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: Yousuf Omar Ali

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

POSITION TITLE: Assistant 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
Ohio Wesleyan University	B.A.	05/2005	Zoology; Env. Studies
University of Miami	Ph.D.	12/2011	Pharmacology
University of Pennsylvania	Postdoc	05/2012	Pathology
Baylor College of Medicine	Postdoc	03/2015	Neuroscience

A. Personal Statement

My main research interests evolve around understanding the intrinsic maintenance mechanisms in neurons required to sustain neuronal health and repair damages upon various insults. Translationally, exploiting such maintenance pathways that can prolong neuronal survival can facilitate to increase the therapeutic window for treating debilitating neurodegenerative diseases, where neuronal integrity is severely compromised.

My training in neurodegenerative diseases and in basic neuroscience of how synapses and neuronal integrity are maintained started during my Ph.D. thesis studies with Dr. Grace R. Zhai in Pharmacology and a brief post-doctoral training with Dr. Virginia Lee in Amyotropic Lateral Sclerosis (ALS). During my graduate studies, I learned molecular biology, histology, and surgical skills for using Drosophila as a model to study the process of neurodegeneration. As a postdoctoral fellow in Dr. Virginia Lee's lab, I became proficient in working with human brain samples and adapt common pathology techniques to study neurodegenerative proteinopathies. I decided to pursue my interests in neuronal maintenance in a second postdoctoral appointment in Dr. Hui-Chen Lu's lab, when I was invited to become a part of the Neurodegenerative Disease Research Consortium at MD Anderson Cancer Institute, where the goal is to find novel drug targets and therapy for Alzheimer's disease. Part of my interest stemmed from the fact that one of the targets they are interested in pursuing for therapy was NMNAT, a protein I worked with during my PhD. In addition, being a part of such a consortium, allowed me to interact with prominent scientists and receive feedback on the progress of my

work, which was invaluable. Moreover, in the Lu Lab, I have expanded my repertoire of expertise to techniques including viral vector construction, stereotaxic injections into live animals and multi-photon imaging. In summary, I have undertaken leadership in several projects that have been successfully completed. My expertise and experience have prepared me to lead the proposed project, and securing funding for this project will help me develop my early scientific career.

1. **Ali YO** *et al.* (2016) NMNAT2:HSP90 complex mediates proteostasis in proteinopathies. PloS Biol., 2016, June 2, 14 (6):e1002472 PMID:27254664
2. Slivicki SA, **Ali YO**, Lu HC, Hohmann A (2016) Impact of genetic reduction of NMNAT2 on chemotherapy-induced losses in cell viability in vitro and peripheral neuropathy in vivo. PLoS One. 2016 Jan 25;11(1):e0147620. PMCID: PMC4726514.
3. Ciupek, S.M., **Ali YO** *et al.* (2015) Progressive functional impairments of hippocampal neurons in a tauopathy mouse model. Journal of Neuroscience. 2015, 35 (21), 8118-31. PMCID: PMC4444537.
4. Majid T, **Ali YO**, Venikraramani D, Jang MK, Lu H-C, Pautler RG. (2014) In Vivo Axonal Transport Deficits in a Mouse Model of Fronto-Temporal Dementia. NeuroImage: Clinical. Mar 31; 4:711-7.
5. **Ali YO**, Li-Kroeger D, Bellen HJ, Zhai RG, Lu, H-C (2013). Sustaining a Healthy Brain: NMNAT Functions as an Essential Endogenous Neuronal Maintenance Factor. Trends Neurosci. 2013, 36 (11), 632-640. PMCID:PMC3857727 *(Featured Cover Article)*

B. Positions and Honors

Positions

2002-2005 Research Assistant with Heather Grunkemeyer, Ph.D., Ohio Wesleyan University
2003-2005 Research Assistant with Anne Fry, Ph.D., Ohio Wesleyan University
2007-2011 Graduate Student with Grace Zhai, Ph.D., University of Miami
2011-2012 Postdoctoral Fellow with Virginia Lee, Ph. D., University of Pennsylvania
2012-2015 Postdoctoral Fellow with Hui-Chen Lu, Ph. D., Baylor College of Medicine
2015- Assistant Scientist, Indiana University

Honors

2001-2005 Faculty Scholar, Ohio Wesleyan University
2002 Lawrence E. Young Award, Department of Zoology, Ohio Wesleyan University
2002 Florence Leas Award, Department of Mathematics, Ohio Wesleyan University
2002 Phi Eta Sigma Honor's Society, Ohio Wesleyan University
2003 Kraus Fellowship, Department of Zoology, Ohio Wesleyan University
2003 Founder's Prize for Expository Writing in the Sciences, Ohio Wesleyan University
2004 All-American Scholar Award, United States Achievement Academy
2009 Second Prize, Poster Session, Division: Science, Research and Creativity Forum, University of Miami
2009 Medical Faculty Association Margaret Whelan Graduate Travel Award, University of Miami, Miller School of Medicine
2011 First Place, Best Graduate Research Award, Medical Faculty Association, University of Miami, Miller School of Medicine
2013 Young Investigator Scholarship, Alzheimer's Drug Discovery Forum (ADDF)

2013 Selected Scientist: Training in Neurotherapeutics Discovery and Development for Academic Scientists, NIH

Other Experiences, Service, and Professional Memberships

2006-2008 The American Society for Pharmacology and Experimental Therapeutics

2006-2016 Society for Neuroscience

2011- Ad hoc reviewer for Molecules, Medical Science Monitor, Behavioral Sciences, PloS One

