BIOGRAPHICAL SKETCH

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NAME: Tharkika Nagendran

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

POSITION TITLE: Senior Scientist

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 Madras, Chennai, India	B. Sc.	04/2000	Zoology
University of Madras, Chennai, India	M. Sc.	04/2002	Biotechnology
Medical College of Georgia, USA	Ph. D.	12/2010	Neuroscience
Duke Ophthalmology Research, Duke University	Postdoctoral	02/12-01/13	Ophthalmology
University of North Carolina, Chapel Hill, NC	Postdoctoral	02/13-01/18	Neuroscience

A. Personal Statement

My research interest is to understand the molecular basis of synaptogenesis and synaptic plasticity during brain development or following damage. Given my extensive neuroscience background and experience using microfluidic platforms in neuroscience research, I am well-qualified to conduct the research detailed in this proposal.

I graduated with a PhD in neuroscience from Augusta University (formerly Medical College of Georgia) where I studied how calcium signaling influences neuronal development and connectivity in the cerebral cortex. My doctoral thesis work was primarily focused on studying developmental neurobiology mechanisms where I utilized cutting-edge gene manipulation tools and imaging techniques to understand the role of CaMKIV in dendritic growth, branching, and synaptogenesis of developing cortical neurons (Nagendran, T. and Hardy, L.R., Neuroscience, 2010). My continued interests in calcium signaling motivated me to join Duke University as a postdoc, where I studied how calcium signaling regulates cytoskeleton molecules and cell-cell adhesion mechanisms in maintaining lens physiology (Maddala, Nagendran et.al., PLoS One 2013). During this opportunity at Duke I received first-hand experience working with several transgenic and novel knock-in strains of mice that expanded my expertise from cell and molecular biology approaches to tackle system-level research questions.

To pursue my career goals, I joined the Neuroscience Center as a postdoctoral fellow at the University of North Carolina (UNC) at Chapel Hill. Using a novel state-of-the-art microfluidic approach to culture primary neurons or stem cell-derived neurons which provides unique access to neurons and their synapses for measurements and manipulations, I studied the molecular mechanisms involved in synaptic remodeling and neuroplasticity following axon injury. A microfluidic approach allowed us to specifically label and axotomize pyramidal neurons away from their physically undisturbed somatodendritic domains. Distal axotomy of pyramidal neurons led to dendritic spine loss on injured neurons followed by a delayed enhancement in presynaptic excitability (Nagendran, T. et.al., Nat Commun. 2017). Thus I developed a reliable *in-vitro* model system for brain injury studies, especially a highly valuable tool for understanding neuron-intrinsic mechanisms following severe

axonal damage resulting from any kind of brain injury. Knowledge gained from these studies can be extended to brain damage caused by stroke, traumatic brain injury, or spinal cord injury.

Given my experience in using microfluidic devices for neuroscience research, I joined Xona Microfluidics, Inc. as a senior scientist. A significant mission of Xona is to be on the forefront of neuroscience research and to maintain a strong research focus. In one of the exciting research projects at Xona, we are presently collaborating with Dr. Cohen's lab at UNC-Chapel Hill to study propagation of axonal tau protein aggregates, one of the hallmarks of Alzheimer's disease (AD) and its effect on neuronal function using microfluidic platform. Interestingly I identified that axonal Aβ stress causes tau relocalization to somatodendritic compartments leading to presynaptic hyperexcitability (Manuscript in preparation) in rat hippocampal neurons. Our findings led to the development of a reliable and robust in vitro model system to study early stages of AD pathology. Further, at Xona I demonstrated culturing primary murine neurons and human stem cell derived neurons in a 3D matrix within microfluidic chips which provides a gateway for identifying more effective therapeutic options for neurological disorders.

1. **Nagendran, T**. and Hardy, L.R. Calcium/calmodulin-dependent protein kinase IV mediates distinct features of basal and activity-dependent dendrite complexity. Neuroscience. 2011 Dec 29;199:548-62.
2. Maddala, R., **Nagendran, T**., and Rao, P.V. L-type calcium channels play a critical role in maintaining lens transparency by regulating phosphorylation of aquaporin-0 and Myosin light chain and expression of connexins. PLoS One. 2013 May 29;8(5):e64676.
3. **Nagendran, T**., Bigler, R.L., Larsen, R., Philpot, B.D., and Taylor, A.M. Distal axotomy enhances presynaptic excitability onto injured pyramidal neurons via trans-synaptic signaling. Nat Commun. 2017 Sep 20;8(1):625. doi: 10.1038/s41467-017-00652-y
4. Kamande J.W., **Nagendran, T**., Harris, J., and Taylor, A.M. Multi-compartment microfluidic device geometry and covalently bound poly-D-lysine influence neuronal maturation. Front. Bioeng. Biotechnol. 2019, 7:84.doi: 10.3389/fbioe.2019.00084.
5. Paranjape, S. R., **Nagendran, T**., Poole, V., Harris, J., Taylor, A. M. Compartmentalization of Human Stem Cell-Derived Neurons within Pre-Assembled Plastic Microfluidic Chips. J. Vis. Exp. 2019; (147), e59250.
6. **Nagendran, T**., Taylor, A.M.* Unique Axon-to-Soma Signaling Pathways Mediate Dendritic Spine Loss and Hyper-Excitability Post-axotomy. Front Cell Neurosci. 2019; 13, 431.

