UNIVERSITY OF MIAMI
EVELYN F. McKNIGHT BRAIN INSTITUTE
ANNUAL PROGRESS REPORT
JANUARY 1, 2016 - DECEMBER 31, 2016

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THE EVELYN F. McKNIGHT BRAIN INSTITUTE
UNIVERSITY OF MIAMI
Preserving memory, enhancing life

January 12, 2017

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Dear Trustees,

Enclosed please find copies of the University of Miami Evelyn F. McKnight Brain Institute Annual Report describing our work and accomplishments from January through December of 2016.

We are looking forward to a successful 2017 with Dr. Rundek as our Interim Scientific Director while we search for Dr. Wright's replacement. We would like to thank you for your support.

Yours Sincerely,

Ralph L. Sacco, M.D., M.S.
Executive Director
Evelyn F. McKnight Brain Institute

Tatjana Rundek, M.D., Ph.D.
Interim Scientific Director
Evelyn F. McKnight Brain Institute

RLS/TR/SSM/bd

cc: Susan Fox Rosellini

Introduction

Scientific Director Leadership Change and Research Program Transition

We start our report with the news that Dr. Clinton B. Wright ended his appointment as the Evelyn F. McKnight Scientific Director at the University of Miami on October 31, 2016. Dr. Tatjana Rundek was appointed as Interim McKnight Scientific Director on November 1, 2016. Dr. Wright was recruited from Columbia University by Dr. Ralph L. Sacco in 2008 to be the first University of Miami Evelyn F. McKnight Scientific Director. Dr. Wright was also appointed as the first Miami Evelyn F. McKnight Chair in Learning and Memory for the Aging. As of October 31, 2016 Dr. Wright ended his appointment at the University of Miami and accepted a prestigious position at the National Institute of Neurological Disorders and Stroke (NINDS) as the Associate Director of the NINDS and the Director of the Division of Clinical Research. Dr. Wright's accomplishments and contributions were acknowledged at a farewell party organized in his honor at the University of Miami. Dr. Wright will be greatly missed at the Evelyn F. McKnight Brain Institute.

In order to assure smooth transition and seamless continuation of the Miami Evelyn F. McKnight Brain Institute research program, Dr. Tatjana Rundek was immediately appointed by Dr. Sacco to be the Interim Scientific Director. She assumed the position on November 1, 2016. Together with Dr. Sacco, she immediately organized the Search Committee for the new Evelyn F. McKnight Scientific Director. This Search Committee is co-chaired by Dr. Rundek and Dr. Sara Czaja, Director of the Miami Center on Aging. The first meeting of the Search Committee was held on November 28, 2016 and the charge for the Committee was established. The Search Committee reviewed an extensive list of potential candidates and ranked them. Numerous emails were sent to potential and highly qualified candidates by Dr. Sacco and Dr. Rundek. Two serious, excellent and highly qualified candidates expressed their interest in the position. The first candidate is scheduled for a visit to Miami on February 2-3, 2017. The advertisement for the Evelyn F. McKnight Scientific Director position was posted in *Neurology* in early November of 2016. It has also been distributed on the *ResearchGate* website and the American Psychological Academy (APA) listserv.

Interim Evelyn F. McKnight Scientific Director

Dr. Rundek's appointment as the interim Evelyn F. McKnight Scientific Director was a logical choice. Similar to Dr. Wright, she was recruited from Columbia University by Dr. Sacco in 2007 in order to help establish a clinical and translational research program in the Department of Neurology at the University of Miami. Dr. Rundek is a Vice Chair of Clinical Research in Neurology and serves on the Executive, Research and other Leadership Committees in the Department of Neurology. She has been involved in research strategic planning for the Department of Neurology as a leader of a research pillar. Dr. Rundek has been a member of the Miami Evelyn F. McKnight Brain Institute since 2008 and has served on the Scientific Advisory Board of the Miami Evelyn F. McKnight Brain Institute.

Dr. Rundek is a Professor of Neurology and Public Health Sciences with tenure and Director of the Clinical Translational Research Division in Neurology. She holds a secondary faculty appointment at the Department of Neurology at Columbia University in New York. Dr. Rundek is a stroke neurologist and clinical translational researcher. She is the Principal Investigator of several NIH/NINDS funded R01 grants on genetic determinants of carotid atherosclerosis and stroke. She has developed extensive research collaborations with various research teams across departments and institutions. For example, Dr. Rundek collaborates with investigators from Columbia University on several large NIH-funded population based studies such as NOMAS (the risk of stroke and cognitive decline), INVEST (oral infections and risk of atherosclerosis), CABLE (cardiac disease and risk of stroke and cognitive decline), PHPT (primary hyperparathyroidism and atherosclerosis) and a large program project U01 eMERGE (on genetics and use of EHR-electronic health records). She also collaborates with Albert Einstein in the Bronx on the NIA-funded Einstein Aging Study (EAS), where she is a co-investigator of the brain hemodynamic study on aging and cognitive decline along with EAS PIs, Dr. Carol Derby and Dr. Richard Lipton. She is a collaborator and site investigator of the large international stroke genetic and atherosclerosis projects and consortia including NINDS SiGN, ISGC, PROG-IMT, and ELSA.

Besides her active role in research and research strategy in the Department of Neurology, Dr. Rundek is an active teacher and educator. She is a Director of a Master of Science degree in the Clinical Translation Investigations at the Miller School of Medicine. At the Miami NIH-funded Clinical Translational Research Institute (CTSI) Dr. Rundek is the Leader of the Educational Component and Director of Clinical Translational Research Bootcamp and Mentor-Mentee Workshops. Dr. Rundek is also a nationally recognized mentor. She is a recipient of a 5-year NINDS K24 award, which allowed for protected time for mentorship. She has recently received an AHA National Mentor award for 3 years to mentor 3 AHA awardees from UF, Johns Hopkins and UT Houston. She is a Training Director of the Miami AHA Bugher Stroke Center of Excellence and Training Director of the NINDS StrokeNet and NeuroNEXT. She serves on the Medical School Admission Committees of the MD/PhD program and PhD program in Public Health Sciences. In the past ten years, Dr. Rundek has mentored over twenty trainees at various stages of their careers. Fourteen completed their MD, PhD, or MS degrees during her

mentorship and obtained NIH grants or other awards (1 K23, 3 K12, 1 R01, 1 K99/R00, 3 AHA, 2 AAN, 1 ANA, 2 FL Biomedical and other institutional/foundation grants).

Dr. Rundek was born and raised in Zagreb, Croatia. She received her medical degree at the University of Zagreb, a PhD degree in Neuroscience in Germany, and trained in neurology at the University of Zagreb, Germany and at Columbia University in New York, where she completed a stroke fellowship. After serving as a physician in MASH during the Balkan War, 1990-1994, Dr. Rundek participated in the international research exchange program and was the first Fulbright Scholar at the Neurological Institute of the Columbia University under the leadership of Dr. Bud Rowland. She was Leader of all Fulbright Scholars in 1996-97, in which role she gave a 45-second presentation on the importance of the international research exchange program at the 1997 annual UN Assembly in New York. While at Columbia, Dr. Rundek was the recipient of the research awards from the Hazel K. Goddess Fund for Prevention of Stroke in Women and the Dr. Gilbert Baum and American Institute of Ultrasound in Medicine Award for best clinical application of ultrasound.

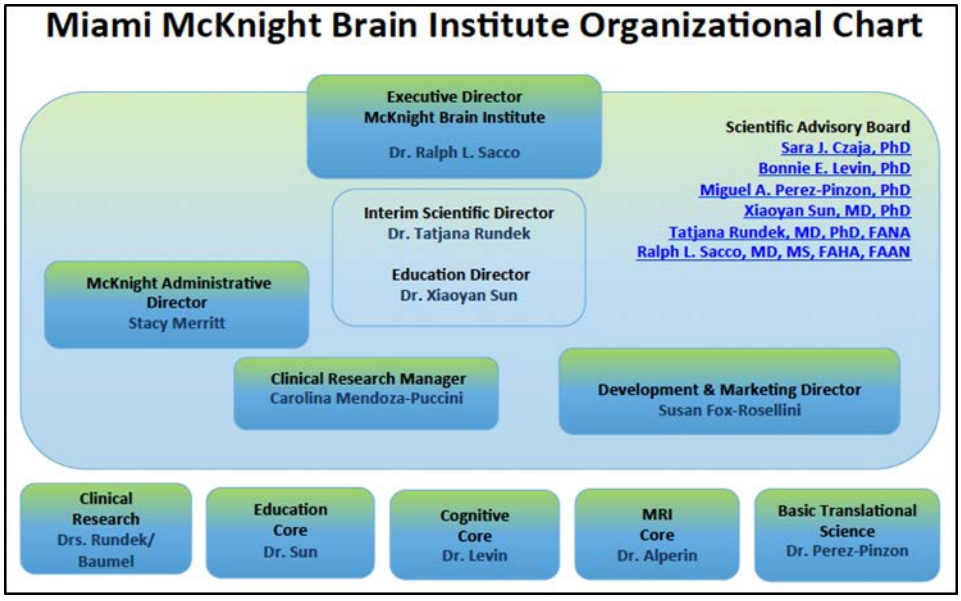
Dr. Rundek serves on the editorial boards of several scientific journals including *Stroke* (Consulting Editor), *Neurology*, *Journal of Ultrasound in Medicine* and *Cerebrovascular Diseases*. She has published over 300 scientific publications, editorials, reviews and book chapters. She is a Fellow of the American Neurological Association and the American Heart Association and a member of the American Academy of Neurology. She is Past President of the Neurosonology Communities of Practice of the American Institute in Ultrasound in Medicine, the largest professional medical ultrasound organization in the US. Dr. Rundek serves on the Intersocietal Accreditation Commission (IAC) Vascular Testing Board of Directors (Secretary), a national organization that accredits clinical ultrasound, echocardiography, nuclear/PET, MRI, CT and carotid stenting programs. Dr. Rundek is a member of the AHA South Florida Board and was recognized as stroke neurologist with AHA Cor Vitae for Stroke Award in 2015.

Transition plan

A clear transition of duties and responsibilities for current McKnight research projects and collaborations from Dr. Wright to Dr. Rundek has been in place since late October of 2016. The plan that was put forth assured a smooth transition of all ongoing McKnight Brain Institute activities that included continuation of all scheduled meetings, conference calls, a visit of the McKnight Trustees and preparation of the 2016 annual report. All research projects are continuing and there has been no lapse in any research program activities. Our Evelyn F. McKnight Brain Institute continues to be a highly *collaborative, integrative, translational and multi-disciplinary* Institute with the **Mission** to discover the causes, conduct treatment and prevention of age-related memory loss and cognitive decline and enhance brain health. Our **Vision** is to become a foremost center of research into the causes, treatment and prevention of age-related cognitive disorders by integrating translational, clinical and population research programs with educational activities.

In the first 2 months of being an Interim Scientific Director, Dr. Rundek's focus was to assure research alignment with our McKnight Brain Institute Mission and Vision. She was focused on addressing research issues by prioritizing research projects and transition activities, as follows:

- Harmonization of the McKnight Brain Aging Registry (MBAR) protocol logistics among McKnight Institutes for individuals 85+ years old, which included harmonization of a detailed neurocognitive battery, a specific MRI protocol, biorepository and data collection, storage, transfer and other data regulatory management issues
- Continuation of current research projects sponsored by the Miami McKnight Brain Institute (*McKnight Brain Institute Cognitive Disorders Clinical and Biorepository Registry; Biomarkers for Early Diagnosis of Cognitive Impairment in the Elderly; Frailty as a Preventive Measure in Maintaining Quality of Life in Aging*; *Retinal Microvascular Dysfunction in Pre-MCI, MCI and Late MCI Patients; Ischemic Preconditioning: Mechanisms of Neuroprotection in animal models, etc.)*
- Continuation of research projects sponsored by the Miami McKnight Brain Institute and the NINDS, NIA and AHA (*Age-Related Cognitive trajectories in NOMAS - NINDS; Augmenting Cognitive Training in older adults (ACT) - NIA; Safety and Tolerability of Aerobic and Resistance Exercise w/without cognitive training post stroke - AHA Bugher)*
- Assuring seamless team transitions and revisiting team members' roles and responsibilities. Dr. Rundek has met with each McKnight Brain Institute project and Core leader and project team to assure research team transitions and no interruption of project activities. Our organizational chart was revisited and clear roles and responsibilities of our executive, research and Core leadership teams were defined (see Organizational Chart below)
- Assuring continuation of education activities (seminars, journal clubs) as scheduled
- Planning for the McKnight Brain Institute activities: McKnight Trustees' Visit to Miami, NIA/McKnight Research Summit on Cognitive Reserve and Resilience in April of 2017 (participation in the planning conference calls), 2016 McKnight Brain Institute Progress Report and 2017 McKnight Brain Institute Budget



New McKnight Brain Institute Activities since October 2016

Collaboration with Center on Aging

Starting in November 2016, we established a more formal partnership between the McKnight Brain Institute and the University of Miami Center on Aging. Dr. Sara Czaja, Director of the Center on Aging has welcomed our stronger collaboration and partnership that will include sharing of educational and training activities and collaboration on intervention research projects in aging.

The following collaborative plan was established:

- Joint Scientific Lecture Series 2016-2017 with monthly lectures. Four external invited speakers are planned and their visits to Miami are co-sponsored by the McKnight Brain Institute and the Center on Aging
- McKnight Grand Rounds on aging and memory is planned for March 2017 with Dr. DeKosky as the guest speaker
- Collaboration on recruitment of research subjects for mutual studies (a list of potential candidates for the MBAR study has already been shared and 3 subjects identified for potential participation in MBAR)
- Jointly working with the Search Committee on selecting the best candidate for the next McKnight Scientific Director

The McKnight Educational Program

Our Educational Program has been evaluated for potential re-organization in order to provide more structured training experiences for our trainees. Neurology residents will have a two-week rotation in the Memory Disorders Clinic where they will see patients with memory complaints and dementia. The Residents will get to discuss the diagnosis and treatment plans with clinicians. In addition they will observe neuropsychological testing and discuss testing results with Neuropsychologists. Residents will also review neuroimaging to learn about imaging modalities and brain changes of patients with neurodegenerative diseases. We will start an initiative to develop a multi-disciplinary mentorship program that will provide our trainees with more skills and knowledge in age-related memory loss and immersion in McKnight projects across our Institute with opportunities for informal training in neuro-cognition, brain imaging and other biomarkers. Our trainees will have an opportunity to actively participate in:

- Seminar Series, Journal clubs, Joint Scientific Lecture Series
- Community education events and programs
- Cross-disciplinary mentorship in collaboration with the MD, MD/PhD, PIBS and MS programs
- Grant and manuscript writing classes (through Miami CTSI under directorship of Dr. Sacco and MS in Clinical Translational Investigations under directorship of Dr. Rundek)
- CTSI classes (clinical trials, study designs, biostatistics)
- Formal MS degree in Clinical Translational Investigations
- Structured Neurocognitive Training program – ***First McKnight Cognitive Fellow will start on July 1, 2017.*** We have established the first cognitive fellowship in our Department of Neurology and identified an excellent candidate for neurocognitive fellowship from our

Neurology Residency Program who is interested in an academic career in cognitive neurology. The Mentorship Team has been created and includes the content mentors, Dr. Baumel, Director of the Cognitive Division in Neurology, Dr. Sun and Dr. Levin; and Dr. Rundek will serve as a career development mentor.

The McKnight Small Pilot Collaborative Research Award Program

Our Leadership Team brainstormed creating a small pilot collaborative research award program. We concluded that 1-2 awards per year for junior faculty or post-doctoral trainees with promising potential to become future successful investigators would greatly improve our McKnight Brain Institute collaborative research project pipeline and support our research talents. One award in the amount of $10,000 is planned for 2017. We will announce this opportunity across our Institution with criteria to include post-doctoral trainee or young investigator according to the NIH definition, a 3-page pilot collaborative research proposal (proposed projects need to include at least 2 different departments) that is aligned with the Mission of our McKnight Brain Institute, and a brief career development statement. Priority will be given to the pilot projects that are clinical-interventional or hold promise of rapid clinical translation and intervention.

In summary, our Executive Director, Dr. Sacco, the collaborative scientific and Core leadership team and dedicated members of the McKnight Institute at the University of Miami are devoted to its Mission and Vision. Our involved investigators and collaborators are talented in their fields and are determined to elucidate the causes, treatment and prevention of age-related memory loss and cognitive decline. Our research transition program has been instituted to successfully continue the next year of the Institute research activities and our Search committee has been actively working to find the best candidate for the next Scientific Director. This report summarizes the accomplishments and work completed as a part of the Miami McKnight Brain Institute in 2016.

1. Summary of Scientific Achievements Since Last Report

A. Clinical and Population-Based Research

A large part of our focus this year was spent harmonizing the McKnight Brain Aging Registry protocol logistics among McKnight Institutes. This entailed continuous collaboration with the McKnight Brain Institutes to finalize the collection of standardized brain MRIs and neuro-psychological assessment data. We worked to strengthen our collaboration with Dr. Czaja at the Center on Aging, whose work focuses on quality of life while aging, which will enhance our clinical research opportunities and will be an important part of our growth in the area of quality of life and healthy aging through the life span. Dr. Czaja's repertoire of research on the aging population has enabled her to build a vast database of healthy older adult research participants. This has already proven to be an asset as we now have a substantial list of potential study participants for the McKnight Brain Aging Registry study.

Additionally, a great effort was put forth to analyze the data from our ongoing McKnight Registry which has resulted in several dynamic findings. This year, Dr. Levin began her important research on frailty in aging. Dr. Sun's research comparing the cerebrospinal fluid (CSF) of APOE and non-APOE carriers showed that carriers had elevated CSF neurogranin levels. This finding suggests that early synaptic damage may contribute to increased risk for Alzheimer's disease in APOE carriers. Her research has been highlighted in Alzheimer's literature. Dr. Sacco was honored with the World Stroke Organization, Global Leadership Award. He is also Co-Investigator studying disparities in stroke outcomes and care delivery in patients with Atrial Fibrillation. Our up and coming Collaborator Joyce Gomes-Osman's transcranial magnetic stimulation (TMS) research has been an instrumental addition to our cross-disciplinary collaborations. While Dr. Jiang's laboratory collaborator Dr. Wang has been contributing to her research correlating the retina and memory change, he became an official McKnight Collaborator this year. Although Dr. Rundek just joined our research leadership team, she has already made important scientific contributions through her active collaborations with national and international groups and consortia on subclinical atherosclerosis and cognitive impairment. Lastly, the abundance of data from the Northern Manhattan Study (NOMAS) has resulted in an array of research projects and manuscripts involving the relationships of lifestyle, heart and brain health in aging. The publication *Leisure time physical activity associates with cognitive decline: the Northern Manhattan Study* concluded that a low level of leisure-time physical activity is independently associated with greater decline in cognitive performance over time across domains. Other research using NOMAS data includes *Sleep disturbances and cognitive decline in the Northern Manhattan Study* which found that sleep symptoms led to worse cognitive performance and predicted decline in executive function in the community-based NOMAS cohort. Another journal article, *Ideal Cardiovascular Health and Cognitive Aging in the Northern Manhattan Study* reported the number of ideal cardiovascular health metrics was associated with less decline in the domains of processing speed and, to a lesser extent, of executive function and episodic memory. In conclusion, ideal cardiovascular health promotion benefits brain health and cognitive aging. The article *MRI markers predict cognitive decline assessed by telephone interview: the Northern Manhattan Study* concluded that simple and short telephone cognitive assessments can quickly detect decline associated with white matter lesions and smaller brain volumes and may be used as an early screening cognitive tool.

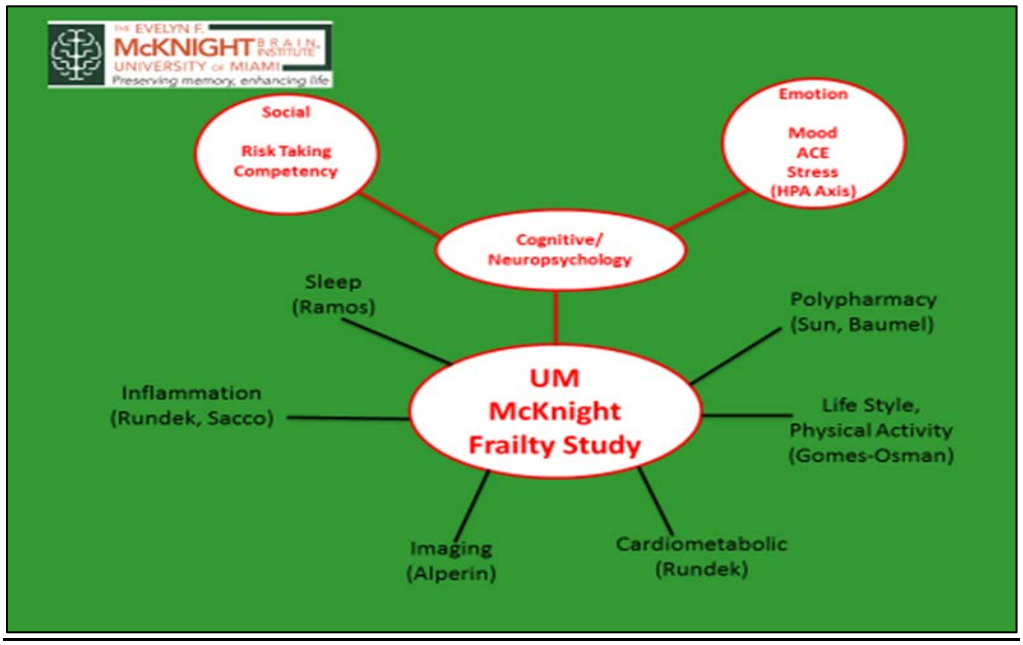
<u>McKnight Brain Aging Registry</u>

Dr. Wright, **Dr. Levin**, **Dr. Alperin** and **Carolina Mendoza-Puccini** spent the year perfecting the McKnight Brain Aging Registry protocol, manual of procedures, and neurocognitive and MRI components. A dedicated team at each of the four McKnight Brain Institutes worked together to tweak even the smallest aspect to ensure a solid and valid research study would result from their efforts. During weekly conference calls we have concentrated on finalizing the protocol, identifying barriers and resolving them. We compiled a list of potential research candidates and have begun study recruitment. The first research participants will be enrolled in the study in early 2017.

Dr. Levin has made significant progress organizing the McKnight Registry in the REDCap database in order to foster more interdisciplinary research in age-related memory loss. The McKnight Registry currently has over 400 study participant entries with detailed demographic, neurologic, neuroimaging, neuropsychological and laboratory data that will serve as a valuable resource for research collaborations. Another accomplishment for Dr. Levin this year is her involvement as the UM site Principal Investigator for the McKnight Brain Aging Registry cognitive component.

McKnight Frailty Study

Dr. Levin and her team of neuropsychologists and trainees initiated the University of Miami McKnight Frailty Study. Beginning in the fall, all individuals referred for neuropsychological evaluations for memory and cognitive complaints receive a formal frailty evaluation as part of their clinical assessment. Each individual receives recommendations to reduce frailty symptoms. The objectives of the study are to identify those most at risk for developing the frailty syndrome; identify the most sensitive biomarkers (behavioral, blood biomarkers, imaging) linking cognition and frailty; understand the inter-relationship between frailty, exercise and cognition; develop interventions targeting frailty symptoms; and to link the current findings to other McKnight Institute multicenter collaborative studies. In addition, Dr. Levin has initiated a community outreach program to introduce the concept of frailty and educate those at risk (pre-frail) on the detection and prevention of this symptom complex.



MRI Markers of Aging-Related Brain Loss

Dr. Alperin is working on several research projects to ascertain if there is a normative pattern of aging-related brain volume loss. His approach is to refine the measurement of annual brain loss by calculating separate mean rate for consecutive decades. This provides information on

how annual rate of loss is changing with age progression. He then further refines the estimate using a nonlinear (spline) approach, and identifies specific critical ages when a change in trend has occurred. He uses FreeSurfer, one of the most comprehensive tools for quantitative study of cortical and subcortical anatomy atlas-based guided brain parcelation. Thus far, some findings include: a) improved precision of normative annual rates of volume loss for cortical and deep brain structures; b) the neocortex ages slower than deep GM structures (Entorhinal cortex); c) volume loss of the hippocampus accelerates around 70 years old with loss rates among the highest measured (in order of 1% per year); d) increased rate of ventricular enlargement occurs at the same time; e) rates of brain loss of some regions slow down at a later age (e.g., parietal lobe); and f) that normative aging is not driven by degenerative processes that lead to dementia.

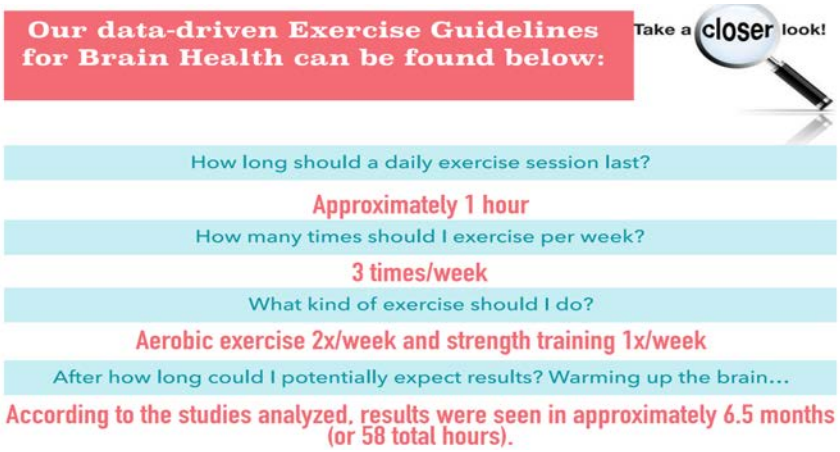
<u>Elucidation of the origin of spaceflight-induced visual impairment in astronauts.</u>
Dr. Alperin and his team presented the results of their study *Role of Cerebrospinal Fluid in Spaceflight-Induced Visual Impairment and Ocular Changes* at the annual meeting of the Radiology Society of North America (RSNA). The RSNA news press release was publicized worldwide. Additionally Dr. Alperin received a second award from NASA to assess the efficacy of head town tilt (HDT) bed rest study as a ground analogue for spaceflight-induced visual impairment syndrome in astronauts.

<u>Biomarkers in Alzheimer's Disease</u>
Dr. Sun's findings thus far were published in *Alzheimer's & Dementia* and highlighted in the journal *Nature Reviews Neurology* in July, 2016. In this study, she examined the levels of CSF neurogranin (Ng), a post-synaptic marker, in the APOE ε4 carriers and non-carriers with normal cognition, mild cognitive impairment (MCI) and AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. She showed that CSF Ng levels were significantly elevated in the APOE ε4 carriers with MCI, as compared to that of the APOE ε4 non-carriers with MCI. The levels of CSF Ng were significantly associated with APOE ε4 status independently of age, education and gender. This is the first human study to provide in vivo evidence that the early synaptic dysfunction is detected in the APOE ε4 carriers at risk of Alzheimer's disease. The level of CSF Ng in the APOE ε4 carriers may be a clinical biomarker for early diagnosis of MCI and provide timing for potential early interventions. The NIH K-grant related to the project has been submitted to the National Institute on Aging (NIA) and positively reviewed (although not funded). The grant will be revised according to the reviewers' comments and resubmitted in 2017.

Disparities in Stroke Outcomes and Care Delivery in Patients with Atrial Fibrillation (AF):
Dr. Rundek was just awarded $800,000 to study health disparities in elderly individuals with Atrial Fibrillation (AF). **Dr. Sacco** will participate as a Co-Investigator. This project aims to identify race/ethnic and gender disparities in stroke care for elderly patients with AF and to propose intervention to reduce these disparities and improve quality of care delivered to elderly patients with AF. The effect of AF on memory loss and cognitive decline is planned for the continuation of this study.

Dr. Sacco was recently honored with the World Stroke Organization's (WSO) President's 2016 Award for Global Stroke Leadership. The prestigious award was presented on October 27 at the WSO's 10th World Stroke Congress in Hyderabad, India. The World Stroke Congress attracts acclaimed international stroke specialists and provides participants opportunities to refine their skills and knowledge in the field of stroke, as well as providing excellent opportunities to strengthen scientific collaborations to improve the care of stroke victims throughout the world.

Exercise Guidelines for Brain Health
After a thorough review of research study results, **Dr. Gomes-Osman** has begun working on a large-scale quantitative systematic review to produce a booklet titled *Exercise Guidelines for Brain Health.* She is avidly recruiting for several clinical studies on brain plasticity involving transcranial magnetic stimulation (TMS). This research using TMS aims to harness neuroplasticity in the form of non-invasive brain stimulation and exercise, and assess its effects on the human nervous system. One of her projects seeks to explore whether short-term exercise (1 month) alters brain physiology and cognitive performance. Another project is to develop evidence-based, dose-specific recommendations to prescribe physical exercise to promote brain health. She has also partnered with our McKnight research team to recruit and enroll study participants for the McKnight Brain Registry. Our efforts to join forces between various research teams to collaborate on study recruitment will ensure the number of subjects needed for vigorous research enrollment this coming year.



The University of Miami American Heart Association/Bugher Center of Excellence
The *Institute of Medicine (IOM) Report on Cognitive Aging* recommended that individuals and families become physically active and that opportunities for physical activity are available. This research project led by **Dr. Wright** (until November of 2016; Dr. Sebastian Koch, Professor of Clinical Neurology and a stroke neurologist has assumed a role of PI after Dr. Wright's departure) is a phase 2A randomized clinical trial aimed to test the effect of physical exercise

and cognitive training on improvement in cognitive memory. Findings from this study have the potential to guide in the development of non-pharmacological interventions which may improve cognition post-stroke in older adults; reduce disability related to cognitive impairment; and promote optimal cognitive and physical health in older persons that could greatly increase the quality of life of stroke patients. This study also explores the relationship between compliance and multiple variables including mood and health related quality of life, and potential social and environment barriers to physical, cognitive and social activities.

CREATE IV (Center for Research and Education on Aging and Technology Enhancement)

Dr. Czaja has accomplished a great deal in moving forward to increase research on quality of life for aging adults through a NIA/NIH funded collaborative research center. One focus of the Center on Aging is ensuring that older adults are able to use and realize the benefits of technology. She received the American Psychological Association (APA) Inaugural Recipient Prize for Interdisciplinary Team Research, CREATE Team in October of 2016. With the aging population exponentially increasing, her research is vital. CREATE strives to develop and evaluate interventions and design solutions to promote successful technology adoption among older adults. Its objectives are to expand our understanding of the needs and preferences of older adults with respect to technology; barriers to access and problems with existing and emerging systems; how person characteristics influence person/technology interactions; design strategies that promote successful technology uptake; and how access to and interactions with technology impact the health, quality of life and independence of older adults.

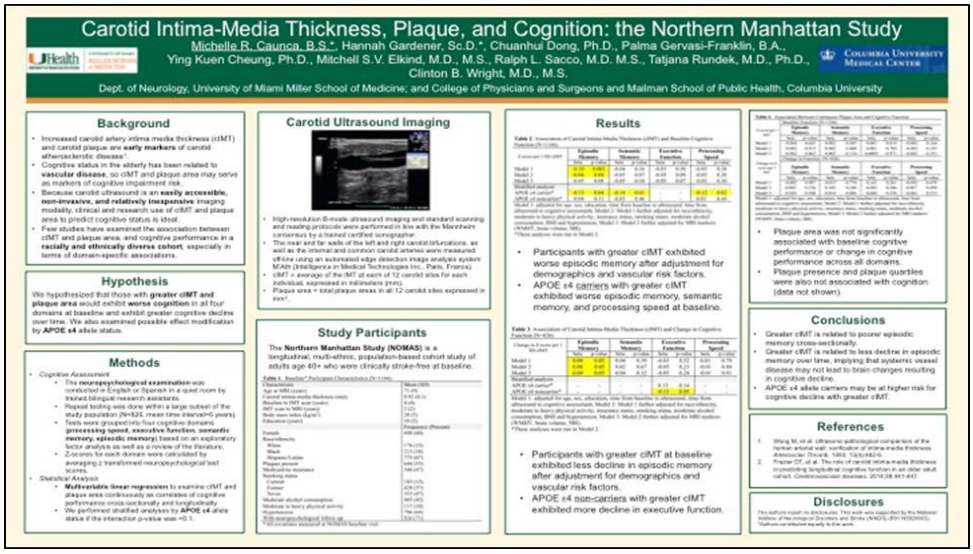
Retinal Microvascular Dysfunction in Pre-MCI, MCI and Late MCI Patients

This year, **Dr. Jiang's** team (including our new McKnight Collaborator **Dr. Wang**) was the first to study the changes of retinal microcirculation, microvascular network density and microstructural alterations with aging, and with or without cognitive function decline. Their findings revealed significant decreases with age in retinal microvascular density, inner retinal layer thickness and retinal venular blood flow velocity. In addition, findings showed significantly decreased retinal microvascular network density in patients with AD and MCI compared to age-matched normal controls, which correlates with thinning of ganglion layer representing neurodegeneration. These findings were presented at the International Retinal Conference in Guangzhou, China in November of 2016 and at the North American Neuro Ophthalmology Society (NANOS) in Tucson, Arizona in early 2016. The manuscript with these results is currently in review.

Carotid Intima-Media Thickness, Plaque, and Cognition: The Northern Manhattan Study

Michelle Caunca is a second year MD/PhD student and the McKnight Brain Institute sponsored trainee who will spend 3-years with our McKnight Brain Institute working on her PhD in MRI markers of cognitive decline. Her poster on the association between subclinical carotid disease and cognitive decline in the NOMAS was chosen by the American Neurological Association (ANA) and the International Stroke Conference (ISC) for presentation at their annual meetings in 2016. She was also given a travel award to attend the ANA meeting and received an Internal Pilot Study grant from the University of Miami Scientific Awards Committee (SAC). She has just submitted her

F30 student project proposal on MRI markers of cognitive decline to the NINDS under Mentorship of Dr. Rundek. Dr. Wright will continue to serve on her Mentorship team in his new position at the NINDS.

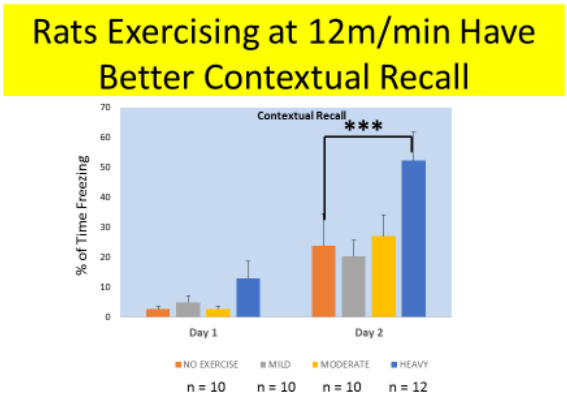


B. Basic and Translational Science Research

The McKnight basic and translational science Members and Collaborators have been working on designing behavioral measures to test the relationship between stroke, exercise and cognition. Additionally, their basic science laboratory has been performing research on effective neuroprotective agents and pharmacological preconditioning in the field of cerebral ischemia and cognitive decline.

<u>Ischemic Preconditioning: Mechanisms of Neuroprotection</u>

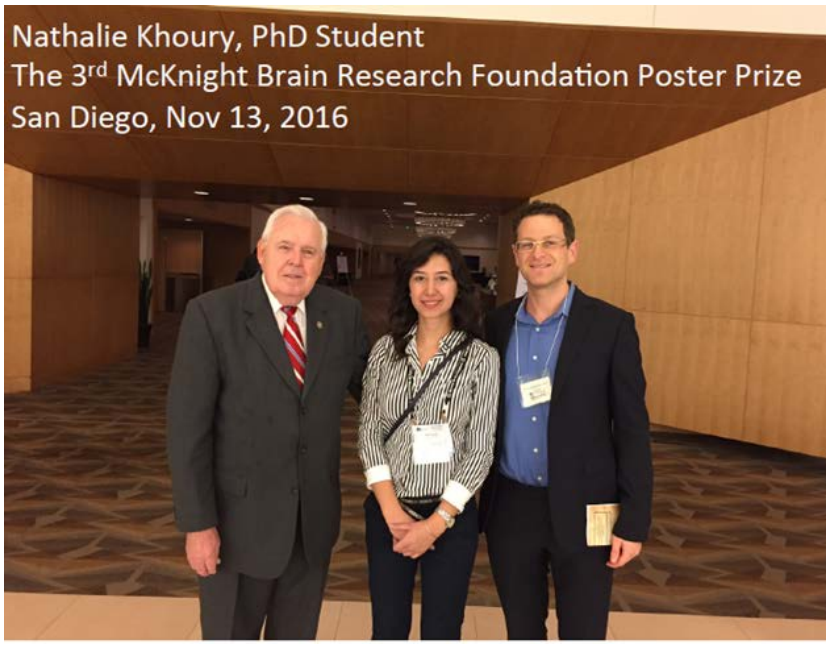
Dr. Perez-Pinzon, **Dr. Dave** and their basic and translational science team developed and established a rat model of white matter disease; which will be used as a model of vascular cognitive impairments for future studies. Their main focus this year was to evaluate the effects of physical exercise on cognitive outcomes following two models of cerebral ischemia using rodent models of focal (ischemic stroke) and global (cardiac arrest) cerebral ischemia. Their work was presented at the International Stroke Conference in California and at the Symposium on Neuroprotection and Neurorepair in Germany this year. They have consistently shown the beneficial effect of heavy exercise on



cognitive outcomes in comparison to no or mild to moderate exercise (as seen below). They are currently working on three peer-reviewed publications from these studies.

<u>Elucidating the molecular mechanism behind the long-term cerebral ischemic tolerance mediated by resveratrol preconditioning</u>

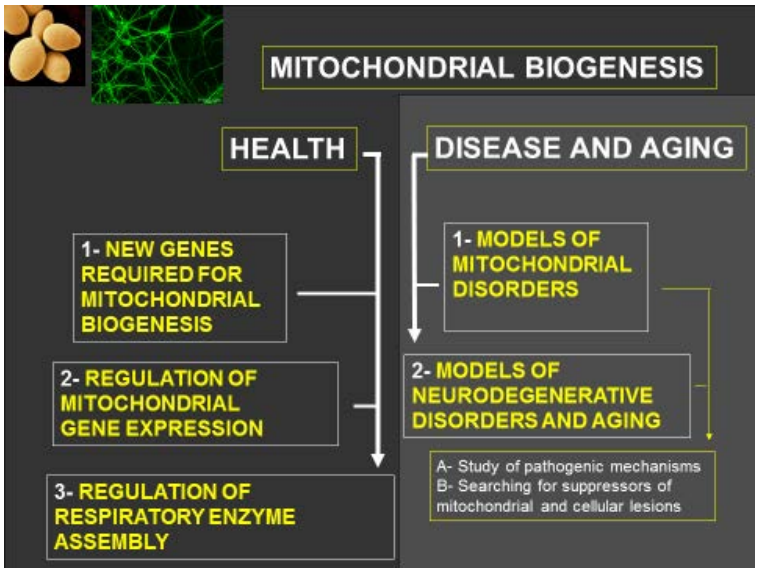
Nathalie Khoury a PhD student in **Dr. Perez-Pinzon's** laboratory was awarded a pre-doctoral fellowship grant from the American Heart Association through 2018.



She also received third place for presenting her poster "Elucidating the molecular mechanism behind the long-term cerebral ischemic tolerance mediated by resveratrol preconditioning" (see photos below) at the Evelyn F. McKnight Brain Research Foundation Poster Reception at the 2016 Society for Neuroscience meeting in San Diego, Ca.

<u>Mitochondrial Biogenesis in Health and Disease</u>

Dr. Barrientos has devised a comprehensive study across two research model organisms of polyQ disorders to explore the protective properties of NAD+ biosynthetic enzymes and their interplay with protective strategies based on enhancement of mitochondrial biogenesis. He proposes that whereas the mechanism involved does not necessarily require mitochondrial OXPHOS function, an enhancement of mitochondrial biogenesis would enhance efficacy, act additively or synergistically and allow the cells to afford stronger protection (see picture below). His team believes the studies will have a significant impact not only on the neurodegeneration field but also on the fundamental biology of molecular chaperones and mitochondrial biogenesis and



physiology in general. He was awarded a National Institutes of Health (NIH)/National Institute of General Medical Sciences (NIGMS) grant for the study of *Mitochondrial Biogenesis in Health and Disease* which will allow him ample time to forge ahead with his promising research without having to continuously seek funding.

