain and Behavior Research Foundation through the NARSAD Young Investigator program. My recently published invited review article (written together with my M.D./Ph.D. student, Taylor Boggess) in the *Journal of Neuroscience Research* attempted to consolidate the current NAS literature and point out areas for further research in the areas of brain structure, function, and cognition. In addition, Taylor's preliminary data included in the current application was recently used as the basis for a *Biorxiv* pre-print, which is in the process of revision for publication. My hope is that our work will yield valuable information on the pathology of NAS and inform future studies aimed at developing therapeutics to improve long-term outcomes for children who have been impacted by the opioid epidemic.

a. Boggess T, **Risher WC**. 2020. Clinical and basic research investigations into the long-term effects of prenatal opioid exposure on brain development. *J Neurosci Res*: Opioids Special Issue. Early View. PMID: 32459039
b. Boggess T, Sexton H, Mazur A, Egleton RD, Grover LM, **Risher WC**. 2020. Alterations in excitatory and inhibitory synaptic development within the mesolimbic dopamine pathway in a mouse model of prenatal drug exposure. *Biorxiv*. DOI: 10.1101/2020.12.18.423503

2. Elucidation of mechanisms underlying thrombospondin/α2δ-1-mediated synaptic development. My postdoctoral fellowship in the lab of Dr. Cagla Eroglu led to several novel findings in the fields of glial biology and developmental neurobiology. I initially began with a review article delineating the importance of astrocyte-secreted thrombospondins (TSPs) to synapse formation and response to injury in development and disease. My investigation of TSPs and their neuronal synaptogenic receptor, alpha-2-delta-1 (α2δ-1) (a.k.a. the gabapentin receptor), with the use of transgenic mice, led me to determine the molecular mechanism of TSP/α2δ-1-induced synaptogenesis and spine maturation to be via postsynaptic NMDA receptors and Rac1; these results were published in a manuscript for the *Journal of Cell Biology*. My work in this area recently resulted in an invited review manuscript (together with Dr. Eroglu, with myself as corresponding author) for *Current Opinion in Neurobiology* summarizing the latest findings in the α2δ field. Our most recent work has resulted in the identification of sex differences in TSP-induced synaptogenesis, opening a novel area of investigation for the field.

a. **Risher WC**, Eroglu C. 2012. Thrombospondins as key regulators of synaptogenesis in the central nervous system. Matrix Biology 31(3): 170-7. PMCID: PMC3961754.
b. **Risher WC**, Kim N, Koh S, Choi JE, Mitev PR, Spence EF, Pilaz LJ, Wang D, Feng G, Silver DL, Soderling SH, Yin H, Eroglu C. 2018. Thrombospondin receptor α2δ-1 promotes synaptogenesis and spinogenesis via postsynaptic Rac1. J. Cell Bio 217(10): 3747-65. PMCID: PMC6168259.
c. **Risher WC,** Eroglu C. 2020. Emerging roles for α2δ subunits in calcium channel function and synaptic connectivity. *Curr Opin Neurobio* 63: 162-9. Cellular Neuroscience Special Issue (Schwarz T and Cline H, Eds.). PMID: 32521436. PMCID: In Progress.
d. Mazur A, Bills EH, Henderson BJ, **Risher WC**. 2021. Astrocyte-derived thrombospondin induces cortical synaptogenesis in a sex-specific manner. *Biorxiv*. DOI: 10.1101/2021.01.04.425242

3. Regulation of dendritic spine maturation by astrocytes. My first major research project in the Eroglu lab studying aberrant synaptic connectivity in the brain led to the development of an innovative technique for identifying and categorizing synapse-associated dendritic spines from Golgi-cox stained tissue. This work was published as a methods paper in 2014 which has already been cited over 80 times according to Google Scholar. This analysis technique was used in a paper from a graduate student in the lab, Spencer McKinstry, to study spine morphology in various mouse models of Huntington's Disease. For my own studies, I used genetically manipulated mice to discover a completely new role for astrocytes as the potential regulators of synaptic competition at dendritic spines. This work, published in the up-and-coming journal *eLife*, also identified the astrocyte-secreted factor hevin as a critical controller of thalamocortical synaptic connectivity. Together with Dr. Eroglu, I recently authored a Book Chapter on the subject.

