BIOGRAPHICAL SKETCH

NAME: Amy R. Nelson

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham, Birmingham, AL	B.S.	05/2005	Biology
University of Alabama at Birmingham, Birmingham, AL	M.S.	12/2006	Biology
University of Alabama at Birmingham, Birmingham, AL	Ph.D.	12/2013	Neuroscience
University of Southern California, Los Angeles, CA	Postdoc	06/2020	Neuroscience

A. Personal Statement

Alzheimer's disease (AD) is a debilitating disease first described more than 100 years ago yet the underlying mechanisms causing sporadic AD remain elusive. Interestingly, many neurodegenerative diseases including ALS, Parkinson's disease, Huntington's disease and AD share several underlying similarities including protein misfolding and programmed cell death. Strikingly, disruption of the blood-brain barrier (BBB) also occurs in these diseases allowing blood-derived cells and toxins to enter the brain. At the same time, this dysfunction impairs proper transport of molecules across the BBB. One key player in BBB maintenance is the pericyte. Notably, pericyte number and coverage are reduced and biomarkers of BBB disruption are elevated in AD post-mortem brain tissue. Unfortunately, little is known about how pericyte reduction alters overall brain function or what causes this cell loss. As a postdoc, I gained extensive insight into the neurovascular unit and BBB key mediators and impairments that occur in AD and other diseases, found that pericytes are contractile cells, and that the loss of pericytes causes reduced cerebral blood flow, tissue oxygenation and metabolism and ultimately behavioral deficit and neurodegeneration. My dissertation work included studies in a cholinergic denervation rat model of AD in which I performed electrophysiology, immunohistochemistry and biochemical studies. In the currently funded R00, the Nelson lab is investigating whether Alzheimer's disease amyloid-beta causes brain pericytes to contract, reducing cerebral blood flow and compromising blood-brain barrier integrity, is worsened in normal aging and is dependent on the p75NTR pathway. Also, we are investigating causes of pericyte degeneration and BBB dysfunction in AD and are particularly interested in post-translational modifications and expression level changes of key receptors at the BBB. The ultimate goal is to discover new therapeutic targets for neurodegeneration by preventing and/or repairing BBB disruption.

B. Positions and Honors

Positions and Employment

2005 - 2008 Teaching Assistant, Department of Biology, University of Alabama at Birmingham, Birmingham, AL

2007 - 2007 Research Assistant, Microbiology Department, University of Alabama at Birmingham, Birmingham, AL

2007 - 2008 Program Director, Community Outreach Development, Science Education, University of Alabama at Birmingham, Birmingham, AL

2007 - 2013 Graduate Student Assistant, Department of Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL

2014 - 2020 Postdoctoral Scholar, Department of Physiology and Biophysics, Center for Neurodegeneration and Regeneration, Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

2014 - 2020 USC Leader/Liason, Los Angeles Brain Bee

2015 - 2017	Executive Board Member (Treasurer), Young Professionals Committee (YPC), Alzheimer's of Greater Los Angeles
2016	Alzheimer's Association, Santa Monica Walk to End Alzheimer's Committee
2017	Alzheimer's Association, Beach Cities Walk to End Alzheimer's Committee
2017-present	Ambassador, Youth Movement Against Alzheimer's
2020-present	Assistant Professor, Department of Physiology and Cell Biology, University of South Alabama, Mobile, AL

Honors

2004 & 2005	UAB Dean's List
2004	Phi Sigma (Biology Honor Society)
2005 - 2006	Graduate Student Fellowship (for academic merit)
2007	Sigma Xi (nominated for scientific achievement)
2007	Golden Key International Honor Society
2007	Teaching Assistantship (selected as 1 of 10 out of 50 applicants)
2008 - 2013	Graduate Student Fellowship (for academic merit)
2008, 2009 & 2012	Graduate Student Association Travel Fellowship
2010	Alzheimer's Association ICAD Travel Fellowship (Honolulu, HI)
2010	Alzheimer's of Central Alabama Research Grant ($10,000)
2011	International Conference of Alzheimer's Disease Volunteer Fellowship (Paris, France)
2011	Alzheimer's Association Scholarship for Advocacy Forum (Washington D.C.)
2013	Society for Neuroscience Award for SfN Capitol Hill Day (Washington D.C.)
2014	Civitan Travel Award for 2014 Glial Symposium (Birmingham, AL)
2018	2018 Trainee Professional Development Award, Society for Neuroscience (SfN)
2018	Best Data Blitz Presentation – Fondation Leducq Meeting (Toronto, CA)

C. Contributions to Science Complete List of Published Work in My Bibliography

BBB dysfunction in Alzheimer's disease and other disorders: Vascular insults kick start cellular and molecular events leading to neurodegeneration, cognitive impairment, and dementia. AD genetic risk factors, impaired clearance of Aβ, as well as other vascular risk factors such as stroke, environment and lifestyle (e.g. air pollution), lead to cerebral blood flow dysregulation and disruption of the neurovascular unit and the blood-brain barrier, contributing to the onset and progression of dementia and AD. Our most recent work shows that *APOE4* leads to early BBB dysfunction predicting human cognitive decline independent of Aβ and tau pathologies.

1. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, Pachicano M, Joe E, **Nelson AR**, D'Orazio LM, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Reiman EM, Caselli RJ, Chui HC, Tcw J, Chen Y, Pa J, Conti PS, Law M, Toga AW, Zlokovic BV. 2020. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 581(7806):71-76. PMCID: PMC7250000.
2. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, **Nelson AR**, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Chui HC, Law M, Toga AW, Zlokovic BV. 2019. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*. 25(2):270-276. PMCID: PMC6367058
3. Sweeney MD, Zhao Z, Montagne A, **Nelson AR**, Zlokovic BV. 2019. Blood-Brain Barrier: From Physiology to Disease and Back. *Physiol Rev*. 99(1):21-78. PMCID: PMC6335099
4. **Nelson, AR**, Sweeney, MD, Sagare, AP, Zlokovic, BV. 2016. Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochimica et Biophysica Acta-Molecular Basis of Disease*. 1862(5):887-900. PMCID: PMC4821735
5. Zhao, ZZ*, **Nelson, AR***, Betsholtz, C, Zlokovic, BV. 2015. Establishment and dysfunction of the blood-brain barrier. *Cell*. 163(5):1064–1078. PMCID: PMC4655822

Pericyte physiology: Pericytes are mural cells along capillaries and their contractility and contributions to red blood cell flow has been debated. We investigated the functional role of pericytes in transgenic mice with reduced

pericyte coverage and found reduced cerebral blood flow, tissue oxygenation and metabolism and ultimately behavioral deficit and neurodegeneration. In more recent work, we found that channelrhodopsin excitation causes pericytes to contract, constrict the underlying capillary and reduce red blood cell flow.

1. Nelson AR, Sagare MA, Wang Y, Kisler K, Zhao Z, Zlokovic BV. 2020. Channelrhodopsin Excitation Contracts Brain Pericytes and Reduces Blood Flow in the Aging Mouse Brain *in vivo*. *Front Aging Neurosci*. 12:108. PMCID: PMC7201096
2. Kisler, K*, **Nelson, AR***, Rege, S*, Ramanathan, A, Boas, DA, Sakadzic, S, Zlokovic, BV. 2017. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. *Nature Neuroscience*. 20(3):406-416. PMCID: PMC5323291
3. Kisler, K*, **Nelson, AR***, Montagne, A*, Zlokovic, BV. 2017. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nature Reviews Neuroscience.* 18(7):419-434. PMCID: PMC5759779

Impaired amyloid-beta clearance in Alzheimer's disease: Low-density lipoprotein receptor-related protein 1 (LRP1) is localized mainly to the abluminal side of the BBB and is the key receptor mediating Aβ transcytosis across the BBB into the circulation. The species of Aβ determines the rate of their transport by LRP1- mediated clearance; for example, $A\beta_{40}$ is cleared at the fastest rate, and $A\beta_{42}$ is cleared at a faster rate than the vasculotropic Dutch Aβ mutants. Also, clusterin binds Aβ and mediates its clearance across the BBB via LRP2. Aβ is taken up into the brain across the BBB by the receptor for advanced glycation end products (RAGE). In several publications, we discuss Aβ transcytosis across the BBB via LRP1 and Aβ uptake across the BBB by RAGE, and discuss how alterations within these pathways can contribute to Aβ accumulation in the brain in AD. We also highlight possible therapeutic opportunities based on restoring the function of Aβ BBB transporters in dementia and AD.

1. Sagare AP*, Sweeney MD*, **Nelson AR***, Zhao Z, Zlokovic BV. 2019. Prion Protein Antagonists Rescue Alzheimer's Amyloid-β-Related Cognitive Deficits. *Trends Mol Med*. 25(2):74-76. PMCID: PMC6377285
2. **Nelson AR***, Sagare AP*, Zlokovic BV. 2017. Role of clusterin in the brain vascular clearance of amyloid-β. *PNAS*. 114(33):8681-8682. PMCID:PMC5565473.
3. **Nelson, AR**, Sagare, AP, Zlokovic, BV. 2016. Chapter 9: Blood-brain barrier transport of Alzheimer's amyloid β-peptide. "Developing therapeutics for Alzheimer's." Edited by Michael S. Wolfe, Elsevier, London. ISBN: 978-0-12-802173-6
4. Ramanathan A, **Nelson AR**, Sagare AP and Zlokovic BV. 2015. Impaired vascular-mediated clearance of brain amyloid beta in Alzheimer's disease: The role, regulation and restoration of LRP1. *Front. Aging Neurosci.* **7**:136. PMCID: PMC4502358.

