BIOGRAPHICAL SKETCH

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NAME: Nicholas H. Varvel, Ph.D.

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

POSITION TITLE: Instructor

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
University of Dayton, Dayton, OH	B.S.	05/2003	Biology
Case Western Reserve University, Cleveland, OH	Ph.D.	01/2009	Neuroscience
Hertie Institute for Clinical Brain Research, Germany	Postdoc	05/2013	Neuropathology
Emory University, Atlanta, GA	Postdoc	12/2015	Neuroimmunology

A. Personal Statement

My long-term scientific goals are to investigate and better understand neuroinflammatory responses in the diseased brain. I hope to achieve these goals by utilizing genetic mouse models, coupled with immunohistological, biochemical, cellular, behavioral, and gene induction analyses. Currently, I am interested in the context by which activation and migration of subsets of myeloid cells are beneficial or harmful in neurological disease. My academic training and research experience have provided me with an excellent background to approach these issues. As a predoctoral student, I gained invaluable knowledge in mouse genetics by utilizing transgenic mouse models of Alzheimer's disease (AD) to investigate the underlying causes of abnormal neuronal cell cycle entry, an event common in AD as well as other neurodegenerative diseases. For my initial postdoctoral training, I secured funding from the Alexander von Humboldt Foundation to perform neuropathological research in Germany. During my time in Germany, I continued to gain experience working with transgenic mouse models. I also became competent in stereotaxic surgery and unbiased stereological quantification of stained brain tissue sections. My research in Tuebingen investigated the potential for circulating monocytes to functionally replace brain-resident microglia in the healthy and diseased brain. While in the Jucker laboratory, I also developed a chemoconvulsant model of epilepsy to track monocyte infiltration into the brain after status epilepticus (SE). In efforts to apply my knowledge of microglia/monocyte cell biology to study the role of myeloid cells after SE, I joined the laboratory of Dr. Raymond Dingledine in June 2013 because of the laboratory's interest and expertise in therapeutically targeting the neuroimmune system to alleviate the deleterious consequences of SE. On January 1, 2016, I was promoted to an independent position as Instructor in the Department of Pharmacology. In summary, I have an established track record of productive scientific research utilizing a range of methodological strategies to bear on the mechanisms underlying neurological disorders.

B. Positions and Honors

Positions and Employment

2016 – Instructor, Emory University, Department of Pharmacology, Atlanta, GA
2013 – 2015 Postdoctoral Fellow, Emory University, Department of Pharmacology, Atlanta, GA
2009 – 2013 Alexander von Humboldt Fellow, Hertie Institute for Clinical Brain Research, Germany
2003 – 2009 Graduate Research Assistant, Case Western Reserve University, Department of Neurosciences, Cleveland, OH

Other Experience and Professional Memberships

2003 – Member, Society for Neuroscience

Honors

2014 American Epilepsy Society Postdoctoral Research Fellowship
2013 Hertie Institute Research Prize – Publication of the Year
2006 Best Poster Presentation, Cleveland Clinic Research Day
2006 Vance Lemon Award for Best Poster Presentation
2003 P.K. Bajpai Award for Excellence in Undergraduate Research, University of Dayton
2002 Mayo Clinic Summer Research Fellowship (SURF) Program

