BIOGRAPHICAL SKETCH

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NAME: Galvan, Veronica

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

POSITION TITLE: Associate Professor

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
CAECE University, Buenos Aires, Argentina	MS	09/94	Molecular Biology
University of Chicago	PhD	12/99	Virology/Molecular Genetics and Cell Biology
Buck Institute for Research on Aging	Postdoctoral	12/05	Neurobiology
Buck Institute for Research on Aging	Postdoctoral	12/08	Neurobiology

A. Personal Statement

My research group is focused on the identification of molecular and biochemical alterations that initiate Alzheimer's disease (AD). We seek to understand how the activity of specific gene products during aging mechanistically lead to AD, and potentially other dementias. To this aim, we use genetic manipulations in mouse models, behavioral, biochemical and molecular biology tools, multiphoton *in vivo* or confocal optical imaging, as well as *in vivo* cerebral blood flow measures to understand the initiating molecular events in AD, determine the effects of potential drug candidate molecules, and define the mechanisms involved. Other interests of my research group are to ascertain the role that signals from the nervous system play in the control of organismal aging in mammals and to develop models of age-associated neurological diseases in non-human primates.

We have demonstrated a key role of the mammalian target of rapamycin (mTOR), a critical driver of mammalian aging, in the maintenance of neuronal and cerebrovascular function during aging and in AD. Because mTOR controls critical aspects of metabolism in most cell types, we hypothesize that mTOR may be involved in cell- and tissue-specific complex disease mechanisms that initiate and then drive neurodegeneration in AD. Thus, to define the role of mTOR in AD, we are studying neuronal and brain vascular mechanisms through which pathways centered on mTOR synergize to precipitate loss of function. We recently discovered that aggregated forms of tau accumulate in brain microvasculature of AD and other tauopathies, triggering cerebrovascular dysfunction. Using Aß- and tau-based mouse models of AD and of 'pure' tauopathy we investigate the mechanisms by which misfolded soluble tau propagates to microvascular cells in AD brain, and how the accumulation of misfolded tau in AD brain vasculature contributes to brain microvascular dysfunction in AD. We are also investigating the role of central and peripheral cell senescence in the pathogenesis of AD-like disease using Aß- and Aß plus tau-based AD models.

B. Positions and Honors

Positions and Employment

1994 - 1999	University of Chicago, Committee on Virology, Department of Molecular Genetics and Cell Biology (Mentor: Dr. Bernard Roizman)	Graduate Student
1999 - 2004	Buck Institute for Age Research (Mentor: Dr.Dale Bredesen)	Postdoctoral Fellow
2004 - 2009	Buck Institute for Age Research (Mentor: Dr.Dale Bredesen)	Staff Scientist
2009 –	Department of Physiology and The Barshop Institute, University of Texas Health Science Center at San Antonio	Assistant Professor

2012 -	Department of Biology, University of Texas at San Antonio	Adjunct Assistant Professor
2015	US Department of Veterans Affairs	Research Health Scientist
2016 -	Department of Cellular and Integrative Physiology and The Barshop Institute, University of Texas Health Science Center at San Antonio	Associate Professor (Tenured)

Other experience and Professional Memberships (selected)

2003- present	Member, Society for Neuroscience
2008- present	Member, International Behavioral Neuroscience Society
2009- present	Member, American Aging Association
2010- present	Co-leader for Cognitive Asessment in Rodents, NIA San Antonio Nathan Shock Center of Excellence in the Basic Biology of Aging
2010- present	Member, Gerontological Society of America
2010- present	Editorial Board member, *Aging and Disease*
2010 - present	Member, National Scientific Advisory Council, American Federation for Aging Research
2012 - present	Editorial Board member, *ISRN Geriatrics*
2012 – present	Scientific Advisory Board member, Rapa Holdings Inc.
2013 – present	Editorial Board member, *Archives of Physiology*
2013 – present	Board, Alzheimer's Association, San Antonio and South Texas Chapter
2014- present	Editorial Board member, *Frontiers in Molecular Biosciences* and *Frontiers in Protein Folding, Misfolding and Degradation*
2015- present	Co-leader, Healthspan and Functional Assessment Core, NIA San Antonio Nathan Shock Center of Excellence in the Basic Biology of Aging
2015 - 2016	Member, Scientific Program Committee, 2016 International Conference on Aging and Disease, Stanford University, October 2016
2015 - 2017	Member, Scientific Program Committee and Young Investigator Committee, BRAIN & BRAINPET 2017, International Symposium
2015 - 2017	Organizer and Chair, 2016 International Conference on Aging and Disease Session III, "*Aging, metabolism and disease*"
2015 – present	Neurobiology D (NURD) Study Section, Veterans Administration Research Service
2016 - present	Associate Editor, AGE – Official Journal of the American Aging Association
2016	Ad Hoc Reviewer, NIH/NIA Special Emphasis Panel ZRG1 MDCN-T PAR-15-358-*Molecular and Cellular Causal Aspects of Alzheimer's Disease*
2017	Organizer, 2017 Barshop Symposium on Aging '*Sex Differences in Aging, Age-related Diseases and Interventions*'
2017	Ad-Hoc reviewer, NIH/NIA Cellular Mechanisms in Aging and Development (CMAD)
2018	Co-organizer, Metabolic/Systemic Signaling and Aging session, 2017 American Aging Association 27th annual meeting