C. Educational Programs

In her second year as the Evelyn F. McKnight Brain Institute Education Director, **Dr. Sun** has been committed to promoting cognitive neuroscience educational programs to graduate students, medical students, Residents, Fellows, faculty and research staff. She provided numerous learning opportunities for the multi-disciplinary departments with whom we collaborate. See Tables 1, 2 and 3 in section 12 of the report. She also worked to increase public awareness of the normal aging process and pathological brain disorders. An endeavor she began last year came to fruition when the Resident Neurology Program at the University of Miami approved a mandatory two-week rotation for neurology residents in the Memory Disorders Clinic. This will have a profound training and educational effect by stimulating the interests of future clinicians in the field of cognitive aging.

The joint venture with the Center on Aging has begun by merging the McKnight Research Seminar series with the Center on Aging's Scientific Lecture series. This provides a tremendous opportunity for the McKnight cross-disciplinary Members, Collaborators and trainees to gain access to the ground-breaking research taking place at the Center on Aging as well as to learn from outside speakers and establish future collaborations.

In November of this year, we held a McKnight Research Seminar in which we showcased the research of the McKnight Institute at the University of Miami. Faculty, students and trainees were in attendance and had the opportunity to see the results and outcomes of the important work being done by the Institute. The presentations surely spawned ideas for future collaborations and research projects. These will be discussed and generated at the next McKnight Members and Collaborators meeting.

In December of 2016, **Dr. Rundek** presented the Miami Cognitive Research and McKnight Brain Institute at an event in a Boca retirement community that was attended by close to 100 participants. She took questions from the audience, arranged for several patients to be seen in our Miami Cognitive Clinic and Boca Neurology Clinic, and created an interest in aging research and research participation. Several research opportunities in investigating anti-viral and anti-infectious medications in memory loss and the use of technology as a negative memory enforcement have been created at that event. Dr. Rundek will follow up with these research ideas and opportunity with the Boca community in 2017.

2. Selected Publications by Institute Members, Collaborators & Trainees (Peer Reviewed)

In 2016, numerous research articles were accepted by peer-reviewed journals for publication written by the UM McKnight Brain Institute team. McKnight Members, Collaborators and trainees across disciplines collaborated on at least 10 publications. Amongst the prestigious scientific journals showcasing our research were 3 articles published in the journal *Neurology.* Some other journals representing work done by the UM McKnight Institute include: *Stroke*, *Journal of the American Heart Association*, *American Journal of Preventive Medicine*, *Sleep*, *Journal of the American Alzheimer's Association*, *American Journal of Human Genetics, American Journal of Geriatric Psychiatry*, *Molecular Neurodegeneration* and the *International Journal of Epidemiology*. Here is a list of the 2016 publications.

Cross-Disciplinary Collaborative Publications

Gardener H, **Wright CB**, **Dong C**, Cheung K, DeRosa J, Nannery M, Stern Y, Elkind MS, **Sacco RL**. Ideal Cardiovascular Health and Cognitive Aging in the Northern Manhattan Study. Journal of the American Heart Association. 2016;5:e002731.

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Sun X, **Dong C**, **Levin B**, **Crocco E**, Loewenstein D, Zetterberg H, Blennow K, **Wright CB**. APOE 4 carriers may undergo synaptic damage conferring risk of Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2016;12:1159-1166.

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Willey JZ*, **Gardener H***, **Caunca MR**, Moon YP, **Dong C**, Cheung YK, **Sacco RL**, Elkind MSV, **Wright CB**. Leisure time physical activity associates with cognitive decline: the Northern Manhattan Study. Neurology. 2016;86:1897-1903. (*Shared first authorship.)

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Trainee (as first authors) Publications

Campos Y, **Diaz M**, Rossetti M, **Dong C**, **Crocco E**, Loewenstein D, **Levin B**, **Sun X**, **Wright C**. Framingham risk score and cognitive outcomes in cognitively normal and subjective memory complaint subjects. Neurology. 2016;86;16 Supplement;2016: P1-090. Published abstract from AAN Annual Conference, Vancouver BC, 2016. Refereed.

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Clinical or Population-Based Publications

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4. Presentations at Scientific Meetings

Cross-Disciplinary Collaborative Presentations

Gardener H*, **Caunca MR***, **Dong C**, Cheung YK, Elkind MSV, **Sacco RL**, **Rundek T**, **Wright CB**. Markers of Carotid Atherosclerosis and Cognition: the Northern Manhattan Study. In preparation. ISC, Los Angeles and ANA, MD 2016. (*Shared first authorship).

Gutierrez J, Cheung K, **Bagci A**, **Rundek T**, **Alperin A**, **Sacco R**, Elkind M, **Wright C.** Brain arterial diameters as biomarkers of cognitive performance: Results from the Northern Manhattan Study. American Academy of Neurology, April 15-21, 2016 - Oral Presentation: Vancouver, BC, Canada.

Zeki Al Hazzouri A, **Caunca MR**, Cespedes S, **Dong C**, Elkind, MSV, **Sacco RL**, DeCarli, C, **Wright CB**. Brain and subclinical brain infarcts, but not white matter lesion load, are associated with depressive symptoms: the Northern Manhattan Study. Poster Session at the Epidemiologic Congress of the Americas, June 21-24, 2016 - Miami, FL.

Dueker ND, Guo S, Beecham A, Wang L, **Blanton SH**, **Dong C**, Cabral D, **Rundek T**, **Sacco RL**. Common and rare variants in previously identified linkage region on chromosome 12p associated with left ventricular mass in Dominican families. Poster Presentation at the 66th Annual Meeting of the American Society of Human Genetics, Vancounver, BC, Canada, October 18-22, 2016, #641/T.

Wang L, Dueker N, Beecham A, **Blanton SH**, **Rundek T**, **Sacco RL**. Sequencing identifies new variants and new genes for carotid intima-media thickness in Dominican Republicans. Poster presentation at the 66th Annual Meeting of the American Society of Human Genetics, October 18-22, 2016 - Vancounver, BC, Canada.

Trainee (as first author) Presentations

Campos Y, **Diaz M**, Rossetti M, **Dong C**, **Crocco E**, Loewenstein D, **Levin B**, **Sun X**, **Wright C**, Framingham risk score and cognitive outcomes in cognitively normal and subjective memory complaint subjects. Neurology. 2016;86;16 Supplement (2016): P1-090. Published abstract from AAN Annual Conference, Vancouver BC, 2016. Refereed.

Caunca MR, **Gardener H**, **Dong C**, Gervasi-Franklin P, Cheung YK, Elkind MSV, **Sacco RL**, **Rundek T**, **Wright CB**. Carotid Intima-Media Thickness and Cognition: the Northern Manhattan Study. International Stroke Conference, February 17- 19, 2016 - Poster Presentation: Los Ángeles, CA.

Caunca MR, **Gardener H**, **Dong C**, Gervasi-Franklin P, Cheung YK, Elkind MSV, **Sacco RL**, **Rundek T**, **Wright CB**. Carotid Intima-Media Thickness, Plaque, and Cognition: the Northern Manhattan Study. American Neurological Association, October 16-18, 2016 - Poster Presentation: Baltimore, MD.

Cohan CH. White matter injury and repair at the McKnight Inter-Institutional Meeting. Tucson, Arizona, April 29th, 2016.

d'Adesky N, de Rivero Vaccari JP, Bhattacharya P, Bramlett H, **Perez-Pinzon MA**, **Raval AP**. Inflammasome activation in the hippocampus of reproductively senescent female rats is down-regulated by Estrogen Receptor Subtype Beta at the Eastern-Atlantic Student Research Forum. Miami, FL, March 2-5, 2016.

d'Adesky N, de Rivero Vaccari JP, Bhattacharya P, Bramlett H, **Perez-Pinzon MA**, **Raval AP**. Inflammasome activation in the hippocampus of reproductively senescent female rats is down-regulated by Estrogen Receptor Subtype Beta at the Center on Aging, University of Miami. Miami, FL, April 11th, 2016.

Khoury N, **Koronowski KB**, Saul I, **Dave KR, Young JI**, **Perez-Pinzon MA**. Elucidating the molecular mechanisms behind the long-term cerebral ischemic tolerance mediated by

resveratrol preconditioning at the Society for Neuroscience Conference. San Diego, November 2016. Abstract # 141.21. Abstract was not refereed.

Koronowski K, **Stradecki H**, Morris-Blanco K, Garrett T, **Perez-Pinzon M.** Effects of Sirt5 deletion and PKCε activation on the brain primary metabolome at the 9th International Symposium on Neuroprotection and Neurorepair. Leipzig, Germany, April, 2016. Abstract # 2-25.

Rehni AK, **Shukla V**, **Dave KR**. Inhibition of glucose transporters attenuate recurrent hypoglycemia-induced increase in intra-ischemic acidosis in insulin-treated diabetic rats at the Society for Neuroscience Conference. San Diego, November, 2016. Abstract # 790.09. Abstract was not refereed.

Shukla V, **Rehni AK**, **Dave KR**. Increased intra-ischemic acidosis in recurrent hypoglycemia exposed rats may activate acid-sensing ion channels in vascular smooth muscle cells at the Society for Neuroscience Conference. San Diego, November, 2016. Abstract # 231.05. Abstract was not refereed.

Stradecki H, **Cohan C**, **Youbi M**, **Dave K**, **Perez-Pinzon M**. Physical exercise after cardiac arrest reduces cognitive deficits and synaptic dysfunction. 9th International Symposium on Neuroprotection and Neurorepair in Leipzig, Germany. April 2016. Abstract # 4-12.

Youbi M, **Cohan CH**, **Stradecki HM**, **Tiozzo E**, **Dave KR**, **Wright CB**, **Sacco RL**, **Perez-Pinzon MA**. Moderate Physical Exercise Promotes Cognitive Recovery Following Focal Cerebral Ischemia in Rats. International Stroke Conference, February 17- 19, 2016 - Poster Presentation: Los Ángeles, CA.

Youbi M, **Cohan C**, **Stradecki H**, **Tiozzo E**, **Dave K**, **Wright C**, **Sacco R**, **Perez-Pinzon M**. Moderate physical exercise promotes cognitive recovery following focal cerebral ischemia in rats at the 9th International Symposium on Neuroprotection and Neurorepair. Leipzig, Germany, April, 2016. Abstract # 4-14.

<u>Clinical or Population-Based Presentations</u>

Alperin N. Is There a Normative Pattern of Aging-Related Brain Volume Loss? At the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. Miami, FL, November 30th, 2016.

Alperin N. Role of Cerebrospinal Fluid in Spaceflight-Induced Visual Impairment and Ocular Changes at the annual meeting of the Radiology Society of North America (RSNA) Chicago, IL, December 2016.

Alperin N. Cranio-Spinal CSF Pulsation: Origin and Clinical Relevance. 1st Annual CSF Disorders

Symposium, Warren Alpert Medical School of Brown University, Providence, RI, June 25, 2016.

Banerjee N, Ironson G, **Levin B**. Executive Functioning, Coping, and Depression in HIV (2016, February). Poster presented at: 44th Annual Meeting of the International Neuropsychological Society, 2016 - Poster Presentation: Boston, MA. Journal of the International Neuropsychological Society. 2016;22.

Blanton SH, Lang S, Dillingham P, Hecht JT. Family-based association analysis of whole exome sequencing data identifies evidence for major role of focal adhesion pathway. Oral Presentation at the 13th International Congress of Human Genetics (ICHG 2016), April 3-7, 2016 - Kyoto, Japan.

Cabral DLF, Barros NB, **Gomes-Osman J**. Repetitive TMS as a therapeutic tool to combat cognitive aging: preliminary results of a systematic review at the Brazilian International Physical Therapy Congress, October 15-18, 2016 - Poster Session: Salvador, Brazil

Cabral DLF, Barros NB, **Gomes-Osman J**. Theta-Burst Stimulation to probe and modulate circuits in the aging brain: preliminary results of a systematic review. Brazilian International Physical Therapy Congress, October 15-18, 2016 - Poster Session: Salvador, Brazil.

Cabral DLF, Richardson M, Barros NB, Oliveira AC, **Gomes-Osman J**. Exercise to promote brain health in older adults: preliminary results of a systematic review for dose-specific recommendations at the XXI Brazilian Physical Therapy Congress, August 31st-September 03, 2016 - Poster Session: Recife, Brazil.

Cabral D, Richardson M, **Gomes-Osman J**. Physical exercise as a potential tool to promote brain health in older adults with and without cognitive deficits: a review of the literature for dose-specific recommendations at the University of Miami Center on Aging, April 11, 2016 - Poster Session: Miami, Florida.

Czaja SJ. Age-Related Changes in Cognition: Risks and Opportunities for Older Adults and Communities at the Annual America Society for Aging Conference. Washington, DC, March, 2016.

Czaja SJ. Computerized simulations of everyday tasks as outcomes measures in treatment measures. Educational track Symposium at the Cognition in Schizophrenia: A Satellite Meeting of the Schizophrenia International Research Society. Florence, Italy, April, 2016.

Czaja SJ. Discussant: Aging with Technologies: Fundamental Positions, Potential, and Challenges at the German Society of Gerontology and Geriatrics. Stuttgart, Germany, September, 2016.

Czaja SJ. Symposium: Forty-Five years of Influence of the Lifespan Developmental Approach – Past, Present, and Future: Methodological Issue at the American Psychological Association Annual Meeting. Denver, Colorado, August, 2016.

Czaja SJ. Symposium: Meeting the Needs of LGBT Individuals across the Lifespan at the American Psychological Association Annual Meeting. Denver, Colorado, August, 2016.

Czaja SJ. Technology and Older Adults Keynote Address at the German Society of Gerontology and Geriatrics. Stuttgart, Germany, September 2016.

Czaja SJ. Technology to Support Independent Aging. Symposium at the HCI International Conference. Toronto, Canada, July, 2016.

Elfassy T, Glymour M, Kershaw K, Carnethon M, Lewis CE, **Zeki Al Hazzouri A**. Sustained Poverty and Increases in Body Mass Index Over Time: Sex and Race Differences in the CARDIA Study. Poster Session at the 2106 Epidemiologic Congress of the Americas. Miami, FL, June 21-24, 2016.

Gomes-Osman J, Roach KE, Tibbett JA, Brisson KR, Field-Fote E. Functional task practice augmented with somatosensory stimulation is superior to resistance training for improving hand strength and function in persons with tetraplegia, IV Step 2016: Prevention, Prediction, Plasticity, and Participation, Cleveland, OH, July 14-19, 2016.

Hecht JT, Chiquet B, Yuan Q, Maili L, Plant R, Letra A, **Blanton SH**. The crispld2 story: From gene function to new NSCLP candidate gene identification. Poster Presentation at the 13th International Congress of Human Genetics (ICHG 2016). April 3-7, 2016 - Kyoto, Japan.

Hu Y, **Jiang H**, Lam B, Delgado S, **Wang J**, Rammohan K. Relationship between fatigue severity score and papillary indices in patients with multiple sclerosis at the 141st Annual meeting of the American Neurological Association. Baltimore, MD, October 16-18, 2016.

Jiang H. Advance ophthalmic imaging of ocular microvasculature in age- related memory loss at the McKnight Inter-Institutional Meeting. Tucson, Arizona, April 29th, 2016.

Jiang H. Correlation of intraretinal thickness and microvasculature in healthy subjects at the 2016 ARVO annual meeting. Seattle, Washington, May 1-5, 2016.

Jiang H. In vivo characterization of retinal microvascular impairment in age-related memory loss at the Ninth McKnight Brain Inter-Institutional meeting. Tucson, Arizona, April 27-29, 2016.

Jiang H. Quantitative analysis of retinal microvascular network in Alzheimer's disease at the 42nd North American Neuro Ophthalmology Society (NANOS). Tucson, Arizona, Feb. 2 -March 3, 2016.

Jiang H. Retinal microvascular impairment in Neurologic diseases at the International Retinal Conference-ZOC 2016. Guangzhou, China, November 4-7, 2016.

Levin B. The role of frailty in normal cognitive aging at the McKnight Inter-Institutional Meeting. Tucson, Arizona, April 29th, 2016.

Lippman S, **Gardener H**, **Rundek T**, Azizi S, Santiago M, Elkind M, **Sacco R**, **Wright C**, **Ramos A**. Sleep Duration is Associated with Depression in the Northern Manhattan Study. American Academy of Neurology, April 15-21, 2016 - Oral Presentation: Vancouver, BC, Canada.

Pandya A, Tekin M, O'Brien AH, **Blanton SH**, Arnos KS. Exploring the characteristics of hearing loss and its etiology in a unique subset of families with hereditary deafness. Poster Presentation at the 66th Annual Meeting of the American Society of Human Genetics, October 18-22, 2016 - Vancounver, BC, Canada.

Sacco RL. Blood Pressure Goals in Stroke Prevention at the Neurology Update 2016. Miami Beach, FL, January 30, 2016.

Sacco RL. FL-PR Registry: In-Hospital Outcomes, and New Pre-Hospital at All SPIRP 2016 Conference. New York, NY, June 22, 2016.

Sacco RL. Fourth Annual Florida Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Stakeholder Meeting. Winter Park, FL, August 26, 2016.

Sacco RL. Primary and Secondary Prevention of Stroke at Mayo Clinic Cardiology Update at South Beach. Miami Beach, FL, January 20, 2016.

Sacco RL. Quality Improvement and Stroke Disparities at the Neurology Update 2016. Miami Beach, FL, January 30, 2016.

Sacco RL. Stroke Innovations in Treatment and Prevention at Palm Beach Round Table. West Palm Beach, FL, January 8, 2016.

Sacco RL. University of Miami Bugher Center Updates for the ASA/Bugher Centers for Excellence in Stroke Research. Miami, FL, October 20, 2016.

Schneider HL, **Sun-Suslow N**, Anderson S, **Segalà L**, Luca C, Jagid J, Singer C, **Levin B**. Assessing DBS candidacy in idiopathic Parkinson's disease: Does RBD influence cognitive outcome? Poster session at the 44th Annual Meeting of the International Neuropsychological Society, 2016 - Poster Session: Boston, MA. Journal of the International Neuropsychological Society. 2016;22.

Segalà L, Delgado SR, Rammohan K, Ortega MR, Hoffman M, **Rooks J**, **Sun-Suslow N**, Schneider HL, Forte M, **Levin BE**. The Effects of Dispositional Optimism on Cognition in Multiple Sclerosis. Poster presented at: 44th Annual Meeting of the International Neuropsychological Society, 2016 - Poster Presentation: Boston, MA. Journal of the International Neuropsychological Society. 2016;22.

Sivasankaran K, Mehta A, Mash DC, Beecham G, Martin ER, Vance J, **Young JL**. Aberrant DNA methylation of the non-coding VTRNA2-1 (MIR886) gene in Parkinson disease. The American Society of Human Genetics 2016 Annual Meeting. Vancouver, CA, October 18-22, 2016.

Sun X. Women's Initiative Health Series: Alzheimer's/Dementia, Holland & Knight LLP. Oct, 2016.

Sun-Suslow N, Schneider HL, Anderson S, **Segalà L**, Luca C, Jagid J, Singer, C, **Levin B**. Components of metabolic syndrome in predicting Deep Brain Stimulation (DBS) outcome in idiopathic Parkinson's disease patients. Poster presented at: 44th Annual Meeting of the International Neuropsychological Society, 2016 - Poster Presentation: Boston, MA. Journal of the International Neuropsychological Society. 2016;2.

Tao F, Beecham G, Rebelo A, **Blanton S**, Abreu L, Baas F, Choi BO, Pareyson D, Reilly M, Shy M, Zuchner S, Inherited Neuropathy Consoritum. Genome-wide association study identifies potential genetic modifiers in Charcot-Marie-Tooth Disease type 1A. Poster presentation at the 66th Annual Meeting of the American Society of Human Genetics, October 18-22, 2016 - Vancounver, BC, Canada.

Vangara S, Wong L, Guerra J, Loewenstein D, **Crocco E**, The Value of LASSI-L for Patients with Mild Cognitive Impairment and Metabolic Risk Factors, Eastern Atlantic Student Research Forum, Poster Presentation (ESRF), Miami, FL, 2016, refereed.

Willey JZ, Moon YP, Cheung YK, **Wright CB**, **Sacco RL**, Elkind MS. Physical Inactivity and Slower Gait Speed in an Elderly Multi-ethnic Population: The Northern Manhattan Study. International Stroke Conference, February 17- 19, 2016 - Poster Presentation: Los Angeles, CA.

Willey JZ, Moon YP, Marquez CE, **Sacco RL**, **Wright CB**, Elkind MS, Cheung YK. Physical Inactivity is a Strong Risk Factor for Stroke in the Oldest Old Findings from the Northern Manhattan Study. American Heart Association Epidemiology and Prevention and Lifestyle and Cardiometabolic Health, March 7-10, 2016 - Moderated Poster Presentation: Phoenix, AZ.

Wong L, Vangara, S, Bhatti B, **Crocco E**, Loewenstein D. Influence of Depression on Neuropsychological Testing in Patients Diagnosed with Mild Cognitive Impairment, Eastern Atlantic Student Research Forum (ESRF), 2016 - Poster Presentation: Miami, FL refereed.

Wright CB. Magnetic resonance imaging to characterize age cognitive decline in the oldest old at the McKnight Inter-Institutional Meeting. Tucson, Arizona, April 28th, 2016.

Basic Science Presentations

Barrientos A. Insights into the Mitoribosome Assembly Pathway at Gordon Conference Mitochondria and Chloroplasts Mount Snow. West Dover, VT, June 2016.

Barrientos A. Molecular biology of mitochondrial gene expression Co-organizer of an EMBO Workshop. Bro, Sweden, May 2016.

Moraes CT. Modulating mtDNA Heteroplasmy with Designer Nucleases at the United Mitochondrial Disease Foundation Annual Meeting. Seattle, WA, June, 2016.

Schatz M, **d'Adesky N**, Bhattacharya P, **Raval AP**, Dietrich WD, Bramlett H. Whole body vibration accelerates recovery of post-ischemic motor function in middle aged female rats at the Center on Aging, University of Miami. Miami, FL, April 11th, 2016.

Yeguez A, Lucas J, Diaz A, Bhattacharya P, **d'Adesky N**, de Rivero Vaccari JP and **Raval AP**. Inflammasome activation in the brain: is there a sex difference? At the Miami Winter Symposium. Miami, FL, January 22-25, 2016.

5. Presentations at Public (Non-Scientific) Meetings or Events

Clinical or Population-Based Presentations

Alperin N. The Origin of the Craniospinal CSF Pulsation: From Historical Perspective to Clinical Relevance. Grand Rounds, Department of Neurology, University of Miami. November 18, 2016.

Crocco E. Alzheimer's Disease and Caregiving Issues, Jewish Community Services of South Florida, Miami, FL, August, 2016.

Crocco EA. The Forget Me Not Tour-Panel Presentation, African Americans Against Alzheimer's/USAgainst Alzheimer's at Florida Memorial University. Miami, FL, May, 2016.

Czaja SJ. Aging and Cognition: The Role of Social Support at the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. Miami, FL, November 30, 2016.

Czaja SJ. CREATE Workshop: Health Care Technologies for Older Adults: Design, Adoption, Implementation & Training Issues. Instructor. University of Miami Miller School of Medicine. Center on Aging offices. February 25-26, 2016.

Czaja SJ. Growing Older Gracefully and Meet the Doc series at the Alumni Center. University of Miami, Coral Gables, FL. September 15, 2016.

Czaja SJ. The Prevalence of Family Caregiving and the Impact on Well-Being. Lecture to Geriatric Fellows at the University of Miami Miller School of Medicine. Center on Aging Offices. Miami, FL, October 17, 2016.

Czaja SJ. The Promotion of Successful Aging: Activities at the Center on Aging at the Women Guild Luncheon. Coral Gables, FL, March 7, 2016.

Czaja SJ. Transitioning to the next Chapter: Life beyond Work to the Greater Miami Chamber of Commerce. Alumni Center, University of Miami, Coral Gables. June 20, 2016.

Gomes-Osman J. Exercise for Brain Health: Plasticity and Data-driven Dose-specific Recommendations at the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. November 30, 2016.

Gomes-Osman, J. Partner at the Brain Fair Training the Brain Exhibit at the Organized and supervised University of Miami Department of Physical Therapy for Students to conduct an exhibit in an event open to the public raise awareness about the nervous system and the relationship between exercise and cognition. Miami, FL, 2016.

Gomes-Osman J. Theta Burst Stimulation of the Human Motor Cortex at the McKnight Journal Club. Miami, FL, June, 2016. Invited lecture.

Levin BE. Understanding Frailty in Normal Aging: The UM McKnight Registry at the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. November 30, 2016.

Merritt S. Dementias, recognizing associated behaviors and enacting the 'Silver Alert' system when someone with dementia is missing at the Miami Police Training Academy. Miami, Florida, June 6, 2016.

Merritt S. Dementias, recognizing associated behaviors and enacting the 'Silver Alert' system when someone with dementia is missing at the Miami Police Training Academy. Miami, Florida, July 18, 2016.

Merritt S. Dementias, recognizing associated behaviors and enacting the 'Silver Alert' system when someone with dementia is missing at the Miami Police Training Academy. Miami, Florida, September 9, 2016.

Merritt S. Dementias, recognizing associated behaviors and enacting the 'Silver Alert' system when someone with dementia is missing at the Miami Police Training Academy. Miami, Florida, November 16, 2016.

Rundek T. Aging, memory loss and cognition: Opportunity for community engagement in research through McKnight Brain Institute. Boca Retirement Home community lecture, Boca, FL, Dec 8, 2016

Sun X. Aging, Hypertension and Cognitive Decline at the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. November 30, 2016.

Zeki Al Hazzouri A. Social and Cardiovascular Determinants of Aging: A Life Course Perspective. At the Department of Clinical Sciences and Community Health, Unit of Medical Statistics, Biometry and Epidemiology, Universita Degli Studi Di Milano, Italy, October 21, 2016.

Basic Science Presentations

Dave K. Exercise Improves Post-stroke Cognitive Outcomes in Young and Elderly Animals at the University of Miami, Evelyn F. McKnight Brain Institute Annual Research Symposium. November 30, 2016.

Moraes CT. Biochemical and genetic basis of mitochondrial encephalopathies. From Pediatric Encephalopathy to Alzheimer's: Linking Mitochondria to Neurological Disease at the Neurobiology of Disease Workshop, Society for Neuroscience Annual Meeting. San Diego, CA, November, 2016.

Moraes CT. Manipulating mitochondrial DNA heteroplasmy with designer nucleases at Baylor College of Medicine, Department of Genetics Seminar Series. Baylor, TX, January, 2016.

Moraes CT. Manipulating the Mitochondrial Genome with Designer Nucleases. Genome Editing for Gene and Cell Therapy at the Herrenhausen Symposium. Hanover, Germany, November, 2016.

Moraes CT. Messing with mtDNA in vivo using mitochondrial targeted nucleases. Molecular biology of mitochondrial gene expression. Bro, Sweden, May 2016.

Moraes CT. Mitochondrial DNA double strand breaks cause a premature aging-like phenotype in mice at the Stem Cell Institute Seminar Series, University of Minnesota. Minneapolis, MN, November, 2016.
Moraes CT. Mitochondrial DNA Double-Strand Breaks: Consequences and Uses. University of Nebraska-Lincoln Biochemistry Department and Redox Biology Center. Lincoln, NE, September, 2016.

Moraes CT. Pharmacological and genetic approaches to treat mitochondrial diseases at the Workshop: Implication of metabolic and epigenetic modifications for neuroprotection: relevance to translational research. Fundação Santa Casa. São Paulo, Brazil. March, 2016.

6. Awards (Other)

Dr. Alperin received a second award from NASA in 2016 to assess the efficacy of head town tilt (HDT) bed rest study as a ground analogue for spaceflight-induced visual impairment syndrome in astronauts.

Dr. Barrientos received significant funding for his research in 2016. He was granted funding from the Muscular Dystrophy Association (MDA) for the research project *Role of cysteine rich proteins in mitochondrial cytochrome c oxidase biogenesis*. He was also awarded a grant from the Biomedical Laboratory Research & Development at the Veteran's Administration (VA) for to research *Slowing Proteotoxic Neurodegeneration by Boosting Mitochondrial Bioenergetics and* funding from the Army Research Office for his research project *Mitochondrial Regulation of Neurodegenerative Proteotoxic Stress*. Last and most important, Dr. Barrientos received a highly prestigious Maximizing Investigators' Research Award (MIRA), or R35 award, from the National Institute of General Medical Sciences (NIGMS). He will be researching *Mitochondrial Biogenesis in Health and Disease.*

Dr. Blanton was appointed to the University of Miami Academic Personnel Board (APB) and was also invited to chair the Clinical Genetics and Dysmorphology 3 session, 13th International Congress of Human Genetics (ICHG2016) in Kyoto, Japan in April of 2016.

Michelle Caunca, the McKnight Student representative received an Internal Pilot Study grant from the University of Miami Scientific Awards Committee (SAC) for Phase II of a pilot study that will be testing the feasibility of a mobile-friendly website curriculum with a small group of stroke caregivers over the course of three months. She also received a travel award from the American Neurological Association (ANA) to attend this year's meeting and present the following abstract and poster: "Carotid Intima-Media Thickness, Plaque, and Cognition: The Northern Manhattan Study".

Dr. Czaja received the American Psychological Association (APA) Inaugural Recipient Prize for Interdisciplinary Team Research, CREATE Team in October of 2016. She was also made a Member of the External Advisory Committee, Great Plains IDeA Center for Clinical and Translational Research this year. She received the prestigious position as Board Member of the Executive Council of Human Factors and Ergonomics Association as of August 2016 through 2020.

Dr. Dave received the NIH funding through 2019 for his research work on red blood cell microparticles (RMPs) to reduce bleeding following hemorrhagic stroke.

Dr. Gomes-Osman received a grant from the Foundation to Support Research in the State of Alagoas, Brazil (Fundacao de Amparo a Pesquisa do Estado do Alagoas- FAPEAL) to support her

trainee Danylo Cabral for the project *The use of exercise as a potential tool for brain health in healthy older adults and individuals with MCI: a systematic review aimed at identifying dose-related exercise recommendations*.

Dr. Jiang received a pilot study award from the North American Neuro-ophthalmology Society (NANOS) to study retinal vascular dysfunction in AD. She was also accepted as a member of the University of Miami Center on Aging.

Nathalie Khoury a PhD student in **Dr. Perez-Pinzon's** lab was awarded a pre-doctoral fellowship grant from the American Heart Association through 2018. She also received third place for presenting *Elucidating the molecular mechanism behind the long-term cerebral ischemic tolerance mediated by resveratrol preconditioning* at the Evelyn F. McKnight Brain Research Foundation Poster Reception this year at the Society for Neuroscience meeting in San Diego.

Dr. Levin received funding through 2021 to examine the inflammatory properties of cannabinoids and determine whether they can be used as a therapeutic intervention in traumatic brain injury (TBI) from Scythian Bioscience. She also received a Department of Defense grant (DoD) to study Utility of MRS Brain Biomarkers of Pain Phenotypes after TBI.

Dr. Perez-Pinzon received an R01 for his research project *Ischemic preconditioning: mechanisms of neuroprotection*. In addition, the NIH awarded him funding for the project *Decellularized extracellular matrix biomaterials as therapy to ameliorate cerebral ischemia damage.*

Dr. Ramos received a K award to evaluate the cerebral hemodynamics as an early marker of cerebrovascular risk in participants with sleep apnea and controls.

Dr. Raval received a Grant-in-aid award from the American Heart Association (AHA) to test how nicotine alters brain oxidative metabolism and exacerbates ischemic brain damage in female adolescent and reproductively senescent rats.

Dr. Rundek was recently awarded a 3-year AHA Mentor grant to mentor 2 trainees nationally for 3 years. She has an NINDS K24 training grant that allows her protected time for research, training and mentorship. She was awarded a 3-year AF grant by BMS/Pfizer Partnership.

Dr. Sacco was recently honored with the World Stroke Organization's President's 2016 Award for Global Stroke Leadership. The prestigious award was presented on Thursday, October 27, at the WSO's 10th World Stroke Congress in Hyderabad, India.

7. Faculty

Faculty is divided by those receiving direct support from the Institute (Members) and those with whom the Institute is collaborating within the University of Miami (Collaborators). Faculty biosketches are attached at the end of the document.

Name	Center Role Members	Area of Expertise
Noam Alperin, PhD	Radiology	Physics (MRI)
Sara Czaja, PhD	Member	Aging, Psychology, Engineering
Kunjan R. Dave, PhD	Member	Neurobiology, Basic Science
Hong Jiang, MD, PhD	Member	Neurology, Neuroscience
Bonnie E. Levin, PhD	Member & Schoninger Professor	Neuropsychology
Tatjana Rundek, MD, PhD	Interim Scientific Director	Epidemiology, Neurology
Ralph L. Sacco, MD, MS	Executive Director	Neurology, Epidemiology, Genetics
Xiaoyan Sun, MD, PhD	Educational Director	Neuroscience, Biochemistry
Clinton B. Wright, MD, MS	Former Scientific Director	Neurology, Epidemiology, Cognition

Name	Center Role	Area of Expertise
Antonio Barrientos, PhD	Collaborator	Neuroscience, Genetics
Susan Blanton, PhD	Collaborator	Genetics
Elizabeth Crocco, MD	Collaborator	Psychiatry
Chuanhui Dong, PhD	Collaborator	Epidemiology, Biostatistics
Hannah Gardener, ScD	Collaborator	Epidemiology
Joyce Gomes-Osman, PhD	Collaborator	Neuroscience
Teshame Monteith, MD	Collaborator	Headache Science
Carlos Moraes, PhD	Collaborator	Neuroscience
Miguel Perez-Pinzon, PhD	Collaborator	Neuroscience
Milena Pinto, PhD	Collaborator	Neurology
Alberto Ramos, MD	Collaborator	Sleep Medicine, Neurology
Ami P. Raval, PhD	Collaborator	Neuroscience, Epidemiology

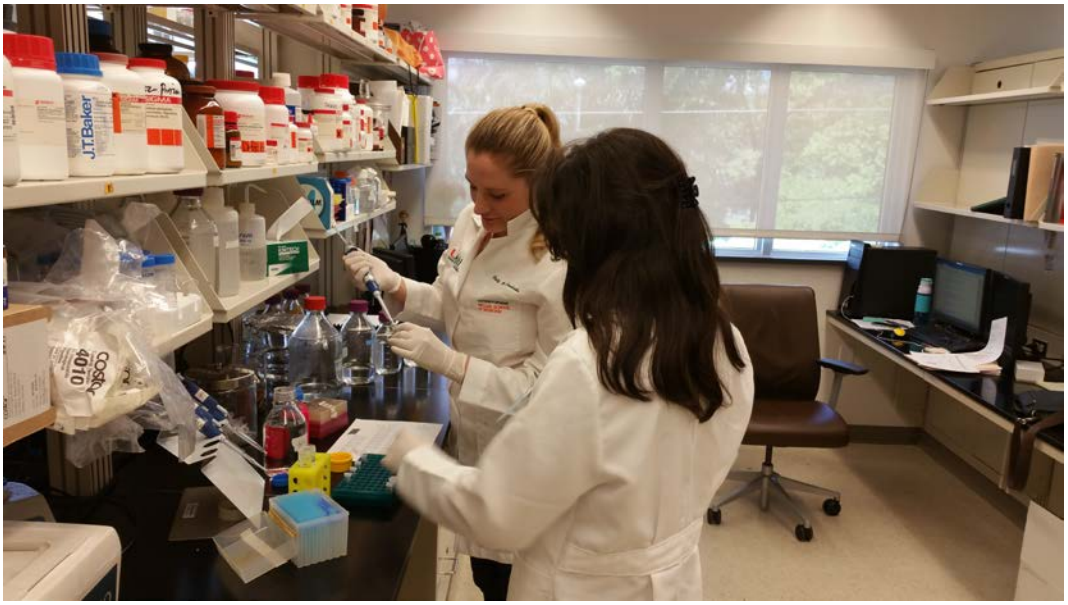
Juan Young, PhD	Collaborator	Genetics
Jianhua Wang, MD, PhD	Collaborator	Neurology, Neuroscience
Adina Zeki Al Hazzouri, PhD	Collaborator	Epidemiology

8. Trainees

Name	Center Role	Area of Expertise
Kyle Andrade-Bucknor	Undergrad Student	Pre-Med
Nikhil Sebastian Banerjee	Graduate Practicum Student	Neuropsychology
Christin I. Bermudez, PhD	Postdoctoral Fellow	Neuropsychology
Myriam Bourens, PhD	Associate Research Scientist	Neuroscience
Annelly Buré-Reyes, MS	Research Associate	Neuropsychology
Yesica Campos, MD	Research Trainee	Neuroscience
Nicholas Cassidy	Undergrad Student	Neurology
Michelle Caunca	Formal McKnight Trainee and MD/PhD Student	Neurology
Austin Choi	PhD Student	Neuroscience
Elise Clark	Undergrad Student	Neuroscience
Charles Cohan, PhD	Postdoctoral Fellow	Neurology
Andres De Leon-Benedetti, MD	Research Assistant	Neurology
Maria Diaz, MD	Research Assistant	Neurology
Katalina Fernàndez McInerney, PhD	Fellow	Neuropsychology
Danylo Lucio Ferreira Cabral, SPT	Research Associate	Physical Therapy/Cognition
Marti Flothmann, BS	Research Assistant	Exercise Physiology
Sarah Getz, PhD	Postdoctoral Fellow	Neuropsychology
Kaylee Kai	Undergrad Student	Neurology
Nathalie Khoury, BS	PhD Student	Neuroscience
Hyun-Jun Kim	PhD Student	Neuroscience
Kevin Koronowski, BS	MD/PhD Student	Neuroscience

Jonathan Landman, MD	Research Assistant	Neurology
Priyanka Maiti, PhD	Post-Doctoral Trainee	Neuroscience
Ava Marsh	Undergrad Student	Biology
Erika Marulanda-Londono	Fellow	Neurology and Stroke
Eva Nyvltova, PhD	Post-Doctoral Trainee	Neuroscience
Sofia Oluwole	MD/PhD Student	Neurology
Elise Picq, DE	Trainee	Neuropsychology
Maya Pinjala	Graduate Practicum Student	Neuropsychology
Ashish Rehni, PhD	Postdoctoral Fellow	Neurology
Jordyn Rice	DPT, PhD Student	Physical Therapy/Cognition
Joshua D. Rooks	Graduate Practicum Student	Neuropsychology
Andrea L. Ruetenik	PhD Student	Neuroscience
Kasra Sarhadi	MD/MPH Student	Physical Therapy/Cognition
Marina Sarno, PhD	Postdoctoral Fellow	Neuropsychology
Laura Segalà, PsyD	Fellow	Neuropsychology
Vibha Shukla, PhD	Postdoctoral Fellow	Neurology
Marialaura Simonetto, MD	Fellow	Neurology
Hesley Solano	Undergrad Student	Neuroscience
Chantel Sorochuk	Graduate Practicum Student	Neuropsychology
Courtney Sparger	Undergrad Student	Neuroscience
Holly Stradecki, BS	MD/PhD Student	Neuroscience
Ni (Sunny) Sun-Suslow	Graduate Practicum Student	Neuropsychology
Alba Timon, PhD	Postdoctoral Trainee	Neuroscience
Eduard Tiozzo, PhD	Fellow	Exercise Physiology/Nutrition
Kristopher Wolford, MPH	Undergrad Student	Public Health
Jing Xu, BS	PhD Student	Neuroscience
Mehdi Youbi, MD	Postdoctoral Fellow	Neurology
Andrew Yu, MS	Research Assistant	Exercise Physiology
Rui Zeng	PhD Student	Neuroscience

Drs. Dave and Perez-Pinzon's Laboratory Trainees



Holly Stradecki, B.S. and Nathalie Khoury, B.S. (Left to Right)

Nathalie Khoury, B.S.