a. **Risher WC**, Ustunkaya T, Singh Alvarado J, Eroglu C. 2014. Rapid Golgi analysis method for efficient and unbiased classification of dendritic spines. PLOS ONE 9(9):e107591. PMCID: PMC4160288.

b. McKinstry SU, Karadeniz YB, Worthington AK, Hayrapetyan VY, Ozlu MI, Serafin-Molina K, **Risher WC**, Ustunkaya T, Dragatsis I, Zeitlin S, Yin HH, Eroglu C. 2014. Huntingtin is required for normal excitatory synapse development in cortical and striatal circuits. J. Neurosci 34(28): 9455-72. PMCID: PMC4087216.
c. **Risher WC**, Patel S, Kim IH, Uezu A, Bhagat S, Wilton DK, Pilaz LJ, Singh Alvarado J, Calhan OY, Silver DL, Stevens B, Calakos N, Soderling S, Eroglu C. 2014. Astrocytes refine cortical connectivity at dendritic spines. eLife 3:e04047. PMCID: PMC4286724.
d. **Risher WC**, Eroglu C. 2020. Astrocytes and synaptogenesis. In "Synapse Development and Maturation, 1st Edition". Rubenstein J, Rakic P (Eds.). Academic Press (Elsevier), Cambridge, MA. Pages 55-75.

4. Role of astrocytes in synaptic deficits after adolescent binge drinking. My *Matrix Biology* review on the synaptogenic abilities of thrombospondin-family proteins led to an ongoing collaboration with Dr. Louise Risher to investigate the role of astrocytes in adolescent ethanol exposure. Thus far, her work has shown that rat hippocampal astrocytes become reactive following an adolescent binge drinking paradigm. Following ethanol, astrocytes significantly alter the secretion levels of various synapse-associated proteins including thrombospondins, hevin, and SPARC. These changes then go on to affect downstream neuronal structure and function, resulting in a prolonged immature-like phenotype that manifests into adulthood. I have been highly active in the conception, execution, and analysis of the experimental design of these ongoing projects, which have been viewed as a highly novel avenue for investigation in the ethanol/addiction field and resulted in Louise's successful application for a 5-year Career Development Award through the U.S. Department of Veteran's Affairs, as well as a NARSAD Young Investigator Award from the Brain and Behavior Research Foundation to understand the role of astrocyte signaling in the development of alcohol addiction. More recently, I collaborated with Louise on a review article focused on the contributions of astrocytes to substance use disorders, including alcohol and opioids.

a. Risher ML, Fleming RL, **Risher WC**, Miller KM, Klein RC, Wills T, Acheson SK, Moore SD, Wilson WA, Eroglu C, Swartzwelder HS. 2015. Adolescent intermittent alcohol exposure: persistence of structural and functional hippocampal abnormalities into adulthood. Alcohol Clin Exp Res. 39(6):989-97. PMCID: PMC4452443.
b. Risher ML, Sexton HG, **Risher WC**, Wilson WA, Fleming RL, Madison RD, Moore SD, Eroglu C, Swartzwelder HS. 2015. Adolescent intermittent alcohol exposure: dysregulation of thrombospondins and synapse formation are associated with decreased neuronal density in the adult hippocampus. Alcohol Clin Exp Res. 39(12):2403-13. PMCID: PMC4712076.
c. Walker CD, **Risher WC**, Risher ML. 2020. Regulation of synaptic development by astrocyte signaling factors and their emerging roles in substance abuse. Cells 9(2):E297. PMID: 31991879