Honors

1995 - 1997	Lucille Markey Scholar in Molecular Medicine
2003	Scholar, National Institute on Aging Summer Institute on Aging Research
2003 - 2005	John D. French Alzheimer's Foundation Fellow
2006	S.D. Bechtel Jr. Foundation Award
2007	US Patent 8329653 B2 "Compositions and methods for suppression of amyloid plaque formation associated with neurodegenerative disorders"
2008	US Patent application EP1744762 A2 "Transgenic Models of Alzheimer's Disease and Uses Thereof In the Treatment of a Variety of Neurodegenerative Diseases
2009	US Patent Application 13/128,800 "Inhibition of mammalian target of rapamycin"
2010	Ellison Medical Foundation New Scholar Award in Aging
2013	US Patent Application "Use of TOR inhibitors to maintain cerebrovascular health and/or restore cerebrovascular dysfunction"
2014	US Patent Application "The use of Inhibitors of mTOR to Improve Vascular Functions in APOE4 Carriers and Reduce Risk for Alzheimer's Disease and other Neurovascular and Psychiatric Disorders"

C. Contribution to Science

h-index=34	***i10index=43***
Total publications: 56	
Total citations: 3,863	*(2,168 citations since 2012)*

1. A major research focus in my laboratory is the investigation of pathways that link the regulation of brain aging to the pathogenesis of Alzheimer's disease and other dementias. We have identified mTOR-dependent inhibition of autophagy in neurons and the inhibition of endothelial nitric oxide (NO) synthase-dependent release of NO in brain vasculature as two critical mechanisms that initiate AD-like pathogenesis in mice. Our work demonstrated that systemic attenuation of mTOR activity with rapamycin can prevent and also *treat* established Alzheimer's-like deficits in mice modeling the disease and that this hinges on two critical mechanisms: The relief of mTOR-dependent inhibition of (a) autophagy, decreasing levels of production of Aβ in brain parenchyma, and (b) restoration of vascular integrity, enabling sustained Aβ clearance from brain in a manner dependent on eNOS-mediated NO release and vasodilation mediated by vascular endothelial cells. Because mTOR inhibitors such as rapamycin and rapalogs are FDA-approved, our studies have significant immediate translational implications for the treatment of Alzheimer's, and potentially other neurological diseases of aging beyond Alzheimer's alone.

a. Spilman P, Podlutskaya N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, Richardson A, Strong R and **Galvan V** (2010) Rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. *PLoS One*. 5:e9979. PMID: 20376313 ***512 citations***
Recommended by Faculty of 1000

b. Halloran JJ, Hussong S, Podlutskaya N, Burbank R, Austad S, Hart MJ, Fischer K and **Galvan V**. (2012) Long-term mTOR inhibition by rapamycin modulates cognitive and non-cognitive components of behavior in mice. *Neurosci*. 223:102-113. ***117 citations***
Recommended by Faculty of 1000

c. Lin A, Halloran JJ, Burbank RR, Korde S, Zheng W, Hussong SA, Podlutskaya N, Strong R, Richardson A, Hart MJ, Fox PT, Lechleiter J, **Galvan V** (2013). Chronic rapamycin restores brain vascular density and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. *J Cereb Blood Flow Metab*. 33:1412. ***61 citations***

d. Jahrling JB, Lin AL, DeRosa N, Hussong SA, Van Skike CE, Girotti M, Javors M, Zhao Q, Maslin LA, Asmis R, **Galvan V**. (2017) mTOR Drives Cerebral Blood Flow and Memory Deficits in $LDLR^{-/-}$ Mice Modeling Atherosclerosis and Vascular Cognitive Impairment. *J Cereb Blood Flow Metab*. E-pub ahead of print. PMID: 28511572

2. Studies from my laboratory recently demonstrated the accumulation of aberrantly phosphorylated, misfolded tau deposits in microvasculature of Alzheimer's and progressive supranuclear palsy (PSP). These suggests that extracellular forms of tau may play a role of in the etiology of cerebromicrovascular dysfunction and disintegration in Alzheimer's disease and potentially other tauopathies. Our ongoing studies seek to define (a) how misfolded, aggregated tau accumulates in brain microvasculature, and (b) the mechanisms by which accumulation of misfolded tau in microvascular cells leads to cerebrovascular dysfunction in AD and other tauopathies.