Barrientos-Fontanesi Research Group- 2015/16

Department of Neurology

Department of Biochemistry and Molecular Biology

Myriam Bourens, PhD, Associate Scientist
Priyanka Maiti, PhD, Postdoctoral Associate
Eva Nyvltova, PhD, Postdoctoral Associate
Alba Timon-Gomez, PhD, Postdoctoral Associate
Rui Zeng, PhD Student (Biochemistry)
Hyun-Jung Kim, PhD Student (Biochemistry)
Andrea Lynema, PhD Student (Neuroscience)
Austin Choi, PhD Student (Neuroscience)

Webpage: Barrientoslab.org

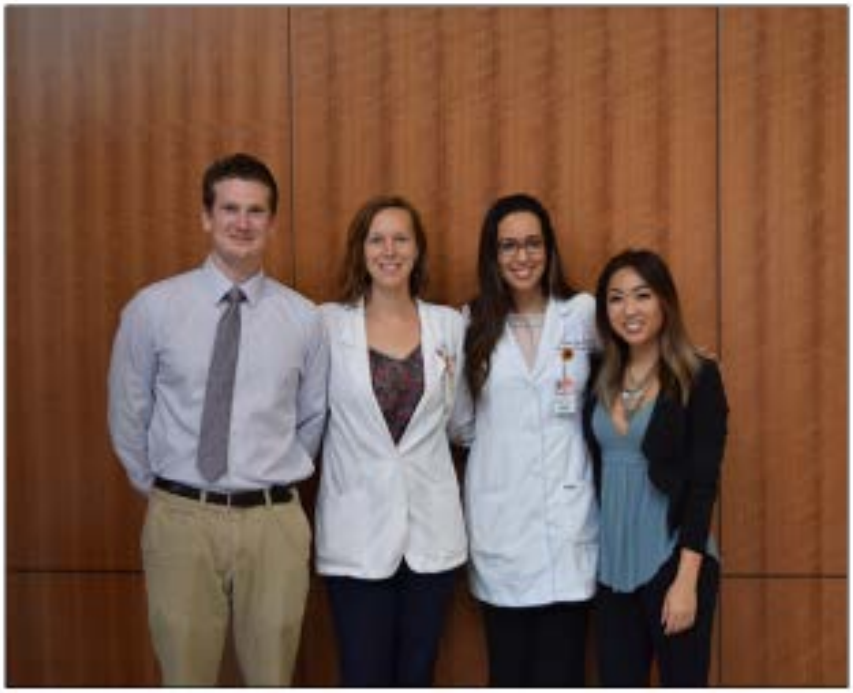
FUNDING:
NIH
AHA
MDA
ARO

Dr. Alejandro Ocampo, PhD

Dr. Jingjing Liu, PhD

Andrea Lynema
Neuroscience

Dr. Gomes-Osman's Lab Team



Nick Cassidy, Jordyn Rice, Dr. Gomes-Osman, Kailee Kai (Left to Right)

9. Clinical /Translational Programs

A. Update on Existing Clinical Studies and Basic Science Research

Dr. Alperin has contributed to the design and evaluation of the McKnight Brain Aging Registry study. He guided and assisted the other McKnight Institutes in implementing the MRI phase contrast scans used for blood flow and brain pulsation assessments. The finalized protocol has been recently implemented and tested on the 3T MRI scanner at UM. He continued working to establish a normative pattern of age-related regional brain volume loss in the Northern Manhattan Study (NOMAS) population. He used the NOMAS data to follow-up on the FreeSurfer brain parcelation analyses of over 900 brain MRI scans.

Dr. Alperin worked on the research project Quantitative assessments of *Hippocampal Subfields in Mild Cognitive Impairment and Normal Aging*. This is a follow-up project to the recently reported assessment of brain regions vulnerable to Alzheimer's Disease. He successfully

completed his NIH funded research *Development and Early Clinical Evaluation of Noninvasive MRI Measurement of ICP i*nvestigating a poorly understood brain disorder (Chiari Malformations Type I) which occurs primarily in female young adults. His research identified quantitative morphological and physiological markers that would help neurosurgeons improve treatment decisions and overall surgical outcomes.

The Stroke Caregiver Support Application Focus Group Study has been completed by **Michelle Caunca** and data will be presented at the International Stroke Conference Nursing Symposium in February of 2017.

Michelle Caunca'**s** pilot study funded by the University of Miami's Scientific Awards Committee (SAC) is currently ongoing. Phase I of the pilot study is to gather more focused feedback on our mobile-friendly website for stroke caregivers through structured interviews with English- and Spanish-speaking stroke caregivers.

Dr. Crocco in her role as Co-Investigator on the research project *Novel Detection of Cognitive and Functional Impairment in the Elderly*, continues to examine the utility of a unique set of neuro-psychological and daily-functioning tests in individuals ranging from cognitively normal (NC) to those with preclinical mild cognitive impairment (preMCI) and those with amnestic mild cognitive impairment (aMCI), in combination with select diagnostic biomarkers and tests such as atrophy on structural MRI, amyloid, tau and phosphorylated tau biomarkers in CSF and in predicting rate of cognitive decline. In addition, she is funded by the ongoing state of Florida Department of Elder Affairs contract.

Dr. Czaja is moving forward with her cutting edge research titled CREATE IV. It is an NIA/NIH funded research center in collaboration with the Georgia Institute of Technology and Florida State University. The focus of the center is on ensuring that older adults are able to use and realize the benefits of technology. The following factors are taken into account: degree of social isolation and support; well-being; quality of life; and functional ability.

This year, with funding from the NINR/NIH, **Dr. Czaja** started the project *A Tailored Technology Intervention for Diverse Family Caregivers of AD Patient*s. This innovative project has an intervention that is 1) tailored to the individual needs of the caregiver using a risk appraisal approach – distinguishing from the "one size fits all" intervention approach; 2) culturally tailored to diverse population of caregivers varying in terms of ethnicity, cultural and other socio-demographic characteristics (e.g., education, SES); 3) employing state-of-the art computer technology to facilitate the delivery of the intervention program; and 4) based on a multi-disciplinary approach including social/behavioral scientists, clinicians and engineers.

Dr. Gomes-Osman has been busy working on a large-scale quantitative systematic review to produce a guide called Exercise *Guidelines for Brain Health*. In addition, she's been conducting an intervention study aimed at characterizing the brain physiology, plasticity and cognitive function of individuals who are sedentary, and assessing changes after a regular exercise regimen.

Dr. Gomes-Osman has also been studying brain plasticity changes in individuals post-stroke who are undergoing combined exercise and cognitive training and exercise in isolation or stretching exercises. Finally, she has an active project that is aimed at acquiring brain plasticity data on individuals who participate in the McKnight Registry which includes patients with memory and cognition complaints.

Dr. Jiang's group along with the University of Miami's Evelyn F. McKnight Collaborator **Dr. Wang** have been using the retina to study the role of vascular dysfunction in the pathophysiology of cognitive function decline. They found that there are decreased retinal microvascular blood flow velocities and microvascular network in both MCI and AD patients, while the retinal ganglion cell layer thickness remains within normal ranges, which indicates that the vascular dysfunction may precede and contribute to the neuronal loss. They are preparing papers such as: "Retinal microvascular impairment prior to ganglion cell loss in mild cognitive impairment and Alzheimer's disease" and "Impaired retinal microcirculation in mild cognitive impairment and Alzheimer's disease." Through their work with AD and MCI patients, they were able to set up the normality lines of age-related retinal microvascular changes by studying a population that ranged from 18 to 85 years old. Their finding suggest that there is age-related decline of retinal microvascular network densities and blood flow velocities.

Under the mentorship of **Dr. Perez-Pinzon** and **Dr. Dave,** their Postdoctoral Fellow **Mehdi Youbi** has been working to analyze the effects of forced treadmill exercise at various speeds on spatial memory tests after focal ischemia in rats. He tested the hypothesis that a moderate intensity treadmill regimen will better ameliorate cognitive deficits and improve functional recovery after focal ischemia compared to the high or mild intensity groups. Experiments were conducted in young (3 months old) Sprague Dawley rats. Focal cerebral ischemia was induced using the middle cerebral artery occlusion model for 90 minutes or sham surgery and were randomly assigned to an exercise intensity group (mild, moderate, heavy or no exercise) for six days starting three days post-surgery. Finally, the rats were subjected to contextual fear conditioning tests. This study concluded that focal cerebral ischemia impairs cognitive function, however moderate intensity physical exercise provided the most beneficial impact on cognitive recovery compared to other exercise intensities. They are also evaluating effects of physical exercise on post-stroke cognitive function in middle-aged rats.

Working on the premise that physical exercise can reduce cognitive deficits after cerebral ischemia by augmenting brain plasticity, **Holly Stradecki** an MD/PhD student in **Dr. Perez-Pinzon's** laboratory performed the following research this year. She examined whether or not forced treadmill exercise improves performance of Sprague Dawley rats on spatial memory tests (Barnes Maze & contextual fear conditioning) and reduces hippocampal long term potentiation (LTP) deficits.

Young Sprague Dawley rats were handled and acclimated to treadmill walking, underwent global ischemia [8 minute asphyxial cardiac arrest (ACA)] or sham surgery and allowed 3 days of recovery. Rats were then subjected to mild (6 m/min), moderate (10 m/min), heavy (15 m/min)

or no treadmill exercise for five days. After the last day of exercise, a subset of rats was subject to the Barnes Maze and contextual fear conditioning tests. Cardiac arrest induced cognitive deficits after global cerebral ischemia as measured by both distance traveled and time spent in target quadrant on the Barnes Maze. When comparing all exercise groups and correcting for multiple comparisons, no statistical difference was found for these parameters. Overall, while ACA impairs cognitive functioning, early induction of exercise restores and improves performance on spatial memory tasks and may restore induction of LTP.

Dr. Ramos has completed enrollment for the Hispanic Community Health Study/Study of Latinos, Sleep as a risk factor of disease (Sueño). The team of researchers have been busy compiling the results and submitting for publication.

The University of Miami Clinical Translational Science Institute (CTSI) continues to build a home for clinical and translational research at the University of Miami under the new leadership of **Dr. Ralph Sacco**. In the last quarter of 2015, the CTSI strategically appointed Dr. Sacco, who maintains an extensive research track record in stroke clinical trials, long-lasting research networks and large-scale disparities research, to direct the CTSI's programmatic focus on network participation and capacity. Under this new purview, the CTSI has enhanced and strengthened professional collaborations and networks. State, national and international partnerships have been initiated and secured with industry leaders and institutes conducting state-of-the-art translational research and/or specializing in training new professionals in translational medicine.

The University of Miami Stroke Prevention Intervention Research Program, Florida-Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) aims to identify race-ethnic and sex disparities in acute stroke care and inform hospital quality improvement through the FL-PR CReSD disparities stroke registry. Led by **Dr. Sacco** this year, along with in-hospital data drawn from hospitals participating in American Heart Association "Get With The Guidelines-Stroke", we featured linked pre-hospital EMS data from the Florida Department of Health's EMSTARS (22,370 linked records to the FL-PR Registry), and in a separate project, linked post-hospital data from CMS (21,630 linked records to the FL-PR Registry). It is expected that analyses of data representing the continuum of stroke care may more specifically reveal underlying factors contributing to higher stroke risk among racial and ethnic minorities, and thereby identify greater opportunities for improvement in prevention, acute stroke care and post-stroke outcomes.

The Northern Manhattan Study (NOMAS)- Stroke Incidence and Risk Factors in a Tri-Ethnic Region, under the leadership of **Dr. Sacco** has just entered its second year of funding within funding cycle 5 (accomplishing 24 years of funding to date). The project continues to collaborate with the Columbia University where the NOMAS cohort is monitored and assessed through annual telephone follow-up on all surviving cohort members (currently N=1,647), and the recall of a subset of subjects who participated in our prior brain MRI sub study (N=960) for in-person cognitive testing and neurological exams. Bi-weekly conference calls between the Columbia University and University of Miami investigators involve discussions on:

improving/trouble-shooting domain coverage in the project's neuropsychological testing battery, and cognitive and functional decline measures; protocol and process for the dementia adjudication committee (yet to be initiated); and manuscript development and status. This year, 14 manuscripts related to risk factors and clinical outcomes, subclinical carotid disease, brain measurements, sleep, migraine, physical activity, cognitive aging and performance have been published.

Dr. Sun continued work as a Co-Investigator in the NIH R01 funded project Novel Detection of Early Cognitive and Functional Impairment in the Elderly. She also spent time collecting CSF samples and monitoring lab measurement of amyloid 42, phosphorylated tau and total tau protein from these samples.

Dr. Sun has been working on the project *Biomarkers in Alzheimer's Disease* using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Her research results were published in *Alzheimer's & Dementia* the journal of the Alzheimer's Association this year. They have also been highlighted in *Nature Reviews Neurology* in July, 2016. The NIH K-grant related to the project has been submitted to the National Institute on Aging and reviewed. The grant will be revised according to the reviewers' comments.

The University of Miami American Heart Association/Bugher Center of Excellence clinical project was led by **Dr. Wright** and as of November 1st, 2016 by Dr. Sebastian Koch. This year the study team has been enthusiastically and successfully enrolling study participants. Additionally this year, through a Supplemental Collaborative Clinical Study, we are testing the viability of an activity-monitoring device (developed at UCLA Bugher Center), which measures physical activity quantitatively in post-stroke participants. The Basic Science Supplementary project, also initiated this year, explores the biology of white matter stroke, one of the leading causes of dementia. These basic science studies will collaborate and corroborate results from studies in mice from our UCLA Bugher Center collaborator. With the aim to improve post-stroke care and prevention of recurrent stroke, results from the study may offer insight towards behavioral/environmental modifications to decrease sedentary behavior.

Dr. Wright and his team made a concerted effort to systematize the data entry process for the *Evelyn F. McKnight Brain Institute Cognitive Disorders Clinical and Biorepository Registry* (McKnight Registry). While the focus until this year has been on enrolling patients into the Registry, this year's goal was to enter the vast data collected from MRI scans and neuropsychological testing into the REDCap database and to develop specific analysis plan. To date, variables including demographics, clinical diagnosis, ability to independently perform activities of daily living (ADLs), education level and living situation for almost 500 study participants is being used to design interventions, future research and write novel grants and manuscripts.

Dr. Young has made progress on his research project *Epigenetic component of Parkinson disease*. He has identified DNA methylation alterations associated with Parkinson disease in early affected brain regions. The manuscript he wrote on these findings is under revision with

the *Annals of Neurology*. He also identified transcriptional changes in Parkinson disease and a manuscript is in production to share these results.

Dr. Zeki Al Hazzouri is working on the project *Lifecourse cardiovascular risk, depression and cognition in black & white adults*. The goal of the study is to address the nature of the associations of cardiovascular risk factors with cognitive function and depressive symptoms, and the role of structural brain changes.

B. New Research Programs

Dr. Alperin will be working next year on the new study *Sleep Apnea, brain volume loss, and cognitive decline.* This is a new multidisciplinary collaborative study he's collaborating on with **Dr. Ramos** and Dr. Curiel at the University of Miami. They will be assessing the effect of sleep apnea on brain volumetry and cognitive performance in healthy elderly individuals.

Phase II of **Michelle Caunca's** pilot study funded by the University of Miami's Scientific Awards Committee will be to test the feasibility of the mobile-friendly website curriculum with a small group of stroke caregivers over the course of three months.

Michelle Caunca submitted the F30 project to NINDS on the *Effects of White and Gray Matter Integrity on Cognition in a Multi-Ethnic Cohort* with hopes of it being funded to start the research next year. She seeks to investigate the associations between macro- and microstructural white matter integrity, grey matter integrity and cognition clinically stroke-free Northern Manhattan Study (NOMAS) population. The study aims support key goals of the National Institute of Neurological Disorders and Stroke (NINDS) Strategic Plan including: investment across the full spectrum of basic, translational and clinical research; promotion of clinical research; and establishment of a data-driven process to identify unmet scientific opportunities and public health need within and across neurological diseases. The proposed research also addresses the NIH BRAIN Initiative by exploring brain networks through MRI metrics of white matter integrity.

Charles Cohan, a Postdoctoral Fellow in **Dr. Perez-Pinzon's** laboratory will be examining the effect of white matter stroke on cognitive outcomes using a rat model. This project is funded by a supplemental grant to the AHA Bugher Center grant.

Dr. Czaja will begin her work on the *DUAL TARGET* research project. This project is an integration of an augmented evidenced-based caregiver intervention and evidenced-based cognitive/functional training for the care recipient. The program will be tailored for the caregiver and emphasizes issues important to caregivers, not only in the earlier stages of caregiving, but will also target issues across the caregiving trajectory to help prepare the caregiver for changes in their role. The program is highly innovative given the focus on a dyadic approach, the use of state-of-the-art technology for intervention delivery, a community-based

and stage-model approach to intervention development and the inclusion of the caregiver as a therapy extender and the cultural tailoring of the program.

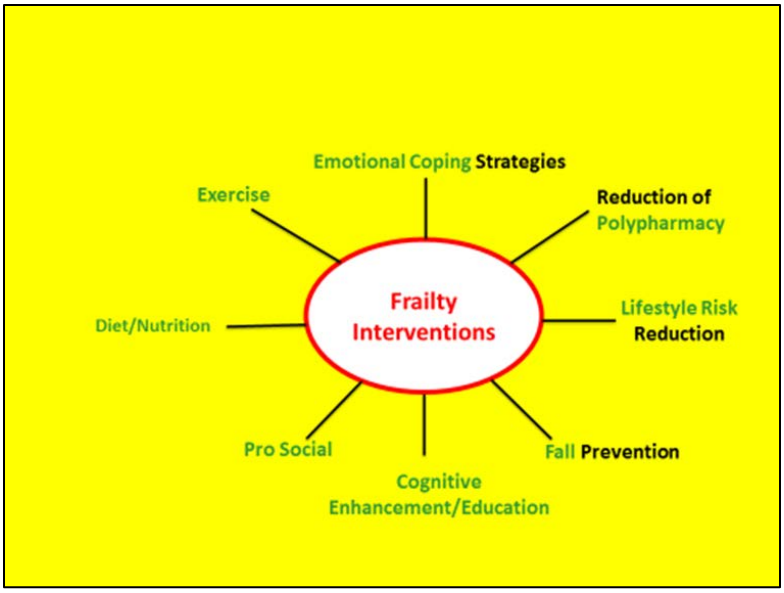
Dr. Czaja will begin working on the NIH/NIA funded Augmenting Cognitive Training in Older Adults (ACT) Study (Dr. Czaja, Site PhD; 2016 Budget: $1,307,013). This adaptive two-phase randomized clinical trial will be done at the University of Florida and the University of Arizona. Phase 1 of the study aims to examine the impact of cognitive training versus an education training control condition. Phase 2 will study the impact of cognitive training augmented by tDCS versus a placebo/sham stimulation condition. This research will test whether transcranial direct current stimulation (tDCS) of frontal cortices enhances neurocognitive and functional outcomes achieved from cognitive training in older adults experiencing age-related cognitive declines. The study will also examine the influence of other clinical and demographic factors (e.g., gender) on neurocognitive, functional and neuroimaging outcomes.

Dr. Czaja will begin her work with the *PARC* study. The study involves a unique industry-university collaboration between the Palo Alto Research Center (PARC) and the University of Miami, Miller School of Medicine (UMMSM), which brings together a multidisciplinary team of behavioral, neural, cognitive and computer scientists, engineers and clinicians. It uses the Fittle Senior System (FSS) which builds on two technology-based systems developed by the investigative team: (1) the computer-based PRISM system, designed for older populations to support social connectivity and well-being and (2) the Fittle+ mobile platform (PARC) designed to support positive health behavior change through integrated online social support and personalized coaching based on artificial intelligence (AI).

Dr. Jiang and **Dr. Wang** plan to continue working on studies of retinal microvascular dysfunction in pre-MCI, MCI and late MCI patients to identify the sensitive ocular biomarkers in predicting cognitive functional decline and monitoring for therapeutic effects.

Dr. Levin is Principal Investigator of the University of Miami cognitive component for the McKnight Brain Aging Registry. Her senior Fellow **Katalina Fernández McInerney**, will be responsible for administering the neuropsychological assessments to the study participants who are healthy individuals age 85 and older. **Dr. Levin** initiated a frailty project, a multi-tiered investigation of frailty and cognitive aging. This project involves numerous collaborations with McKnight members and will address multiple components of the frailty syndrome including comorbid cognitive status, emotional well-being, lifestyle risk factors, sleep dysregulation, cardiometabolic health, polypharmacy, imaging parameters and inflammatory biomarkers (see picture below). She also initiated a community outreach program involving her McKnight Postdoctoral Fellows working with undergraduate and graduate students. It was created to build a database consisting of fully independent older adults who are not experiencing subjective cognitive complaints. This database is the control group for the frailty project as well as other future promising McKnight endeavors.

Dr. Levin is collaborating with the McKnight Brain Institutes (proposal under consideration) on research to examine risk factors contributing to increased susceptibility to deception in aging. This project addresses a growing public health concern pertaining to the expanding number (1 in 5 over the age of 65 years) of older Americans who fall victim to some form of financial abuse. This proposed study will determine specific processes associated with susceptibility to scamming and propose effective interventions to increase deception detection.



Katalina Fernández McInerney with her mentor **Dr. Levin** is part of a working group collaboration (proposal under consideration) examining the role of chronic stress and hypothalamic–pituitary–adrenal (HPA) axis dysregulation on age-associated changes of memory and executive function. The proposed project incorporates an experimental (rodent) and clinical study to identify the critical mechanisms that mediate the relationship between cortisol release associated with chronic stress, sleep dysregulation and cognition.

Dr. Rundek and **Dr. Sacco** are Co-Investigators of the new research study "Disparities in Stroke Outcomes and Care Delivery in Patients with Atrial Fibrillation: FLorida PuErto Rico Atrial Fibrillation Stroke Study (FLiPER – AF)," which was recently funded by Bristol-Myers Squibb/Pfizer Alliance. Scheduled to begin in 2017, the project aims to identify race/ethnic and gender gaps in stroke care for elderly patients with Atrial Fibrillation. Results from these studies will contribute to the development of targeted interventions to reduce disparities, as well as improve quality of systems of care for elderly AF patients. The effect of AF on memory and cognitive decline is planned in the future studies.

Dr. Sun will be working on her K-grant re-submission to the NIA in 2017. The grant will be revised according to the reviewers' comments.

Dr. Young and his team plan to analyze the methylome and transcriptome data in the context of neurodegeneration by comparing Parkinson disease associated changes with changes observed in Alzheimer's disease.

10. Technology Transfer

N/A

11. Budget Update

Status of matching funds, if applicable (see attached).

Projected budget for coming year (see attached).

Extramural Funding

Stroke Incidence and Risk Factors in a Tri-ethnic Region
Source: NIH, NINDS (R01 NS029993)
Principal Investigator: **Ralph Sacco**
2016 Budget: $1,716,978

University of Miami ASA/Bugher Foundation Center for Excellence in Stroke Collaborative Research
Source: American Heart Association Bugher Foundation
Principal Investigator: **Ralph Sacco**
2016 Budget: $604,000

Miami Clinical and Translational Science Institute
Source: NIH//NCRR/NIMHD
Principal Investigator: **Ralph Sacco**
2016 Budget: $3,405,890

Family Study of Stroke Risk and Carotid Atherosclerosis
Source: NIH/NINDS R01 NS040807
Principal Investigators: **Ralph Sacco** and **Tatjana Rundek**
2016 Budget: $577,652

Mentor/AHA Mentee Award
Source: American Heart Association (MM26340000)
Principal Investigator: **Tatjana Rundek**
2016 Budget: $15,000

The Accreditation and Utilization of Cardiac Echo Laboratories in Medicare Beneficiaries: The VALUE-ECHO Study
Source: Intersocietal Accreditation Commission (IAC)
Principal Investigator: **Tatjana Rundek**
2016 Budget: $75,000

Protocol adc- 047-tcad: A Phase 2 Multi-center, Randomized, Double Blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of t-817ma in Patients with Mild to Moderate Alzheimer's Disease
Source: Toyama Chemical Co., Ltd.
Co- Investigator: **Xiaoyan Sun**
2016 Budget: $473,346

University of Miami Memory Disorder Clinic
Source: State of Florida, Division of Elder Affairs
Co-Investigator: **Xiaoyan Sun**
2016 Budget: $222,801

Novel Detection of Early Cognitive and Functional Impairment in the Elderly
Source: NIH/NIA
Co-Investigator: **Xiaoyan Sun**
2016 Budget: $498,219

The Effects of Cannabinoids on TBI
Source: Scythian Biosciences
Co-Investigator: **Bonnie Levin**
2016 Budget: $953,121

Increased Cerebral Ischemic Injury by Repeated Hypoglycemic Episodes in Diabetes.
Source: NIH, NINDS (R01 NS073779)
Principal Investigator: **Kunjan Dave**
2016 Budget: $271,096

Red Blood Cell Microparticles (RMPs) to Reduce Bleeding Following Hemorrhagic Stroke
Source: NIH, NINDS (R2121 NS094896)
Principal Investigator: **Kunjan Dave**
2016 Budget: $307,000

Ischemic Preconditioning: Mechanisms of Neuroprotection.
Source: NIH, NINDS (R01NS034773)
Principal Investigator: **Miguel Perez-Pinzon**
2016 Budget: $335,781

Ischemic Preconditioning: Mechanisms of Neuroprotection/Supplement for Research on Sex/Gender Differences
Source: NIH, NINDS (R01NS034773-S1)
Principal Investigator: **Miguel Perez-Pinzon**
2016 Budget: $100,000

Decellularized Extracellular Matrix Biomaterials as Therapy to Ameliorate Cerebral Ischemia Damage
Source: NIH, NINDS (R21 NS098896)
Principal Investigator: **Miguel Perez-Pinzon**
2016 Budget: $175,875

Activity-Dependent Mechanisms of White Matter Repair after Stroke.
Source: Supplemental award: American Stroke Association-Bugher Foundation Centers for Excellence in Stroke Collaborative Research for Regeneration, Resilience and Secondary Prevention,
Site Principal Investigator: **Miguel Perez-Pinzon**
2016 Budget: $101,529

Neuroprotective mechanisms of resveratrol pre-conditioning.
Source: NIH/NINDS F31 Ruth L. Kirschstein National Research Service Award Predoctoral Fellowship # 1F31NS089356-01A1
Principal Investigator: **Kevin B. Koronowski** (PhD student in **Perez-Pinzon** lab)
2016 Budget: $37,176

Elucidating the mechanism behind the long-term cerebral ischemic tolerance mediated by resveratrol preconditioning
Source: AHA, Greater Southeast Affiliate Winter 2016 Predoctoral Fellowship (16PRE29170004)
Principal Investigator: **Nathalie Khoury** (PhD student in **Perez-Pinzon** lab)
2016 Budget: $25,950

ORCATECH Collaborative Aging (in Place) Research Using Technology CART
Source: NIH/NIA (1U2CAG054397-01)
Site PI: **Sara Czaja**
2016 Budget: $1,948,567

Augmenting Cognitive Training in Older Adults – the ACT Grant
Source: NIH/NIA
Site PI: **Sara Czaja**
2016 Budget: $1,307,013

A non-pharmacological intervention for patients with Alzheimer's disease and family caregivers
Source: NIH/NIA (1 R01 AG054009-01)
Principal Investigator: **Sara Czaja**
2016 Budget: $749,437

A Personalized Health Behavior System to Promote Health and Well-Being in Older Adults
Source: NIH (1 R01 AG053163-01)
Principal Investigator: **Sara Czaja**
2016 Budget: $834,282

Center for Research and Education for Aging and Technology Enhancement (CREATE IV)
Source: NIA/NIH (5PO1AG0172-17)
Principal Investigator: **Sara Czaja**
2016 Budget: $1,597,545

Novel Detection of Early Cognitive and Functional Impairment in the Elderly
Co-Investigator: **Sara Czaja**
Source: NIH (1R01AG047649-01A1)
2016 Budget: $582,363

A Tailored Technology Intervention for Diverse Family Caregivers of AD Patients
Source: NINR/NIH (1R01NR014434-01)
Principal Investigator: **Sara Czaja**
2016 Budget: $459,484

A Non-Pharmacological Intervention for Patients with Alzheimer's disease and Family Caregivers
Source: Florida Department of Health – FLDOH)
Principal Investigator: **Sara Czaja**
2016 Budget: $249,095

The Role of Retinal Microvascular Impairment on neurodegeneration in Multiple Sclerosis
Source: National Multiple Sclerosis Society
Principal Investigator: **Hong Jiang**
2016 Budget: $180,278

Imaging of Conjunctival Microvasculature During Contact Lens Wear
Source: Johnson and Johnson contact lens study
Principal Investigator: **Hong Jiang**
2016 Budget: $91,000

12. Educational Programs Focusing on Age-Related Memory Loss

A. General Education Program

Michelle Caunca along with undergraduate and other medical students participated in community health fair events throughout the greater Miami area. They performed memory

screening tests and educated attendees on normal aging changes and those requiring medical attention. Those who displayed questionable memory impairment were given information on the appropriate resources.

Dr. Crocco through the Miami Area Geriatric Education Center (MAGEC) contributes to the planning, development and implementation of educational programs to diverse health care professionals who provide services to older adults in a variety of settings in the South Florida area. Select lectures provided include intensive psychiatric courses in agitation in dementia, geriatric depression and other aging issues.

Dr. Crocco as part of the Florida Department of Elder Affairs Alzheimer's Disease Initiative (ADI), provides caregiver training seminars on Dementia in Miami-Dade County. She also leads the ADI Caregiving Training Program on Dementia to ADI Respite Care and Day-Care Centers in Monroe County. She developed a 4-hour state-mandated training for caregivers, ADI Respite, Day-Care professionals and para-professionals for CEU accreditation on an annual basis in both English and Spanish. She also developed and coordinates 4 hours of state-mandated dementia training to caregivers in Respite and Day Care Centers in Monroe County.

Dr. Czaja orchestrates the CREATE Workshop - Health Care Technologies for Older Adults: Design, Adoption, Implementation and Training Issues. This workshop brings together representatives from companies, large and small, who are involved in the healthcare industry or healthcare product development who have an interest in meeting the needs of older adults.

Led by **Dr. Levin**, neuropsychologists from the McKnight Institute provided outreach to the community by introducing education on frailty detection and prevention mechanisms.

Stacy Merritt attended a regional memory and cognitive disorders event hosted by the Alzheimer's Association. This was a great opportunity to speak with family and loved ones of those with memory/cognitive issues as well as people concerned about their cognitive health.

Stacy Merritt has been training graduating cadets of the Miami-Dade Police Department on Florida's Silver Alert program, understanding memory and cognitive changes/disorders in aging as well as resources and strategies to work with this population.

Dr. Sun and **Michelle Caunca** were involved in outreach aimed at neuroscience undergraduate students and medical students. They participated in a panel discussion about career planning answering relevant questions from undergraduate students.

Dr. Sun represented the McKnight Institute through her participation in the "Women's Initiative Annual Health Series" at the Holland and Knight law firm. Dr. Sun and a fellow neurologist in our department who is also a McKnight collaborator, Dr. Baumel, gave lectures about the latest research on Alzheimer's Disease and related disorders and their diagnosis and treatment.

Dr. Sun, **Stacy Merritt**, and **Michelle Caunca** hosted an exhibition table at the University of Miami Brain Fair in March of 2016 in which the Evelyn F. McKnight Brain Institute, its efforts and mission were showcased. We provided educational information and demonstrations by way of memory games to the participants who ranged from children to older adults. This endeavor was well received and we reached a wide-ranging audience.

Dr. Sun organizes monthly Research Seminars. We invite basic and clinical scientists from inside and outside of the Institution to present their research projects. Monthly Research Seminars are a forum for researchers to present their current work and to promote ideas for collaboration on new projects. The 2016 Research Seminars are listed in Table 1 below.

This year, the Evelyn F. McKnight Brain Institute established a joint scientific lecture series with the University of Miami Center on Aging under **Dr. Czaja**. It is a natural collaboration and one we are looking forward to building upon. Speakers will present on research related to aging, memory loss and cognitive decline both within and outside of the University for an exchange of ideas, and to foster new collaborations. The 2016/17 Scientific Lecture Series is listed in Table 2 below.

We have organized a monthly Journal Club for the department of neurology, McKnight Members and Collaborators and researchers and scientists from partnering departments to enhance knowledge of the current research on cognitive neurosciences and memory related disorders. The Journal Club articles are focused on cognitive aging in neuropsychology, neurochemistry, neuro-epidemiology and clinical aspects of memory and cognitive disorders. The 2016 Journal Clubs are listed in Table 3 below.

We have organized annual grand rounds and invite expert researchers/scientists in their field to update us on current advances in aging and memory disorders. In January of 2016, Dr. Henrik Zetterberg, MD, PhD, presented on "Blood biomarkers for CNS disorders - feasible or too much of a challenge?".

Dr. Rundek serves as director and strategist of the work force development component of the University of Miami CTSI. She is the Vice Chair of Clinical Research and Director of the Clinical Translational Research Division in Neurology and Director of the Master of Science program in Clinical Translational Investigations. She also creates the core curriculum and teaches courses in team science and scientific writing. Through her role as Training Director of the NINDS StrokeNet and NeuroNext programs, she mentors 1-2 scholars each year. As Training Director of the Miami American heart Association Bugher Stroke Center, she trains 2 scholars per year in Miami and 1-2 scholars at two other AHA Bughers sites (UCLA and University of Colorado, Denver). She fosters a robust research environment and facilitates multi-disciplinary research training in vascular neurology and epidemiology for graduate and post-graduate trainees. She is the director of the Neurology Residents and Fellows Clinician Researcher Program, a 3-year program aimed at providing research and career development mentorship in neurology where she mentors and advises 2-3 residents and fellows per year. She will be the career development mentor for the first McKnight Brain institute clinical fellow starting in June of 2017.

Table 1. 2016 Evelyn F. McKnight Brain Institute Research Seminar Series

Speaker	Area of Expertise	Date	Title
Dr. Gaurav Saigal, MD	Neuroradiology	1/13/16	*High Resolution Steady State Blood Volume Maps in Glioblastoma Using MRI*
Maria Diaz, MD	Neurology	2/17/16	*Framingham Risk Score and Cognitive Outcomes in Cognitively Normal and Subjective Memory Complaint*
Rosanna Squitti, PhD	Neuroscience	3/23/16	*Copper studies in Alzheimer's disease and other neurological disorders*
David Loewenstein, PhD	Neuropsychology	4/13/16	*Novel Cognitive Stress Paradigms, Biomarkers and the Earliest Detection of Alzheimer's Disease and Related Disorders*
Andres De Leon-Benedetti, MD	Neurology	5/11/16	*Synaptic Function and Mild Cognitive Impairment: the Role of Neurogranin*
Holly Stradecki	Neuroscience	6/8/16	*Physical Exercise in the Reduction of Cognitive Deficits After Cardiac Arrest*
Charles Cohan, PhD	Neurology	7/13/16	*Protection against ischemic injury and aging*

Table 2. 2016 University of Miami Evelyn F. McKnight Brain Institute/Center on Aging Scientific Lecture Series

Speaker	Area of Expertise	Date	Title
Rosie E. Curiel Cid, PsyD	Neuropsychology	10/3/16	*Precision-based Assessment of Mild Cognitive Impairment in Older Adults*
Jianhua Wang, MD, PhD	Ophthalmology & Neurology	10/12/16	*Conjunctival microvascular imaging on aged related memory loss*

Alberto Ramos, MD, MSPH, FAASM	Neurology	11/9/16	*Are sleep disturbances a risk factor for dementia?*
Antoni Barrientos, PhD	Neuroscience, Genetics	12/14/16	*NAD+ biosynthetic pathways open new frontiers for neuroprotection*

Table 3. 2016 Evelyn F. McKnight Brain Institute Journal Club Presentations

Speaker	Area of Expertise	Date	Title
Andres DeLeon-Benedetti, MD	Neurology	1/27/16	*Effects of vascular risk factors and APOE e4 on white matter integrity and cognitive decline*
Yesica Campos, MD	Neuroscience	2/17/16	*Vascular burden and Alzheimer disease pathologic progression*
Maria Diaz, MD	Neurology	3/16/16	*PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease*
Katalina Fernàndez McInerney PhD	Neuropsychology	4/20/16	*PET Imaging of Tau Deposition in the Aging Human*
Laura Segalà, PsyD	Neuropsychology	5/18/16	*Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons*
Joyce Gomes-Osman, PT, PhD	Physical Therapy & Neurology	6/15/16	*Theta Burst Stimulation of the Human Motor Cortex*
Carolina Mendoza-Puccini, FMG, CCRC	Neurology	7/20/16	*Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study*

Michelle Caunca	Neurology	8/17/16	*Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study*
Eddie Tiozzo, PhD	Exercise Physiology, Nutrition	9/21/16	*Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies*
Marialaura Simonetto, MD	Neurology	10/19/16	*Coordinated Gene Expression of Neuroinflammatory and Cell Signaling Markers in Dorsolateral Prefrontal Cortex during Human Brain Development and Aging*
Ni (Sunny) Sun-Suslow, MS	Neuropsychology	11/16/16	*Declines and Impairment in Executive Function Predict Onset of Physical Frailty*
Jordyn Rice, PT, DPT	Physical Therapy, Cognition	12/21/16	*Strength and Aerobic Exercises Improve Spatial Memory in Aging Rats Through Stimulating Distinct Neuroplasticity Mechanisms*

B. Education of Trainees: Undergraduate, Medical and Doctoral Students, Post-Docs, Fellows and Residents

Dr. Barrientos continued his effort to maintain and improve the Journal Club for the MD/PhD program.

Michelle Caunca, the McKnight student representative and trainee recruited medical and PhD students to attend the McKnight monthly Research Seminars and Journal Club presentations. She also has an attentive forum for generating information to the student community on McKnight events.

Dr. Crocco leads Doctoring II: Dementia Small Groups Miller/UM SOM for small groups of 20-25 medical students in diagnosis and evaluation of cognitive disorders and aging. She also leads Doctoring II: Neuroscience and Behavioral Science, mood and anxiety disorders and addiction for small groups Miller/UM for small groups of 20-25 medical students in evaluation and management of common psychiatric disorders in aging and the Geriatric Psychiatry Lecture Series Miller/UM SOM 3rd year psychiatry clerkship.

Dr. Crocco also develops and implements comprehensive geriatric psychiatry lectures in psychiatric clerkship to all 3rd year medical students. This includes topics including: aging and normal aging, late-life depression and anxiety, ECT, bereavement, neurodegenerative disorders, Alzheimer's, vascular and Lewy body disease.

Dr. Crocco is also involved with the Jackson Memorial Hospital (JMH) General Psychiatry Residency Training Program: 1) Psychiatry Lecture Series. She develops and implements comprehensive geriatric specialty lectures in all 4 years of general psychiatric residency training. Topics include: normal aging, late-life schizophrenia, late-life depression, ECT, bereavement, neurodegenerative disorders, Alzheimer's, Vascular, Lewy body disease and caregiving issues. 2) Geriatric Psychiatry Seminar – She also develops and implements on a weekly basis the core curriculum-focused conference that covers knowledge and skill areas that are necessary for the successful completion of the geriatric psychiatry training program and commonly seen diagnoses in geriatric psychiatry.

As part of the JMH Geriatric Psychiatry Training Program, **Dr. Crocco** has a weekly case conference. She coordinates and supervises all geriatric psychiatry Fellows' weekly presentations of patient case history, including biological, psychological and sociological data and formulates an integrated treatment plan with special emphasis on aging. She holds a weekly journal club overseeing the coordination and supervision of all geriatric psychiatry Fellows with the objective of critical evaluation of peer-reviewed, original research articles and applies this knowledge to the care of their geriatric patients and aging issues.

Dr. Czaja oversees the Certificate in Gerontology Program at the University of Miami's Center on Aging. The Certificate Program provides education and training on the science of aging with the aim to increase the number of qualified providers to work with and study the growing aging population.

Dr. Dave and **Dr. Perez-Pinzon** mentor and train 4 Postdoctoral Fellows, 1 MD/PhD student and 3 PhD students in their labs.

This year **Dr. Gomes-Osman** taught a 3-credit graduate level class to physical therapy students - *Neuroscience II 641*. In this class, students learned about the clinical neurophysiology functional performance in the healthy nervous system and in neurologic conditions.

She continues to mentor a PhD Student from the Department of Physical Therapy who will be conducting studies about brain plasticity, exercise and cognitive function. **Dr. Gomes-Osman** is also a mentor to two undergraduate students she's teaching through studies being carried out in her lab. In addition to these local students, she serves as a mentor for a physical therapy student in Alagoas, Brazil who is currently working on the *Exercise for Brain Health* review and educational booklet.