C. Contributions to Science

1. **The role of Aβ and inflammation in neuronal cell cycle events in Alzheimer's disease mouse models.** My major research accomplishment as a graduate student was to provide insights into the underlying causes of abnormal neuronal cell cycle entry in Alzheimer's disease (AD). At the time I began my graduate work, multiple independent laboratories reported that post-mitotic neurons showed evidence of having entered a mitotic cell cycle, such as expression of cyclins and DNA synthesis, during the death process in multiple neurodegenerative conditions in man and in neuronal cultures. Indeed, Dr. Karl Herrup's laboratory documented the appearance of neuronal cell cycle events (CCEs) in post-mortem human AD brain tissue in neuronal populations susceptible to death in AD, but not in neuronal populations spared in the disease. In addition, CCEs were also found in disease-relevant neuronal populations in brain tissue from individuals that died with Mild Cognitive Impairment (MCI), an early clinical presentation of AD, just prior to my joining his laboratory. One of the outstanding issues was the factor(s) responsible for inducing neuronal CCEs. To address this I initiated a collaborative effort with Dr. Bruce Lamb, an expert and creator of genomic-based mouse models of AD. First, I documented the appearance of neuronal CCEs in a mouse model of AD prior to the onset of amyloid deposition, offering me the ability to utilize the model to investigate the causes of neuronal cell cycle entry in model organism. Second, utilizing genetic knockout approaches, I identified amyloidogenic processing of the amyloid precursor protein necessary for the induction of CCEs. Finally, by treating the animals with two different non-steroidal anti-inflammatory drugs (NSAIDs) I was able to block the appearance of neuronal CCEs, but I could not reverse CCEs once the process had initiated. Taken together, my findings provided evidence that beta-amyloid-induced neuroinflammation was an initiator of CCEs in transgenic mouse models of AD and by extension the human condition. These studies, and work by others, led to the now widely held view that AD therapeutics need to be administered well in advance of the clinical manifestations of the disease to be efficacious. This work sparked my interest in both neuroinflammation and neuropathology in more detail for my post-doctoral fellowships.

    a. Yan Y*, Varvel NH*, Lamb BT and Herrup K. Ectopic cell cycle events link human alzheimer's disease and amyloid precursor protein transgenic mouse models. (2006) *J Neurosci* 26(3): 775-784. *co-first authors. PMID: 16421297 http://www.jneurosci.org/content/26/3/775.full.pdf+html
    b. Varvel NH*, Bhaskar K*, Patil A, Pimplikar SW, Herrup K and Lamb BT. (2008) Abeta oligomers induce neuronal cell cycle events in Alzheimer's disease. *J Neurosci* 28(43): 10786-10793. *co-first authors. PMCID: PMC2680286

c. Varvel NH, Bhaskar K, Kounnas MK, Wagner SL, Yang Y, Lamb BT and Herrup K. (2009) NSAIDs prevent, but do not reverse, neuronal cell cycle re-entry in Alzheimer's disease mouse models. *J Clin Invest* 119(12): 3692-3702. PMCID: PMC2786797

d. Bhaskar K, Maphis N, Xu G, Varvel NH, Kokiko-Cochran ON, Weick JP, Staugaitis SM, Cardona A, Ransohoff RM, Herrup K, Lamb BT. (2014) Microglial derived tumor necrosis factor-α drives Alzheimer's disease-related neuronal cells cycle events. *Neurobiol Dis* Feb;62:273-85. PMCID: PMC3877710

2. **Replacement of brain-resident microglia with blood-borne monocytes in health and disease.** During my postdoc in Germany I studied the potential for circulating monocytes to functionally replace brain-resident microglia in health and disease. Neuroinflammation research has led to tremendous advances in our understanding of the brain's response to injury and disease in the last few years. Lineage tracing studies have provided evidence that brain-resident innate immune cells, microglia, arise from embryonic tissue distinct from tissues that give rise to adult innate immune cells. Thus, microglia are ontogenetically distinct from adult innate immune cells, including blood-derived monocytes. In addition, the microglial population can sustain itself without peripheral contribution, and invasion of blood-borne monocytes into the healthy brain is rare. However, damage or disease can induce robust infiltration of blood-derived monocytes that in turn contribute to the neuroinflammatory response. Interestingly, the inflammatory response of monocytes can promote tissue healing or exacerbate brain damage depending on the disease context. My postdoctoral studies addressed two issues. First, can blood-derived monocytes replace brain-resident microglia? Second, does replacement of brain-resident myeloid cells with blood-derived monocytes clear β-amyloid deposits in AD mouse models? To address these questions, I utilized a genetically-modified mouse in which nearly all microglia could be ablated within two weeks. Astonishingly, in the absence of microglia, peripheral, circulating monocytes rapidly infiltrate CNS brain tissue, engraft in the brain for over six months and behave in remarkable similar fashion as brain resident microglia, such as parenchymal coverage and movement toward purinergic agonists. My data identifies a robust homeostatic CNS drive to maintain the innate immune population. I next asked whether replacement of brain-resident microglia with blood-borne monocytes alters amyloid deposition in AD mouse models. In contrast to microglia, which are encountered in close proximity to amyloid deposition, tightly clustering around the deposits, the monocytes did not cluster around the deposits. Strikingly, monocyte repopulation for up to six months did not modify amyloid load. These data argue against a long-term role of brain-invading monocytes that is distinct from microglial function during cerebral β-amyloidosis. Taken together my findings indicate monocytes have the potential to functionally replace microglia in the healthy brain, but replacement of brain-resident microglia with monocytes is not likely to be effective as a therapeutic approach for AD.