B. Positions and Honors

Positions and Employment

2003-2004 Lecturer in the Department of Industrial Biotechnology, Madha Engineering College, Chennai, India
2005-2010 Graduate Research Assistant, Biomedical Sciences, Augusta University (formerly Medical College of Georgia), Augusta, GA
2010-2011 Temporary Technical/Paraprofessional, Dr. Lawrence Layman, Department of OB/GYN and IMMAG, Medical College of Georgia, Augusta, GA
2012-2013 Postdoctoral associate, Dr. Vasanth Rao, Duke Ophthalmology Research, Duke University School of Medicine, Durham, NC
2013-2018 Postdoctoral associate, Dr. Anne M. Taylor, University of North Carolina, Chapel Hill,NC
2018-2019 Research Scientist, Dr. Anne M Taylor, University of North Carolina, Chapel Hill, NC
2019- Senior Scientist, Xona Microfluidics, Inc.

Other Experience and Professional Memberships

2007-2009 Sponsored membership of AAAS/Science Program for Excellence in Science
2008- Member, Society for Neuroscience
2012-2013 Member, ARVO- The Association for Research in Vision and Ophthalmology
2017- Reviewer for 'Scientific Reports' from Nature Publishing group.
2018- Reviewer for Neural Regeneration Research.
2018- Reviewer for Biomedical Microdevices.
2019- Reviewer for Journal of Molecular Neuroscience.
2019- Reviewer for Journal of Depression and Anxiety.
2019- Reviewer for NeuroMolecular Medicine.
2019- Reviewer for Brain Research.

Honors

2007 Greenbaum Travel Award, 28th Annual Meeting of the Southeastern Pharmacology Society.
2010 Travel award to joint South East Nerve Net and Georgia-South Carolina Neuroscience Consortium conference.
2015 Featured poster in Perl Memorial Lecture and Research day, UNC-CH.
2016 UNC Postdoctoral Scholar Travel Award recipient for attending Society for Neuroscience (SFN) Annual meeting 2016.

C. Contributions to Science

1. CaMKIV regulates dendrite arborization and synaptogenesis

Intrinsic ability of neurons to make connections within and other brain regions, termed neuronal circuits, is indispensable for proper brain functions. Formation of neuronal circuits during brain development depends on establishing dendritic and synaptic connections. Dendritic arbors and spines work in concert to relay information between circuits, where dendrites receive and process information from their synaptic inputs. Although several molecular mechanisms have been implied in the formation and maintenance of neuronal connectivity, a role for neuronal activity evoked mechanisms is poorly understood. In my graduate training I identified a novel role for Calcium/Calmodulin-dependent protein kinase IV (CaMKIV) during basal and activity-induced dendrite complexity using elegant genetic tools, to both potentiate and negate CaMKIV expression, and by imaging techniques (**Nagendran, T**. and Hardy, L.R., Neuroscience, 2010). Using gene manipulation strategies, I found that CaMKIV regulates connectivity by influencing filopodia and spine formation. Above findings are significant for developing therapeutic strategies in several neurodevelopmental disorders caused by abnormal neuronal connections.

A. **Nagendran, T**. and Hardy, L.R. Calcium/calmodulin-dependent protein kinase IV mediates distinct features of basal and activity-dependent dendrite complexity. Neuroscience. 2011 Dec 29;199:548-62.

2. Calcium channels and cell-cell adhesion molecules maintain lens morphology

Vertebrate organ morphogenesis depends on cell-cell junction formation, cell adhesive interactions, establishment of cell polarity and migration. Studying molecular mechanisms that regulate cell adhesive interactions and cell polarity are critical for understanding the structural and functional architecture of tissues and organs. In my postdoctoral training with Dr. Vasanth Rao at Duke University, I used crystalline lens as a model system to explore how intracellular calcium homeostasis influences cell-cell adhesion and cytoarchitecture. Consisting of epithelial cells and fiber cells the

simple structure of lens serves as a valuable tool to study how cell-cell adhesion plays a crucial role in maintaining organ structure and function. Using ex-vivo mouse lens cultures we identified that L-type calcium channels regulate expression of cell junction and cytoskeletal proteins, which indeed are essential for maintaining morphological integrity and lens function (Maddala, **Nagendran** et.al., PLoS One 2013). Subsequently by using conditionally deficient mice I identified that Rap1, a Ras-like small GTPase, mediates maintenance of lens epithelial phenotype and morphogenesis (Maddala, **Nagendran** et.al., Dev. Biol. 2015). Experience gained investigating a role for calcium signaling in the maintenance of cytoarchitecture of lens could be extended to neurobiology and beyond.