The Division of Neuropsychology under the supervision of **Dr. Levin** had mentorships for 2 undergraduate students this year. She taught a 3 credit upper level graduate class for advanced PhD students examining the foundations of clinical neuroscience and neuropsychology. This 12 week course focuses on age-related memory loss and other changes across the life span and neural circuitry underlying cognition and behavior.

Dr. Levin also continues to lead bi-weekly neuropsychology rounds for practicum students and interns that includes clinical case conferences, assessments, scoring and interpretation of data and group supervision. Case discussions include all patients seen in the Memory Disorders Clinic where students are trained in the evaluation and assessment of age-related and non-age-related memory loss.

Dr. Levin leads a bi-weekly neuropsychology rounds for Post-doctoral Fellows that includes clinical case conferences, assessments, scoring and interpretation of data and group supervision. Case discussions include all patients seen in the Memory Disorders Clinic where students are trained in the evaluation and assessment of age-related and non-age-related memory loss. All trainees are closely supervised in the assessment of cognition and emotion. In addition, the trainees spend a minimum of one day per week testing referrals from the Memory Disorders Clinic and receive ongoing supervision as part of the Schoninger Training Program.

Dr. Sun instituted a curriculum focused on memory disorders for medical and PhD students and Residents. For the medical and PhD students, the lectures were focused on providing an overview of dementia and aphasia. She has also continued giving annual lectures to the Residents. The lecture topics covered mental status examinations in dementia, pathology of neurocognitive diseases, Alzheimer's disease, Lewy Body dementia, fronto-temporal dementias, vascular cognitive impairment, introduction to neuropsychological testing and psychiatric aspects of dementia.

Along with **Dr. Zeki Al Hazzouri**, **Dr. Sun** proposed a neuro-epidemiology course to the Curriculum Development Committee of the Masters/PhD epidemiology program this past academic year. We will re-propose the neuro-epidemiology course for the upcoming academic year.

Dr. Sun has been working with **Michelle Caunca**, the McKnight Brain Institute trainee and MD/PhD student representative, to improve medical education in the field of neurology. Ms. Caunca initiated a student survey collecting opinions regarding timing of neurology rotations among third and fourth year students who have completed the neurology clerkship. The goal of the survey was to advocate for an early neurology clerkship for medical students. Early neurology rotation would help medical students to understand neurology and consider neurology Resident training programs in the future. The result of these efforts is that a mandatory cognitive neurology clinic rotation curriculum for neurology Residents has been approved by our Resident Neurology Program and implemented in 2016. Neurology Residents are required to have a minimum 2-week rotation in the memory disorders clinic. Residents at memory disorders clinic will see patients with memory related disorders, perform screening

assessments for cognitive impairment and interact with clinicians and neuropsychologists to diagnose and formulate treatment plans individuals with memory complaints. In addition, the Residents will be required to observe cognitive testing and participate in scoring of the tests. This represents an important component in ferreting out cognitive and memory deficits.

As part of the educational program, we hold an annual lecture series for neurology Residents in memory disorders aimed at understanding memory related disorders. We work with faculty and Chief Residents to choose the lecture topics. The topics include neurodegenerative diseases and an introduction of neuropsychological testing and management of dementia-related psychiatric symptoms. **Dr. Crocco**, a geriatric psychiatrist and McKnight collaborator contributes to the cognitive neurology lecture series. Starting in 2017, **Dr. Rundek** together with **Dr. Sun** and Chief resident **Dr. Danielle Spengler** will implement a mandatory, one per semester, discussion on aging and memory complaints with relevant literature review during the regular neurology resident Journal Clubs.

13. Collaborative Programs with other McKnight Institutes, Institutions and Research Programs

Our collaboration with the three McKnight Institutes at the Universities of Florida, Arizona and Alabama at Birmingham has continued this year on *The McKnight Brain Aging Registry.* Together, we have made great strides on the development of a standardized brain MRI protocol and neurocognitive assessment battery that will allow the collection of data on those age 85 and over without cognitive impairment. Our site will begin enrolling study patients in early 2017.

All four McKnight Institutes have partnered this year on a Frontiers in Aging Neuroscience Topic. Drs. Alexander, Cohen, Visscher, Woods and Wright are the Special Topic editors focusing on neuroimaging for the study and assessment of cognitive aging.

The research project proposal ***Augmenting Cognitive Training in Older Adults; the ACT Study was funded*** this year with **Dr. Woods** at the University of Florida as the Principal Investigator and the University of Arizona also participating. The grant was initially submitted to the NIA in response to the NIA/McKnight RFA and was subsequently redesigned and successfully re-submitted. This multisite RCT leverages the infrastructures of the cross-institutional McKnight Brain Institutes. The main objective is to examine the individual and combined impact of pairing cognitive training with transcranial direct current stimulation (tDCS) in older adults experiencing cognitive decline but not AD or MCI. Outcomes will include a comprehensive neurocognitive and clinical status, and multimodal neuroimaging of brain structure, function and metabolic state.

A Clinical Translational Workgroup was initially formed and convened at the annual Inter-Institutional meeting in Miami in 2015 to begin to address the long-term objectives. At that meeting, considerable discussion was directed at areas of expertise, interest and potential inter-institute research collaboration. Several translational, clinical and interventional translational topics were identified. It was decided that following the meeting, the Workgroup would organize these topics and consider how to move forward. Next, the group organized a brain and cognitive health working group at the 2016 Inter-Institutional meeting at the University of Arizona. ***On July 22nd 2016, the Trustees of the McKnight Brain Research Foundation approved the proposal to establish the McKnight Inter-Institutional Cognitive Aging and Memory Intervention Core (the Intervention Core)***.

Thus far, **the Intervention Core** has made significant progress toward the primary goal of rapid translation and implementation of effective interventions to reduce memory complaints, cognitive aging, memory loss, and improve brain health. Our initial timeline for completion of review of potentially effective interventions was planned for the end of 2016. We are currently on track in reaching this goal. The Intervention Core is intensively working on expedited completion of potential list of interventions at each site and on prioritizing these interventions on the basis of feasibility, resources and infrastructure across the institutions. In addition, mining the available resources in the forms of the McKnight Brain Institute annual reports, inter-institutional meeting programs and MBI websites were a valuable resource for collation of initial review. With the completion of the recent request for intervention information from the identified MBI investigators, we were able to increase the number of identified candidate cognitive aging and memory interventions. This provides the Intervention Core with a rich pool of candidate interventions for further consideration, as well as an excellent foundation towards our goal of facilitating multi-MBI site cognitive aging and memory interventions. Following the success of this initial phase (Phase 1) of the Core, we look forward to submission of a full proposal to the Trustees for the next Phase 2 of the Cognitive Aging and Memory Intervention Core.

14. Collaborative Programs with Non-McKnight Institutes, Institutions and Research Programs

Dr. Czaja is moving forward with her cutting edge research titled CREATE IV. It is an NIA/NIH funded research center in collaboration with the Georgia Institute of Technology and Florida State University. The focus of the center is on ensuring that older adults are able to use and realize the benefits of technology. This collaborative project, involving 3 universities, evaluates the impact of an innovative easy to use computer-based Personalized Reminder Information and Social Management System (PRISM 2.0) software application. It is especially designed for older adults, on the degree of social isolation and support, well-being, quality of life and functional ability among a diverse sample of older adults who live alone and are at risk for

social isolation. The study will examine the impact of PRISM 2.0 on social connectivity, engagement, social support and loneliness.

The University of Miami McKnight Institute will continue collaborating with the Northern Manhattan Study (NOMAS) at Columbia University and the Einstein Aging Study (EAS) at Albert Einstein in New York; the AHA Bugher Centers of Excellence at UCLA and the University of Colorado, Denver; and the Hispanic Communities Health Study-Study of Latinos at Michigan State. Recruitment for the Systolic Pressure Intervention Trial (SPRINT) at Wake Forest has completed enrollment and the data is in the analyses and the manuscript in preparation.

15. Briefly describe plans for future research and/or clinical initiatives

We are excited about the upcoming plans for 2017. The McKnight research projects will be in full-swing. The McKnight Brain Aging Registry will be underway as we are ready to enroll study participants. The McKnight Registry and Biorepository enrollments will surge as we pair with Dr. Gomes-Osman and her TMS research and collaborate with Dr. Levin's team on her frailty study.

Included in our repertoire of clinical initiatives is Dr. Alperin's multidisciplinary work involving sleep apnea, brain volume loss and cognitive decline in healthy elderly individuals. Another is the new research which aims to identify race/ethnic and gender gaps in stroke care for elderly patients with Atrial Fibrillation by Dr. Sacco and Dr. Rundek. Dr. Czaja will begin the multi-site ACT Study and the DUAL TARGET research project. (These projects are described in Section 9 of the report.)

Our basic science team will be examining the effect of white matter stroke on cognitive outcomes in a novel rat behavioral model. This is a new animal model in our basic science laboratory and will require a considerable amount of validity testing before using it for novel interventional approaches.

Our McKnight trainee Michelle Caunca, a MD/PhD Student will be researching the Effects of White and Gray Matter Integrity on Cognition in a Multi-Ethnic Cohort. This was a proposal submitted to the NINDS for the F30 award. She will conduct this research as a part of her PhD thesis regardless of obtaining the NIH funding.

16. If applicable, please provide endowment investment results for the report period.

See the most recent report attached. The next report will be available in mid-January, 2017.

17. Were any funds used for a Prohibited Purpose during the report period?

No funds were used for prohibited purposes.

18. Do you recommend any modification to the Purpose or mandates in the Gift Agreement?

No.

19. Did all activities during the report period further the Purpose?

Yes.

20. Please describe any negative events (loss of personnel, space, budget, etc.) that occurred during the report period and the possible impact on carrying out the Gift Agreement.

With the departure of our Scientific Director Dr. Clinton Wright, we have taken the opportunity to re-assess, build on and improve the University of Miami Evelyn F. McKnight Brain Institute,

while successfully continuing and maintaining the high quality of our research and educational portfolio.

We have started an official search for the Scientific Director of the UM Evelyn F. McKnight Brain Institute. We formed a cross-disciplinary Search Committee co-chaired by Drs. Czaja and Rundek. The Search Committee has already established and reviewed an extensive list of potential candidates. We have already had initial conversations with several potential candidates. We have posted a position in the *Neurology* journal and on several research websites and a listserv. Following our first search committee meeting Drs. Sacco and Rundek had several telephone interviews with two potential highly qualified candidates in December. An in-person interview with the first candidate has been scheduled for February 2-3, 2017. We will continue to update the Trustees on the Search Committee progress throughout the 2017.

21. Please provide any general comments or thoughts not covered elsewhere – a response is not required. Please respond only if you would like to add something not otherwise covered elsewhere.

N/A

22. What do you consider your most important scientific achievement this year?

We would like to highlight four important scientific achievements this year:

1. Dr. Sun conducted novel research on novel biomarkers in Alzheimer's Disease. This is the first human study to provide in vivo evidence that the early synaptic dysfunction is detected in the APOE ε4 carriers at risk for Alzheimer's disease. Dr. Sun's findings were published in Alzheimer's & Dementia and highlighted in Editorial commentary of the journal Nature Reviews Neurology in July of 2016.

2. Michelle Caunca, a second year MD/PhD student and our formal McKnight trainee received a competitive Internal Pilot Study grant from the University of Miami Scientific Awards Committee (SAC). The funding is for Phase II of a pilot study that will be testing the feasibility of a mobile-friendly website curriculum with a small group of stroke caregivers over the course of three months.

3. Dr. Sacco was honored with the World Stroke Organization's (WSO) President's 2016 Award for Global Stroke Leadership at the WSO's 10th World Stroke Congress in Hyderabad, India. The World Stroke Congress attracts acclaimed international stroke specialists and provides participants opportunities to refine their skills and knowledge in the field of stroke, as well as providing excellent networking opportunities and strengthening scientific collaborations to improve the care of stroke victims throughout the world.

4. Dr. Barrientos received a highly prestigious Maximizing Investigators' Research Award (MIRA), or R35 award, from the National Institute of General Medical Sciences (NIGMS). The five-year NIH grant, totaling more than $4.5 million, consolidates three R01 awards and gives Dr. Barrientos the status of "NIH investigator." He will be researching *Mitochondrial Biogenesis in Health and Disease*. The MIRA program, currently in a pilot testing phase, supports investigators' overall research programs through a single, unified grant rather than individual project grants. The goal is to provide investigators with greater stability and flexibility, thereby enhancing scientific productivity and the chances for important breakthroughs.

23. Signature, date, and title of person submitting the report.

Tatjana Rundek

Tatjana Rundek, M.D., Ph.D.
Interim Scientific Director
Evelyn F. McKnight Brain Institute

1/12/2017

Date

FINANCIAL

AND

BUDGET

SHEETS

McKnight053116

Summary

Evelyn F. McKnight Brain Institute's Endowments
at the Miller School of Medicine
Market Value Analysis
05/31/2016

2002 Gift & Match

McKnight Contribution	$5,000,000
UM Match	5,050,913
Transfers from Other University Funds	1,362,153
Investment Return	3,926,990
Distributions for Spending	(4,485,689)
05/31/16 Endowment Balance	$10,854,368
Unmatched Balance	$0

2014 Gift & Match

McKnight Contribution	$1,500,000
UM Match	2,000,000
Transfers from Other University Funds	0
Investment Return	1,194
Distributions for Spending	(96,002)
05/31/16 Endowment Balance	$3,405,192
McKnight Foundation Pledge Balance	$500,000

McKnight053116
Annual

University of Miami
Evelyn F. McKnight Brain Institute's Endowments
Summary Analysis at Market Value
June 1, 2015 - May 31, 2016

2002 Gift & Match

	Evelyn F. McKnight 262080	F.Peterson/ McKnight 262293	Schoninger Professorship in Neurology 262453	Schoninger Neuropsychology Clinic 262454	Other sources	Total
Beginning Balance at Market, 6/1/15	$7,245,253	$1,120,910	$1,017,780	$2,544,450	$0	$11,928,394
Investment Return	(318,634)	(49,296)	(44,760)	(111,900)		(524,589)
Distributions for Spending	(333,725)	(51,630)	(46,880)	(117,200)		(549,436)
Transfers from other University funds						0
Matching gifts						0
Ending Balance at Market, 05/31/16	$6,592,895	$1,019,983	$926,140	$2,315,350	$0	$10,854,368

2014 Gift & Match

	Schoninger Professor in Memory Disorders 262471	Evelyn F. McKnight Endowed Chair 262490				Total
Beginning Balance at Market, 6/1/15	$2,084,226	$1,033,569	$0	$0	$0	$3,117,795
Investment Return	(91,661)	(24,940)				(116,601)
Distributions for Spending	(96,002)	0				(96,002)
Transfers from other University funds						0
Matching gifts						0
McKnight Foundation gifts		500,000				500,000
Ending Balance at Market, 05/31/16	$1,896,564	$1,508,628	$0	$0	$0	$3,405,192

McKnight - FY17 Budget For Annual Report
June 1, 2016 - May 31, 2017

			Budget	Actual as of December 31, 2016	Projected at Year End
Revenue			***645,437.96***	***301,501.30***	***645,437.96***
Personnel					
Faculty	***Role In Project***	***Effort***			
Clinton Wright, MD (end Oct 2016)	Scientific Director	20%			
Tatjana Rundek (star t Oct 2016)	Interim Scientific Director	20%			
Ralph Sacco, MD	Executive Director	5%			
Xiaoyan Sun, MD	Educational Director	25%			
Xiaoyan Sun, MD	Research for Age-related Cog Disorder	25%			
Bonnie Levin, PHD	Neuropsychology	20%			
Noam Alperin	Radiology	5%			
Kunjan Dave	Basic Science	5%			
Jiang Hong	Neurologist	3%			
Sara Czaja	Psychiatry	4%			
Subtotal Faculty Salary and CFB			***273,632.42***	***128,737.87***	***279,618.88***
Staff	***Role in Project***	***Effort***			
Stacy Merritt	McKnight Project Manager	55%			
Ahmet Bagci	Radiology	20%			
Maria Mendoza-Puccini (end Jan 2017)	Clinical Research Coordinator	16%			
TBA / Mendoza-Puccini replacement -(start Feb 2017)	Clinical Research Coordinator	59%			
Andres DeLeon (start Aug 2016)	Research Assistant	33%			
Lucas Lages	Research Assistant	6%			
Isabel Saul	Research Support Specialist-Basic Science	28%			
Katalina McInerney	Neuropsychology	23%			
Laura Segala (endAug 2016)	Post Doctoral Associate	33%			
Annelly Bure	Research Asst for Neuro-Psychology	42%			
Sarah Getz	Post Doctoral Associate	83%			
Marina Sarno	Post Doctoral Associate	26%			
Subtotal Staff and CFB			***307,289.83***	***136,244.15***	***283,791.40***
Total Personnel			***580,922.25***	***264,982.02***	***563,410.28***
Non Personnel Expenses					
Communcations			3,500.00	1,528.60	3,500.00
Internal UM Services Provided/Animal Purchase/Supplies			10,000.00	-	10,000.00
Conference,Registration,Dues,Memberships,Travel,Postage,Freight,Printing,Publishing, etc.			10,100.00	3,752.90	16,449.07
BioRepository			1,000.00	-	1,000.00
Blood sample storage			5,000.00	-	5,000.00
Pilot awards			-	10,000.00	10,000.00
Other			21,500.00	20,187.68	21,187.68
Total Non Personnel Expenses			***63,290.93***	***36,519.28***	***82,027.68***
Grand Total Expenses			***644,213.18***	***301,501.30***	***645,437.96***
Net Operating Income			1,224.78	0.00	0.00

McKnight - FY18 - Budget Proposal
June 1, 2017 - May 31, 2018

			Budget Summary
Revenue			**738,196.08**
Personnel			
Faculty	***Role In Project***	***Effort***	
TBA - Scientific Director start date 1/1/2018	Scientific Director (5 months)	20%	24,958.33
Tatjana Rundek - supplement interim until 12/31/2017	Interim Scientific Director (7 months)	10%	17,255.11
Tatjana Rundek	Education/Professorship	10%	29,580.18
Ralph Sacco, MD	Executive Director	5%	36,407.08
Xiaoyan Sun, MD	Educational Director	10%	20,767.21
Xiaoyan Sun, MD	Research for Age-related Cognitive Disorder	25%	51,918.03
Bonnie Levin, PhD	Neuropsychology	20%	44,379.36
Kunjan Dave, PhD	Neurology - Basic Science	6%	9,161.28
Noam Alperin, MD	Radiology	10%	25,681.07
Jiang Hong, MD	Neurologist	5%	8,662.26
Sara Czaja, MD	Psychiatry	5%	19,621.50
David della Morte, PhD	Neurology		18,500.00
			-
Subtotal Faculty Salary and CFB			***306,891.40***
Staff	***Role in Project***	***Effort***	
Stacy Merritt	McKnight Project Manager	100%	106,962.08
Ahmet Bagci	Radiology	40%	14,608.81
Sang Lee	Radiology	20%	-
Digna Cabral - Main	Neurology	7%	6,925.75
TBA - Replacement Mendoza-Puccini - Main	Clinical Research Coordinator	50%	41,919.50
Andres DeLeon (start date 8/8/2016) + TBA replacing Andres	Clinical Research Coordinator	20%	10,515.40
Michelle Caunca	MD/PhD Student - Neuro	100%	28,500.00
Isabel Saul	Research Support Specialist-Basic Science	15%	15,681.33
Katalina McInerney (end 6/30/2016) - Shonninger	Neuropsychology	7%	4,493.64
Annelly Bure - end 10/31/2018	Neuropsychology	25%	16,048.70
TBA Post Doc - Clinical	Neuropsychology	25%	16,048.70
TBA Post Doc - Clinical	Neuropsychology	25%	16,048.70
TBA Post Doc - Research	Neuropsychology	100%	64,194.81
			-
Subtotal Staff and CFB			***341,947.43***
			-
Total Personnel			***648,838.84***
Non Personnel Expenses			
Communcations	phones/other		2,000.00
Internal UM Services Provided?animal purchasing/Supplies/Chemicals	Animal purchasing, shipping, DVR surcharge, Per Diem -KD		17,000.00
Conference,Registration,Dues,Memberships,Travel,Postage,Freight,Printing,Publishing, etc.	Travel - other personnel		29,857.24
Blood sample storage	Blood sample storage		3,500.00
Two 10K - Pilot awards	Two 10K - Pilot awards		20,000.00
Other			17,000.00
Total Non Personnel Expenses			***89,357.24***
Grand Total Expenses			***738,196.08***
Net Operating Income			0.00

MEMBER

AND

COLLABORATOR

BIOSKETCHES

Ralph L. Sacco, M.D., M.S., FAHA, FAAN
Evelyn F. McKnight Brain Institute Executive Director
Chairman, Department of Neurology
Olemberg Family Chair in Neurological Disorders
Miller Professor of Neurology, Public Health Sciences,
Human Genetics and Neurosurgery
Chief of Neurology Service, Jackson Memorial Hospital
University of Miami, Miller School of Medicine

Tatjana Rundek, M.D., Ph.D. FANA
Evelyn F. McKnight Brain Institute Interim Scientific Director
Professor of Neurology, Epidemiology and Public Health
Vice Chair, Clinical Research in Neurology
Director, Clinical Translational Research Division
Director, MS Degree Program in Clinical Translational Investigations
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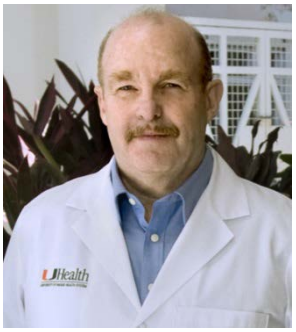

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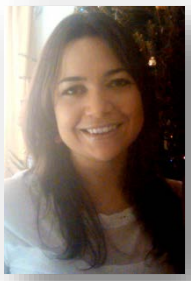

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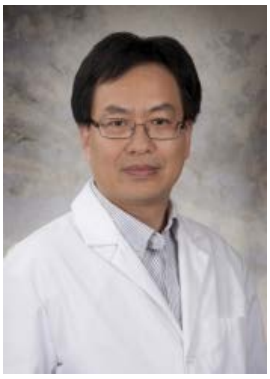
Evelyn F. McKnight Brain Institute Collaborator



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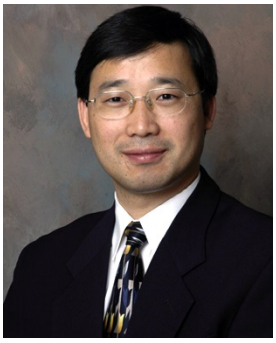
Department of Ophthalmology Bascom Palmer Eye Institute
University of Miami, Miller School of Medicine
Evelyn F. McKnight Brain Institute Collaborator



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Assistant Professor of Epidemiology
Department of Public Health Sciences
University of Miami, Miller School of Medicine
Evelyn F. McKnight Brain Institute Collaborator

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: Alperin, Noam

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

POSITION TITLE: Professor of Radiology and Biomedical Engineering

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 Tel Aviv, Israel	B.Sc.	10/1980	Physics
Hebrew University, Jerusalem		08/1983	Medicine
University of Chicago, Chicago, IL	Ph.D	8/1992	Medical Physics
University of Chicago, Chicago, IL	Postdoctoral	10/1994	MRI

A. Personal Statement

Even before attending graduate school I was attracted to medical imaging. I started my career in imaging working as a physicist in the R&D department of a medical imaging company developing digital subtraction angiography systems. During graduate school I shifted my focus to MRI, fascinated by the ability to image blood vessels and flow without the need to inject contrast agent. One of my early publications utilized blood vessels as landmarks for registering X-ray with MR angiography data (1). During my postdoctoral training I was introduced to Chiari Malformations, a poorly understood and debilitating neurosurgical problem associated with altered cerebrospinal fluid (CSF) dynamics. I used velocity-encoding MR to image and measure CSF pulsation in the cranio-spinal system and was puzzled by the large inter-individual variability, even among healthy subjects. We were among the first to investigate the relationship between CSF and blood flow pulsations and the first to demonstrate that the cranio-spinal CSF pulsation is driven by the change in the intracranial blood volume during the cardiac cycle (2). The characterization of the driving force for the CSF pulsation has clarified what information can be derived from the CSF pulsation and to the development of a novel methodology to noninvasive measure intracranial compliance and pressure by MRI (MRICP) (3). I was fortunate to receive R21 grant to demonstrate the feasibility of the MRICP method followed by RO1 grant to apply the method in the clinical setting of Chiari Malformation (the same disorder that got me involved in CSF dynamics). This effort resulted with advancement and new insight into this disorder (4). Consistent focus on the CSF physiology and dedicated research effort helped establish our group among the leaders in this field.

In the current application, we identify another CSF related clinical challenge that can benefit from the MRICP technique, the need for reliable noninvasive test to assess CSF shunt function. Incorporating the MRICP as part of a shut function test will likely yield a reliable test, which in turn, will have a significant impact on management of many pediatric and adult patients with CSF shunts. Our track record and my previous experience leading a multi-disciplinary teams will benefit the project and the likelihood for successful completion.

1. Alperin N, Levin DN, and Pelizzari CA. (1994). Retrospective registration of x-ray angiograms with MR images by using vessels as intrinsic landmarks. Journal of Magnetic Resonance Imaging, 4:139-144
2. Alperin N, Vikingstad EM, Gomez-Anson B, Levin DN. (1996). Hemodynamically-independent analysis of CSF and brain motion observed with dynamic phase-contrast MRI. Magn. Reson. in Med., 35:741-754
3. Alperin N, Lee SH, Loth F, Raksin P, Lichtor T. (2000). MR-Intracranial Pressure (ICP): A method for noninvasive measurement of intracranial pressure and elastance. Baboon and Human Study. *Radiology*, 217 (3); 877–885.
4. Alperin N, Loftus JR, Oliu CJ, Bagci AM, Lee SH, Ertl-Wagner B, Green B, Sekula R. (2014). MRI measures of Posterior Cranial Fossa Morphology and CSF Physiology in Chiari Malformation Type I. Neurosurgery 75:515–522 (Editor's Choice)

B. Positions and Honors

POSITIONS AND EMPLOYMENT

1985-1987 Physicist, Elscint Medical Imaging, Inc.
1987-1988 Product Manager, Mennen Medical, Inc.
1989-1994 Research Associate, MRI Center, University of Chicago
1994-1995 MRI Application Scientist, SMIS Inc.
1995-2001 Assistant Professor, Departments of Radiology and Bioengineering, Uni. of Illinois, Chicago
2001-2009 Associate Professor, Departments of Radiology and Bioengineering, Uni. of Illinois, Chicago
2009- Professor, Department of Radiology and Biomedical Engineering, University of Miami

Other Experience and Professional Memberships

1990-2008 Member, American Association of Medical Physicists
1994- Member, American Society of Magnetic Resonance in Medicine
2004- Ad hoc member, reviewer for several NIH study sections
2011- Member of the American Society of Neuroradiology

C. Contribution to Science

1. My early publications related to the investigations of the CSF flow dynamics aimed to characterize the origin of the cranio-spinal CSF pulsation (a-d). Effort to explain the origin of CSF pulsation started in the early 1940s where invasive measurements showed that CSF pressure pulsation is synchronous with the blood pressure pulsation. In each decade since till the late 1970s a new view of the origin of CSF pulsation was proposed, from only arterial origin through only venous origin and sometimes a complex combination of the two. In the 1990s, MRI provided new perspective into CSF pulsation, enabling quantitation of the volumes of blood and CSF entering and leaving the cranium during the cardiac cycle. Our publications adopted a system approach to describe the CSF volumetric flow rate dynamics and proposed transfer function to describe the link between CSF and blood flow, where the CSF is the output driven by the momentary difference between arterial inflow and venous outflow (the input). The CSF flow is also modulated by the mechanical properties of the intracranial compartment (i.e., compliances and resistances). This provided the first subject-specific noninvasive estimation of the lamped mechanical properties of the cranio-spinal system. This approach however, does not yield individual parameters such as the intracranial compliance, but instead, it provides measures, such as the natural frequency of the system, which is a combination of several parameters. Therefore, an alternative approach was needed to obtain a measurement of intracranial compliance from which intracranial pressure is derived.

   Alperin N, Bagci AM, Lee SH, Lam BL. Role of Cerebrospinal Fluid in Spaceflight-Induced Ocular Changes and Visual Impairment in Astronauts. Radiology (in press)

   Loewenstein D, Curiel R, Sun X, Alperin N, et al. Recovery from Proactive Semantic Interference in Mild Cognitive Impairment and Normal Aging: Relationship to Atrophy in Brain Regions Vulnerable to Alzheimer's Disease. JAD (in press)

   Obeid JP, Stoyanova R, Kwon D, Patel M, Padgett K, Slingerland J, Takita C, Alperin N, Yepes M, Zeidan YH. Multiparametric evaluation of preoperative MRI in early stage breast cancer: prognostic impact of peri-tumoral fat. Clin Transl Oncol. 2016 Jun 30. [Epub ahead of print]

   4Alperin N, Bagci AM, Lee SH, Lam B.L. Automated Quantitation of Spinal CSF Volume and Measurement of Craniospinal CSF Redistribution following Lumbar Withdrawal in Idiopathic Intracranial Hypertension. AJNR Am J Neuroradiol. 2016 Jun 9. [Epub ahead of print]

   Alperin N, Loftus JR, Bagci AM, Lee SH, Oliu CJ, Shah AH, Green BA. MRI-Based Measures Predictive of Short-Term Surgical Outcome in Chiari Malformation Type I: A Pilot Study. J Neurosurg Spine. 2016 Aug 5:1-11. [Epub ahead of print]

Alperin N, Vikingstad EM, Gomez-Anson B, Levin DN. (1996). Hemodynamically-independent analysis of CSF and brain motion observed with dynamic phase-contrast MRI. Magn. Reson. in Med., 35:741-754.

Chu D, Levin DN, and Alperin N. (1998). Assessment of the biomechanical state of intracranial tissue by dynamic MRI of Cerebrospinal fluid pulsations: a phantom study. Magn. Reson. Imag. 16:(9)1043- 48.

Alperin N, Kulkarni K, Loth F, Mafee M, Lichtor T. (2001). Analysis of MRI-Based Blood and CSF Flow Measurements in Patients with Chiari I Malformations: A System Approach. Neurosurgical Focus, 11(1):1-10.

Tain and RW, Alperin N. (2009). Noninvasive Intracranial Compliance from MRI-Based Measurements of Transcranial Blood and CSF Flows: Indirect vs. Direct Approach; IEEE Transaction in Biomedical Engineering, 56(3):544-54.

2. Following efforts were focused on developing a direct measure of intracranial compliance based on its physical definition, the change in volume for a given change in pressure (i.e., dV/dP). Our effort was motivated by the possibility to derive ICP noninvasively by MRI. Because of the mono-exponential relationship between intracranial pressure and intracranial volume, intracranial compliance is inversely related to intracranial pressure (ICP). Our initial publication demonstrated the feasibility of the MRICP

method using flow phantom, nonhuman primate model and a small number of humans (a). The volume change was derived from volumetric flow rate of blood and CSF to and from the cranium, and the pressure change was derived from the change in the pressure gradient. The following publications describe important improvements that made the MRICP method more robust. The first was the modeling of the CSF flow in the cervical canal in order to formulate the relationship between the pulse pressure and the pulse pressure gradient replacing the previous empirical relationship (b). The second important contribution was the development of a novel method for automated segmentation of lumens conducting non-steady flow for reliable quantitation of volumetric CSF and blood flow rates by MRI (c). Our lumen segmentation method incorporates temporal information in multiple images compared to available methods that are primarily based on spatial information in a single image. This method has been adopted by other investigators who utilize velocity-encoded MRI for flow quantitation (e.g., Huang et al 2004). The MRICP method is now beginning to be used independently by other groups (e.g., Muehlmann et al 2013) and by other investigators in collaboration with our group who assists with guidance and with the data analyses. For example, the MRICP methodology was very recently employed to investigate the elusive pathophysiology of *Acute Mountain Sickness*. Results published in the Annals of Neurology revealed that the severity of headaches symptoms is correlated with the change in ICP between the normal and the hypoxic conditions (d).

a. Alperin N, Lee SH, Loth F, Raksin P, Lichtor T. (2000). MR-Intracranial Pressure (ICP): A method for noninvasive measurement of intracranial pressure and elastance. Baboon and Human Study. *Radiology*, 217 (3); 877–885.

b. Loth FM, Yardimici MA, and Alperin N. (2001). Hydrodynamic modeling of Cerebrospinal Fluid Motion within the spinal cavity. Jour. of Biomechanical Engineering, 123:71-79,

c. Alperin N, Lee SH. (2003). PUBS: Pulsatility based segmentation of lumens conducting nonsteady flow, Magnetic Resonance in Medicine, 49:934–44.

d. Lawley J, Alperin N, Bagci A, Lee S, Mullins O, Oliver S, Macdonald J. (2014). Acute mountain sickness: Elevated brain volume and intracranial hypertension. Annals of Neurology. 75(6):890-8.

3. Our recently completed RO1 project focused on the potential role of the MRICP in the setting of Chiari Malformation Type I (CMI). Adult CMI affects primarily women with onset of symptoms occurring during childbearing age. Symptoms include severe headaches and motor and sensory deficits. If left untreated, patients experience poor quality of life and deficits worsen. A surgical procedure, termed decompression, where a portion of the skull base is removed, was found to provide symptomatic relief. However, due to a lack of reliable diagnostic criteria (currently diagnosis is based on an arbitrary radiologic finding of tonsilar herniation greater than 5mm), 3 to 4 out of 10 patients undergoing surgery do not improve. Therefore, there is a clear need for a fresh look at this disorder. During the award period, we collected data from CMI patients and healthy subjects. It was evident that cranial morphology, especially of the posterior cranial fossa (PCF), plays a role and should be considered together with the CSF hydrodynamics. We therefore developed an automated method for PCF parcelation (a), computed over 20 morphologic and hydrodynamic measures, and assessed differences between CMI and the control cohorts. In addition, these measures were correlated with symptomatology. The results of this work have led to a new characterization of CMI using combined morphologic-physiologic quantitative measures. We identified 10 measures that were significantly different in the CMI and were strong differentiators of CMI (b). Outcome analyses reveal that some of these new CMI markers were outside the CMI range in patients that had poor outcome following surgery. We therefore hypothesize that the combined morphologic-physiologic criterion for CMI would significantly improve diagnostic accuracy and surgical outcome. Interestingly, MRICP was among the predictive parameters and is moderately elevated in CMI. Increased ICP was proposed as a possible mechanism for CMI by the discoverer of CMI, H. Chiari, in 1891. Our latest paper on CMI addresses the different types of headaches reported in CMI (c). This work is important because neurosurgeons rely on specific symptoms for surgery consideration. We found that headaches worsen with Valsalva maneuver, which is considered a hallmark symptom of CMI, is associated with lower compliance and higher MRICP due to a smaller intracranial volume and not, as previously suggested, smaller PCF. This information has implications on utilization of symptoms in the diagnosis of CMI.

a. Bagci AM, Lee SH, Nagornaya N, Green BA, Alperin N. (2013). Automated posterior cranial fossa volumetry by MRI: applications to Chiari malformation type I. AJNR 34(9):1758-63.

b. Alperin N, Loftus JR, Oliu CJ, Bagci AM, Lee SH, Ertl-Wagner B, Green B, Sekula R. (2014*). MRI measures of Posterior Cranial Fossa Morphology and CSF Physiology in Chiari Malformation Type I*. Neurosurgery 75:515–522. (Editor's Choice)
c. Alperin N, Loftus JR, Oliu CJ, Bagci AM, Lee SH, Ertl-Wagner B, Sekula R, Lichtor T, Green AB. (2015). *Imaging-Based Features of Headaches in Chiari Malformation Type* I. Neurosurgery. Mar 23.

4. In 2010, after relocating my lab to the University of Miami I initiated collaboration with the Bascom Palmer Eye Institute focusing on another complex CSF related disorder, idiopathic intracranial hypertension (IIH). IIH is characterized by elevated ICP of unknown cause and is manifested mainly by severe headaches and often with visual impairments caused by increased CSF pressure that compresses the optic nerve and the eye globe. IIH can occur both in males and females of a wide age range, though it is most frequent in overweight women of childbearing age. Our research focused on the obesity related IIH that often presents with edema of the optic nerve (papilledema). We since published 5 important publications that were well received. Two were selected by Biomed Updater as 1st and 3rd in a list of top 20 articles in this domain published since 2013 and another article featured by AJNR news digest. Our first contribution employed our lamped parameter modeling of the cranio-spinal system to document reduced spinal canal compliance in IIH, which likely explains the associated with obesity through increased abdominal pressure (a). The following paper provided evidence for impaired CSF homeostasis and the involvement of the extra cranial venous drainage in the etiology of IIH (b). We documented increased intracranial CSF volume in the extra-ventricular spaces in IIH, consistent with the reduced ability of the spinal canal to accommodate the increased CSF volume. We made an important contribution by developing an automated method for quantitation of the eye globe deformation in IIH that provide quantitative measures of the optic nerve protrusion and posterior sclera flattening (c). Using these novel quantitative measures we found that the degree of papilledema severity is proportional to the nerve protrusion length, an observation that favors a "mechanical" over a "vascular cause of papilledema. We then correlated MRI and Optical coherence tomography (OCT) imaging of the globe and were able to translated the method to measured nerve protrusion with OCT, which is a more widely used imaging modality for the eye globes

    a. Tain RW, Bagci AM, Lam BL, Sklar EM, Ertl-Wagner B, Alperin N. (2011). Determination of cranio-spinal canal compliance distribution by MRI: Methodology and early application in idiopathic intracranial hypertension. Jour. Magn. Reson. Imag. 34:1397-404.
    b. Alperin N, Ranganathan S, Bagci AM, Adams DJ, Ertl-Wagner B, Saraf-Lavi E, Sklar E, Lam BL. (2013). MRI Evidence of Impaired CSF Homeostasis in Obesity-Associated Idiopathic Intracranial Hypertension. AJNR. 34(1):29-34.
    c. Alperin N, Bagci AM, Lam BL, Sklar E. (2013). Automated quantitation of the posterior scleral flattening and optic nerve protrusion by MRI in idiopathic intracranial hypertension. AJNR Am J Neuroradiol. 34(12):2354-9.
    d. Chang YC, Alperin N*, Bagci AM, Lee SH, Rosa PR, Giovanni G, Lam BL (2015). Relationship between Optic Nerve Protrusion Measured by OCT and MRI and Papilledema Severity. Invest Ophthalmol Vis Sci. 2015 Mar 17 (*co-first author)

5. In this section we report two recent important contributions. The first relates to another disorder of impaired CSF homeostasis that occurs in the elderly, idiopathic normal-pressure hydrocephalus (iNPH). iNPH is a reversible syndrome of gait impairment, dementia, and incontinence. Currently, the only effective treatment is surgical implantation of a shunt. The need for a pharmacologic adjunctive treatments due to high failure rates and mortality associated with shunt has been already noted at several NIH workshops. I initiated a collaboration with Weill Cornell Medical College in New York to assess the effect of acetazolamide (a drug that is effective in IIH). Results of this pilot study were recently reported in Neurology and included first radiologic evidence for the potential efficacy of pharmacologic treatment in iNPH- reversal of periventricular white matter hyperintensities in patients who had improved gait following treatment (a).