5. Acute cellular and synaptic injury and recovery after stroke-induced depolarizations. As a graduate student in the lab of Dr. Sergei Kirov, my thesis project sought to understand the mechanisms of injury and recovery of both neurons and astrocytes following ischemic stroke. Using acute mouse brain slices, I discovered the ability of astrocytes to rapidly expand and contract in response to osmotic and ischemic stress. However, in an intact in vivo stroke model, astrocytes did not recover to the same extent. This was likely due to their role in neuroprotection, allowing neurons that were damaged following stroke to recover their form and function as long as adequate blood flow was maintained. Acute neuronal injury following stroke can be prevented or lessened with the sodium channel blocker dibucaine, an effect that I tested on tissue obtained from human patients in a highly translational collaboration with pediatric neurosurgeons at the Medical College of Georgia.

a. **Risher WC**, Andrew RD, Kirov SA. 2009. Real-time passive volume responses of astrocytes to acute osmotic and ischemic stress in cortical slices and in vivo revealed by two-photon microscopy. Glia 57(2): 207-21. PMCID: PMC2635108.
b. **Risher WC**, Ard D, Yuan J, Kirov SA. 2010. Recurrent spontaneous spreading depolarizations facilitate acute dendritic injury in the ischemic penumbra. J. Neurosci 30(29): 9859-68. PMCID: PMC2918261.
c. **Risher WC**, Lee MR, Hess DC, Kirov SA. 2011. Dibucaine mitigates spreading depolarization in human neocortical slices and prevents acute dendritic injury in the ischemic rodent neocortex. PLOS ONE 6(7): e22351. PMCID: PMC3137632.

d. **Risher WC**, Croom D, Kirov SA. 2012. Persistent astroglial swelling accompanies rapid reversible dendritic injury during stroke-induced spreading depolarizations. Glia 60(11): 1709-20. PMCID: PMC3435464.

D. Additional Information: Research Support

Current Research Support

NIH/NIMH 1 R15 MH126345-01 Risher (PI) 04/01/21-03/31/24
Title: Investigating Sex Differences in Astrocyte-Mediated Synaptic Development
This application is for continued support of our investigation into novel sex-dependent mechanisms of astrocyte-dependent synaptogenesis. As part of the R15 REAP program, this award is focused on exposing students to meritorious research.

Pilot Award, Chronic Disease Research Program Risher (PI) 09/01/20-08/31/22
Title: Effects of prenatal opioid exposure on astrocyte-mediated synaptic connectivity
These pilot funds were awarded by the West Virginia IDeA Network of Biomedical Research Excellence (WV-INBRE) as part of their addiction focus. This project will identify novel regulators of astrocyte-mediated synaptic development and astrocyte maturation using novel *in vivo* proximity-based proteomic screening.

NARSAD Young Investigator 27662 Risher (PI) 01/15/19-07/21/21
Title: Astrocytic regulation of synaptic connectivity in neonatal abstinence syndrome
The Brain and Behavior Research Foundation recently funded this project, which was designed to understand interactions between opioids and the α2δ-1 ligand gabapentin in a rodent cell culture model of neonatal abstinence syndrome (NAS). The project was recently sponsored by the John and Polly Sparks Foundation as part of the BBRF's Research Partners Program.

Marshall University Startup Funds Risher (PI) 03/05/18-03/04/21

Completed Research Support

NINDS F32 NS083283 Risher (PI) 07/01/13-06/30/15
Title: Control of excitatory synapse formation and maturation by astrocytes.
This fellowship was designed to provide training in cellular and molecular biology while investigating the roles of the astrocyte-secreted proteins thrombospondin, hevin and SPARC in synapse formation and development.
Role: PI (Sponsor: Cagla Eroglu, Co-Sponsors: Vann Bennett, Nicole Calakos)

NINDS T32 NS511566 Eroglu (PI) 02/04/11-02/03/12
Title: Investigation of the functional role of astrocyte-mediated synaptogenesis in vivo.
This training grant allowed me to investigate the roles the thrombospondin receptor, alpha-2-delta-1, in developmental and injury-mediated synaptogenesis *in vivo*.
Role: Trainee

NINDS F31 NS064753 Kirov (PI) 03/01/10-12/10/10
Title: Neuronal and astroglial injury and recovery from stroke-induced depolarizations.
The goal of this fellowship was to understand the mechanism of cellular injury and recovery in the wake of ischemic depolarizations while receiving training in mouse models of stroke.
Role: Trainee