Synaptic plasticity and hippocampal function: During my PhD studies, I investigated several topics related to synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), and hippocampal function. In one study, we investigated the benefits of estrogen replacement therapy (ERT) on cognition. In rats, we found that estrogen replacement restored LTP up to 15 months post-ovariectomy. This beneficial effect was no longer observed 19 months post-ovariectomy. Our studies suggested that there is a critical period during which ERT is beneficial for cognition. In another study, we investigated cholinergic denervation and sympathetic sprouting in Alzheimer's disease. Cholinergic degeneration occurs in AD and can be mimicked in rats by lesioning cholinergic neurons in medial septum. Hippocampal cholinergic denervation disrupts retrograde transport of nerve growth factor (NGF), leading to its accumulation, which subsequently triggers sprouting of noradrenergic sympathetic fibers from the superior cervical ganglia into hippocampus. Coincident with this sprouting, there is an increase in cholinergic innervation that correlates with a recovery of M1 muscarinic receptor dependent plasticity at CA3-CA1 synapses and visual cortex. M1 mAChRs have been a recent focus as a therapeutic target for AD given their role in cognition and non-amyloidogenic processing of amyloid beta-protein precursor (AβPP). Therefore, we tested the hypothesis that noradrenergic sympathetic sprouting and the associated increase in cholinergic innervation maintains non-amyloidogenic AβPP processing that is dependent upon M1 mAChRs. We found that NGF stimulates sprouting and that sprouting maintains non-amyloidogenic AβPP processing. Furthermore, we showed that $A\beta_{42}$ is not only toxic to central cholinergic fibers innervating hippocampus, but it prevents and reverses noradrenergic sympathetic sprouting and the accompanying cholinergic reinnervation. Lastly, we found that the post-translational modification, OGlcNacylation, induces hippocampal LTD via the AMPA receptor GluR2.

1. Dyer-Reaves, K, Goodman AM, **Nelson, AR**, McMahon, LL. 2019. Alpha1-adrenergic receptor mediated long-term depression at CA3-CA1 synapses can be induced via accumulation of endogenous norepinephrine and is preserved following noradrenergic denervation. *Frontiers of Synaptic Neuroscience.* 11:27. PMCID: PMC6794465
2. **Nelson AR**, Kolasa K, McMahon LL. 2014. Noradrenergic sympathetic sprouting and cholinergic reinnervation maintains non-amyloidogenic processing of AβPP. *Journal of Alzheimer's Disease*. 38(4):867-79. PMCID: PMC4047988
3. Taylor ET, Wang K, **Nelson AR**, Bredemann TM, Fraser FB, Clinton SM, Marchase RB, Chatham JC, McMahon LL. 2014. O-GlcNAcylation of AMPA receptor GluA2 is associated with a novel form of LTD at hippocampal synapses. *Journal of Neuroscience*. 34(1):10-21. PMCID: PMC3866478
4. Smith CC, Vedder LC, **Nelson AR**, Bredemann TM, and McMahon LL. 2010. Duration of estrogen deprivation, not chronological age, prevents estrogen's ability to enhance hippocampal synaptic physiology. *PNAS*. 107(45):19543-8. PMCID: PMC2984203

Cancer gene therapy: My earliest work utilized conditionally replicative adenovirus as a cancer gene therapy modality for breast and pancreatic cancer. We developed adenovirus with EGFP core labeling for virus visualization and tracking for *in vivo* imaging. Also, we performed *in vitro* and *in vivo* experiments and found a synergistic effect between an adenovirus developed by the lab that was in early phase clinical trials and commonly used chemotherapeutic agents.

1. **Nelson AR**, Davydova J, Curiel DT, Yamamoto M. 2009. Combination of conditionally replicative adenovirus and standard chemotherapies shows synergistic antitumor effect in pancreatic cancer. *Cancer Science*. 100(11):2181-7. PMCID: PMC4569096
2. Le LP, Le HN, **Nelson AR**, Matthews DA, Yamamoto M, Curiel DT. 2006. Core Labeling of Adenovirus with EGFP. *Virology*. 351(2):291-302. PMCID: PMC1781517

***Denotes equal authorship**

D. Research Support

Current Research Support

K99AG058780/ R00AG058780 (Nelson) 07/15/18 – 07/14/23
NIH/NIA
Brain pericyte contractility, cerebral blood flow and blood-brain barrier integrity are impaired by normal aging and Alzheimer's disease amyloid-beta and are dependent on p75NTR
This project investigates the novel hypothesis that normal aging and Alzheimer's amyloid-beta oligomers impair pericyte contractility, and thereby cerebral blood flow, and also blood-brain barrier integrity, via p75NTR.
Mentor: Dr. Berislav Zlokovic

Completed Research Support

Alzheimer's of Central Alabama 2010 - 2011
Sympathetic Sprouting in Human AD Hippocampus: A Potential Novel Therapeutic Target
The goal was to determine the presence of noradrenergic sympathetic sprouting density in post-mortem human hippocampus from Alzheimer's patients as compared to age-matched no cognitive impairment subjects.
Role: Principal Investigator