   The second contribution is related to the validity of the MRICP method. In 2005, we applied the MRICP methodology to study the effect of posture on CSF physiology in humans (b). In this publication, ICP was measured in healthy subjects noninvasively in the upright and supine positions. MRICP was lower, as

expected, in the upright posture with an average value of about 4mmHg compared to 10mmHg in the supine posture. Apparently, neurosurgeons expect mainly negative ICP values in the upright posture. We further investigated this discrepancy and found that it is related to a difference in the location of the pressure reference. We now account for the effect of the hydrostatic pressure gradient and estimate a pressure value at a more central cranial location that is compatible with invasive measurements in the upright posture (c). Mean MRICP value after adjusting for the hydrostatic pressure component is now negative, -3.4±1.7 mmHg compared to the previously unadjusted value of +4.3 ±1.8 mmHg.

a. Alperin N., Oliu CJ, Bagci AM, Lee SH, Kovanlikaya I Adams D, Katzen H, Relkin N. (2014). Low-Dose Acetazolamide Reverses Periventricular White Matter Hyperintensities in iNPH. Neurology 82:1347–1351.
b. Alperin N, Lee S, Sivaramakrishnan A, Hushek S. (2005). Quantifying the Effect of Posture on Intracranial Physiology in Humans by MRI Flow Studies, Jour. Magn. Reson. Imag. 22(5):591-596.
c. Alperin N, Lee SH, Bagci AM. (2015). MRI Measurements of Intracranial Pressure in the Upright Posture: The Effect of the Hydrostatic Pressure Gradient. J Magn Reson Imaging. Mar 9

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Alperin+N

D. Research Support

Ongoing Research Support

NNX14AB51G Alperin (PI) 08/01/14-08/31/16
Analyses of MR Imaging of CSF flow dynamics Pre and Post Space Flights
The goal of this directive contract from NASA is to identify hydrodynamic measures that are associated with developing elevated ICP in microgravity.
Role: PI

Completed Research Support

R01 NS052122 Alperin (PI) 08/01/08-01/31/14
Development and Early Clinical Evaluation of Noninvasive MRI Measurement of ICP
The goal of the study is to implement an MRI-based measurement of intracranial compliance and pressure (MR-ICP) in the clinical setup of Chiari Malformations and evaluate the role of intracranial compliance in the pathophysiology of this relatively common but poorly understood neurological problem.
Role: PI

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: **BARRIENTOS, Antoni**

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

POSITION TITLE: **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	FIELD OF STUDY
Univ. of Barcelona. Teachers' School. SPAIN	B.S.	1981-1984	Science Education
Univ. of Barcelona. School of Biology. SPAIN	B.S.	1986-1992	Fundamental Biology
Univ. of Barcelona. School of Medicine. SPAIN	Ph.D.	1993-1997	Mitochondrial Biochemistry
Uni. of Miami. School of Medicine. FL. USA	Post-doctoral fellow	1997-1999	Mitochondrial Genetics and Biochemistry
Columbia University. New York. NY. USA	Post-doctoral fellow	1999-2000	Yeast mitochondrial Genetics and Biochemistry

A. Personal Statement

The study of mitochondria and their function is critical to the understanding of key cellular functions. There are still significant gaps in knowledge about the mechanisms regulating the assembly of multisubunit membrane protein complexes, which have a dual genetic origin (nuclear and mitochondrial). The study of mitochondria is also critical to understand aging and the pathogenesis of several diseases with wide social impact, such as neurodegenerative disorders. Alterations in mitochondrial energy production are also the cause of fatal childhood diseases, mostly encephalomyopathies.

I have devoted my entire career to mitochondrial research, initially studying samples from patients and later developing novel mammalian and yeast culture models. My main research interest focuses on the **biogenesis of mitochondrial membrane complexes in health and neurological disease.** Over the last five years we have been extensively working on mitochondrial translational regulation and on the biogenesis of mitochondrial respiratory chain. We have also worked extensively on the development and characterization of yeast and mammalian cell culture models of proteotoxicity to study suppression mechanisms involving mitochondrial and cellular metabolism in the context og aging.

B. Positions and Honors

Positions:

1985-1992. Permanent position as Teacher of Sciences in Secondary Public Schools. Barcelona. SPAIN.
2000-2003. Associate Research Scientist. Dept Biological Sciences. Columbia University (New York, NY).
2003-2007. Tenure-earning track Assistant Professor. Department of Neurology. The John Macdonald Foundation. Center for Medical Genetics. University of Miami (Miami. FL)
2005-2007. Tenure-earning track Assistant Professor. Department of Biochemistry and Molecular Biology. University of Miami (Miami. FL)
June 2007 – June 2009. Tenure-earning track Associate Professor. Department of Neurology and Department of Biochemistry & Molecular Biology. University of Miami (Miami. FL)
June 2009 - June 2013. Tenured Associate Professor. Department of Neurology and Department of Biochemistry & Molecular Biology. University of Miami (Miami. FL)
June 2013 until present. Tenured Professor. Department of Neurology and Department of Biochemistry & Molecular Biology. University of Miami (Miami. FL)

Honors:

1993-1996. Pre-Doctoral Scholarship from the Spanish Government: Education of University' Professors.
1997-1999. Post-Doctoral Scholarship from the Spanish Government: Program for Research Profs. Abroad.

2003-2004. Selected candidate to represent the University of Miami for the Pew Award in Biomedical Sciences.
2004-2005. Selected candidate to represent the University of Miami for the Ellison Foundation award in Aging Research.

Editorial Responsibilities:

Ad hoc reviewer for: Cell Metabolism, Nature Genetics, Journal of Biological Chemistry, Human Molecular Genetics, Molecular Biology of the Cell, Journal of Molecular Biology, Trends Mol Med, Mitochondrion, Antioxidants and Redox Signaling, Biochemical Journal, FEBS Letters, Aging: clinical and experimental Research, Genetics in Medicine, Annals of Neurology and Neurology.

Advisory panels:

Federal Agencies

(**i**) Ad hoc reviewer for the Cellular Mechanisms of Aging and Development (CMAD) study section (NIH) and the Membrane Biology and Protein Processing (MBPP) Study Section (2011-2013). (**ii**) Ad hoc reviewer for R13 Scientific Conference Grant (NIH) since 2011. (**iii**) Stage 1 reviewer for The Fellowships ZRG1 F05-Cell Biology and Development study section (NIH) (2010). (**iv**) Stage 1 reviewer for Recovery Act RC1 (2009) and RC4 (2010) applications (NIH). (**v**) Regular member of the Membrane Biology and Protein Processing (MBPP) Study Section since 2014.

Reviewer of research grants from:

Muscular Dystrophy Association (MDA) (*ad hoc* reviewer since 2008); Italian Telethon (*ad hoc* reviewer since 2006); The British Medical Research Council (MRC) (*ad hoc* reviewer since 2008); The Spanish National Evaluation and Foresight Agency (ANEP) from the Spanish Government Ministry of Education and Science - Secretary for Universities and Research (permanent reviewer since 2004).

C. Contribution to Science

I believe I have significantly contributed to the field of mitochondrial biogenesis in health, disease and aging. Some of my most notable contributions are:

(i) Discovered a translational negative feed back regulatory system that coordinates the synthesis of mitochondrial cytochrome *c* oxidase (COX) subunit 1 with the assembly of the multimeric COX enzyme. COX, the terminal oxidase of the respiratory chain, is a hetero-oligomeric enzyme formed by subunits encoded in the nuclear and the mitochondrial DNA. Because COX contain highly reactive heme A and copper prosthetic groups, the biogenesis of this enzyme must be tightly regulated to prevent the accumulation of pro-oxidant assembly intermediates. Over the last 13 years we have discovered and characterized in yeast mitochondria the existence of a negative feedback translational regulatory system. This system coordinates the synthesis of Cox1, a mtDNA-encoded catalytic subunit containing heme A and copper centers, with its assembly into the holoenzyme. Studies during my postdoctoral training at Columbia University had shown that most COX mutants had low levels of Cox1 synthesis. Subsequently, we identified a COX1 mRNA-specific translation activator, Mss51, as the key element of the system [1]. Mss51 is a bi-functional protein that interacts with the 5'UTR of COX1 mRNA to promote translation and subsequently interacts with the newly synthesized Cox1 protein to facilitate its stability in pre-assembly complexes. Mss51 does not act alone. The mitochondrial Hsp70 chaperone Ssc1 [2] and the COX specific chaperones Cox14 [1] and Coa3 [3] dynamically interact with Mss51-containing complexes to coordinate Cox1 synthesis and assembly, and to facilitate Mss51 recycling between its two functions. Our discoveries sparked lines of investigations in several groups who have contributed to the understanding of the translational regulatory mechanism in yeast and in mammalian cells. More recently, we discovered that Mss51 binds heme [4]. This specific finding has provided a key element for a regulatory mechanism that coordinates assembly of COX, the major oxygen-consuming mitochondrial enzyme, with heme and oxygen availability for respiration and aerobic energy production. Over the last few years, researchers have found similar translational regulation mechanisms operating on the assembly of other mitochondrial OXPHOS complexes, namely the bc_1 complex or complex III and the F_oF_1 ATPase.

1 Barrientos, A.*, et al.* (2004) Mss51p and Cox14p jointly regulate mitochondrial Cox1p expression in *Saccharomyces cerevisiae*. ***EMBO J.*** 23, 3472-3482

2 Fontanesi, F.*, et al.* (2010) Mss51 and Ssc1 facilitate translational regulation of cytochrome *c* oxidase biogenesis. ***Mol. Cell. Biol.*** 30, 245-259

3 Fontanesi, F.*, et al.* (2011) Cox25 teams up with Mss51, Ssc1, and Cox14 to regulate mitochondrial COX subunit 1 expression and assembly in *Saccharomyces cerevisiae*. ***J. Biol. Chem.*** 286, 555-566

4 Soto, I.C.*, et al.* (2012) A heme-sensing mechanism in the translational regulation of mitochondrial cytochrome *c* oxidase biogenesis. ***Cell Metab.*** 16, 801-813

(ii) Discovered that mitochondrial supercomplexes or repirasomes are assembled by incorporation of individual complex subunits rather than by assembly of preexisting fully assembled complexes [5]. The structural and functional organization of the mitochondrial respiratory chain (MRC) has been a matter of debate for more than 50 years. Two models have been historically hypothesized. Following the "fluid state" model, individual MRC complexes diffuse freely in the mitochondrial inner membrane and electron transport occurs when the complexes randomly collide. Conversely, the "solid state" model proposes that OXPHOS complexes are organized in rigid higher-order assemblies known as supercomplexes or respirasomes. It is currently accepted that both organizations probably coexist, giving rise to the "dynamic aggregate" or "plasticity" model. This model suggests that OXPHOS complexes switch from freely moving to fixed structures and vice versa to adapt to changes in cellular metabolism. The mechanisms that regulate the biosynthesis of mitochondrial supercomplexes remain largely unsolved. It has been thought that supercomplexes originate by the direct association of single preassembled complexes. However, some observations had suggested that they could also form through a coordinated association of partially assembled complexes and free subunits. In collaboration with Dr. Cristina Ugalde (Spain), we reported the first human mitochondrial respirasome assembly pathway, which involves a paradigm-shifting model. Our data indicate that respirasome biogenesis involves a complex I assembly intermediate acting as a scaffold for the combined incorporation of complexes III and IV subunits, rather than originating from the association of preassembled individual holoenzymes [5]. This model allows us to explain the requirements for CI assembly, the structural interdependences among OXPHOS complexes, and why certain genetic defects affecting a single complex may lead to combined RC enzyme defects in patients. Multiple research groups are now contributing to define the proposed pathway and to identify respirasome assembly factors as facilitators the assembly process [6].

5 Moreno-Lastres, D.*, et al.* (2012) Mitochondrial Complex I Plays an Essential Role in Human Respirasome Assembly. ***Cell Metab****.* 15, 324-335
6 Barrientos, A. and Ugalde, C. (2013) I Function, Therefore I Am: Overcoming Skepticism about Mitochondrial Supercomplexes. ***Cell Metab.*** 18, 147-149

(iii) Discovered the first DEAD box RNA helicases that play roles in the assembly of the mitochondrial ribosomes in yeast and in mammals. Over the last few years we have been working on the biogenesis of the mitochondrial ribosomes. Our interest is timely because in the years of 2014-15 the structure of yeast, porcine and human mitochondrial ribosomes have been resolved by cryo-EM at 3.4-3.9 Å resolution. The process of mitoribosome assembly is complicated by the fact that the two mitoribosomal RNAs (rRNAs) are universally mitochondrion-encoded whereas all ribosomal proteins (with a single exception in yeast) are encoded in the nuclear DNA. Despite recent advances, a detailed map of the mitoribosome assembly pathway is yet to be determined. Several factors may have contributed to the paucity of information on this process both, in yeast and human cells. First, many assembly factors are yet to be identified. In this regard, we described MTG1 as the first conserved GTPase involved in the assembly of the large subunit (LSU) [7] and more recently we have characterized the first DEAD box helicase that plays a role in LSU assembly, called Mrh4 in yeast [8] and DDX28 in mammals [9]. For example, we have reported that Mrh4 binds to the 21S rRNA to facilitate the incorporation of three late-assembly LSU subunits [8]. Second, yeast ribosome assembly mutants tend to lose their mitochondrial DNA, therefore complicating their analyses. To bypass this challenge in yeast we have recently identified genetic suppressors that maintain mtDNA stability in the absence of mitoribosome assembly, thus allowing the study of assembly intermediates [8].

A recent breakthrough on mitoribosome assembly relates to the mitochondrial compartmentalization of this process**.** At least three distinct types of foci relevant to mtDNA expression have been identified and visualized within the mitochondrial matrix of human cells. Those are the mitochondrial nucleoids, RNA granules and the RNA degradosome. While it has been proposed that mitoribosome assembly could start near the nucleoids, our results show that the distinct compartment in the vicinity of the nucleoids are the RNA granules, where DDX28 and several other assembly factors localize [9]. Newly transcribed rRNAs and/or early mitoribosome assembly intermediates are probably transferred from nucleoids to the RNA granules, where mitoribosome assembly is completed. These RNA granules are therefore reminiscent of the nucleolus. Within the nucleus, the membrane-less nucleolus is organized around the chromosomal regions that contain the genes for the rRNAs, and is the site of rRNA transcription and processing, and of ribosome assembly. Equivalent features pertain to the mitochondrial RNA granule, which we have proposed to term "the mitochondriolus" [9].

7 Barrientos, A.*, et al.* (2003) *MTG1* codes for a conserved protein required for mitochondrial translation. ***Mol. Biol. Cell*** 14, 2292-2302.
8 De Silva, D.*, et al.* (2013) The DEAD-Box protein Mrh4 functions in the assembly of the mitochondrial large ribosomal subunit. ***Cell Metab****.* 18, 712-725

9 Tu, Y.T. and Barrientos, A. (2015) The Human Mitochondrial DEAD-Box Protein DDX28 Resides in RNA Granules and Functions in Mitoribosome Assembly. ***Cell Rep****.* 12, 00058-00053

(iv) Discovered that mitochondrial respiratory thresholds and ROS signaling regulate yeast chronological life span and its extension by TORC1 inhibition or caloric restriction (CR). Metabolic and mitochondrial abnormalities are a prominent feature of aging and neurodegeneration. However, the literature reports conflicting results concerning the extent and causality of the aging associated aerobic energy production decline and mitochondrial ROS-induced damage, as well as their interplay with nutritional cues. Single cell models have provided key information concerning mechanisms of aging and neurodegeneration. In collaboration with Dr. G. Shadel (Yale University), we have gained insight into the mechanism by which *tor1* mutations extend yeast chronological lifespan. We discovered that TORC1 inhibition leads to increased mitochondrial respiration and enhanced ROS production, which induced an adaptive signaling that enhances stress resistance and extends chronological life span [10]. This is an example of mitohormesis, where low levels of a stressor (i.e. ROS) promote adaptive changes resulting in stress resistance. Furthermore, we have characterized the role of mitochondrial respiration in regulating yeast lifespan and its extension by CR. We have shown that a 40% of wild-type respiration is enough to support regular life span and to allow the cells to benefit from CR-induced life span extension. However, while CR increases respiratory capacity and ROS production during growth, it induces shutdown of OXPHOS and ROS generation during chronological aging, thus contributing to extend life span [11]. Together, our data support a model in which ROS signaling and respiratory thresholds are complementary aging modulators that utilize two distinct mechanisms to achieve the same adaptive endpoint: increased stress resistance, efficient use of energy stores, and probably other beneficial effects in the stationary phase, all of which extend chronological life span [12].

10 Pan, Y.*, et al.* (2011) Regulation of yeast chronological life span by TORC1 via adaptive mitochondrial ROS signaling. ***Cell Metab****.* 13, 668-678.
11 Ocampo, A.*, et al.* (2012) Mitochondrial respiratory thresholds regulate yeast chronological life span and its extension by caloric restriction. ***Cell Metab****.* 16, 55-67
12 Barrientos, A. (2012) Complementary roles of mitochondrial respiration and ROS signaling on cellular aging and longevity. ***Aging*** *(Albany NY)* 4, 578-579

(vi) Discovered that proteotoxicities can be suppressed in yeast models by either enhancement of mitochondrial biogenesis or by increasing the levels of $NAD^{\pm}$ salvage biosynthetic enzymes.
Transgenic yeast expressing human neurodegenerative disease-relevant proteins recapitulate key features of neuronal proteotoxicity. They have facilitated the elucidation of basic cellular mechanisms of toxicity triggered by human neurotoxic proteins. For example, we reported that they reproduce the mitochondrial defects seen in patients [13]. More recently, we have developed novel models to screen for suppressors of proteotoxicity. We found that proteotoxicity can be suppressed by enhancement of mitochondrial biogenesis [14], which brought to a similar discovery in mouse models. We showed that proteotoxicity can be suppressed by overexpressing several enzymes in the NAD+ salvage biosynthetic pathway, specifically NMA1/2, QNS1, NPT1 and PNC1 [15]. Our results are consistent with those obtained in fly models for NMNAT (NMA1 homologue). We are now establishing collaborations with Dr. Grace Zhai (Molecular & Cellular Pharmacology, University of Miami) and with Dr. Lisa Ellerby (Bucks Institute, California) to test whether the four enzymes act as suppressors respectively in Drosophila and patient derived-iPSC-neuronal models of polyglutamine disorders. Results from ongoing experiments indicate that suppression is independent of sirtuins and of the catalytic activity of the enzymes. Rather, under stress, these proteins act as molecular chaperones to combat proteotoxicity [15].

13 Solans, A.*, et al* (2006) Cytotoxicity of a mutant huntingtin fragment in yeast involves early alterations in mitochondrial OXPHOS complexes II and III. ***Hum. Mol. Genet****.* 15, 3063-3081
14 Ocampo, A.*, et al.* (2010) Suppression of polyglutamine-induced cytotoxicity in *Saccharomyces cerevisiae* by enhancement of mitochondrial biogenesis. ***FASEB J****.* 24, 1431-1441
15 Ocampo, A.*, et al* (2013) NAD^{+} salvage pathway proteins suppress proteotoxicity in yeast models of neuro-degeneration by promoting the clearance of misfolded/oligomerized proteins. ***Hum. Mol. Genet****.* 22, 1699-1708

Public URL for my bibliography collection in My NCBI is http://www.ncbi.nlm.nih.gov/sites/myncbi/antoni.barrientos.1/bibliography/41138774/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

7-1-2016 / 6-39-2021. MIRA (R35) grant from NIHGMS. "*Mitochondrial biogenesis in health and disease*". We use the yeast *Saccharomyces cerevisiae* and human cultured cells as models to study assembly pathways of mitochondrial respiratory chain complexes and of mitochondrial ribosomes in wild-type strains/cell lines and other carrying mutations in evolutionary conserved respiratory chain and mitoribosome assembly factors, relevant for human mitochondrial diseases. **PI:** Antoni Barrientos.

1-1-2014 / 12-31-2018. (will be integrated in the MIRA grant by 1-1-2017) RO1 grant from NIH (NIH # R01 GM105781A). "*The biogenetic pathway of mitochondrial respirasomes*". We use yeast and human cultured cells as models to study the assembly of mitochondrial supercomplexes and respirasomes. **PI:** Antoni Barrientos.

3-1-2015 / 2-28-2019. (will be integrated in the MIRA grant by 1-1-2017) RO1 grant from NIH (NIH # R01 GM105781A). "*Biogenesis of the Mitochondrial Translation Machinery*". We use the yeast and human cultured cells as models to study the assembly of mitochondrial ribosomes, with a focus on the function of DEAD box proteins. **PI:** Antoni Barrientos.

2-1-2016 / 1-31-2019. Research Grant from the Muscular Dystrophy Association (MDA # 381828**).** "*Role of cysteine rich proteins in the assembly of human mitochondrial cytochrome c oxidase*" We study the role on COX assembly of several human proteins located in the intermembrane space. **PI:** Antoni Barrientos.

6-1-2016 / 5-30-2019. Research Grant from the Department of the Army (ARO # 65594-LS). *"Mitochondrial Regulation of Neurodegenerative Proteotoxic Stress".* We use yeast and mammalian models of polyQ diseases and α-synucleinopathies to investigate how increased mitochondrial mass, ROS-mediated signaling and mitochondrial uncoupling regulate expression of proteotoxic phenotypes. **PI:** Antoni Barrientos.

Completed Research Support over the last three years

1-1-2012 / 6-30-2016. RO1 grant from NIH (NIH # 2 R01 GM071775-06A1). "*Cytochrome c oxidase assembly in health and disease*". We use the yeast *Saccharomyces cerevisiae* and human cultured cells as models to study cytochrome *c* oxidase (COX) assembly in wild-type strains and other carrying mutations in evolutionary conserved COX assembly factors, relevant for human mitochondrial diseases. **PI:** Antoni Barrientos.

1-1-2013 / 6-30-2016. Supplement to RO1 grant from NIH (NIH # 2 R01 GM071775-06A1S3). "Macromolecular assemblies in cells". We use the human cell culture models to study COX assembly and how it is regulated at the translational level though dynamic protein-protein interactions. PI: Antoni Barrientos.

2010-2013. Research Challenge grant form the Florida Department of Health / James & Esther King Biomedical Research Program. "*Slowing degenerative processes by bolstering cellular bioenergetics*" **PI**: Antoni Barrientos, **PI**: C. T. Moraes (multiple PI grant).

2006-2011. RO1 grant from NIH (NIH # R01GM071775). Research project: "*Cytochrome c oxidase assembly in health and disease*". **PI:** Antoni Barrientos.

2009-2011. Competitive ARRA supplement NIGMS 3 R01 GM071775-04S1. Research project: "*Cytochrome c oxidase assembly in health and disease*". **PI**: Antoni Barrientos.

2011-2013. Research Grant from the Muscular Dystrophy Association. Research project: "*Characterization of novel conserved cytochrome c oxidase chaperones*". **PI**: Antoni Barrientos.

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: Blanton, Susan Halloran

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

POSITION TITLE: Professor of Human Genetics

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
Virginia Commonwealth University, Richmond VA	B.S.	1980	Biology
Virginia Commonwealth University, Richmond VA	Ph.D.	1985	Human Genetics
University of Pittsburgh, Pennsylvania	(Post-Doc)	1986	Biostatistics
Fox Chase Cancer Center, Philadelphia PA	(Post-Doc)	1988	Population Oncology

A. Personal Statement

1. I am a Genetic Epidemiologist with an interest in cognitive decline and its relationship to cardiovascular disease. I have been involved in mapping genes for complex disorders and traits for nearly three decades. These disorders include birth defects such as cleft lip/palate and clubfoot and common quantitative traits such as carotid plaque and intima media thickness. These carotid phenotypes are important for their role in cardiovascular disease and stroke. They may also impact cognition. Working with the NOMAS dataset, we are identifying primary loci associated with cognition and cognitive decline.
    a. Adams HH, Hibar DP, Chouraki V, Stein JL, Nyquist PA, Rentería ME, Trompet S, Arias-Vasquez A, Seshadri S, Desrivières S, Beecham AH, Jahanshad N, Wittfeld K, Van der Lee SJ, Abramovic L, Alhusaini S, Amin N, Andersson M, Arfanakis K, Aribisala BS, Armstrong NJ, Athanasiu L, Axelsson T, Beiser A, Bernard M, Bis JC, Blanken LM, **Blanton SH**, ….., Medland SE, Ikram MA, Thompson PM. Novel genetic loci underlying human intracranial volume identified through genome-wide association. Nat Neurosci. 2016 Oct 3. doi: 10.1038/nn.4398. [Epub ahead of print]
    b. NINDS Stroke Genetics Network (SiGN); International Stroke Genetics Consortium (ISGC). Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study. Lancet Neurol. 2015 Dec 18. pii: S1474-4422(15)00338-5. doi: 10.1016/S1474-4422(15)00338-5. PMCID: PMC4912948 [Available on 2017-06-18].
    c. Lu W, Bacino CA, Richards BS, Alvarez C, VanderMeer JE, Vella M, Ahituv N, Sikka N, Dietz FR, **Blanton SH**, Hecht JT. Studies of TBX4 and chromosome 17q23.1q23.2: an uncommon cause of nonsyndromic clubfoot. Am J Med Genet A, Jul;158A(7):1620-7, 2012. PMCID: PMC3381434.
    d. Weymouth KS, **Blanton SH**, Bamshad MJ, Beck AE, Alvarez C, Richards S, Gurnett CA, Dobbs MB, Barnes D, Mitchell LE, Hecht JT. Variants in genes that encode muscle contractile proteins influence risk for isolated clubfoot. Am J Med Genet A, Sep;155(9):2170-9, 2011. PMCID: PMC3158831.

B. Positions and Honors

Positions and Employment

1980-1983	Graduate Asst, Dept of Human Genetics, VCU, Richmond
1983-1985	Graduate Asst, Div of Human Genetics, Univ of Maryland at Baltimore
1985-1986	Research Assoc, Dept of Biostatistics, U of Pittsburgh, Pittsburgh, PA
1987-1988	Postdoc, Population Oncology, Fox Chase Cancer Ctr, Philadelphia PA
1988-1989	Instructor, Dept of Pediatrics, U of Conn Health Center, Farmington
1989-1991	Asst Professor-Research, Medical Genetics Center, U of TX, Houston
1991-1996	Asst Professor of Research, Dept of Pediatrics, UVA, Charlottesville
1996-2006	Assoc Professor of Research, Dept of Pediatrics, UVA, Charolottesville
1997-2007	Assoc Professor, Collateral Faculty, Dept of Human Genetics, VCU, Richmond, VA
2006	Assoc Research Professor, Center for Human Genetics, Duke, Durham, NC
2007-2015	Assoc Professor, Dr. John T. Macdonald Foundation Department of Human Genetics,

University of Miami Leonard M. Miller School of Medicine, Miami, Florida

2012-2015 Executive Director, John P. Hussman Institute for Human Genomics
University of Miami Leonard M. Miller School of Medicine, Miami, Florida
2015-present Associate Director, Collaborations and Compliance, John P. Hussman Institute for Human Genomics University of Miami Leonard M. Miller School of Medicine, Miami, Florida
2015-present Professor, Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Leonard M. Miller School of Medicine, Miami, Florida
2015-present Professor, Department of Otolaryngology
University of Miami Leonard M. Miller School of Medicine, Miami, Florida

Honors

1980 Phi Kappa Phi, Virginia Commonwealth University
1980 Biology Award to Outstanding Senior, Virginia Commonwealth University, Dept. of Biology
1980-1983 NIH Pre-Doctoral Fellowship, Medical College of Virginia
1982 Alpha Sigma Chi, Virginia Commonwealth University
1983-present Sigma Zi
1994 IBM Shared University Resource Award

Other Experience and Professional Memberships

1990-1995 Member, Tuberous Sclerosis Advisory Board
1995-1998 Research Proposal Reviewer, MD Anderson Cancer Center
1995-2000 Research Proposal Reviewer, Wellcome Trust, England
1997 Ad Hoc, NIDDK NIH study section
2001-2003 Ad Hoc, NINDS NIH study section NSD-C
2002/2005 Research Proposal Reviewer, Alzheimer's Association
2003-2005 Member, NINDS NIH study section NSD-C
2005/2006 Member, Special emphasis panel, NINDS
2005-2007 Member, Ad Hoc, NINDS study section NST
2007-2011 Member, NINDS study section NST
2008-2013 Editorial Board, Journal of Biomedicine and Biotechnology
2008 Reviewer, March of Dimes
2011 NCBDDD, Fragile X/Rare Disorders special emphasis panel
2012 Research proposal Reviewer, Gallaudet Research Institute
2014 Field Reviewer, CDC study section, Center for Research and Training to Promote the Health of People with Developmental and Other Disabilities
2015 Member, NICHD, ZHD1 DRG-D (13), special emphasis panel (April 8, 2015)

C. Contribution to Science

1. I have played a major role in the mapping of Mendelian disorders since the early days of linkage analysis. For some of these disorders, this was the first gene identified, providing insight into the underlying mechanism. While my role has primarily revolved around the analysis of the data, I am also involved in other aspects, including study design, phenotype definition and sample collection.

    a. **Halloran SL**, Boughman JA, Dryja TP, Mukai S, Long D, Roberts DF and Craft AW. Accuracy of detection of the retinoblastoma gene by esterase D linkage. Arch Ophthal, 103(9):1329-1331, 1984
    b. **Blanton SH**, Heckenlively JR, Cottingham AW, Freidman J, Sadler LA, Wagner M, Freidman LH and Daiger SP. Linkage mapping of autosomal dominant retinitis pigmentosa (RP1) to the pericentric region of human chromosome 8. Genomics, 11:857-869, 1991.
    c. Kumar A, Girimaji SC, Duvvari MR, **Blanton SH**. Mutations in *STIL,* encoding a pericentriolar and centrosomal protein, cause primary microcephaly. Am J Hum Genet, Feb;84(2):286-290, 2009. PMCID: PMC2668020.
    d. Sullivan LS, Koboldt DC, Bowne SJ, Lang S, **Blanton SH**, Cadena E, Avery CE, Lewis RA, Webb-Jones K, Wheaton DH, Birch DG, Coussa R, Ren H, Lopez I, Chakarova C, Koenekoop RK, Garcia CA, Fulton RS, Wilson RK, Weinstock GM, Daiger SP. A Dominant Mutation in

Hexokinase 1 (HK1) Causes Retinitis Pigmentosa. Invest Ophthalmol Vis Sci. 2014 Sep 4;55(11):7147-58. PMCID: PMC4224580.

2. In addition to identification of the loci for a variety of Mendelian disorders, I have also played a key role in the establishment of heterogeneity and phenotype-genotype correlations in these disorders. This information is critical for reliable counseling of affected individuals and their families, as well as providing insight into disease etiology.

   a. Northrup H, Kwiatkowski DJ, Roach ES, Dobyns WB, Lewis RA, Herman GE, Rodriguez E, Daiger SP and **Blanton SH.** Evidence for genetic locus heterogeneity in tuberous sclerosis: one locus on chromosome 9 and at least one locus elsewhere. Am J Hum Genet, 51(4):709-720, 1992. PMCID: PMC1682771.
   b. Cook A, Raskind W, **Blanton SH**, Pauli RM, Gregg RG, Francomano CA, Puffenberger E, Conrad EU, Schmale G, Schallenberg G, Wijsman E, Hecht JT, Wells D, Wagner MJ. Genetic heterogeneity in families with hereditary multiple exostoses. Am J Hum Gen, 53:71-79, 1993. PMCID: PMC1682231.
   c. Daiger SP, Bowne SJ, Sullivan LS, **Blanton SH**, Weinstock GM, Koboldt DC, Fulton RS, Larsen D, Humphries P, Humphries MM, Pierce EA, Chen R, Li Y. Application of Next-Generation Sequencing to Identify Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa (adRP). Adv Exp Med Biol, Mar 25;801:123-9, 2014. PMCID: PMC4121110.
   d. **Blanton SH,** Burt A, Garcia E, Mulliken JB, Stal S, Hecht JT. Ethnic Heterogeneity of IRF6 AP-2a Binding Site Promoter SNP Association With Nonsyndromic Cleft Lip and Palate. Cleft Palate Craniofac J, Nov;47(6):574-7, 2010. PMCID: PMC3039881.

3. I have been studying different aspects of deafness for almost two decades. In addition to mapping novel genetic loci for Mendelian forms, I have contributed to the delineation of the heterogeneity, phenotype-genotype correlations, and population genetics, as well as social aspects of hearing loss.

   a. **Blanton SH**, Nance WE, Norris VW, Welch KO, Burt A, Pandya A, Arnos KS. Fitness among individuals with early childhood deafness: studies in alumni families from Gallaudet University. Ann Hum Genet, Jan;74(1):27-33, 2010. PMCID: PMC2804774.
   b. Dodson KM, **Blanton SH**, Welch KO, Norris VW, Nuzzo RL, Wegelin JA, Marin RS, Nance WE, Pandya A, Arnos KS. Vestibular dysfunction in DFNB1 deafness. Am J Med Genet A, May;155(5):993-1000, 2011. PMCID: PMC3080433.
   c. Lasisi A, Bademci G, Foster J, **Blanton S**, Tekin M. Common Genes for Non-syndromic Deafness are uncommon in Sub Saharan Africa: A report from Nigeria. Int J Pediatr Otorhinolaryngol. 2014 Nov;78(11):1870-3. doi: 10.1016/j.ijporl.2014.08.014. PMCID: PMC4208623 [Available on 2015-11-01].
   d. Tekin D, Tutar E, Ozturkmen Akay H, **Blanton S**, Foster J 2nd, Tekin M. Comprehensive genetic testing can save lives in hereditary hearing loss. Clin Genet. 2014 Apr 2. doi: 10.1111/cge.12376. [Epub ahead of print], 2014. PMC Journal-In-Process.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/susan.blanton.1/bibliography/43755049/public/?sort=date&direction=ascending

D. Research Support

Most Relevant Research Support

7R01NS040807-09 (Sacco, Ralph) 10/01/09-06/30/17
NINDS
"Family Study of Stroke Risk and Carotid Atherosclerosis"
The purpose of this grant is to identify genetic determinants of quantitative cerebrovascular risk phenotypes. Role: Co-investigator

Ongoing Research Support

2 P50 DC000422-26 (Dubno, J) (Med Univ SC) 10/01/13–09/30/18
NIH/NIDCD
(Liu, X – subcontract Project 3)
"Experimental and Clinical Studies of Presbyacusis –
Project 3: Identification of Susceptibility Genes for Age-Related Hearing Loss"
This proposal will investigate the genetic and molecular basis of human presbyacusis.
Role: Co-Investigator on Project 3

1R01 DC012836-04 (Tekin, M) 03/01/13-02/28/18
NIH
"Genetic Studies of Inner Ear Anomalies"
The goals of the project are to identify new genes for deafness associated with inner ear anomalies and to establish a resource for research in inner ear anomalies including biological samples and clinical data from large numbers of affected families. Role: Co-Investigator

1R01DC012115-01A1-04 (Liu, X) 03/08/13 – 02/28/18
NIH
"Implementing Genomic Medicine in Clinical Care of Deaf Patients"
We will develop a comprehensive genetic testing platform and genomic deafness database for clinical care of deaf individuals to: 1) improve the clinical care of deaf and hard of hearing persons; and 2) determine the epidemiology of hereditary hearing loss in the United States. The successful completion of the proposed aims will significantly improve our ability to provide genetic counseling for affected patients/families and to expand our knowledge on the genomic basis of hereditary hearing.
Role: Co-Investigator

1 R01 DC009645-01A2-07 (Tekin, M) 06/01/10-05/31/16 *(no-cost extension)*
NIH
"*A Collaborative Search for New Genes for Non-Syndromic Deafness"*
The purpose of this grant is to identify new genes for deafness in inbred families from Turkey.
Role: Co-investigator

2R01DE011931-13 (Hecht, J; Blanton S) University of Texas 12/26/12-11/30/17
NIH-NIDCR
"Mapping nonsyndromic cleft lip and palate genetic loci"
Nonsyndromic cleft lip with or without cleft palate (NSCLP) is a common birth defect affecting 4000 newborns in the US and 135,000 worldwide each year. The etiology is poorly understood and currently, only 20% of the NSCLP genetic liability has been identified, limiting our ability to identify at-risk individuals or provide accurate counseling for families. In these studies, we apply the newest technology to identify the genetic variation underlying NSCLP in families with multiple cases, will test the variants for expression and functionality in a fish model and develop ethnic-specific risks. The results of this study will ultimately be utilized to identify and test for potential at-risk genotypes.
Role: Principal Investigator

Completed Research Support *(Last Three Years)*
1R01NS065114-05 (Tatjana Rundek, Susan Blanton) 07/01/10-06/30/16 *(no-cost extension)*
NIH-NINDS
"Novel factors for unexplained extreme phenotypes of subclinical atherosclerosis"
The purpose of this grant is to identify genes associated with extreme phenotypes of subclinical atherosclerosis.
Role: Principal Investigator

1U54NS0657-12-03 (Shy, ME) 09/01/09-08/31/14
NIH/RDCRC/WSU
"Inherited Neuropathies Consortium - Project 2: Inherited neuropathies; an integrated approach leading to therapy".

The proposed CMT consortium will deliver high quality clinical data and collect a large number of CMT families/patients;. apply innovative study designs using the latest technology to tackle some of the most pressing genetic issues in CMT that will ultimately pave the way for new therapeutic approaches.
Role: Senior Statistical Geneticist and Epidemiologist

2 T15 HG000026-17 (Scott, WK) 03/01/10-11/30/14
NIH/NHGRI
"Genetic Analysis Methods for Medical Researchers"
In order to successfully move into the next phase of disease gene mapping, and thus attain one of the primary goals of the Human Genome Initiative, it is critical that physician scientists and laboratory scientists be educated with respect to pedigree ascertainment, sampling and basic gene localization experimental design along with the understanding of the plethora of analytic tools available.
Role: Co-course organizer.
(Dong, C) 07/01/11-06/30/13
James and Esther King Biomedical Research
"Gene-Smoking Interactions and Athersoclerosis"
Role: Collaborator

5R01NS047655-07 (Rundek) PI – University of Miami 01/01/04-03/31/13
"Genetic Determinants of Subclinical Carotid Disease"
The main goal of this research is to study the genetic polymorphisms associated with carotid IMT and distensibility in the three race/ethnic groups (whites, blacks and Hispanics) from the Northern Manhattan Study (NOMAS) cohort.
Role: Co-Investigator

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: Crocco, Elizabeth A.