2013 American Heart Association, Council on Stroke.

C. Contribution to Science

1. My early contributions as a graduate student uncovered the molecular and biochemical basis of a novel neuroprotective agent, NMNAT. Using Drosophila, mouse and cell-based models, I uncovered the transcriptional mechanisms by which this potent molecule can impart such robust neuroprotection in various models of stress and degeneration. In addition, I also explored whether NMNAT has endogenous molecular partners, and identified that it imparts protection at the synapse by directly interacting with and stabilizing structural components of the active zone. Moreover, I also showed that NMNATs can be very neuroprotective in Alzheimer's disease models and an early reduction in NMNAT levels, prior to the onset of neurodegeneration, can be an underlying factor in disease progression.

   a) Zang S*, **Ali YO***, Ruan K, Zhai RG. (2012) *Drosophila* NMNAT maintains the dynamic presynaptic active zone structure through interaction with BRP. *EMBO Reports,* 14(1): 87-92*.* PMCID:PMC3537136. *Co-First Authors *(Featured Cover Article) Highlighted in EMBO Reports in* Chaperoning the synapse-NMNAT protects Bruchpilot from crashing
   b) Ljunberg C*****, **Ali YO***, Zhu J, Oka K, Zhai RG, Lu HC. (2011) CREB-activity and nmnat2 transcription are down-regulated prior to neurodegeneration, while NMNAT2 over-expression is neuroprotective, in a mouse model of human tauopathy. *Human Molecular Genetics*. 21(2):251-67. PMCID:PMC3276285
      *Co-First Authors.
   c) **Ali YO**, Ruan K, Zhai RG (2011) NMNAT suppresses Tau-induced neurodegeneration by promoting clearance of hyperphosphorylated Tau oligomers in a Drosophila model of tauopathy. *Human Molecular Genetics*. 21(2):237-50. PMCID:PMC3276290 *(Featured Cover Article)*
   d) **Ali YO**, McCormack RM, Darr A, Zhai RG (2011) Nicotinamide mononucleotide adenylyltransferase (NMNAT) is a stress response protein regulated by the HSF/HIF1A pathway*. J Biol Chem.,* 286(21):19089-99. PMCID:PMC3099722

2. In addition to understanding the role of a novel neuroprotective agent, I also uncovered the structural and molecular basis of aggresome formation by discovering the crystal structure of HDAC6 in complex with ubiquitinated substrate. The aggresome pathway is activated when proteasomal clearance of misfolded proteins is hindered. Misfolded polyubiquitinated protein aggregates are recruited and transported to the aggresome via the microtubule network by a protein complex consisting of histone deacetylase 6 (HDAC6) and the dynein motor complex. These results provide structural and mechanistic bases for the role of HDAC6 in aggresome

formation and further suggest a novel ubiquitin-mediated signaling pathway, where the exposure of ubiquitin C termini within protein aggregates enables HDAC6 recognition and transport to the aggresome. The aggresome pathway has emerged as a potential therapeutic target for cancer treatment. Our studies suggest the ZnF-UBP domain of HDAC6 as a site of interest.

a) Ouyang H*, **Ali YO***, Ravichandran M, Dong A, MacKenzie F, Dhe-Paganon S, Zhai RG, and Arrowsmith C. (2011) Protein aggregates are recruited to the aggresome by histone deacetylase 6 via unanchored ubiquitin C-termini. *J Biol Chem.,* 20;287(4):2317-27. PMCID:PMC3268394 *Co-First Authors

3. Training under a team of experienced neuropathologists, I contributed to one of the first papers observing C9orf72 expansions as the most common leading cause of sporadic and familial ALS. C9ORF72-hexanucleotide repeat expansions and ubiquilin-2 (UBQLN2) mutations are recently identified genetic markers in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We investigated the relationship between C9ORF72 expansions and the clinical phenotype and neuropathology of ALS and FTLD. Our study indicated that this pathology is associated with alterations in clinical phenotype, and suggests that the presence of C9ORF72 repeat expansions may indicate a worse prognosis in ALS.

   a) Johannes Brettschneider, Vivianna van Deerlin, John Robinson, Linda Kwong, Edward B Lee, **Yousuf O Ali** *et al*. (2012) Pattern of ubiquilin pathology in ALS and FTLD indicates presence of C9ORF72 hexanucleotide expansion. *Acta Neuropathologica,* 2012, 123(6):825-39. PMCID:PMC3521561

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Ali%20YO

D. Research Support

Completed Research Support

2009-2011 **American Heart Association** GSA Spring 09 Predoctoral Fellowship (09PRE2250608)
Project Title: Transcriptional Regulation of a Neuroprotective Factor NMNAT upon Oxidative Stress

Current Research Support

2015-2016 **CTSI Core Pilot** (22-315-21) "*Understanding the development of cardiac dysfunction in Alzheimer's Disease.*"

2015-2016 **CTSI Core Pilot** (22-315-20)"*Elucidating the mechanistic insights of NMNAT2, a key neuronal maintenance factor and a potent drug target for neurodegenerative diseases.*"

2016-2018 **CTSI Project Development Team Award** "*Mechanisms of cardiac dysfunction in Alzheimer's Disease*" Role: PI