A. Maddala, R., **Nagendran, T**., and Rao, P.V. L-type calcium channels play a critical role in maintaining lens transparency by regulating phosphorylation of aquaporin-0 and Myosin light chain and expression of connexins. PLoS One. 2013 May 29;8(5):e64676.
B. Maddala, R., **Nagendran, T**., Lang, R.A., Morozov, A., and Rao, P.V. Rap1 GTPase is required for mouse lens epithelial maintenance and morphogenesis. Dev Biol. 2015 Oct 1;406(1):74-91

3. Retrograde trans-synaptic remodeling following axon injury

Axons of pyramidal neurons that project to distant areas of the central nervous system (CNS), to establish neuronal circuits, are susceptible to damage as seen in stroke, spinal cord injury or traumatic brain injury. Brain injury induces synaptic reorganization and hyperexcitability in an effort to reinstall new connections in CNS. Due to the extreme polarization of pyramidal neurons and the difficulty in experimentally accessing remote subcellular compartments *in-vivo*, the underlying mechanisms for this synaptic remodeling remain unknown. To investigate these mechanisms, I used microfluidic tools developed by my mentor Dr. Anne M.Taylor to access the undisturbed somatodendritic domains following distal axon injury and studied the cellular mechanism of this injury induced synaptic remodeling. Using time-lapse imaging, I specifically monitored retrograde tracer labeled injured neurons on the microfluidic devices and identified that distal axotomy of pyramidal neurons lead to dendritic spine loss on injured neuron followed by a delayed enhancement in presynaptic excitability that is transcription-dependent. Additionally, I found that local activity in axons during injury presumably causes axotomy-induced spine loss. (**Nagendran** et.al., Nat Commun. 2017). This sophisticated approach of using microfluidic devices, immensely enhanced my ability to document the progression of events leading to retrograde trans-synaptic changes dynamically.

A. **Nagendran, T.**, Bigler, R.L., Larsen, R., Philpot, B.D., and Taylor, A.M. Distal axotomy enhances presynaptic excitability onto injured pyramidal neurons via trans-synaptic signaling. Nat Commun. 2017 Sep 20;8(1):625. doi: 10.1038/s41467-017-00652-y
B. **Nagendran, T.**, Poole, V., Harris, J., Taylor, A.M.* Use of Pre-Assembled Plastic Microfluidic Chips for Compartmentalizing Primary Murine Neurons J Vis Exp, 2018 (141), e58421, doi:10.3791/58421
C. **Nagendran, T**., Taylor, A.M.* Unique Axon-to-Soma Signaling Pathways Mediate Dendritic Spine Loss and Hyper-Excitability Post-axotomy. Front Cell Neurosci. 2019; 13, 431.

D. Research Support

Ongoing Research Support

1R21NS109750-01A1 Taylor (PI) 04/2020-03/2022
NIH/NINDS
Title: The Role of ER in Axon-to-Soma Injury Signaling in Pyramidal Cells
The goal of this grant is to investigate calcium-dependent axon-to-soma signaling following axotomy that causes somatic ER stress and synapse loss.
Role: Senior Scientist

1R41NS108895-01 Taylor (PI) 09/2018-08/2020 (No cost Extension)
NIH/NINDS
Title: A user-friendly microfluidic chip for anti-epileptogenic drug screening
The goal of this grant is to develop a new anti-epileptogenic drug screen using Xona's patented platform technology.
Role: Research Scientist

Completed Research Support

1R42MH097377 Taylor (PI) 05/2013-08/2019
A user-friendly scalable microfluidic platform for enhanced neuron-cell culture
The goal of this Phase II small business technology transfer grant is to develop user-friendly and robust technology for neuron-cell culture including the development of novel technology to examine and manipulate synapses.
Role: Research Scientist

Mead Johnson Nutrition Taylor (PI) 05/2015-04/2016
Effects of nutrients on synapse development
This project is a continuation of a previous project to test the effects of several nutrients on synapse development using assays previously developed by the Taylor lab.
Role: Postdoc

17GRNT33700108 Taylor (PI) 07/2017-06/2019
American Heart Association
Molecular mechanisms triggering synaptic remodeling following stroke
The goal of this project to identify the critical signaling mechanisms that trigger synaptic remodeling following axon damage and the information gained form this research helps us identify potential therapeutic targets to improve recovery following stroke.
Role: Research Scientist