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

POSITION TITLE: Associate Clinical Professor of Psychiatry and Behavioral Sciences

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
Douglas College, Rutgers University, New Brunswick, NJ	B.A.	05/1989	Biology
Rutgers-Robert Wood Johnson Medical School, Piscataway, NJ	M.D.	05/1993	Medicine
Mount Sinai Medical Center, New York, NY	Residency	06/1997	General Psychiatry
Mount Sinai Medical Center, New York, NY	Admin.Chief Resident	06/1997	General Psychiatry
University of Miami/Jackson Memorial Hospital, Miami, FL	Fellowship/ Chief Fellow	06/1998	Geriatric Psychiatry

A. Personal Statement

I am currently the Director of the Memory Disorders Clinic (MDC) at the University Of Miami Miller School Of Medicine. I am Board-Certified in the sub-specialty of Geriatric Psychiatry. As the Director of the University of Miami Memory Disorder Clinic, I am an expert in conduct comprehensive memory disorder evaluations and other patient examinations and participate in multidisciplinary staffing conferences to determine patient diagnosis and treatment in neurodegenerative diseases as part of our Registry. I am a key educator on aging and aging issues for medical students, residents, and fellows at UM/Jackson Memorial Hospital as well as the South Florida Community. I am also involved in support, education and interventions to assist their caregivers. In the UM Center on Aging, I have collaborated on several successful caregiving intervention studies with Dr. Sara Czaja. I have had a significant role in both developing and testing novel neuropsychological and functional measures developed to detect Mild Cognitive Impairment (MCI) and preclinical MCI leading to Alzheimer's Dementia (AD).

a. **Crocco, EA**, Sabbag, S, Curiel, R. Bipolar Disorder in the Elderly, In: *The Bipolar Book: History, Neurobiology and Treatment,* A Yildiz, P Ruiz, CB Nemeroff, ed., Oxford University Press: NY, Chapter 40, 2015**.** ISBN: 978-0-199-30053-2

b. **Crocco, EA**, Eisdorfer, C. Research in Mental Health and Caregiving, In: *The Challenges of Mental Health and Caregiving,* RC Talley, GL Fricchion, BG Druss ed., Springer, NY, 205-221, 2014. ISBN: 978-1-4614-8791-3

c. Ownby, R.L., Hertzog, C., **Crocco, E.**, & Duara, R. (2006). Factors related to medication adherence in memory disorder clinic patients. Aging and Mental Health, 10(4), 378-385. PMCID: PMC3543157.

d. **Crocco, EA**, Sabbag, S (in Press). Cholinesterase Inhibitors and Memantine, In: *Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Tenth Edition*, BJ Sadock, VA Sadock, P Ruiz ed., Lippincott Williams & Wilkins: Philadelphia, PA

B. Positions and Honors

Positions and Employment

1998-2006	Clinical Director of Psychiatry, Wien Center for Memory Disorder, Mount Sinai Medical Center, Miami Beach, FL
1998-2015	Clinical Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL
2001-	Director, Geriatric Psychiatry Training Program, Jackson Memorial Hospital, Department of Psychiatry and Behavioral Sciences, Miami, FL
2001-2006	Clinical Director of Consultation-Liaison Psychiatry, Mt. Sinai Medical Center, Miami Beach, FL
2000-2006	Medical Director, Mount Sinai Medical Center Geriatric Psychiatry Inpatient Unit, Miami, FL
2006-	Medical Director, Geriatric Medical/Psychiatry Inpatient Unit, Jackson Memorial Hospital, Miami, FL
2010-	Director, Memory Disorder Center, Department of Psychiatry and Behavioral Sciences, Miller School of Medicine at University of Miami, FL
2009-	Division Chief, Geriatric Psychiatry, Department of Psychiatry and Behavioral Sciences, Miller School of Medicine at University of Miami, Miami, FL
2015-	Associate Clinical Professor, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL

Other Experience and Professional Memberships

1994-2009	Member, American Psychiatric Association
1998-	Member, American Association of Geriatric Psychiatry
2003-	Florida Psychiatric Society
2009-2014	Fellow, American Psychiatric Association
2013-	Associate Member, Academy of Medical Educators, University of Miami Miller School of Medicine
2014-	Distinguished Fellow, American Psychiatric Association
2014-	Member, The American College of Psychiatrists
2014-	Member, Gerontological Society of America
2014-	Member, Anxiety and Depression Association of America

Honors

2007, 2008	Geriatric Psychiatry Training Program Teacher of the Year Award, JMH, Miami, FL
2010	University of Miami/Miller School of Medicine Faculty Citizenship Award, Miami, FL
2010	Nancy C.A. Roeske, M.D., Certificate of Recognition for Excellence in Medical Student Education, American Psychiatric Association
2011	Irma Bland Certificate of Excellence in Teaching Residents, American Psychiatric Association
2012	Geriatric Fellowship Excellence in Teaching Award, JMH, Miami, F

C. Contribution to Science

1. **Early detection of Alzheimer's disease and Mild Cognitive Impairment (MCI):** I have had a significant role in both developing and testing novel neuropsychological and functional measures developed to detect Mild Cognitive Impairment (MCI) and preclinical MCI leading to Alzheimer's Dementia (AD). The importance of early detection of AD is crucial to the current science in testing and developing disease-modifying treatment for this neurodegenerative disease. I have served as Co-PI on 1 NIA-funded grant previously (2003-2008) and am currently Co-PI on a current 5 year study predicting rates of cognitive decline in the elderly using these measures over 5 years in conjunction with other select diagnostic biomarkers and tests such as atrophy on structural Brain MRI, amyloid, tau and phosphorylated tau in CSF as well as ApoE4 genotype. I have worked closely with both Dr. David Loewenstein and Dr. Sara Czaja in

this important field and have had several significant publications documenting this important work.

a. **Crocco, E.**, Curiel, R.E., Acevedo, A., Czaja, S.J., & Loewenstein, D.A. (2014). An evaluation of deficits in semantic cueing and proactive and retroactive interference as early features of Alzheimer's disease. The American Journal of Geriatric Psychiatry*,* 22(9), 889-897.

b. Curiel, R., **Crocco, E.,** Duara, R., Acevedo, A. & Loewenstein, D.A. (2013). A new scale for the evaluation of proactive and retroactive interference in Mild Cognitive Impairment and early Alzheimer's disease. Journal of Aging Science*,* 24(10): 804-813.

c. Loewenstein, D.A., Acevedo, A., Small, B.J., Agron, J., **Crocco, E.**, & Duara, R. (2009). Stability of different subtypes of mild cognitive impairment among the elderly over a 2-to 3-year follow-up period. Dementia and Geriatric Cognitive Disorders*,* 27(5), 418-23. PMCID: PMC2814021.

d. Loewenstein, D.A., Acevedo, A., Agron, J., Isaacson, R., Strauman, S., **Crocco, E.**, Barker, W., & Duara, R. (2006). Cognitive profiles in Alzheimer's disease and in mild cognitive impairment of different etiologies. Dementia and Geriatric Cognitive Disorder, 21(5-6), 309-315.

2) **Depression and Cognition**: The relationship between depression and cognitive impairment in the elderly is important but is not well delineated. The role of depression as risk factor, prodromal event, or symptom of dementia is not well understood. I have published several journal articles related to cognition and dementia in the elderly. This includes a widely cited meta-analysis and meta regression analysis relating early depression as a risk factor for Alzheimer's disease (AD). I have also published on the relationship of depression and other psychiatric symptoms in MCI and cognitive changes related to geriatric depression in general.

a. Ownby, R.L., **Crocco, E.**, Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer's disease: systematic review, meta-analysis and meta-regression analysis.The Archives of General Psychiatry,63(5), 530-538. PMCID: PMC3530614.

b. **Crocco, E.A.**, Castro, K., & Loewenstein, D. (2010). How late-life depression affects cognition: neural mechanisms. Current Psychiatric Reports, 12(1): 34-38.

c. **Crocco, E.** & Loewenstein, D.A. (2005). Psychiatric aspects of mild cognitive impairment. Current Psychiatric Reports, 7(1), 32-36.

d. Duara, R, Loewenstein, DA, Wright, C, **Crocco, E**, Varon, D. Mild Cognitive Impairment, In: *Neurology in Practice: Dementia*, J Quinn ed.,Wiley-Blackwell Pub, UK, Chapter 6, 2014 ISBN: 978-0-470-67424-6

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Pg52WCUHj95C/bibliography/47914940/public/?sort=date&direction=ascending

D. Research Support
Ongoing Research Support

XZ203 State of Florida Department of Elder Affairs Crocco(PI) 05/2010-Present
Alzheimer's Disease Initiative/Memory Disorder Clinic
The University of Miami Memory Disorders Clinic (MDC) is funded by an ongoing state of Florida Department of Elder Affairs contract. The role of the Principal Investigator in the clinic is to provide clinical and diagnostic services, research and training for individuals about Alzheimer's disease or related disorders, as well as to their caregivers.
Role: Principal Investigator

1R01AG047649-01A1 Loewenstein (PI) 02/01/15-01/31/20
National Institute on Aging
Novel Detection of Cognitive and Functional Impairment in the Elderly
The role of the Co-investigator is to examine the utility of a unique set of neuropsychological and daily functioning tests in individuals ranging from cognitively normal (NC) to those with preclinical mild cognitive impairment (preMCI) and those with amnestic mild cognitive impairment (aMCI), in combination with select diagnostic biomarkers and tests such as atrophy on structural MRI, amyloid, tau and phosphorylated tau biomarkers in CSF and in predicting rate of cognitive decline.
Role: Co-Investigator

1 R01 AG047146-03 Devanand (PI) 2015-2018
National Institute on Aging
Treatment of Psychosis and Agitation in Alzheimer's Disease (Lithium Study)
I am a Co PI with a subcontract involved in the recruitment of patients in this study examining the effects of lithium on psychosis ad agitation in Alzheimer's disease.
Role: Co-Investigator

PI: Avanir Pharmaceuticals. A Phase 3, Multicenter, Long-term, Extension Study of the Safety and Efficacy of AVP-786 (deuterated [d6] dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type, 2016-

PI: Avanir Pharmaceuticals. A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type. 2016-

PI: Neurim Pharmaceuticals. Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Rannfing study of Piromelatine in patients with mild dementia due to Alzheimer's disease
Sponsor. 2016-

Co-Investigator: Merk & Co. A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial to Study the Efficacy and Safety of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal AD). 2016-

Co-Investigator: Toyama Chemical Co. LTD. Protocol T817MAUS202: A Phase 2 multi-center, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild to moderate Alzheimer's Disease (US202) 2014-

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: **Sara J. Czaja, PhD**

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

POSITION TITLE: **Professor/Director Center on Aging**

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	FIELD OF STUDY
State University of NY College at Buffalo, NY	B.S.	1975	Psychology
State University of NY at Buffalo, NY	M.S.	1976	Industrial Engineering
State University of NY at Buffalo, NY	Ph.D.	1980	Human Factors/Industrial Engineering

A. Personal Statement

Overall, I am well recognized for my expertise in aging and behavioral intervention research. Specifically I have extensive experience in interventions aimed at diverse populations of family caregivers of patients with AD as well as older adults of varying levels of cognitive and functional status. I served at these PI for the Miami site of the Resources for Enhancing Alzheimer's Caregivers Health (REACH II) program; the PI of the REACH Community Program and the VideoCare projects. Each of these projects were concerned with developing and delivering interventions to family caregivers of older adults. I am currently the PI of an NIH funded study (Caring for the Caregiver Network), which is evaluating an technology-based psychosocial interventions for diverse family caregivers of AD patients. I am also serving on an Institute of Medicine (IOM) Committee that is focusing on family caregivers of older adults and recently I served on an IOM Committee concerned with cognitive aging. I am also the PI of a project which is evaluating a functional skills training program, using computer-based simulations of everyday tasks developed at the UM Center on Aging, with Schizophrenia patients and non-impaired older adults. In addition, I have vast expertise with technology-based interventions and with the implementation of these interventions with diverse older adult populations including the oldest old. A particular focus of our work at the Center on Aging at the University of Miami Miller School of Medicine of which I am the Director, has been on aging and cognition and on strategies to enhance the functional performance of older people. Our approach to interventions is based on a person-centered design approach, which is commensurate with my background in Industrial Engineering. I am also the Director of the NIH, multi-site Center for Research on Aging and Technology Enhancement (CREATE). CREATE has been funded for the past 16 years and focuses on the interaction of older adults with technology systems in living, work and healthcare settings. We recently completed a cross-site trial, The PRISM Trial, which evaluated the efficacy of a software application in enhancing the well-being and social connectively of older adults (aged 65+) who live alone in the community and were at risk for social isolation. I have received extensive funding from the NIH in these areas and am also well published (examples provided below in the description of my scientific contributions).

B. Positions and Honors

1980-1982Senior Research Associate, Buffalo Organization for Social and Technological Innovation, Inc
1984-1988Assistant Professor, Department of Industrial Engineering, SUNY at Buffalo
1988-1991Associate Professor, Tenured, Department of Industrial Engineering, SUNY at Buffalo
1989-1990Research Associate, Professor, Department of Industrial Engineering, University of Miami
1988-1993Research Director, Stein Gerontological Institute, Miami, FL
1991-1994Associate Professor, Department of Industrial Engineering, University of Miami
1993-1999Director, Center on Human Factors & Aging Research, University of Miami School of Medicine
1994-present Professor, Dept. of Psychiatry and Behavioral Sciences, University of Miami School of Medicine
1994-present Professor, Department of Industrial Engineering, University of Miami, Coral Gables, FL
1999-present Director, Center on Aging and Technology Research, University of Miami School of Medicine
2002-present Co-Director, Center on Aging, University of Miami, Miami, FL
2010-present Scientific Director, Center on Aging, University of Miami Miller School of Medicine
2016-present Director, Center on Aging, University of Miami Miller School of Medicine

Honors
APA Inaugural Recipient Prize for Interdisciplinary Team Research, CREATE Team, October 2016
M. Powell Lawton Distinguished Contribution Award for Applied Gerontology, August 2015
Panel Member, Nobel Prize Week Dialogue, Stockholm Sweden, December 2014
Jack A. Kraft Award for Innovation, Human Factors and Ergonomics Society, 2013
Social Impact Award for the Association of Computing Machinery (ACM), Special Interest Group for Human Computer Interaction (SIGCHI), 2013
The Scottish Informatics & Computer Science Alliance Distinguished Visiting Professor, School of Computing, University of Dundee, March, 2010.
IBM, University Cooperative Research Award, 2007-2009.
IBM Faculty Award, 2006
Provost's Scholarly Activity Award, 1998.
Researcher of the Year, College of Engineering, University of Miami, 1995.

C. Contribution to Science

1. A key area of my research has been on issues surrounding family caregiving. I have a very active research portfolio and publication record in the area of family caregiving for the past several decades. My work has focused on diverse family caregiver populations for a broad range of patient populations including patients with dementia, spinal cord injury, cancer, chronic fatigue syndrome and LGBT elders. This work has been funded by the National Institutes of Health, the Administration on Aging, the Retirement Research and Langeloth Foundations, Johnson & Johnson, AT&T, Cisco and the Community Alliance Against Aids.
In terms of specifics, I served as the PI for the Miami site for the Resources to Enhance Caregiver Health (REACH) project and as the Co-PI on a study examining caregiving issues for family caregivers of Spinal Cord Injured Patients. I am currently the PI of a study that is evaluating efficacy of a technology-based culturally tailored psychosocial intervention for minority family caregivers and Co-PI on a project that is examining partners of patients with chronic fatigue syndrome. The NIH has provided support for all of these projects. I completed a project that examined issues confronted by working caregivers and a demonstration project, funded by the Administration on Aging, that involved collaboration with a community agency to translate the evidenced-based REACH II intervention in community settings. A unique feature of my work in the area of caregiving has been on the examination of the use of technology to deliver programs and services to family caregivers in diverse contexts. Examples of relevant publications include

Czaja, S.J. (2016). Long term care services and supports for older adults: The role of Technology. *American Psychologist*, Vol 71, No. 4, 294-301.
Czaja, S.J., Sabbag, S., Lee, C.C., Schulz, R., Lang, S., Vlahovic, T., Jaret, A.J., Thurston, C. (2015). "Concerns about aging and caregiving among middle-aged and older Lesbian and Gay Adults". *Aging & Mental Health*, doi:10.1080/13607863.2015.1072795.
Czaja, S.J., Loewenstein, D., Schulz, R., Nair, S.N., Perdomo, D. (2013) A Videophone Psychosocial Intervention for Dementia Caregivers. Nov; 21(11):1071-81. doi: 10.1016/j.jagp.2013.02.019. E pub 2013 Jul 3. Am J of Geriatric Psychiatry.
Czaja, S.J., Gitlin, L.N., Schulz, R., Zhang, S., Burgio, D., Stevens, A.B., Nichols, L.O., Gallagher-Thompson, D. (2009) Development of the Risk Appraisal Measure (RAM): A Brief Screen to Identify Risk Areas and Guide Interventions for Dementia Caregivers*. J AM Geriatr Soc 57:1064-1072.*
Czaja, S.J. (contributing author) (2006). Enhancing the Quality of Life of Hispanic/Latino, Black/African American, and White/Caucasian Dementia Caregivers: The REACH II Randomized Controlled Trial REACH II Investigators. *Annals of Internal Medicine, 145, 727-738.*
Belle, S. H., Zhang, S., **Czaja, S.J**., Burns, R., & Schulz, R. (2004). Cognitive enhancement medication utilization among persons with Alzheimer's disease who have a family caregiver: Findings from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) project. *American Journal of Geriatric Psychiatry, 12,* 250-257.
Eisdorfer, C. E., **Czaja, S. J**., Loewenstein, D. L., Rubert, M. P., Arguelles, S., Mitrani, V., & Szapocznik, J. (2003). The effect of a family therapy and technology-based intervention on caregiver depression. *The Gerontologist, 43 (4)* 521-531.

2. A second key area is related to cognition and functional assessment in diverse older populations. A central focus of this work is on understanding the implications of normative age-related changes in cognition for everyday functioning and the performance of everyday tasks. An additional focus is on understanding how conditions such as mild cognitive impairment or persistent mental illnesses such as schizophrenia impact on cognition and everyday functioning. In addition we are examining the efficacy of cognitive remediation strategies in improving functional performance. I currently am the PI (Dr. Philip Harvey and Dr. David Loewenstein are Co-PIs) of a grant from the National Institute on Aging that is focusing on these issues with older adults with Schizophrenia (Czaja, S.J., Harvey, P., Loewenstein, D., PI's 1R21AG041740-01, NIH/NIA, Title: "Improving the Functional Outcomes in Older Adults with Schizophrenia".) Some relevant publications in this area include:

Crocco, E., Curiel, R.E., Acevedo, A., **Czaja, S.J**., Loewenstein, D.A. (2014). An Evaluation of Deficits in Semantic Cuing, Proactive and Retroactive Interferences as Early Features of Alzheimer's Disease. The American Journal of Geriatric Psychiatry, Vol. 22, Issue 9, pg. 889-897, September. Harvey, P.D., Stone, L., Loewenstein, D., **Czaja, S.J**., Heaton, R.K., Twamley, E.W., Patterson, T.L. (2013) The convergence between self-reports and observer ratings of financial skills and direct assessments of financial capabilities in patients with schizophrenia: More detail is not always better. Schizophrenia Research 147 (2013) 86-90.
Harvey, Phillip D., Loewenstein, D., **Czaja, S.J**. (2013) Hospitalization and Psychosis: Influences on the Course of Cognition and Everyday Functioning in People with Schizophrenia. Neurobiology of Disease 53 (2013) 18-25. **Czaja S. J.** & Loewenstein, D. (2013) Cognition and Functional Status in Adult and Older Patients with Schizophrenia. In P.D. Harvey (Ed.). Cognitive Impairment in Schizophrenia). London: Cambridge University Press (pp. 110-125).

3. A third key area of my contribution relevant to this application is in behavioral intervention research. Most notably, in the use of technology to deliver interventions to diverse populations of older adults and family caregivers. I have also received extensive NIH funding and funding from foundations such as the Retirement Research Foundation and the Langeloth Foundation for this work and am widely published in this area. For example, I am currently the Principal Investigator of a study funded by the National Institute of Nursing Research (NINR) that is examining the efficacy of an evidenced-based caregiver intervention delivered via technology for minority caregivers of patients with dementia (1R01NR014434-01, Czaja, S.J., PI NINR/NIH A Tailored Technology Intervention for Diverse Family Caregivers of AD Patients".) As

noted, in my personal statement, I also recently served as PI for an NIH funded (as part of CREATE) multi-site randomized clinical trial that examined the efficacy of a software application in enhancing the well-being and social connectively of older adults (aged 65+) who live alone in the community and were at risk for social isolation (The PRISM TRIAL). Examples of relevant publications in this area include:

Czaja, S. J., Zarcadoolas, C., Vaughon, W., Lee, C. C., Rockoff, M., & Levy, J. (2015). The Usability of Electronic Personal Health Record System for an underserved Adult Population. Human Factors. Vol. 57, No. 3, pp. 491-506, DOI: 10.1177/0018720814549238 May.

Czaja, S. J., Boot, W. R., Charness, N., Rogers, W. A., Sharit, J., Fisk, A. D., Lee, C. C., & Nair, S. N. (2014).The Personalized Reminder Information and Social Management System (PRISM) Trials: Rationale, Methods, and Baseline Characteristics. Contemporary Clinical Trials 40 (2015) 35-46. November.

Taha, J., **Czaja, S.J.,** Sharit, J., Morrow, D.G. (2013) Factors Affecting Usage of a Personal Health Record (PHR) to Manage Health. Psychology and Aging, Vol. 28, No.4, 1124-1139.

D. Research Support

Czaja, S.J. (PI) 9/1/16 – 8/31/2020
ORCATECH Collaborative Aging (in Place) Research Using Technology CART
NIH/NIA
The CART program will develop and validate an infrastructure for rapid and effective conduct of research utilizing technology to facility aging in the place. The demonstration project is designed as a feasibility study of the technology system, testing whether the CART system measures and detects maintenance of independence and/or functional declines and transitions leading to greater dependency. The project will be focusing on the oldest-old with chronic disease, veterans living in rural communities, minorities and social isolated seniors of low income.

Czaja, S.J. (PI) 9/1/16 – 4/30/2021
Augmenting Cognitive Training in Older Adults – the ACT Grant
NIH/NIA
This is a randomized clinical trial to test whether transcranial direct current stimulation (tDCS) of frontal cortices enhances neurocognitive and functional outcomes achieved from cognitive training in older adults experiencing age-related cognitive declines. The study will also examine the influence of other clinical and demographic factors (e.g., gender) on neurocognitive, functional, and neuroimaging outcomes.

Czaja, S.J. (PI), Loewenstein, D., (Co-Investigator) 9/1/2016-4/30/2021
1 RO1 AG054009-01
NIH/NIA
A non-pharmacological intervention for patients with Alzheimer's disease and family caregivers
The proposed study is extremely relevant to public health concerns. The prevalence of individuals with AD and family caregivers is projected to increase in the upcoming decades. To address this pressing issue, the focus of the proposed study is to evaluate the acceptability and efficacy of an innovative intervention program, delivered through state-of-the art computer tablet technology that targets both ethnically/culturally diverse family caregivers of patients with Alzheimer's Disease (AD) and AD patients. The program augments an evidenced-based caregiver intervention with an evidenced-based cognitive/functional training intervention for the patient. The overall goals of the project are to improve the lives of family caregivers; the ability of caregivers to provide care to their loved ones; to improve the lives of individuals with AD; and to reduce disparities in access to needed services and support among caregiver and patient populations.

Czaja, S.J., Pirolli, P., (PI's) 9/1/2016-4/30/2021

1 RO1 AG053163-01
NIH
A Personalized Health Behavior System to Promote Health and Well-Being in Older Adults
This proposed project is addressing a critical public concern. The population is aging and chronic conditions such as hypertension, diabetes and obesity are common among older adults especially ethnic minorities. This study will develop and evaluate a mobile technology-based intervention designed to support positive health behavior change among diverse older adults through integrated online social support, personalized coaching and goal setting.

Czaja, S. J., PI 7/1/15-3/30/20
NIA/NIH
Center for Research and Education for Aging and Technology Enhancement (CREATE IV)
This application is a request for continued support for the Center for Research and Education on Aging and Technology Enhancement (CREATE), an established multidisciplinary, cohesive Center that focuses on aging and technology. CREATE's goal is to ensure that older adults are able to use and realize the benefits of technology. Our objectives are to: develop a database on user preferences, needs, and problems with emerging and existing systems; assess the efficacy of design solutions; gather information on the value of technology; promote new research; support new investigators; and disseminate outcomes to a broad community.

1R01AG047649-01A1 2/1/2015-1/31/2020
Loewenstein, David, PI
Czaja, S.J., Co-Investigator
NIH
Novel Detection of Early Cognitive and Functional Impairment in the Elderly
This is an innovative longitudinal study that will examine the utility of two novel cognitive measures (LASSI-L; MPMT) and a series of newly developed computer-based functional task stimulations (FTS) in the detection of amnestic mild cognitive impairment (aMCI) and PreMCI versus normal elderly subjects. We will examine performance on these novel measures with changes in brain MRI volumes over time as well as associations with amyloid, tau, and phosphorylated tau biomarker levels in the CSF.

1R01NR014434-01 (Czaja, S.J.) 4/1/13-3/31/18
NINR/NIH
A Tailored Technology Intervention for Diverse Family Caregivers of AD Patients
The aims of this project are to evaluate the acceptability and efficacy of a culturally tailored technology-based psychosocial intervention for reducing the stress and burden and enhancing quality of life of diverse family caregivers of AD patients. The intervention is designed to address known areas of caregiver risk and to foster the ability of caregivers to leverage the type of supports they need for themselves and the AD patient. The target population is Black/African American, Hispanic, and White non-Hispanic family caregivers of AD patients.

Czaja, S.J., PI 2/1/16-9/30/17
FLDOH
6AZ04
A Non-Pharmacological Intervention for Patients with Alzheimer's disease and Family Caregivers
The proposed developmental study will develop and test the efficacy and feasibility of an integrated, dyadic-based intervention program (DT), delivered through technology that will include cognitive/functional training for the AD patient and engage the caregiver (CG) as a therapy extender. The program will also include an evidenced-based caregiver component that emphasizes issues important in the earlier stages of caregiving and helps CGs prepare for caregiving transitions.

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: Kunjan R. Dave

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

POSITION TITLE: Research 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
Gujarat University, Ahmedabad, India	B.Sc.	12 / 1993	Biochemistry
The M. S. University of Baroda, Vadodara, India	M.Sc.	12 / 1995	Biochemistry
The M. S. University of Baroda, Vadodara, India	Ph.D.	06 / 2000	Biochemistry
University of Miami School of Medicine, Miami	Post-doc	05 / 2003	Neurology

A. Personal Statement

I completed my training in the field of cerebral ischemia at the Cerebral Vascular Disease Research Center (CVDRC), University of Miami Miller School of Medicine. Since joining CVDRC I have participated in several projects studying different aspects of cerebral ischemia which resulted in over 30 peer-reviewed publications. Presently, my laboratory works on research projects with ultimate goal of lowering the incidence and severity of cerebral ischemia. One of the projects is focused on improving neurological health of diabetics by decreasing the severity and incidence of cerebral ischemia in diabetics as cerebral ischemia and heart disease are the most serious complications of diabetes, accounting for more than 84% of the mortality among diabetics. In this collaborative project, with Dr. Jy and colleagues, we propose to determine efficacy of RMP in preventing hematoma growth following experimental sICH in rats. Part of the preliminary results presented in this application were generated using a small budget internal seed grant (PI: Dave, Co-PI: Jy). Besides my expertise, my versatile team is comprised of a stroke clinician with special interest in sICH, an expert on RMP, pharmacologists and a statistician, who together have the training, experience and environment needed to translate these findings to the clinic.

B. Positions and Honors

Professional experience:

- Associate Director (2014 – present), Cerebral Vascular Disease Research Laboratories, Department of Neurology, University of Miami Miller School of Medicine, Miami, FL.
- Affiliate faculty Neuroscience Graduate Program (2014 – present), University of Miami Miller School of Medicine, Miami, FL.
- Research Associate Professor (2013 – present) Department of Neurology, University of Miami Miller School of Medicine, Miami, FL.
- Research Assistant Professor (2006 - 2013) Department of Neurology, University of Miami Miller School of Medicine, Miami, FL.
- Assistant Scientist (2003 - 2006) Department of Neurology, University of Miami Miller School of Medicine, Miami, FL.
- Biochemist (September, 1999 – February, 2000) Pharmacology Division, Research and Development, The Zandu Pharmaceutical works, Mumbai (Bombay), India.

Scholarship / Award:

- Stanley J. Glaser Foundation biomedical research award, University of Miami Miller School of Medicine 2007 - 2008.

- Recipient of award of Bursaries for young scientists to attend Brain'05 conference (Amsterdam, The Netherlands, June 2005) organized by the International Society for Cerebral Blood Flow and Metabolism.
- Received "Hari Ohm Ashram Prerit Shri Bhaikaka Inter-University Smarak Trust" Award, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India for two research papers in year 1999-2000.
- Recipient of award of The Lady Tata Memorial Trust Research Scholarship, Mumbai (Bombay), India for years 1996-98.
- Recipient of Scholarship from Higher Education Commissioner, Government of Gujarat, India for year 1996.

Membership in Professional Societies:

- Society for Neurosciences
- International Society for Cerebral Blood Flow and Metabolism
- American Heart Association.

C. Contribution to Science

1. Cerebral ischemia and heart disease are the most serious complications of diabetes, accounting for more than 84% of the mortality among diabetics. Epidemiological studies of cerebral ischemia suggest that diabetes increases both the risk of incidence and exacerbates the consequences of cerebral ischemia. Hyperglycemia is one of the contributing factors. In clinical studies, intensive anti-diabetic therapy was able to delay the onset and slow the progression of secondary complications of diabetes. The major side-effect of intensive diabetic therapy is hypoglycemia. Using the streptozotocin-diabetic rat, we observed that recurrent hypoglycemia (RH) renders the insulin-treated diabetic (ITD) rat brain more sensitive to global cerebral ischemia and results in greater brain damage. Presently, we are investigating the mechanism by which RH increases ischemic damage in ITD.
   a. Dave K. R., Pileggi A., Raval A. P. Recurrent hypoglycemia increases oxygen glucose deprivation-induced damage in hippocampal organotypic slices. Neurosci Lett. 496:25-9, 2011.
   b. Dave K. R., Tamariz J, Desai KM, Brand FJ, Liu A, Saul I, Bhattacharya SK, Pileggi A. Recurrent hypoglycemia exacerbates cerebral ischemic damage in streptozotocin-induced diabetic rats. Stroke. 42:1404-11, 2011.
   c. Rehni A. K., Nautiyal N., Perez-Pinzon M. A., Dave K.R. Hyperglycemia / hypoglycemia-induced mitochondrial dysfunction and cerebral ischemic damage in diabetics. Metab Brain Dis. 2014 (In press)

2. Ischemic tolerance in brain develops when a sublethal ischemic insult occurs before a period of "lethal" cerebral ischemia. While working at Dr. Perez-Pinzon's laboratory, I participated in studies aimed to determine mechanisms of ischemia tolerance induced by cerebral ischemia and pharmacological preconditioning.
   a. Della-Morte D., Dave K. R., Defazio R. A., Bao Y. C., Raval A. P., Perez-Pinzon M. A. Resveratrol pretreatment protects rat brain from cerebral ischemic damage via a sirtuin 1 - uncoupling protein 2 pathway. Neuroscience. 159:993-1002, 2009.
   b. Dave K. R., DeFazio R. A., Raval A. P., Torraco A., Saul I., Barrientos A., Perez-Pinzon M. A. Ischemic preconditioning targets the respiration of synaptic mitochondria via protein kinase C epsilon. J Neurosci. 28:4172-82, 2008.
   c. *Raval A. P., Dave K. R., Perez-Pinzon M. A. Resveratrol mimics ischemic preconditioning in the brain, J Cereb Blood Flow Metab, 26:1141-7, 2006.
   d. *Dave K. R., Lange-Asschenfeldt C., Raval A. P., Prado R., Busto R., Saul I., Perez-Pinzon M. A. Ischemic preconditioning ameliorates excitotoxicity by shifting glutamate/gamma-aminobutyric acid release and biosynthesis, J Neurosci Res., 82:665-673, 2005.
   e. Dave K.R., Saul I., Busto R., Ginsberg M. D., Sick T. J., Perez-Pinzon M. A. Mitochondrial function following global cerebral ischemia in rat hippocampus. Journal of Cerebral Blood Flow and Metabolism, 21:1401-1410, 2001.

3. Cardiopulmonary arrest remains one of the leading causes of death and disability in the U.S.A. Cardiac arrest with its consequent disruption of blood flow sets in motion a cascade of cellular and systemic derangements that result in selective brain damage. I participated in project aimed to determine the mechanism of neuronal death following cardiac arrest-induced cerebral ischemia.
   a. Lin H. W., Gresia V. L., Stradecki H. M., Alekseyenko A., Dezfulian C., Neumann J. T., Dave K. R., Perez-Pinzon M. A. Protein kinase C delta modulates endothelial nitric oxide synthase after cardiac arrest. J Cereb Blood Flow Metab. 2014, 34:613-20.

b. Dave K. R., Della-Morte D., Saul I., Prado R., Perez-Pinzon M. A. Ventricular fibrillation-induced cardiac arrest in the rat as a model of global cerebral ischemia. Transl Stroke Res. 2013, 4:571-8.
c. Dave K. R., Bhattacharya S. K., Saul I., DeFazio R. A., Dezfulian C., Lin H. W., Raval A. P., Perez-Pinzon M. A. Activation of protein kinase C delta following cerebral ischemia leads to release of cytochrome C from the mitochondria via bad pathway. PLoS One. 6:e22057, 2011.
d. Raval A. P., Dave K. R., Prado R., Katz L. M., Busto R., Sick T. J., Ginsberg M. D., Mochly-Rosen D., Perez-Pinzon M. A. Protein kinase C delta cleavage initiates an aberrant signal transduction pathway after cardiac arrest and oxygen glucose deprivation, J Cereb Blood Flow Metab, 25:730-741, 2005.
e. Dave K.R., Raval A. P., Prado R., Katz L. M., Sick T. J., Ginsberg M. D., Busto R., Perez-Pinzon M. A. Mild cardiopulmonary arrest promotes synaptic dysfunction in rat hippocampus. Brain Res, 1024:89-96, 2004.

4. Amyotrophic lateral sclerosis (ALS) is a devastating disease, which results in degeneration of both upper and lower motor neurons of the brain, brain stem and spinal cord. The cause of most types of ALS remains uncertain, and the disease is incurable. I participated in projects aimed to determine mechanisms of cell death in mouse models of motor neuron disease.
   a. Dave K. R., Raval A. P., Purroy J., Kirkinezos I. G., Moraes C. T., Bradley W. G., Perez-Pinzon M. A. Aberrant deltaPKC activation in the spinal cord of Wobbler mouse: a model of motor neuron disease. Neurobiol Dis, 18:126-133, 2005.
   b. Dave K. R., Bradley W. G., Perez-Pinzon M. A. Early mitochondrial dysfunction occurs in motor cortex and spinal cord at the onset of disease in the Wobbler mouse. Experimental Neurology, 182:412-420, 2003.
   c. Dave K. R., Prado R., Busto R., Raval A. P., Bradley W. G., Torbati D., Perez-Pinzon M. A. Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in the wobbler mice. Neuroscience, 120:113-20, 2003.
   d. Xu, G-P, Dave K. R., Moraes C. T., Busto R., Sick T. J., Bradley W. G., Perez-Pinzon M. A. Dysfunctional mitochondrial respiration in the Wobbler mouse brain. Neuroscience Letters, 300:141-144, 2001.

5. Arctic ground squirrels (AGS; Spermophilus parryii) is a species of heterothermic mammals; i.e., a species that hibernates. Hibernating creatures experience fluctuating metabolic rates and body temperatures as they cycle into and out of periods of prolonged torpor. One of the main reasons for their ischemia tolerance during hibernation is hypothermia. However, during euthermia several ischemia tolerance pathways are active in AGS. In an experiment aimed to determine if AGS tolerate cerebral ischemia during euthermia, we demonstrated that AGS can be readily resuscitated from prolonged cardiac arrest (CA) without evidence of neuropathology. Tolerance to global cerebral ischemia was observed even when animals were not hibernating and when brain temperature was maintained at 37 °C. In another study we observed that epsilon PKC activation delays the collapse of ion homeostasis during ischemia in AGS but not rat.
   a. Dave K. R., Christian S. L., Perez-Pinzon M. A., Drew K. L. Neuroprotection: lessons from hibernators. Comp Biochem Physiol B Biochem Mol Biol. 162:1-9, 2012.
   b. Dave K. R., Defazio R. A, Raval A. P., Dashkin O., Saul I., Iceman K. E., Perez-Pinzon M.A., Drew K.L. Protein kinase C epsilon activation delays neuronal depolarization during cardiac arrest in the euthermic arctic ground squirrel. J Neurochem. 110:1170-9, 2009.
   c. Dave K. R., Prado R., Raval A. P., Drew K. L., Perez-Pinzon M. A. The arctic ground squirrel brain is resistant to injury from cardiac arrest during euthermia, Stroke, 37:1261-1265, 2006.

Complete List of Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&term=%22Dave%20KR%22

D. Research Support

1R01NS073779 Dr. Dave, P.I. 3/1/2012 – 12/31/2016
NIH/NINDS
Increased cerebral ischemic injury by repeated hypoglycemic episodes in diabetes.
The major goal of this project is to determine the mechanism by which repeated hypoglycemic episodes increases cerebral ischemic injury in diabetics.
Role: Principal Investigator

American Stroke Association-Bugher Foundation Centers for Excellence in Stroke Collaborative Research for Regeneration, Resilience and Secondary Prevention, Ralph S. Sacco (PI): Project 2: Enriched Environment, Exercise and Neurotherapeutics to Enhance Functional Recovery Following Stroke. Project PI: Dr. Perez-Pinzon
4/1/2014 – 3/31/2018 Role: co-investigator project 2

2R01NS034773 Dr. Perez-Pinzon, P.I. 6/1/2015 – 5/31/2020
NIH/NINDS
Ischemic preconditioning: mechanisms of neuroprotection.
The major goals of this project are to define the specific molecular targets of resveratrol preconditioning that promote ischemic tolerance and to further define the molecular mechanisms of a chronic ischemic tolerant state.
Role: co-investigator

R21NS094896 (IGNITE mechanism) Dr. Dave, P.I. R21 phase: 2/1/2016 – 1/31/2017
R33 phase: 2/1/2017 – 1/31/2019
NIH/NINDS (R33 phase will depend on results of R21 phase)
Red blood cell microparticles (RMPs) to reduce bleeding following hemorrhagic stroke.
The major goal of this project is to lower hematoma growth following intracerebral hemorrhage using RMPs.
Role: Principal Investigator

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: Chuanhui Dong

eRA COMMONS USER NAME (credential, e.g., agency login): CHDONG07

POSITION TITLE: Research 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
Tongji Medical University, Wuhan, China	M.D.	07/1984	Preventive Medicine
Hubei Medical University, Wuhan, China	M.A.	06/1989	Epidemiology
Shanghai Medical University, Shanghai, China	Ph.D.	07/1998	Molecular Epidemiology
Karolinska Institute, Stockholm, Sweden	Post-Doc	12/2000	Genetic Epidemiology
University of Pennsylvania, Philadelphia	Post-Doc	10/2003	Statistical Genetics

A. Personal Statement

I am a biostatistician and research associate professor in the Department of Neurology at the University of Miami. Over 10 years, my research interest has been focused on investigation of independent and interactive effects of social-demographic, environmental, behavioral, metabolic and genetic factors on the risk of complex diseases such as cognition impairment, depression, subclinical and clinical cardiovascular diseases, and efficacy of drug treatment in animal models and clinical trials. With the successful collaboration with many researchers, I have published over 100 peer-reviewed research articles.

1. Wright, C.B., **Dong, C.,** Caunca, M.R., DeRosa, J., Cheung, Y., Rundek, T., Elkind, M.S., DeCarli, C., Sacco, R.L. (2016). MRI Markers Predict Cognitive Decline Assessed by Telephone Interview: The Northern Manhattan Study. *Alzheimer disease and associated disorders*. [Epub ahead of print]

2. **Dong C,** Zadeh N, Caunca MR, Cheung Y, Rundek T, Elkind MSV, DeCarli C, Sacco RL, Stern Y, Wright CB (2015). Cognitive correlates of white matter lesion load and brain atrophy: The Northern Manhattan Study. Neurology 85(5):441-9.

3. **Dong C,** Rundek T, Wright CB, Anwar Z, Elkind MS, and Sacco RL (2012). Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks, and hispanics: the northern Manhattan study. Circulation 125, 2975-2984.

4. **Dong C,** Della-Morte D, Rundek T, Wright CB, Elkind MS, and Sacco RL (2016). Evidence to maintain the systolic blood pressure treatment threshold at 140 mm Hg for stroke prevention: The Northern Manhattan Study. Hypertension 67(3):520-526.

B. Positions

Positions and Employment

1998-2000 Research Fellow, Epidemiology, Dept. of Biosciences, Karolinska Institute, Stockholm, Sweden

2001-2003 Postdoctoral Researcher, Statistical Genetics, Dept. of Psychiatry, University of Pennsylvania, PA
2003-2006 Research Associate, Statistical Genetics, Dept. of Psychiatry, University of Pennsylvania, PA
2006-2007 Research Biostatistician, Clinical Research, American College of Radiology, PA
2007-2009 Research Assistant Professor, Dept. of Psychiatry & Behavioral Sci., University of Miami, FL
2009-2014 Research Assistant Professor, Dept. of Neurology, University of Miami, FL
2014- Research Associate Professor, Dept. of Neurology, University of Miami, FL

Professional Memberships

2012- Member, American Heart Association
2002- Member, American Association of Human Genetics
2008- Member, International Genetic Epidemiology Society
2008- Member, American Statistical Association
2002-2006 Member, International Epidemiological Association

C. Contribution to Science

1. In the collaboration with clinicians, one of my major research activities was to evaluate the cognitive correlates in population-base cohort. As a statistician, I served as the analyst in several projects.

    a. Glazer, H., **Dong, C.,** Yoshita, M., Rundek, T., Elkind, M.S.V., Sacco, R.L., DeCarli, C., Stern, Y., Wright, C.B. (2015) Subclinical cerebrovascular disease inversely associates with learning ability: The NOMAS Study. Neurology 84(23):2362-2367

    b. Wright, C.B., Gardener, H., **Dong, C.,** Yoshita, M., DeCarli, C., Sacco, R.L., Stern, Y., Elkind, M.S.V. (2015). Infectious Burden and Cognitive Decline in the Northern Manhattan Study. Journal of the American Geriatrics Society 63(8):1540-5

    c. Levin, B.E., Llabre, M.M., **Dong, C.,** Elkind, M.S., Stern, Y., Rundek, T., Sacco, R.L., and Wright, C.B. (2014). Modeling metabolic syndrome and its association with cognition: the northern Manhattan study. Journal of the International Neuropsychological Society 20, 951-960.

    d. Ramos, A.R., **Dong, C.,** Elkind, M.S., Boden-Albala, B., Sacco, R.L., Rundek, T., and Wright, C.B. (2013). Association between sleep duration and the mini-mental score: the Northern Manhattan study. Journal of Clinical Sleep Medicine 9, 669-673.