Castillo-Carranza DL, Nilson AN, Van Skike CE, Jahrling JB, Patel K, Garach P, Gerson JE, Sengupta U, Abisambra J, Nelson P, Troncoso J, Ungvari Z, **Galvan V** and Kayed R (2017) Cerebral microvascular accumulation of tau oligomers in Alzheimer's disease and related tauopathies. *Aging Dis.* 8: 257-266. PMID: 28580182

3. The amyloid precursor protein (APP) is causally involved in Alzheimer's disease through the generation of amyloid-beta (Aβ), a peptide that results from cleavage of APP at its extracellular and intramembranous domains. APP is a classic transmembrane protein with a short intracellular domain that assembles signaling complexes and is part of transcriptional complexes after its release by intramembranous cleavage of the precursor. The role of the intracellular domain of the amyloid precursor protein (APP) in the pathogenesis of AD had not yet been explored. My postdoctoral work provided the first *in vivo* evidence for a novel proteolytic cleavage of the amyloid precursor protein (APP) as critical to the etiology of synaptic and cognitive deficits of AD-like disease in model mice. These studies resulted in 13 publications and contributed to expanding our understanding of various APP preoteolytic products and the functional interplay among them, providing novel insights into mechanisms of AD neurodegeneration. The knowledge generated by these studies resulted in 2

patents and led to a clinical trial that started in 2014.

a. **Galvan V**, Gorostiza OF, Banwait S, Ataie M, Logvinova AV, Sitaraman S, Carlson E, Sagi SA, Chevallier N, Jin K, Greenberg DA, Bredesen DE. (2006) Reversal of Alzheimer's-like pathology and behavior in human APP transgenic mice by mutation of Asp664. *Proc Natl Acad Sci USA*. 103:7130. ***Recommended by Faculty of 1000*** ***230 citations***

b. **Galvan V**, Chen S, Lu D, Koo EH and Bredesen DE. (2002) Caspase cleavage of members of the amyloid precursor family of proteins. *J Neurochem.* 82: 283-4. ***102 citations***

c. Saganich MJ, Schroeder BE, **Galvan V**, Bredesen DE, Koo EH, Heinemann SF. (2006) Deficits in synaptic transmission and learning in APP transgenic mice require C-terminal cleavage of APP. *J Neurosc*. 26:13428. ***101 citations***

d. Calheiros F, **Galvan V**, Corset V, Llambi F, Bredesen DE, and Mehlen P. (2009) Netrin-1 acts as an APP ligand and suppresses amyloid-ß production. *Cell Death Differ*. 16:655. ***59 citations*** ***Recommended by Faculty of 1000***

3. My first major contributions were in the field of herpes simplex virology. With my doctoral studies I made the initial discovery of pathways of activation and inactivation of programmed cell death upon the initial contact of herpes simplex type 1 (HSV-1) virions with host cells. These studies provided the first evidence that infection by herpes simplex virus 1 (HSV-1) activates several checkpoints of programmed cell death, and has evolved functions to block all cellular programmed death pathways. The publications that arose from these studies contributed to open a novel area of research in the biology of HSV-1-host cell interactions that led to important insights into the initial steps of both productive and latent infection by HSV-1, and prompted similar or divergent discoveries in other members of the Herpesvirus family. Galvan and Roizman (1998) provided a foundation for subsequent high-impact studies and also contributed to the development and use of mutant HSV-1 vectors as oncolytic agents.

a. **Galvan V** and Roizman B. (1998) Herpes simplex virus 1 induces and blocks apoptosis at multiple steps during infection and protects cells from exogenous inducers in a cell-type-dependent manner. *Proc. Natl. Acad. Sci. USA* 95:3931-36. PMID: 9520470 ***251 citations***

b. **Galvan V**, Brandimarti R and Roizman B. (1999) Herpes simplex virus 1 blocks caspase-3-independent and caspase-dependent pathways to cell death. *J Virol.* 73:3219-26. ***99 citations***

c. **Galvan V**, Brandimarti R, Munger J and Roizman B. (2000) Bcl-2 blocks a caspase-dependent pathway of apoptosis activated by HSV-1 infection in HEp-2 cells. *J Virol.* 74:1931-38 ***63 citations***

d. Zou G, **Galvan V**, Campadelli-Fiume G and Roizman B. (2000) Glycoprotein D or J delivered in trans blocks apoptosis in SK-N-SH cells induced by a herpes simplex virus 1 mutant lacking intact genes expressing both glycoproteins. *J Virol.* 74:11782-91. ***157 citations***

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1jkK1ehNbwzQp/bibliography/48168264/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1R01AG057964-01 (**Galvan**, PI/MPI) 09/15/2017 – 06/30/22
Brain cellular senescence as a driver of Alzheimer's disease
The goal of this project is to determine the role of brain cellular senescence in the pathogenesis of Alzheimer's disease.