a. Varvel NH*, Grathwohl SA*[§], Baumann F, Liebig C, Brawek B, Thal DR, Charo IF, Heppner FL, Aguzzi A, Garaschuk O, Ransohoff RM, Jucker M. (2012) Microglial repopulation model reveals a robust homeostatic process for replacing CNS myeloid cells. *Proc Natl Acad Sci USA* 109(44):18150-5. *co-first authors. PMCID: PMC3497743

b. Varvel NH, Grathwohl SA, Degenhardt K, Resch C, Bosch A, Jucker M, Neher JJ. (2015) Replacement of brain-resident myeloid cells does not alter cerebral β-amyloid deposition. *J Exp Med* 212(11):1803-9 PMCID: PMC4612086

3. **The role of brain-invading Ccr2+ monocytes after status epilepticus.** Currently my research aims to understand the innate immune response in the hours and days after status epilepticus (SE). Concomitant with my aforementioned studies in Germany, I utilized a genetically modified mouse that allowed me to differentiate brain-invading monocytes from brain-resident microglia on histological tissue sections after kainate- or pilocarpine-induced SE. Using this animal model I documented brain infiltration of approximately 80,000 Ccr2+ monocytes three days, but not one day after SE, indicating a delayed inflammatory response. Blocking brain entry of the monocytes was beneficial, reducing neuronal damage, accelerating weight regain, maintaining the blood-brain barrier coupled with reduced levels of the proinflammatory cytokine IL-1β in the hippocampus, which was explained by higher expression of the cytokine in circulating and brain-invading monocytes in wild-type mice. These findings indientify brain-

infiltrting monocytes as a myeloid-cell subclass that contributes to neuroinflammation and morbidity after SE. Inhibiting brain invasion of CCR2+ monocytes could represent a viable method for alleviating the deleterious consequences of SE.

a. Dingledine R, Varvel NH, Dudek FE. (2014) When and how do seiaures kill neurons, and is cell death relevant to epileptogenesis? *Adv Exp Med Biol*. 813:109-22. PMCID: PMC4624106
b. Varvel NH, Jiang J, Dingledine R. (2015) Candidate drug targets for prevention or modification of epilepsy. *Annu Rev Pharmacol Toxicol*. 55:229-47. PMCID: PMC4427904
c. Varvel NH, Neher JJ, Bosch A, Wang W, Ransohoff RM, Miller RJ, Dingledine R. (2016) Infiltrating monocytes promote brain inflammation and exacerbate neuronal damage after status epilepticus. *PNAS.* 113(38):E5665-74. PMCID: PMC5035862

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1lUQz_e_4neQc/bibliography/48654107/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

My salary and research interests are currently funded through Dr. Ray Dingledine's grant

Title – Inflammatory control of blood-brain barrier integrity and epileptogenesis after seizures
Agency – NIH/NINDS
Type – RO1 NS097776-01
Period – 5/15/2016 – 4/30/2021

Completed Research Support

Postdoctoral Research Fellowship 01/01/2014 – 12/31/2014
American Epilepsy Society
Title – The role of brain-infiltrating monocytes after status epilepticus
The major goal of this project was to compare the induction of pro- and anti-inflammatory cytokines and chemokines in monocytes to brain resident microglia and determine if inhibiting monocyte infiltration after status epilepticus attenuated or exacerbated neuronal damage.
Role: PI