2. As a collaborator, I served as the statistician to evaluate the response of various medications in clinical studies and examined the factors influencing response of treatments.

    a. Wong ML, **Dong C,** Flores DL, Ehrhart-Bornstein M, Bornstein S, Arcos-Burgos M, and Licinio J (2014). Clinical Outcomes and Genome-Wide Association for a Brain Methylation Site in an Antidepressant Pharmacogenetics Study in Mexican Americans. The American Journal of Psychiatry 171, 1297-1309. PMID: 25220861

    b. Waldrop-Valverde, D, **Dong C,** and Ownby RL (2013). Medication-taking self-efficacy and medication adherence among HIV-infected cocaine users. The Journal of the Association of Nurses in AIDS Care 24, 198-206.

    c. Yavagal DR, Lin B, Raval AP, Garza PS, **Dong C,** Zhao W, Rangel EB, McNiece I, Rundek T, Sacco RL, et al. (2014). Efficacy and dose-dependent safety of intra-arterial delivery of mesenchymal stem cells in a rodent stroke model. PloS One 9, e93735.

d. **Dong C,** Wong ML, Licinio J (2009). Sequence variations of ABCB1, SLC6A2, SLC6A3, SLC6A4, CREB1, CRHR1 and NTRK2: association with major depression and antidepressant response in Mexican-Americans. Mol Psychiatry, 14(12):1105-1118. PMID: 19844206

3. In population-based and clinical studies, I took a lead in many data analyses to identify the factors influencing the subclinical and clinical outcomes.

   a. Nirav S, **Dong C,** Elkind MS, Sacco RL, Mendez A, Barry H, Silverberg S, Wolf M, Rundek T, and Wright CB, (2015). Fibroblast Growth Factor 23 is associated with Carotid Plaque Presence and Area: the Northern Manhattan Study. Arteriosclerosis, Thrombosis, and Vascular Biology 35(9):2048-53

   b. **Dong C,** Della-Morte D, Beecham A, Wang L, Cabral D, Blanton SH, Sacco RL, Rundek T (2015) Genetic variants in LEKR1 and GALNT10 modulate sex-difference in carotid intima-media thickness: A genome-wide interaction study. Atherosclerosis 240:462-7

   c. Dhamoon MS, **Dong C,** Elkind MS, Sacco RL (2015). Ideal cardiovascular health predicts functional status independently of vascular events: The northern manhattan study. Journal of the American Heart Association 4(2), e001322

   d. Xu WH, **Dong C,** Rundek T, Elkind MS, and Sacco RL (2014). Serum albumin levels are associated with cardioembolic and cryptogenic ischemic strokes: Northern Manhattan Study. Stroke 45, 973-978.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1piUox9klssQ2/bibliography/42015963/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

R01 NS 29993 Ralph Sacco (PI) 02/03-03/20
Stroke Incidence and Risk Factors in a Tri-Ethnic Region
To determine the effects of risk factors for stroke, MI, and vascular death in a prospective cohort study of 3 race-ethnic groups from Northern Manhattan.
Role: Statistician

R01MD009164, Olveen Carrasquillo (PI) 07/14-03/19
Hispanic Secondary Stroke Prevention Initiative (HISSPI)
To examine the effectiveness of a combined multilevel intervention consisting of Community Health Workers and mobile based phone technologies in lowering of systolic blood pressure which is the most important risk factor for recurrent stroke.
Role: Statistician

14BFSC17690000 Ralph Sacco (PI) 04/14-03/18
American Heart Association/ASA-Bugher Foundation
To evaluate the effects of a Combined Aerobic and Resistance Exercise Training (CARET) program, a Cognitive Training Intervention (CTI), and the combination of the CARET and CTI interventions on cognitive performance in stroke patients.
Role: Co-investigator/Statistician

1U54NS081763, Ralph Sacco (PI) 01/13-12/17
Hispanic stroke prevention intervention research program
To create the Florida Puerto Rico Stroke Registry to identify and reduce stroke disparities in acute stroke and secondary prevention.
Role: Co-investigator/Statistician

Completed Research Support (within the last three years):

R01 HL108623-01A1 Clinton Wright (PI) 03/12-02/16
FGF-23 and the Risk of Stroke and Cognitive Decline
To examine the relationship between FGF-23 and the risk of stroke and cognitive decline.
Role: Co-investigator/Statistician

NATL MULTIPLE SCLEROSIS SOCIETY, Melissa Ortega (PI) 12/12-11/15
(Fast-Forward) A Randomized Double-Blind Placebo-Controlled Study of Caprylic Triglyceride for Cognitive Impairment in Subjects with Multiple Sclerosis
To determine the efficacy of Caprylic Triglyceride for Cognitive Impairment in Subjects with Multiple Sclerosis
Role: Biostatistician

R01NS065114 Tatjana Rundek (PI) 07/10-06/15
Novel factors for unexplained phenotypes of subclinical carotid atherosclerosis
To identify genetic variants influencing unexplained phenotypes of subclinical carotid atherosclerosis.
Role: Co-investigator/Statistician

2KN01, Florida JEK Program, Chuanhui Dong (PI) 07/11-06/14
Gene-smoking interactions and atherosclerosis
To identify genetic moderators in the association between smoking and atherosclerosis.
Role: PI/Statistician

2KN09, Florida JEK Program, Dileep Yavagal (PI) 07/11-06/14
Intra-arterial mesenchymal stem cell delivery in a canine model of acute ischemic stroke
To evaluate safety sub-acute endovascular intra-carotid administration of MSCs in a canine stroke model.
Role: Co-investigator/Statistician

1U01NS069208 Kittner Steven(PI) 07/10-06/14
NINDS Ischemic Stroke Genetics Consortium
To assemble ischemic stroke phenotypic data and DNA samples from 11 stroke studies.
Role: Statistician

1K02NS059729-01A1 Clinton Wright (PI) 09/08-08/13
Vascular Risk and Cognition in a Multi-ethnic Cohort
To examine vascular risk factors for cognitive dysfunction in a stroke-free multi-ethnic sample.
Role: Statistician

The Miami CTSI, CTSI-2013-P02, Dileep Yavagal (PI) 01/13-12/13
Time Window of Intracarotid Mesenchymal Stem Cell Therapy in a Large Animal Model of Stroke
To determine the time window of intracarotid mesenchymal stem cell therapy in animal model of stroke.
Role: Co-investigator/Biostatistician

2R01NS040807 Ralph Sacco (PI) 09/09-08/13
Family study of stroke risk and carotid atherosclerosis
To investigate genes influencing carotid atherosclerosis through linkage and association studies.
Role: Statistician

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: **Hannah Gardener, ScD**

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

POSITION TITLE: **Associate 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
Dartmouth College	AB	06/2000	Psychological and Brain Sciences
Harvard School of Public Health	ScD	08/2007	Epidemiology

A. Personal Statement

Hannah Gardener, ScD, Assistant Scientist in the Department of Neurology at the University of Miami, is an epidemiologist with a particular interest in neuroepidemiology and the epidemiology of aging. She received her doctorate in Epidemiology in 2007 from the Harvard School of Public Health. She has been conducting research on risk factors for clinical and subclinical vascular outcomes in the Northern Manhattan Study for over nine years. She is particularly interested in dietary behavior and other modifiable vascular risk factors in relation to vascular events, carotid disease, and age-related changes in brain structure and cognitive decline. She is responsible for study design, data management, design and completion of statistical analyses, interpretation of results, presentations and manuscript writing.

B. Positions and Honors

POSITIONS AND EMPLOYMENT

Traineeship

2002-04 Senior Research Assistant
Department of Society, Human Development and Health, Harvard School of Public Health
2007-09 Epidemiology Post-Doctoral Fellow
Department of Neurology, University of Miami Miller School of Medicine

Academic Appointments:

2016-present Associate Scientist Department of Neurology, University of Miami Miller School of Medicine
2009-2016 Assistant Scientist Department of Neurology, University of Miami Miller School of Medicine
2009 Research Assistant Professor Departments of Neurology and Pediatrics,
University of Miami Miller School of Medicine

Memberships:

2008- American Academy of Neurology
2007-2008 Society for Epidemiologic Research

Honors:

2006-2007 Certificate of Distinction in recognition of outstanding accomplishments and contributions in teaching: Harvard School of Public Health, Department of Epidemiology
2004-2006 National Research Service Award grant from the Training Program in Psychiatric Epidemiology and Biostatistics (T32 MH17119):
2000 Phi Beta Kappa, Dartmouth College
2000 Benner Award for Excellence in Research, Dartmouth College

C. Contribution to science

C.1. Predictors of cognitive function and decline in the population. An area of research focus is the role of novel and traditional vascular risk factors in cognitive performance and decline over time. Most notable is our finding of a role for

infectious burden in executive function as well as memory decline over time, and our studies showing relationships between sleep disturbance, physical activity, and cardiovascular health factors with decline in cognitive domains.

1. Ramos AR, **Gardener H**, Rundek T, Elkind MS, Boden-Albala B, Dong C, Cheung YK, Stern Y, Sacco RL, Wright CB. Sleep disturbances and cognitive decline in the Northern Manhattan Study. Neurology. 2016;87(14):1511-1516.
2. Willey JZ, **Gardener H***, Caunca MR, Moon YP, Dong C, Cheung YK, Sacco RL, Elkind MS, Wright CB. Leisure-time physical activity associates with cognitive decline: The Northern Manhattan Study. Neurology. 2016;86(20):1897-903.
3. **Gardener H**, Wright CB, Dong C, Cheung K, DeRosa J, Nannery M, Stern Y, Elkind MS, Sacco RL. Ideal Cardiovascular Health and Cognitive Aging in the Northern Manhattan Study. Neurology. 2016;86(20):1897-903.
4. **Gardener H**, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. Nat Rev Neurol. 2015;11(11):651-7.
5. Wright CB, **Gardener H***, Dong C, Yoshita M, DeCarli C, Sacco RL, Stern Y, Elkind MS. Infectious burden and cognitive decline in the Northern Manhattan Study. *J Am Geriatr Soc*. 2015;63(8):1540-1545.
6. Del Brutto OH, Mera RM, Del Brutto VJ, Maestre GE, **Gardener H**, Zambrano M, Wright C. Influence of depression, anxiety and stress on cognitive performance in community-dwelling elders living in rural Ecuador. Results of the Atahualpa Project. *Geriatr Gerontol Int*. 2015;15(4):508-514.
7. Del Brutto OH, **Gardener H**, Del Brut to VJ, Maestre GE, Zambrano M, Montenegro JE, Wright CB. Edentulism Associates with Worse Cognitive Performance in Community-Dwelling Elders in Rural Ecuador: Results of the Atahualpa Project. *J Community Health*. 2014;39(6):1097-1100.
8. **Gardener H**, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. *Nat Rev Neurol*. 2015;11(11):651-657.

C.2. MRI markers of vascular damage. A primary area of research focus has been examining the role of vascular risk factors in predicting MRI markers of vascular damage, which may be mediators in the pathways between cardiovascular health indices and both stroke and cognitive function and decline. We have shown that migraine is a risk factor for subclinical brain infarcts imaged using MRI, and that diastolic blood pressure, lipid levels, and adherence to a Mediterranean-style diet are predictive of white matter hyperintensity volume, a risk factor for both stroke and dementia. We have also examined the prevalence and risk factors for cerebral microbleeds in our urban multiethnic cohort.

1. Caunca MR, Del Brutto V, **Gardener H**, Shah N, Dequatre-Ponchelle N, Cheung YK, Elkind MS, Brown TR, Cordonnier C, Sacco RL, Wright CB. Cerebral Microbleeds, Vascular Risk Factors, and Magnetic Resonance Imaging Markers: The Northern Manhattan Study. J Am Heart Assoc. 2016;5(9).
2. Monteith T, **Gardener H**, Rundek T, Dong C, Yoshita M, Elkind MSV, DeCarli C, Sacco RL, Wright CB. Migraine, White Matter Hyperintensities, and Subclinical Brain Infarction in a Diverse Community: The NOMAS Study *Stroke*. 2014;45(6):1830-1832.
3. Willey JZ, **Gardener H**, Moon MY, Sacco RL, Elkind MSV, Wright CB. Lipid profile components and subclinical cerebrovascular disease in the Northern Manhattan Study. *Cerebrovascular Diseases*. 2014;37(6):423-430.
4. Modir R, **Gardener H**, Wright C. Blood pressure and white matter hyperintensity volume – a review of the relationship and implications for stroke prediction and prevention. *European Neurological Review,* 2012;7(3):174–7.
5. **Gardener H**, Scarmeas N, Gu Y, Boden-Albala B, Elkind MSV, Sacco RL, DeCarli C, Wright CB. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. *Archives of Neurology*. 2012;69(2):251-256.
6. Marcus J, **Gardener H***, Rundek T, Elkind MSV, Sacco RL, DeCarli C, Wright CB. Baseline and longitudinal increases in diastolic blood pressure are associated with greater white matter hyperintensity volume: The Northern Manhattan Study. *Stroke.* 2011;42(9):2639-2641.

C.3. Epidemiology of stroke. Over the past 8 years I have pursued research in stroke epidemiology. I have examined novel and traditional risk factors for stroke and vascular-related death in a multi-ethnic population-based study with an emphasis on understanding race/ethnic disparities. In particular, a primary research interest is the role of dietary factors in the etiology of vascular outcomes. Specifically, I have published on the role coffee and tea, soft drinks, sodium, and egg consumption as well as adherence to a Mediterranean-style diet in relation to risk of stroke, cardiovascular disease, and vascular death. Other novel vascular risk factors that I have examined in a multiethnic population-based sample include migraine, adiponectin and HOMA insulin resistance. Most recently I have contributed to research on sex disparities in acute stroke care in Florida and Puerto Rico, and I have studied short-term outcomes in patients with mild and rapidly improving stroke symptoms using Get With The Guidelines-Stroke data.

1. Asdaghi N, Romano JG, Wang K, Ciliberti-Vargas MA, Koch S, **Gardener H**, Dong C, Rose DZ, Waddy SP, Robichaux M, Garcia EJ, Gonzalez-Sanchez JA, Burgin WS, Sacco RL, Rundek T. Sex Disparities in Ischemic Stroke Care: FL-PR CReSD Study (Florida-Puerto Rico Collaboration to Reduce Stroke Disparities). Stroke.

2016;47(10):2618-26.
2. Romano JG, Smith EE, Liang L, **Gardener H**, Campo-Bustillo I, Khatri P, Bhatt DL, Fonarow GC, Sacco RL, Schwamm LH. Distinct Short-Term Outcomes in Patients With Mild Versus Rapidly Improving Stroke Not Treated With Thrombolytics. Stroke. 2016;47(5):1278-85.
3. Monteith TS, **Gardener H**, Rundek T, Elkind MS, Sacco RL. Migraine and risk of stroke in older adults: Northern Manhattan Study. *Neurology*. 2015;85(8):715-721.
4. Romano JG, Smith EE, Liang L, **Gardener H**, Camp S, Shuey L, Cook A, Campo-Bustillo I, Khatri P, Bhatt DL, Fonarow GC, Sacco RL, Schwamm LH. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With the Guidelines-Stroke registry. *JAMA Neurol*. 2015;72(4):423-431.
5. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet*. 2014;383(9921):970-983.
6. **Gardener H**, Rundek T, Wright CB, Elkind MSV, Sacco RL. Coffee and tea consumption are inversely associated with mortality. *J Nutr*. 2013;143(8):1299-1308.
7. **Gardener H**, Goldberg R, Mendez AJ, Wright CB, Rundek T, Elkind MSV, Sacco RL. Adiponectin and risk of vascular events in the Northern Manhattan Study. *Atherosclerosis*. 2013;226(2):483-489.
8. **Gardener H**, Rundek T, Wright CB, Elkind MSV, Sacco RL. Dietary sodium and risk of stroke in the Northern Manhattan Study. *Stroke*. 2012;43(5):1200-1205.
9. **Gardener H**, Rundek T, Markert M, Wright CB, Elkind MSV, Sacco RL. Diet soft drink consumption is associated with an increased risk of vascular events in the Northern Manhattan Study. *Journal of General Internal Medicine*. 2012;27(9):1120-1126.
10. The Global Burden of Disease Stroke Expert Group: Bennett DA, Anderson LM, Nair N, Truelsen T, Barker-Collo S, Connor M, **Gardener H**, Krishnamurthi R, Lawes CMM, Moran A, O'Donnell M, Parag V, Sacco RL, Ezzati M, Mensah G, Feigin VL. Methodology of the global and regional burden of stroke study. *Neuroepidemiology*. 2011;38(1):30-40.
11. **Gardener H**, Wright CB, Gu Y, Demmer RT, Boden-Albala B, Elkind MSV, Sacco RL, Scarmeas N. A Mediterranean-style diet and the risk of ischemic stroke, myocardial infarction, and vascular death: The Northern Manhattan Study. *American Journal of Clinical Nutrition.* 2011;94(6):1458-1464.
12. Rundek T, **Gardener H**, Xu Q, Goldberg RB, Wright CB, Boden-Albala B, Disla N, Paik MC, Elkind MSV, Sacco RL. Insulin resistance and risk of ischemic stroke among non-diabetic individuals from the Northern Manhattan Study. *Archives of Neurology*. 2010;67(10):1195-1200.
13. Sacco RL, Khatri M, Rundek T, Xu Q, **Gardener H**, Boden-Albala B, Di Tullio M, Homma S, Elkind MSV, Paik MC. Improving global vascular risk prediction with behavioral and anthropometric factors: the multi-ethnic Northern Manhattan Cohort Study. *Journal of the American College of Cardiology*. 2009;54(24):2303-2311.

C.4. Epidemiology of atherosclerosis and imaging markers of carotid disease. A primary research focus has been examining the associations of vascular risk factors with carotid atherosclerosis phenotypes to better understand their impact on clinical and subclinical vascular disease. In particular, I have studied the roles of diet (egg consumption and adherence to a Mediterranean-style diet) and genetics in the etiology of carotid atherosclerosis. I have examined the relationship between two important and distinct measures of carotid atherosclerosis measured using B-mode ultrasound – carotid intima-media thickness and carotid plaque – and have explored multiple ways to quantify plaque burden including total plaque area. In addition to diet, modifiable vascular risk factors for carotid atherosclerosis phenotypes that I have published include cigarette smoking, soluble RAGE levels, lipid levels, homocysteine, and adiponectin.

1. Tiozzo E, **Gardener H**, Hudson BI, Dong C, Della-Morte D, Crisby M, Goldberg RB, Elkind MS, Cheung YK, Wright CB, Sacco RL, Desvarieux M, Rundek T. Subfractions of High-Density Lipoprotein-Cholesterol and Carotid Intima-Media Thickness: The Northern Manhattan Study. Stroke. 2016;47(6):1508-13.
2. Haussen DC, Rose DZ, Drazin D, Newsome SD, **Gardener H**, Edgell RC, Boulos A, Bernardini G, Rundek T, Yavagal DR. Ipsilateral infarct in newly diagnosed cervical internal carotid artery atherosclerotic occlusion. *Interv Neurol*. 2015;3(3-4):142-148.
3. Yang D, Iyer S, **Gardener H**, Della-Morte D, Crisby M, Dong C, Cheung K, Mora-McLaughlin C, Wright CB, Elkind MS, Sacco RL, Rundek T. Cigarette smoking and carotid plaque echodensity in the Northern Manhattan Study. *Cerebrovasc Dis*. 2015;40(3-4):136-143.
4. Rundek T, **Gardener H**, Della-Morte D, Dong C, Cabral D, Tiozzo E, Roberts E, Crisby M, Cheung K, Demmer R, Elkind MS, Sacco RL, Desvarieux M. The relationship between carotid intima-media thickness and carotid plaque in the Northern Manhattan Study. *Atherosclerosis*. 2015;241(2):364-370.

5. Hudson BI, **Gardener H**, Liu-Mares W, Dong C, Cheung K, Elkind MS, Wright CB, Sacco RL, Rundek T. Serum soluble RAGE levels and carotid atherosclerosis: the Northern Manhattan Study. *Atherosclerosis*. 2015;240(1):17-20.
6. Tiozzo E, **Gardener H**, Hudson BI, Dong C, Della-Morte D, Crisby M, Goldberg RB, Elkind MS, Cheung YK, Wright CB, Sacco RL, Rundek T. High-density lipoprotein subfractions and carotid plaque: the Northern Manhattan Study. *Atherosclerosis*. 2014;237(1):163-168.
7. Goldberg S, **Gardener H***, Tiozzo E, Cheung YK, Elkind MSV, Sacco RL, Rundek T. Egg Consumption and Carotid Atherosclerosis in the Northern Manhattan Study*. Atherosclerosis.* 2014;235(2):273-280.
8. **Gardener H**, Wright CB, Cabral D, Scarmeas N, Gu Y, Cheung K, Elkind MS, Sacco RL, Rundek T. Mediterranean diet and carotid atherosclerosis in the Northern Manhattan Study. *Atherosclerosis*. 2014;234(2):303-310.
9. Alsulaimani S, **Gardener H**, Elkind MSV, Cheung K, Sacco RL, Rundek T. Elevated homocysteine and carotid plaque area and densitometry in the Northern Manhattan Study. *Stroke*. 2013;44(2):457-461.
10. Della-Morte D**,** Beecham A, Dong C, Wang L, McClendon MS, **Gardener H**, Blanton SH, Sacco RL, Rundek T. Association between variations in coagulation system genes and carotid plaque. *Journal of the Neurological Sciences*. 2012;323(1-2):93-98.
11. Kuo F, **Gardener H**, Dong C, Cabral D, Della-Morte D, Blanton SH, Santiago M, Elkind MSV, Sacco RL, Rundek T. Traditional cardiovascular risk factors explain only small proportion of the variation in carotid plaque. *Stroke*. 2012;43(7):1755-1760.
12. **Gardener H**, Sjoberg C, Crisby M, Goldberg R, Mendez A, Wright CB, Elkind MSV, Sacco RL, Rundek T. Adiponectin and carotid intima-media thickness in the Northern Manhattan Study. *Stroke*. 2012;43(4):1123-1125.
13. Markert MS, Della-Morte D, Cabral D, Roberts EL, **Gardener H**, Dong C, Wright CB, Elkind MS, Sacco RL, Rundek T. Ethnic differences in carotid artery diameter and stiffness: the Northern Manhattan Study. *Atherosclerosis.* 2011;219(2):827-832.
14. **Gardener H,** Beecham A, Cabral D, Yanuck D, Slifer S, Wang L, Blanton SH, Sacco RL, Juo SH, Rundek T. Carotid plaque and candidate genes related to inflammation and endothelial function in Hispanics from Northern Manhattan. *Stroke.* 2011;42(4):889-896.
15. Wang L, Yanuck D, Beecham A, **Gardener H,** Slifer S, Blanton SH, Sacco RL, Rundek T. A candidate gene study revealed sex-specific association between the ORL1 gene and carotid plaque. *Stroke.* 2011;42(3):588-592.
16. Ramos A, Wohlgemuth WK, **Gardener H**, Lorenzo D, Dib S, Wallace D, Nolan B, Boden-Albala B, Elkin MSV, Sacco RL, Rundek T. Snoring and insomnia are not associated with subclinical atherosclerosis in the Northern Manhattan Study (NOMAS). *International Journal of Stroke*. 2010;5(4):264-268.
17. Morte D, **Gardener H**, Denaro F, Boden-Albala B, Elkind MSV, Paik, MC, Sacco RL, Rundek T. Metabolic syndrome increases arterial stiffness: The Northern Manhattan Study. *International Journal of Stroke*. 2010;5(3):138-144.
18. **Gardener H**, Morte D, Elkind MSV, Sacco RL, Rundek T. Lipids and carotid plaque in the Northern Manhattan Study (NOMAS). *BMC Cardiovascular Disorders*. 2009;9:55.
19. Sacco RL, Blanton SH, Slifer S, Beecham A, Glover K, **Gardener H,** Wang L, Sabala E, Juo SH, Rundek T. Heritability and linkage analysis for carotid intima-media thickness: The family study of stroke risk and carotid atherosclerosis. *Stroke.* 2009;40(7):2307-2312.

*Shared first authorship

Link to my full list of publications:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Gardener+h

D. Research Support

1. NOMAS
   R01 NS 029993 (PI: Sacco) **02/01/03-07/31/20**
   NIH/NINDS
   Stroke Incidence and Risk Factors in a Tri-Ethnic Region
   The goals of this project are to determine the effects of risk factors for stroke, MI, and vascular death, as well as evaluate predictors of cognitive impairment and the importance of subclinical MRI findings in a prospective cohort study of 3300 persons from 3 race-ethnic groups from Northern Manhattan.

2. SPIRP
   U54 NINDS SPIRP U54NS081763 (PI: Sacco) **01/01-12/31/17**

NIH/NINDS

Stroke Prevention/Intervention Research Program in Hispanics (& supplement FL-PR CReSD-W)

The goal of this project is to develop high-impact stroke disparities interventions and research projects that have the ability to reduce stroke disparities in the two distinct Hispanic groups in Miami and Puerto Rico using effective and culturally appropriate methods.

3. FGF-23 (ended 10/31/16)

1 R01 HL108623 (PI: Wright) **3/16/2012-10/31/16**

NIH/ NHLBI

FGF-23 and the Risk of Stroke and Cognitive Decline

Elevated fibroblast growth factor 23 and serum phosphate are novel risk factors for cerebrovascular disease and cognitive decline. This study takes advantage of an ongoing population-based cohort study that includes Hispanic, black, and white people living in the same community, to examine elevated serum FGF23 and phosphate and the risk for stroke, subclinical small and large vessel injury, and cognitive decline. Elevated serum phosphate is modifiable and the results of this study have therapeutic potential that can be tested in randomized clinical trials.

4. Genentech

Genentech (PI: Romano) **12/14/11 – 10/30/20**

Coordinating Center: University of Miami

Mild and Rapidly Improving Stroke Study (MaRISS) This research project encompasses two phases, a *retrospective* analysis of the existing entire Get With The Guidelines-Stroke Registry to determine prevalence and short-term outcomes among patients with mild and rapidly improving stroke symptoms and a *prospective* study in 100 select GWTG hospitals to elucidate the long-term outcomes of patients that suffered mild or rapidly improving stroke.

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: Joyce Gomes-Osman

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

POSITION TITLE: Assistant Professor, Departments of Physical Therapy and Neurology
Research Fellow, Berenson-Allen Center for Non-Invasive Brain Stimulation

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
Escola Bahiana de Medicina e Saude Publica	B.S.	06/07	Physical Therapy
University of Miami Miller School of Medicine	Ph.D.	09/13	Motor Control
Harvard Medical School	Post-Doc	09-13 (to present)	Non-Invasive Brain Stimulation

A. Personal Statement

I am a rehabilitation scientist with expertise in clinical research that aims at harnessing plasticity in the form of non-invasive brain stimulation (NIBS) and exercise, and assessing its effects on the human nervous system. In my career, I have explored pertinent questions regarding the potential for non-invasive brain stimulation (including transcranial magnetic stimulation [TMS] and transcranial direct current stimulation [tDCS]) to aid in the characterization of remaining function, and augment rehabilitation approaches aimed at restoring functional hand use after impairment due to spinal cord injury. As a result of these previous experiences, I have successfully carried out all aspects of research projects (subject recruitment, data analysis, data synthesis and manuscript preparation) effectively, as can be seen in my publication record. During my postdoc at Harvard Medical School, I had the opportunity to improve my knowledge in NIBS, advanced TMS-based plasticity measures and cognitive neurology. In my newly established Neuromotor Plasticity Laboratory, I collaborate with different investigators in the Evelyn F. McKnight Brain Institute on projects that apply my knowledge of neuroplasticity and functional performance to better understand the influence of exercise and its potential to improve function and promote neuroplasticity throughout the lifespan.

B. Positions and Honors

Positions and Employment

2016- Collaborator, Center on Aging, University of Miami Miller School of Medicine, USA.

2014- Collaborator, Evelyn F. McKnight Brain Institute University of Miami Miller, School of Medicine, USA.

2014- Assistant Professor, Departments of Physical Therapy and Neurology, University of Miami Miller School of Medicine, USA.

2013- Faculty. Transcranial Magnetic Stimulation Intensive Course. Berenson-Allen Center for Non-invasive Brain Stimulation. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (http://www.tmslab.org/educationintensive.php; 5 day intensive course, three times per year).

2013- Postdoctoral Research Fellow, Beth Israel Medical Center, Harvard Medical School, USA.

2010-2013 Research Support Specialist, The Miami Project to Cure Paralysis, University of Miami, Florida, USA

2007-2010 Research Associate, the Miami Project to Cure Paralysis, University of Miami, Florida, USA

Honors

2007 Humberto de Castro Lima Award by the Bahiana School of Medicine and Public Health-Salvador, Brazil as Outstanding Student in the year of 2007.

2005 First Scholarship for young Scientists among the Physical Therapy Students in the State of Bahia, Brazil by the Foundation to Support Research in the State of Bahia (Fundacao de Amparo a Pesquisa do Estado da Bahia - FAPESB)

Other Experience and Professional Memberships

2015 Peer Review Committee: Journal of Neuroscience, *ad hoc reviewer*
2015 Peer Review Committee: Annals of Neurology, *ad hoc reviewer*
2015 Peer Review Committee: Frontiers in Psychology, *ad hoc reviewer*
2015 Peer Review Committee: The Lancet Neurology, *ad hoc reviewer*
2014 Peer Review Committee: European Journal of Neuroscience, *ad hoc reviewer*
2010- Member, American Physical Therapy Association
2010- Member, Society for Neuroscience
2009- Peer Review Committee: Journal of Neurologic Physical Therapy, *ad hoc reviewer*

C. Contribution to Science

1. My early work was focused on comparing different NIBS approaches in their potential for harnessing plasticity to augment motor function, both in neurologically healthy individuals and individuals with chronic incomplete tetraplegia. In neurologically healthy individuals, I found that bi-hemispheric tDCS applied to both primary motor cortices augments fine motor hand function. In individuals with chronic incomplete tetraplegia, I found that repetitive TMS augmented the effects of neurorehabilitation exercise programs designed to improve fine motor hand function. In addition, I found differences in the potential for NIBS techniques to augment an exercise program that targeted fine motor hand use. Direct stimulation to the motor cortex (tDCS) was the most promising approach, when compared with peripherally applied stimulation (transcutaneous electrical nerve stimulation [TENS] and vibratory stimulus [VIB]). By demonstrating that harnessing plasticity in the form of NIBS, it is possible to further extend the benefits of exercise interventions designed to improve

hand function. Therefore, this body of work provides alternatives for physical therapists and patients to advance the quality of their rehabilitation programs. I served as primary author on all these publications.

1. **Gomes-Osman, J.**, Field-Fote EC. Improvements in Hand Function in Adults With Chronic Tetraplegia Following a Multiday 10-Hz Repetitive Transcranial Magnetic Stimulation Intervention Combined With Repetitive Task Practice. **J Neurol Phys Ther.** 2015.

2. **Gomes-Osman, J.**, Field-Fote EC. Cortical vs. afferent stimulation as an adjunct to functional task practice training: A randomized, comparative pilot study in people with cervical spinal cord injury. **Clin Rehabil.** 2015.

3. **Gomes-Osman, J.**, Field-Fote EC. Bihemispheric anodal corticomotor stimulation using transcranial direct current stimulation improves bimanual typing task performance. **J Mot Behav.** 2013.

2. Recognizing that electrophysiological measures with TMS may show substantial variability from one individual to the next, among a group of scientists, I carried out a study to determine the internal consistency of different TMS measures (single-pulse TMS, paired-pulse TMS, theta-burst TMS), and the minimum number of pulses that will lead to accurate estimation of the mean, around the 95% confidence interval for these measures. This work adds to the literature by providing guidelines to achieve reliable measurements using TMS, and has the potential to decrease the variability often seen with TMS measures across the literature.

1. Chang, W.H., Fried, P.J., Saxena, S., Jannati, A., **Gomes-Osman, J.**, Kim, Y.H., Pascual-Leone, A. Optimal number of pulses as outcome measures of neuronavigated transcranial magnetic stimulation. Clin Neurophysiol. 2016.

Complete List of Published Work in My Bibliography, and also below:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Joyce+Gomes
http://www.ncbi.nlm.nih.gov/pubmed/?term=Gomes-Osman

1. Chang, W.H., Fried, P.J., Saxena, S., Jannati, A., **Gomes-Osman, J.**, Kim, Y.H., Pascual-Leone, A. Optimal number of pulses as outcome measures of neuronavigated transcranial magnetic stimulation.
Clin Neurophysiol. 2016.

2. **Gomes-Osman J.**, Cortes M., Guest J., Pascual-Leone A. A systematic review of experimental strategies aimed at improving motor function after acute and chronic spinal cord injury. **J Neurotrauma.** 2015.

3. **Gomes-Osman, J.**, Field-Fote EC. Improvements in Hand Function in Adults With Chronic Tetraplegia Following a Multiday 10-Hz Repetitive Transcranial Magnetic Stimulation Intervention Combined With Repetitive Task Practice. **J Neurol Phys Ther.** 2015.

4. **Gomes-Osman, J.**, Field-Fote EC. Cortical vs. afferent stimulation as an adjunct to functional task practice training: A randomized, comparative pilot study in people with cervical spinal cord injury. **Clin Rehabil.** 2015.

5. **Gomes-Osman, J.**, Field-Fote EC. Bihemispheric anodal corticomotor stimulation using transcranial direct current stimulation improves bimanual typing task performance. **J Mot Behav.** 2013.

6. **Rios-Gomes, J**., De Ornelas, M., Ponski, E, Field-Fote EC. Bilateral excitatory transcranial

direct current stimulation (tDCS) improves bimanual motor performance in non-disabled individuals-A pilot study. **Neuroscience 2010**. Poster November 2010.

7. Baptista AF, Goes BT, Menezes D, Gomes FC, Zugaib J, Stipursky J, **Gomes JR**, Oliveira JT, Vannier-Santos MA, Martinez AM PEMF fails to enhance nerve regeneration after sciatic nerve crush lesion. **J Peripher Nerv Syst**. 2009.

8. Baptista AF, **Gomes J.R.**, Oliveira JT, Santos SM, Vannier-Satos MA, Martinez AMB. High and low frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration in the mouse. J Perypher Nerv Syst, 2007.

9. Baptista AF, **Gomes J.R**., Oliveira JT, Santos SM, Vannier-Satos MA, Martinez AMB. A new approach to assess function after sciatic nerve lesion in the mouse-Adaptation of the sciatic static index. **J Neurosci Methods.** 2007.

C. Research Support

Completed

2007-2012 **National Institutes of Health (NIH) R01 HD053854.** Improving Arm and Hand Function in Individuals with SCI. This project consisted of a comparison of different approaches to improve upper extremity function in individuals with tetraplegia using repetitive task practice and peripherally applied electrical stimulation. Principal Investigator: Edelle Field-Fote, PT, PhD. **Role: Project Coordinator**.

2010-2011 **National Institutes of Health (NIH) R01HD053854-03S1.** Improving Arm and Hand Function in Individuals with SCI. This project consisted of a comparison of different approaches to improve upper extremity function in individuals with tetraplegia using repetitive task practice and repetitive transcranial magnetic stimulation. Principal Investigator: Edelle Field-Fote, PT, PhD. **Role: Project Coordinator**

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: Jiang, Hong

eRA COMMONS USER NAME (agency login): HongJiang

POSITION TITLE: Clinical Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Zhejiang Medical University, Hangzhou, Zhejiang	MD	07/1988	Medicine
Zhejiang Medical University, Hangzhou, Zhejiang	MS	07/1993	Neurology
University of Hong Kong, Hong Kong	PHD	07/2001	Neuroscience
Zhejiang Medical University, Hangzhou, Zhejiang	Other training	07/1990	Internship (Internal Medicine)
University of Rochester, Rochester, New York	Postdoctoral Fellow	07/2005	Neuroscience
Rochester General Hospital, Rochester, New York	Other training	07/2006	Intership (Internal Medicine)
Jackson Memorial Hospital/University of Miami, Miami, FL	Resident	07/2010	Neurology
Bascom Palmer Eye Institute, University of Miami, Miami, FL	Fellow	07/2011	Neuro-Ophthalmology

A. Personal Statement

Vascular dysfunction is a possible contributor to the age-related cognitive decline. We proposed to study the relationship between ocular microvascular dysfunction and cognitive decline in patients with mild cognitive impairment and Alzheimer's disease (AD) by using advanced ophthalmic imaging techniques. The goal is to identify the role of vascular derangement in the pathogenesis of AD. The preliminary data obtained with the grant support from North American Neuroophthalmology Society (NANOS) and University of Miami revealed ocular microvascular dysfunction and retinal microstructural alterations exist in age-related cognitive decline. As a neurologically trained neuroophthalmologist, I have a broad background in both basic and clinical research. I am a member of McKnight Brain Institute at the University of Miami and have been participating in AD clinical trials. Working with the exceptional and experienced scientists and engineering team at the Bascom Palmer Eye Institute, I have been involved in advanced structural and functional ophthalmic imaging for more than 5 years. My work has been reflected in my recent publications as the corresponding author in the field of retina and conjunctiva functional imaging. I have initiated Functional Slit-lamp Biomicroscopy (FSLB) imaging for the conjunctival microvasculature, which yielded the invention of single shot microvascular network quantification. I also explored the Retinal Function Imager (RFI) while studying various diseases like diabetic retinopathy, cerebral small vessel diseases, multiple sclerosis and other ocular diseases. The build-up of the versatile FSLB and further development of the RFI imaging processing approach indicate that the team is well capable of conducting the proposed study. In summary, my expertise and experience make me well equipped and qualified for working in this proposed project.

1. Jiang H, Abukhalil F, Shen M, Gregori G, Lam BL, Wang Y, Wang J. Slit-lamp-adapted ultra-high resolution OCT for imaging the posterior segment of the eye. Ophthalmic Surg Lasers Imaging. 2012 Jan-Feb;43(1):76-81. PubMed PMID: 22251848.

2. Jiang H, Ye Y, DeBuc DC, Lam BL, Rundek T, Tao A, Shao Y, Wang J. Human conjunctival microvasculature assessed with a retinal function imager (RFI). Microvasc Res. 2013 Jan;85:134-7. PubMed PMID: 23084966; PubMed Central PMCID: PMC3534915.
3. Jiang H, Debuc DC, Rundek T, Lam BL, Wright CB, Shen M, Tao A, Wang J. Automated segmentation and fractal analysis of high-resolution non-invasive capillary perfusion maps of the human retina. Microvasc Res. 2013 Sep;89:172-5. PubMed PMID: 23806780; PubMed Central PMCID: PMC3773708.
4. Jiang H, Zhong J, DeBuc DC, Tao A, Xu Z, Lam BL, Liu C, Wang J. Functional slit lamp biomicroscopy for imaging bulbar conjunctival microvasculature in contact lens wearers. Microvasc Res. 2014 Mar;92:62-71. PubMed PMID: 24444784; PubMed Central PMCID: PMC3960300.