R21 (Jakob) Role: Co-I 09/01/2016 - 08/31/2021
NIH/NIA
"A role of polyphosphate in Alzheimer's disease"
The goal of this project is to define the role of the several million year-old molecule polyphosphate, present in every eukaryotic cell and tissue, in the formation of Aß fibrils in Alzheimer's disease.

1 I01 BX002211-01A2 (**Galvan**) 01/26/15 – 01/25/2019
Veterans Administration Research and Development Merit Award
Inhibiting the TOR Pathway to Combat Alzheimer's Disease
Goals of this project are to establish the therapeutic potential for rapamycin or other TOR inhibitors in the treatment of Alzheimer's disease (AD) and to determine rapamycin's mechanisms of action in AD brain.

2 P30 AG013319-21 (Strong) 07/01/15 – 06/30/2020
NIH/NIA SA Nathan Shock Center of Excellence in the Biology of Aging

This project supports the San Antonio Nathan Shock Center whose goal is to provide services to enable research in the biology of aging and in age-associated diseases.
Role: Co-Leader, Healthspan and Functional Assessment Core

Kleberg Foundation Award (Paukert) 01/01/15 –12/31/2019
Robert J. Kleberg and Helen C. Kleberg Foundation
"Mechanisms of neurodegeneration and the role of astrocytes: Insights into Alzheimer's and its progression"
The goal of this project is to determine the role of astrocytes in the early stages of Alzheimer's disease.

SAMF 2014 (**Galvan**) 08/01/14 – 07/31/2017
San Antonio Medical Foundation
Interdisciplinary approaches to age-associated neurodegenerations and cognitive decline
The goal of this project is to establish the Neurobehavioral Functional Assessment Laboratory, a comprehensive testing facility available to all investigators at the UT Health Science Center and its research partners to advancing research in neurological diseases in our community.

Private (**Galvan**) no expiration
Robert L. Bailey and daughter Lisa K. Bailey Alzheimer's Fund
The goal of this project is to determine the mechanisms that link signaling through the mTOR pathway and the production of nitric oxide in vascular endothelial cells.

<u>Completed Research Support</u> (last 3 years)

IIMS/CTSA (**Galvan**) 11/01/15-10/30/2016
NIH Institute for Integration of Medicine and Science
Neurovascular tau in dementia
The goal of this project is to determine the role of misfolded and oligomerized tau in neurovascular dysfunction associated with Alzheimer's disease and other dementias.

JMR Barker Foundation (**Galvan**, Curiel) 01/06/14 – 05/31/2016
Exploring the potential for rapamycin as a therapy for Alzheimer's disease and other dementias
The goal of this project is to determine whether rapamycin can restore cerebral blood flow in AD or MCI patients.

OWENS FND 2016 (**Galvan**) 01/01/2016 - 12/31/2016
William & Ella Owens Medical Research Foundation
Rapamycin as a therapy for vascular damage in Alzheimer's disease
The goal of this project is to determine whether rapamycin maintains memory in AD mice by blocking Aß-induced vessel damage.

AG-NS-0726-10 (**Galvan**) 08/01/2011 - 07/31/2015
Ellison Medical Foundation-New Scholar Award in Aging
"Neuronal mTOR in Mammalian Aging"
Goal: To determine the role of mTOR signaling from the nervous system in the control of aging in mammals.

1IO1VX001454-01 (Hornsby) 10/01/2011 - 09/30/2015
Regenerative medicine
Veterans Administration Research and Development Merit Award
The project will establish a non-human primate model for the safety and efficacy of autologous cell transplantation using iPS cells. Role: Key Personnel

1 R03 AG045481-01/NIH (Hornsby) 08/15/2013 - 05/31/2015
Stress resistance in neurons from primate iPS cells
This project will establish whether differentiated motor neurons derived from three primate species of very different longevities exhibit differential resistance to physiological stresses. Role: Key Personnel

OWENS FND 2014 (**Galvan**) 01/01/2013 - 12/31/2014
William and Ella Owens Medical Research Foundation
Rapamycin as a therapy for vascular damage in Alzheimer's disease
The goal of this continuation project is to determine whether rapamycin maintains memory in AD mice by blocking Aß-induced vessel damage.