B. Positions and Honors

Positions and Employment

1990 - 1997	Neurologist, Second Affiliated Hospital of Zhejiang Medical University, Hangzhou
2011 - 2012	Clinical Instructor, Neuro-ophthalmology and Neurology, Bascom Palmer Eye Institute, University of Miami, Miami, FL
2012 -	Clinical Assistant Professor, Neuro-ophthalmology & Neurology, Bascom Palmer Eye Institute & Dept. of Neurology, University of Miami, Miami, FL

Other Experience and Professional Memberships

2001 -	Member, American Academy Of Neurology
2010 -	Member, Association for Research in Vision and Ophthalmology
2010 -	Member, American Association of Ophthalmology
2012 -	Member, North American Neuro-Ophthalmology Society
2012 -	Member, Member of American Heart Association

Honors

1997	Lady Ivy Wu Fellowship , University of Hong Kong
1999	Travel Grant, International Federation of Parkinson's disease Foundations
2000	Young Investigator Award for Best Oral Presentation, Queen Mary Hospital
2000	Travel and Conference Award , Dr. Lo Kwee Seong Education Foundation
2008	Travel Award, Florida Society of Neurology
2011	ARVO Travel Grant, National Eye Institute

C. Contribution to Science

1. To image microvasculature on the conjunctiva in studying cerebral small vessel diseases, a system called functional slit-lamp biomicroscope (FSLB) was developed and a patent of single shot for generating conjunctival microvascular network map was filled. This novel system enables easily imaging the conjunctival microvascular network and small vessel blood flow velocity.

    a. Jiang H, Ye Y, DeBuc DC, Lam BL, Rundek T, Tao A, Shao Y, Wang J. Human conjunctival microvasculature assessed with a retinal function imager (RFI). Microvasc Res. 2013 Jan;85:134-7. PubMed PMID: 23084966; PubMed Central PMCID: PMC3534915.
    b. Jiang H, Zhong J, DeBuc DC, Tao A, Xu Z, Lam BL, Liu C, Wang J. Functional slit lamp biomicroscopy for imaging bulbar conjunctival microvasculature in contact lens wearers. Microvasc Res. 2014 Mar;92:62-71. PubMed PMID: 24444784; PubMed Central PMCID: PMC3960300.
    c. Stuebiger N, Smiddy W, Wang J, Jiang H, DeBuc DC. Assesment of Conjunctival Microangiopathy in a Patient with Diabetes Mellitus Using the Retinal Function Imager. J Clin Exp Ophthalmol. 2015 Feb;6(1)PubMed PMID: 26301125; PubMed Central PMCID: PMC4541803.

d. Jiang H, Delgado S, Liu C, Rammohan KW, DeBuc DC, Lam BL, Wang J. In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis. Ophthalmology. 2015 Aug 20;PubMed PMID: 26299696.

2. I have initiated the development of automatic segmentation of retinal microvascular network obtained using Retinal Function Imager (RFI) for studying retinal microvascular changes in multiple sclerosis, AD, diabetics and cerebral small vessel diseases.

   a. Jiang H, Debuc DC, Rundek T, Lam BL, Wright CB, Shen M, Tao A, Wang J. Automated segmentation and fractal analysis of high-resolution non-invasive capillary perfusion maps of the human retina. Microvasc Res. 2013 Sep;89:172-5. PubMed PMID: 23806780; PubMed Central PMCID: PMC3773708.

   b. Jiang H, Delgado S, Liu C, Rammohan KW, DeBuc DC, Lam BL, Wang J. In vivo characterization of retinal microvascular network in multiple sclerosis. *Ophthalmology,* 2015 Aug 20 [Epub ahead of print] PubMed PMID 26299696

3. To study retinal degeneration in neurological diseases such as multiple sclerosis, I have contribute to the development of slit-lamp based ultra-high resolution OCT for imaging the retina. Our segmentation software can segment 9 retinal sub-layers. Recent development of segmentation software enables automatic segmentation of 6 maps of retinal sub-layers.

   a. Jiang H, Abukhalil F, Shen M, Gregori G, Lam BL, Wang Y, Wang J. Slit-lamp-adapted ultra-high resolution OCT for imaging the posterior segment of the eye. Ophthalmic Surg Lasers Imaging. 2012 Jan-Feb;43(1):76-81. PubMed PMID: 22251848.

   b. Wang Y, Jiang H, Shen M, Lam BL, DeBuc DC, Ye Y, Li M, Tao A, Shao Y, Wang J. Quantitative analysis of the intraretinal layers and optic nerve head using ultra-high resolution optical coherence tomography. J Biomed Opt. 2012 Jun;17(6):066013. PubMed PMID: 22734769; PubMed Central PMCID: PMC3381522.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1buofoatUF5Q8/bibliography/48052483/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2015/04/01 – 2018/3/31
National Multiple Sclerosis Society
The Role of retinal microvascular impairment on Neurodegeneration in Multiple Sclerosis
The goal of this study is to test if impaired retinal microvasculature proceeds and contributes to neurodegeneration.
Role: PI

2015/10/1 – 2020/9/30
Sun Yat-sen University collaboration award
Jianhua Wang (PI)
Clinical applications of advanced ophthalmic imaging
Role: co-PI

2013/11/21-2018/05/31
US202, Toyama (pharmaceutical company)
Clinton Wright (PI)

A Phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild to moderate Alzheimer's Disease (US202)
Role: Co-Investigator

2016/04/01 –
US20140371439
Bylon Lam (PI)
A Phase 2/3, randomized, double-masked, sham-controlled trial of QPI-1007 delivered by single or multi-dose intravitreal injection(s) to subjects with acute nonarteritic anterior ischemic optic neuropathy (NAION)
Role: sub-investigator

2014/12/01-2016/12/31
JJVC, Johnson & Johnson Vision Product Clinical Research
Jiang, Hong (PI)
Conjunctival microvascular characterization of contact lens wear
The purpose is to characterize conjunctiva microvasculature in contact lens wearer.
Role: PI

Completed Research Support

NANOS Pilot 2015, North American Neuro-Ophthalmology Society
Hong Jiang (PI)
04/15/15-10/15/16
Retinal microvascular alteration as a possible biomarker in Alzheimer's disease
The purpose of this project is to characterize the retinal microvascular dysfunction and optical properties of Retinal nerve fiber layer in AD patients.
Role: PI

NMSS Pilot 2014, National Multiple Sclerosis Society
Jiang, Hong (PI)
07/01/14-04/30/15
Retinal vascular dysfunction in multiple sclerosis
The purpose of this project is to characterize the retinal microvascular dysfunction and optical properties in MS patients using the Retinal Function Imager (RFI) and Polarization Sensitive Optical Coherence Tomography (PS-OCT).
Role: PI

R01EY020607S, NIH supplemental award
Delia Cabrera DeBuc (PI)
02/01/12-01/31/14
Advanced imaging for diabetic retinopathy
This award (R01 supplement for 2 years) provides support under the Research Supplements to Promote Diversity in Health-Related Research Program to Dr. Jiang who studies retinal neurodegenerative diseases by using the unique prototype of UHR-OCT with added oximetry capability and the Retinal Function Imager (RFI).
Role: Co-Investigator

Start-up research project, Bascom Palmer Eye Institute
Jiang, Hong (PI)
07/01/11-06/30/12
Functional Imaging of optical coherence tomography

The purpose of this project was to assess retinal hemodynamics and structure morphology differences between normal healthy subjects and multiple sclerosis using spectral analysis of images obtained with ultra-high resolution optical coherence tomography.
Role: PI

US202, Toyama (pharmaceutical company)
Clinton Wright (PI)
11/21/13-05/31/18
A Phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild to moderate Alzheimer's Disease (US202)
Role: Co-Investigator

UM SAC 2015-27R1 , University of Miami
Jianhua Wang (PI)
01/01/15-12/31/15
Conjunctival Microvasculature and its association with tear protein biomarkers in dry eye syndrome
The purpose is to characterize conjunctival microvasculature in dry eye
Role: Co-Investigator

UM RSA 2015-41, University of Miami
Hong Jiang (PI)
12/01/14-12/31/15
Ocular microvascular biomarkers in Alzheimer's disease
This project is a clinical trial for further studying tear dynamics after treatment with Restasis in dry eye patients.
Role: PI

Novartis FTY720/Fingolimod, Novartis
Khema Shama (PI)
12/01/12-11/30/15
Efficacy and safety of fingolimod in CIDP patients
This study is a double-blind, randomized, multicenter, placebo-controlled, parallel-group study to study the efficacy and safety of fingolimod in CIDP patients.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Bonnie E. Levin, Ph.D.	Professor of Neurology and Psychology
eRA COMMONS USER NAME bonnie_levin	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Georgetown University	BS	1974	Psychology
Temple University	Ph.D.	1983	Psychology

A. Personal Statement

My role is to direct and implement all cognitive and behavioral assessments carried out in the Division of Neuropsychology, Department of Neurology at the University of Miami Miller School of Medicine. Currently, I hold the Bernard and Alexandria Schoninger Professorship in Neurology and I am the founder and Director of the Division of Neuropsychology. I direct the Neuropsychology Assessment Teaching Program and supervise the clinical activities of PhD graduate students in the Child Clinical, Adult Clinical and Behavioral Medicine tracks. I have taught the graduate level course in Foundations of Neuropsychology for over 25 years. I have had a long history of collaborations with numerous research teams in neurology, psychology and radiology, and participated in multiple projects examining cognitive, behavioral and imaging changes associated with normal aging and neurodegenerative disease. I am currently the site PI of a study examining cognitive and behavioral changes, including symptoms of frailty, among the oldest old, funded by the Mcknight Brain Research Institute. I am also a co-investigator on the NIH-funded population based Northern Manhattan Study, in which I am a member of the neuropsychology team and the dementia adjudication consensus panel. I am also a co-investigator on the Bugher AHA grant and a recently approved study (Dept of Defense) examining brain metabolites underlying pain associated with traumatic injury. I believe I have the qualifications, expertise and administrative and leadership abilities serve as the PI or Co-I on studies of examining cognitive function over the life span.

These peer reviewed publications highlight my experience and qualifications for this project:

1. **Levin BE**, Llabre MM, Dong C, Elkind MS, Stern Y, Rundek T, Sacco RL, Wright CB. Modeling metabolic syndrome and its association with cognition: the northern Manhattan study.J Int Neuropsychol Soc. 2014 Nov;20(10):951-60.
2. Maudsley A, Govind V**, Levin B**, Saigal G, Harris LT, Sheriff S. Distributions of MR Diffusion and Spectroscopy Measures with Traumatic Brain Injury.J Neurotrauma. 2014 Oct 21. [Epub ahead of print] PMID: 25333480
3. **Levin BE**, Katzen HL, Maudsley A, Post J, Myerson C, Govind V, Nahab F, Scanlon B, Mittel A.Whole-brain proton MR spectroscopic imaging in Parkinson's disease. J Neuroimaging. 2014 Jan-Feb;24(1):39-44

B. Positions and Honors

POSITIONS AND EMPLOYMENT

Academic Appointments

1979-1980	Fellow in Psychology, Department of Psychiatry, Harvard Medical School, Boston, MA
1979-1980	Intern, Clinical Pediatric Neuropsychology, Children's Hospital Center, Boston, MA.
1980	Extern, Boston Veteran's Administration Hospital, Boston, MA
1981-1982	Instructor, Department of Neurology, University of Miami
1981	Director, Division of Neuropsychology, Department of Neurology, University of Miami
1986-1992	Assistant Professor, Department of Neurology, University of Miami
1992-2011	Associate Professor (with tenure), Department of Neurology, University of Miami Miller School of Medicine

2011- Professor of Neurology, Department of Neurology, University of Miami Miller School of Medicine

Honors

Cum Laude, Georgetown University; Psi Chi Honor Society1974
Fellow, Mahoney Residential College
International Neuropsychology Society (INS) Program Chair-1997
INS Board of Governors 1998-2001
NINDS Study Section Member NSD-K, 2001-2005
NINDS AD hoc Reviewer-NSD-A 2001, 2002
NINDS Special Emphasis Panels 7/1998, 8/1999, 12/1999, 5/2000, 8/2000, 10/2000, 12/2001, 6/2001, 10/2001, 8/2002, 12/2002, 1/2004, 8/2004, 12/2004, 2/2005, 1/2006, 10/2006, 11/2006, 11/2006, 6/2007, (6/24 & 6/29) 3/2008, 4/2008.
NINDS Ad hoc reviewer, NSD-K, 2006 - 2008
Alzheimer Association Medical and Scientific Council Reviewer, 1999, 2002
Consultant: University of Miami Brain Endowment Bank, Department of Neurology; Clinical Neuroscience Unit, UM Department of Neurology
Member, National Acute Brain Injury Study: Hypothermia II: Data Safety of Monitoring Board
Pediatrics; UM Sleep Center, Department of Neurology.
Professional Advisory Board: Epilepsy Foundation of South Florida
Editorial Boards: Neuropsychology, Journal of International Neuropsychology Society, Neuropsychology Review, Aging, Neuropsychology and Cognition
Alexandria and Bernard Schoninger Endowed Professorship in Neurology, 2009

C. Contributions to Science

C.1. Over the past 30 years, I have focused on cognitive and behavioral changes over the life course. My research projects are largely in the field of aging, examining age related cognitive decline and early biomarkers of behavioral and cognitive decline in normal aging and neurodegenerative disease. As the Schoninger Professor or Neurology, I oversee the Division of Neuropsychology, a major training and research site that evaluates over 300 patients a year examining age related cognitive change as well as pathological behavioral alterations associated with degenerative disease. I have published extensively on cognitive change across the lifespan.

1. Kelley, R.E., Chang, JY, Scheinman, NJ, **Levin, BE**, Duncan, RC, Shih-Chang, L: Transcranial doppler ultrasonographic assessment of cerebral artery flow velocity during cognitive activity. Stroke, 1992; 23:9-14.
2. Tomer, R**, Levin, BE**, Differential affects of aging in two verbal fluency tasks. Perceptual and Motor Skills, 1993; 76: 465-466
3. **Levin, BE**, Katzen, H.L., Klein, B., Llabre, M. Cognitive decline affects subject attrition in longitudinal research. Journal of Clinical and Experimental Neuropsychology. 2000, 22 (5), 580-586.
4. Grossman A, Levin B, Katzen H, Lechner S. PTSD symptoms and onset of neurologic disease in elderly trauma survivors. Journal of Clinical and Experimental Neuropsychology 2004: 26(5): 698-705.

C.2.Our group was among the earliest investigators to document and describe non-motor changes in Parkinson's disease. I have also examined how gait and other lateralized motor changes are linked to cognitive and behavioral symptoms and PD progression. These studies reflect my longstanding interest in gait, movement and cognition.

1. **Levin, BE**, Llabre, MM, Weiner, WJ: Cognitive impairments associated with early Parkinson's disease. Neurology, 1989, 39:557-561.
2. **Levin, BE**, Llabre, MM, Weiner, WJ, Brown, MC: Visuospatial decline in Parkinson's disease. Neurology, 1991; 41:365-369.
3. Tomer, R, **Levin, BE**, Weiner, WJ: Side of motor onset influences cognition in Parkinson's disease. Annals of Neurology, 1993; 34:579-584.
4. Katzen, H, **Levin, BE**, Llabre, M: Age of onset influences cognition in Parkinson's disease. Journal of International Neuropsychological Society, 1998, 4, 285-290.

C.3. I am currently involved in several studies examining the relationship between MRS metabolites and cognitive changes in normative aging, TBI, ALS and Parkinson's disease. These studies utlize a unique whole brain analysis that permits a study of a large fraction of the brain volume, including the cortical mantle. My role as the neuropsychologist on these projects is to identify sensitive outcome measures and to work with my collaborators linking the behavioral presentation associated a traumatic injury or neurologic illness with distributions of proton magnetic resonance spectroscopy (MRS) observed metabolites throughout the whole brain.

1. **Levin BE**, Katzen, HL, Maudsley, A, Post, J, Myerson, C, Govind, G, Nahab, F, Scanlon, B, Mittel. A Whole-brain proton MR spectroscopic imaging in Parkinson's disease. Journal of Neuroimaging, 2014, 24, 39-44
2. Maudsley, A, Govind, V, **Levin, BE**, Saigal, G, Harris, L, Sheriff, S Distributions of MR Diffusion and Spectroscopy Measures with Traumatic Brain Injury. J. Neurotrauma. 2015; 32 (14): 1056-1063
3. Widerstrom-Noga, E, Govind, VB, Adcock, J**, Levin, BE**, Maudsley, A Subacute Pain after TBI is associated with lower insular N-acetyl-aspartate concentrations. Journal of Neurotrauma (in press)

Complete List of Published Work at NCBI:
http://www.ncbi.nlm.nih.gov/pubmed/?term=(%22levin%2C%20bonnie%22%5BAll%20Fields%5D)&cmd=DetailsSearch

D. Research Support

Ongoing Research Support

Scythian Bioscience **08/01/2016-7/30/2021**
The Effects of Cannabinoids on TBI ($16,000,0000)
B. Levin, Co-Investigator, Director of Clinical Trials
This study will examine the inflammatory properties of cannabinoids and determine whether they can be used as a therapeutic intervention in traumatic brain injury

7 R01 NS 029993 (PI, Sacco) NIH/NINDS **02/01/03-03/31/21** **1.20 calendar**
Stroke Incidence and Risk Factors in a TriEthnic Region **$1,795,509**
(B. Levin, Co-Investigator)
The goals of this project are to determine the effects of risk factors for stroke, MI, and vascular death, as well as evaluate predictors of cognitive impairment and the importance of subclinical MRI findings in a prospective cohort study of 3300 persons from 3 race-ethnic groups from Northern Manhattan.

09/28/12-09/27/15 **1.20 calendar**
National Multiple Sclerosis **$169,003**
Fast Forward a Randomized Double Blind Placebo Controlled (PI: Ortega; B. Levin, Co-Investigator)
To evaluate the therapeutics effects of caprylic triglyceride administered once a day for 90 days on cognitive impairment in subjects with multiple sclerosis.

AHA/ASA 14BFSC1759000 (PI: Sacco) **04/01/14 – 03/31/18** **0.6 calendar**
AHA (B. Levin, Co-Investigator) **$234,667**
Bugher Center Foundation Center of Excellence in Stroke Award
This award will conduct two projects evaluating the effects of physical activity and cognitive training on animals and stroke survivors on cognitive recovery

DoD/CDMRP/USAMRMC (PI: Widerstrom-Noga) **11/2015-10/2018** **.84 calendar**
(B. Levin, Co-Investigator) **$977,099** (direct)
Utility of MRS Brain Biomarkers of Pain Phenotypes after TBI
Goals are to evaluate advanced metabolic imaging methods for injury assessment and prognosis following mild and moderate traumatic brain injury.

Prior Research Support

NINDS 1 UO1 NS052478-01A2 (Adelson) **7/30/07 – 6/30/2011**
Pediatric Traumatic Brain Injury Consortium: Hypothermia
This is a multicenter clinical trial to determine the efficacy of early induced moderate hypothermia after severe TBI in a pediatric sample. Subject mortality at 3 months is the primary measure of outcome. Secondary outcome measures included functional assessment and performance based neuropsychological measures. Role: Study Principal Investigator of the Outcome Center.

NIH/NINDS 2U01NS38529-07A1 (Benavente/ Romano, site PI) **02/01/2008 – 6/30/2011**
Secondary Prevention of Small, Subcortical Strokes (SPS3)

NIH/NINDS R01 NS055107 (Maudsley) **6/1/2006 – 12/31/2012**
Volumetric MRSI Evaluation of Traumatic Brain Injury
Goals are to evaluate advanced metabolic imaging methods for injury assessment and prognosis following mild and moderate traumatic brain injury.

NIH/NINDS R01 NS060874 (Govind) **1/1/2009 – 8/31/2012**

Brain Metabolic Imaging in Amyotrophic Lateral Sclerosis

The major goal of this project is to examine the efficacy of whole-brain proton MRSI and DTI methods for evaluating cerebral pathological changes in ALS.

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: **Teshamae S. Monteith, M.D.**

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

POSITION TITLE: **Assistant Professor of Clinical Neurology**

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
Florida International University, Miami, FL	BS	12/98	Biology
University of Miami Miller School of Medicine, Miami, FL	MD	05/04	Medicine
Albert Einstein-Montefiore Medical Center, NY, NY	Intern	06/05	Internal Medicine
New York University School of Medicine, NY, NY	Residency	06/08	Neurology
Thomas Jefferson University School of Medicine, Philadelphia, PA	Fellowship	06/09	Headache
University of California, San Francisco, CA	Fellowship	06/11	Headache

A. Personal Statement

My research focus has been on headache disorders, migraine in particular, and the cross section between migraine and vascular risk factors and stroke outcomes. As a collaborator for the McKnight Brain Institute, I aim to investigate cognitive impairment in subjects with headache disorders. I have a secondary interest in understanding the impact of obesity, metabolic disorders, and dietary factors on migraine and cognition.

B. Positions and Honors

POSITIONS AND EMPLOYMENT

Traineeship:

2004-2005	Intern	Montefiore Medical Center, Bronx, New York
2005-2008	Neurology Resident	New York University, New York, NY
2008-2009	Headache Fellowship	Thomas Jefferson University, Philadelphia, PA
2009-2011	Headache Fellowship	University of California, San Francisco, San Francisco, CA

Academic Appointments:

2011-Present	Assistant Professor of Clinical Neurology	Department of Neurology, University of Miami School of Medicine, Miami, FL

OTHER EXPERIENCE AND PROFESSIONAL MEMBERSHIPS

Ad Hoc Reviewer for the Professional Journals: Headache, European Journal of Neurology, Cephalalgia.

Memberships:

1996-	American Academy of Neurology
2008-	American Headache Society

2008- American Academy of Neurology Brain PAC Founder's Club
2008 New York State Neurological Society
2008 National Headache Foundation
2009 Pennsylvania Neurological Society
2009- International Headache Society
2013- Florida Society of Neurology, board member
2014- International Association for the Study of Pain

HONORS

1993 Florida International University Tuition Scholarship, Miami, FL
1994 National Institutes of Health, Minority Biomedical Research Support Program
1998 AMSA Outstanding Commitment Award, Minority Committee Chairman
1998 Florida International University Honors Program
2000 Leonard Miller School of Medicine at the University of Miami Tuition Award
2001 McClleland Brown Trust Rotary Scholarship Award
2006 American Neurological Association Resident's Program Scholarship
2007 National Headache Foundation Travel Award
2008 American Headache Society /Merck US Human Health Scholarship Award
2010 Palatucci Co-Advocate of the Year Award, American Academy of Neurology
2013 Harold G. Wolff Lecture Award, presented at the American Headache Society meeting
2014 Doctor of Excellence, Leaders in Healthcare Network
2014 Fellow, American Headache Society
2015 South Florida, Top Black Educator, Legacy Magazine

C. Contribution to Science

1. I have made significant contributions to the understanding of migraine pathophysiology and vascular complications. Through PET imaging during nitroglycerin triggered migraine attacks, our group determined several brain regions that were activated before migraine pain was experienced during the premonitory phase. This critical study was awarded the Wolff award for the key finding that confirmed migraine as a central brain disorder as opposed to a peripheral nerve disorder. The findings have implications for targeted drug approaches.
    a. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014;137(Pt 1):232-41
    b. Maniyar FH, Sprenger T, Monteith T et al. The premonitory phase of migraine - what can we learn from it? Headache. 2015; 55(5):609-20.

2. Through a NINDS funded supplement award to promote health related diversity research, our study findings have contributed a better understanding of the impact of migraine on silent brain lesions, cardiovascular risks and vascular outcomes through analysis of the multi-ethnic cohort from the Northern Manhattan Study. We found that compared to people without migraine, those with migraine (confirmed by International Classification of Headache Disorders-2 criteria) had a 2-fold increased odds of subclinical brain infarction (adjusted odds ratio [OR], 2.1; 95% confidence interval [CI], 1.0 - 4.2). These results were confirmed in a diverse older cohort with a high burden of cardiovascular risk factors such as hypertension. However, the association between migraine and silent brain infarction was independent of sociodemographic and cardiovascular factors. In a study accepted to Neurology, I also found that the impact of migraine on stroke differed among smokers and non-smokers which is consistent with other studies. Further work is needed to determine the role of lifestyle intervention, genetics, and vascular risk reduction in improving migraine complications such as stroke and other vascular disorders.
    a. Gardener H, Monteith T, Rundek et al. Hypertension and Migraine in the Northern Manhattan Study. Ethn Dis. 2016; 3:323-30.
    b. Monteith T, Gardener H, Rundek T et al. Migraine and risk of stroke in older adults: Northern Manhattan Study Neurology. 2015; 85:1–7.
    c. Monteith TS, Gardener H, Rundek et al. White Matter Hyperintensities, and Subclinical Brain Infarction in a Diverse Community: The NOMAS Study. Stroke. 2014; 45(6):1830-2.

Complete List of Published Work:
http://www.researchgate.net/profile/Teshamae_Monteith/publications

D. Research Support

Ongoing Research Support

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache. Eli Lilly. Site PI, 2015.

Completed Research Support

The Relationship between Migraine, Subclinical Brain Lesions, and Biomarkers of Subclinical Cardiovascular Disease in a Tri-Ethnic Region: Supplement to Promote Diversity in Health-Related Research (R37 NS 29993) – NINDS PI, 2011-2015.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Carlos T. Moraes	Professor
eRA COMMONS USER NAME cmoraes	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Escola Paulista de Mediclna, Sao Paulo, Brazil	B.Sc.	1983	Biomedical Sciences
Escola Paulista de Mediclna, Sao Paulo, Brazil	M.Sc.	1987	Molecular Biology
Department of Genetics and Development, Columbia University	M.A.	1991	Genetics & Development
Department of Genetics and Development, Columbia University	Ph.D.	1993	Genetics & Development

A. Personal Statement

Although I have been working on mitochondrial diseases since 1987, my independent group at the University of Miami was established in 1993 and in the last two decades has been studying mitochondrial diseases and the role of mitochondrial dysfunction in neurodegenerative diseases. Our work has been continuously funded by the NIH since 1994. Mentoring Ph.D. students and postdoctoral fellows has been an important part of my career's mission. I have graduated 10 Ph.D. students since starting my independent lab and almost all have continued in an academic career. There are 2 Ph.D. students currently developing their projects in my lab. I have also trained 17 Postdoctoral fellows, 3 of whom are still in the lab.

B. Positions and Honors.

PROFESSIONAL APPOINTMENTS

2014 -	Esther Lichtenstein Endowed Chair in Neurology
2005 -	Professor (Tenured). Dept. of Neurology, University of Miami, Miami, FL.
1998 – 2005	Associate Professor (Tenured). Dept. of Neurology, University of Miami, Miami, FL.
1993 – 1998	Assistant Professor. Dept. of Neurology, University of Miami, Miami, FL.
1992 – 1993	Postdoctoral Research Fellow. Dept. of Neurology, Columbia University, New York, NY.

AWARDS AND OTHER PROFESSIONAL ACTIVITIES:

2005	Provost Award for Scholarly Activity, University of Miami
2002 - 2006	NIH Scientific Review Panel Member (GHD)
2010- 2013	NIH Scientific Review Panel Member (NOMD)
2007- Present	Scientific Advisory Committee member, Muscular Dystrophy Association
2005- Present	Scientific Advisory Committee member, United Mitochondrial Disease Foundation
2009- Present	Chair, Scientific Advisory Committee, United Mitochondrial Disease Foundation
1999 - 2004	Scientific Advisory Committee member, Muscular Dystrophy Association
1995 - 1999	PEW Scholar in the Biomedical Sciences
1997	National Eye Institute Committee on "Development of a National Plan for Vision Research
1997	National Heart, Lung, and Blood Institute Scientific Review Committee for RFA: HL-96-013
1998	Chemistry and Related Sciences Special Emphasis Review Panel (NIH).
1998	Molecular Cytology Special Emphasis Panel (NIH).

C. Contribution to Science

1. I became involve with mitochondrial genetics during my Ph.D.. Working with Drs. Salvatore DiMauro and

Eric Schon at Columbia University, we were the first to show that mtDNA deletions were associated with ocular myopathy. We were also the first to show how mtDNA deletions are generated and how they segregate. Besides mtDNA deletions, we also identified several pathogenic mtDNA point mutations and, described a new genetic abnormality, namely a mtDNA depletion, caused by defects in the nuclear genome.

a. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. **Moraes. C.T**., DiMauro, S., Zeviani, M., Lombes, A., Shanske. S., Miranda, A. F et al., *New England Journal of Medicine,* 320: 1 293-1299 (1989).
b. Molecular analysis of the muscle pathology associated with mitochondrial DNA deletions. **Moraes, C. T.**, Ricci, E., Petruzzella, V., Shanske, S., DiMauro, S., Schon, E.A. and Bonilla, E. *Nature Genetics,* 1: 359-367 (1992).
c. A mitochondrial tRNA anticodon swap associated with a muscle disease. **Moraes. C.T**., Ciacci, F., Bonilla, E., Ionascescu, V., Schon, E.A., and DiMauro, S. *Nature Genetics,* 4:284-287 (1993).
d. Mitochondrial DNA depletion with variable tissue expression: A novel genetic abnormality in mitochondrial diseases. **Moraes. C.T**., Shanske, S., Trishler HJ., Aprille, J.R.. Andreetta, F., Bonilla, E., Schon, E.A. and DiMauro, S. *American Journal of Human Genetics,* 48: 492-501 (1991).

2. As an independent investigator, I continued to study mitochondrial diseases, but became interested in the co-evolution of nuclear and mitochondrial genomes. Using cross-species transmitochondrial (xenomitochondrial) cybrids we were able to determine the timing of evolutionary divergency for functional interaction between these genomes. We showed that although the nucleus of a human cell could maintain a functional mtDNA from chimpanzee or gorilla, it could not do so with orangutan or other species of primates (old world, new world, lemurs). However, even human-Chimp xenomitochondrial cybrids had a defect in complex I, showing how co-evolution shaped these interactions. These findings are important to better understand how mutations in the mtDNA cause disease. They may not be obviously deleterious for the function of the enzyme, but may disrupt critical interactions with nuclear counterparts.
    a. Expanding the functional human mitochondrial DNA database by the establishment of primate xenomitochondrial cybrids. Lesley Kenyon and **Carlos T. Moraes**. *Proceedings of the National Academy of Sciences USA* 94:9131-9135 (1997).
    b. Human xenomitochondrial cybrids. Cellular models of mitochondrial complex I deficiency. Antoni Barrientos, Lesley Kenyon and **Carlos T. Moraes**. *J Biol Chem*, 273:14210-7 (1998).
    c. Cytochrome *c* Oxidase Assembly in Primates is Sensitive to Small Evolutionary Variations in Amino Acid Sequence. Antoni Barrientos, Stefan Müller, Runu Dey, Johannes Wienberg and **Carlos T. Moraes**. *Molecular Biology and Evolution*, 17: 1508-1519 (2000)
    d. Fast Adaptive Co-evolution of Nuclear and Mitochondrial Subunits of ATP Synthetase in Orangutan. Maria Pilar Bayona-Bafaluy, Stefan Müller, **Carlos T. Moraes**. *Mol. Biol. Evol.* 22:716-724 (2005).

3. In the early-mid 2000, I decided to create mouse models of mitochondrial disease, as the pathogenesis studies and development of therapies would require them. We created conditional knockout models of defects in complexes IV, III and I, as well as a model of mtDNA depletion by expressing restriction endonuicleases targeted to mitochondria. These models have been shared to multiple groups and are deposited at Jackson laboratories. They have been used to study the role of mitochondrial oxidative phosphorylation defects in neurodegenerative diseases and to test therapies.
    a. Cytochrome c Oxidase Deficiency in Neurons Decreases both Oxidative Stress and Amyloid Formation in a Mouse Model of Alzheimer's Disease. Hirokazu Fukui, Francisca Diaz, Sofia Garcia and **Carlos T. Moraes**. *Proc Natl. Acad. Sci*. *USA* 104 :14163–14168 (2007).
    b. Striatal Dysfunctions Associated with Mitochondrial DNA Damage in Dopaminergic Neurons of a Mouse Model of Parkinson's Disease. Alicia M. Pickrell, Milena Pinto, Aline Hida and **Carlos T. Moraes**. *The Journal of Neuroscience;*31:17649-58 (2011).
    c. A defect in the mitochondrial Complex III, but not Complex IV, triggers early ROS dependent damage in defined brain regions. Francisca Diaz, Sofia Garcia, Kyle R. Padgett and **Carlos T. Moraes**. *Human Molecular Genetics,* 21:5066-77 (2012).
    d. Partial Complex I deficiency due to the CNS conditional ablation of Ndufa5 results in a mild encephalopathy and no increase in oxidative damage. Susana Peralta, Alessandra Torraco, Tina

Wenz, Sofia Garcia, Francisca Diaz and **Carlos T. Moraes**. *Hum. Mol. Genet. 23:1399-412 (2014)*

4. My interest in developing therapies to mitochondrial diseases led us to explore the role of increased mitochondrial biogenesis in mitochondrial myopathies. We found that overexpression of PGC-1a in muscle counteracted the deleterious effect of an OXPHGOS defect in mice. Moreover, we showed that some drugs, such as bezafibrate could partially mimic this effect. This work opened a new area of investigation, where increase in mitochondrial biogenesis was analyzed in several disorders suspected to have a mitochondrial component.
    a. PGC-1α/β induced expression partially compensates for respiratory chain defects in cells from patients with mitochondrial disorders. Sarika Srivastava, Francisca Diaz, Luisa Iommarini, Karine Aure, Anne Lombes and **Carlos T. Moraes**. *Human Molecular Genetics* 18:1805-12. (2009)
    b. Increase Mitochondrial Biogenesis in Muscle Improves Aging Phenotypes in the mtDNA Mutator Mouse. Lloye M. Dillon, Sion L. Williams, Aline Hida, Jacqueline D. Peacock, Tomas A. Prolla, Joy Lincoln and **Carlos T. Moraes**. *Human Molecular Genetics, 21:2288-97 (2012).*
    c. Pioglitazone ameliorates the phenotype of a novel Parkinson's disease mouse model by reducing neuroinflammation. Pinto Milena, Nissanka Nadee, Peralta Susana, Brambilla Roberta, Diaz Francisca, **Moraes Carlos**. *Molecular Neurodegeneration*, 11:25 (2016).
    d. Sustained AMPK activation improves muscle function in a mitochondrial myopathy mouse model by promoting muscle fiber regeneration
    *Susana Peralta, Garcia Sofia, Han Yang Yin, Arguello Tania, Francisca Diaz and **Carlos T. Moraes**. Hum. Mol. Genet. 2016 Jun 10.*

5. We also developed a genetic approach to treat mtDNA diseases. Shortly, we used mitochondria-targeted restriction endonucleases that could digest exclusively a specific mtDNA haplotype. In heteroplasmic cells, it leads to a reduction in the mutant mtDNA load and restoration of OXPHOS activity. We showed this approach to be effective in vivo, using several viral vectors to deliver the mitoRestriction Endonuclease. More recently, we adapted TALENs to this approach (mitoTALENs), which overcomes the limitation of few sites recognition posed by the bacterial endonucleases. This approach can also be used to prevent transmission of mutant mtDNA.
    a. Organ-specific shifts in mtDNA heteroplasmy following systemic delivery of a mitochondria-targeted restriction endonuclease. Bacman SR, Williams SL, Garcia S, **Moraes CT**. *Gene Ther*. 17:713-20. (2010).
    b. Manipulation of mtDNA heteroplasmy in all striated muscles of newborn mice by AAV9-mediated delivery of a mitochondria-targeted restriction endonuclease. Bacman SR, Williams SL, Duan D, **Moraes CT**. *Gene Ther*.;19:1101-6 (2012).
    c. Specific elimination of mutant mitochondrial genomes in patient–derived cells by mitoTALENs. Sandra R. Bacman, Siôn L. Williams, Milena Pinto, Susana Peralta and **Carlos T. Moraes**. *Nature Medicine, 19:1111-3. (2013).*
    d. MitoTALEN: A general approach to reduce mutant mtDNA loads and restore oxidative phosphorylation function in mitochondrial diseases.
    Hashimoto M, Bacman SR, Peralta S, Falk MJ, Chomyn A, Chan DC, Williams SL, **Moraes CT.** *Mol Ther.* 23:1592-9 (2015)
    e. Selective Elimination of Mitochondrial Mutations in the Germline by Genome Editing.
    Pradeep Reddy, Alejandro Ocampo, Keiichiro Suzuki, Jinping Luo, Sandra R. Bacman, Sion L. Williams, Atsushi Sugawara, David Lam, Nuria Monsterrat, Concepcion Rodriguez Esteban, Salva Civico, Francesc Cardellach, Maria del Mar O'Callaghan, Josep Maria Campistol, **Carlos T. Moraes**, Juan Carlos Izpisua Belmonte.
    Cell. 161, 459–469 (2015)

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/carlos.moraes.1/bibliography/40679402/public/?sort=date&d

irection=ascending

D. Research Support.

Active

*5R01EY010804-18 (*Moraes, C.T.) 12/01/94-4/30/21
NIH/NEI
"Setting the stage for the replacement of mitochondrial genes"
The objective of this project is to use mitochondria-targeted restriction endonucleases to modify mtDNA heteroplasmy.
Role: PI

*1R01NS079965-03 (*Moraes, C.T.) 07/01/2012 – 05/31/2017
NIH/NINDS
"Cellular and Molecular Consequences Of Respiratory Chain Defects In Neurons"
The objective of this project is to investigate the phenotypic differences of mitochondrial encephalopathies caused by defects in different respiratory complexes. Genetically modified mice with defects in complexes I, III ad IV are analyzed and compared.
Role: PI

1R01AG036871-07 (Moraes, C.T.) 06/01/2010 – 05/30/2020
NIH/NIA
"Mitochondrial Dysfunction in Neurodegeneration and Compensatory Approaches"
The goals of this project is to analyze the role of mtDNA deletions and depletion in aging.
Role: PI

UMDF (Moraes, C. T.) 09/01/2014-09/01/2016
Developing Specific Nucleases to Eliminate Mutant mtDNA
The objective of this project is to develop mitoTALEN against common mtDNA mutations and test delivery by adenovirus.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Miguel A. Perez-Pinzon, PhD, FAHA	Professor
eRA COMMONS USER NAME mperezpinzon	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Panama	B.Sc.	1983	Biology
University of Miami (RSMAS)	M.Sc.	1987	Marine Biology
University of Miami (RSMAS/Neurology)	PhD	1991	Neuroscience
New York University	Postdoc	1992	Neurophysiology
Stanford University	Postdoc	1993	Neuroscience

A. Personal Statement

Although I have been working on cerebral anoxia/ischemia since 1987, my independent group at the University of Miami was established in 1995 and in the last two decades has been studying cerebral ischemia and one of my research emphasis is mitochondrial dysfunction. I currently direct the Cerebral Vascular Disease Research Center at the University of Miami since 2005, which was established approximately 45 years ago by Dr. Pertiz Scheinberg (first Chair of Neurology at UM). Many seminal investigators of the field directed or were part of this center (e.g., Kyuya Kogure, Mordecai Globus, Dalton Dietrich). Dr. Myron Ginsberg led the center until 2005. I am a Professor of Neurology and Neuroscience and I am Vice-Chairman of Basic Sciences in the Department of Neurology. My main research expertise is in the area of cerebral ischemia, which results from cardiac arrest or a stroke. My research focuses on the areas of synaptic, vascular and mitochondrial dysfunction that ensue following cerebral ischemia. Over the last 20 years, my laboratory has investigated the signaling pathways that lead to neuroprotection against ischemia following ischemic preconditioning (IPC). Our goal is to develop new therapies for pre- and post-treatment in stroke and cardiac arrest patients. Our center uses a large number of techniques that include imaging, electrophysiology, behavior, stereotaxic surgeries, and molecular biology techniques.

I have a long track record of collaborations with Drs. Barrientos and Moraes. My interest in mitochondrial dysfunction not only in cerebral ischemia and anoxia, but also on neurodegenerations has been part of my collaborations with both colleagues. Dr. Zhai has been a dissertation committee member of 3 of my PhD students and since then we have been developing significant collaborations. Her expertise in NAD^+ metabolism complements my interest on NAD^+ and cerebral ischemia, which has been the subject of research in my lab since the 1990's. I think the expertise of all four PIs are complementary.

B. Positions and Honors.

PROFESSIONAL APPOINTMENTS

1995 – 2001 Assistant Professor, Department of Neurology, University of Miami School of Medicine.
1999 – 2006 Co-Director of Cerebral Vascular Disease Center, University of Miami School of Medicine, Miami, Fl (Dr. Ginsberg, Director)
2001 – 2006 Associate Professor, Department of Neurology, University of Miami School of Medicine.
2005 – present Director of Cerebral Vascular Disease Center, University of Miami, Miller School of Medicine, Miami, Fl
2006 – present Professor, Department of Neurology, University of Miami Miller School of Medicine, Miami, Fl
2007 – 2010 Associate Chair for Basic Science, Department of Neurology, University of Miami Miller School of Medicine, Miami, FL

2010 – present Vice-Chair for Basic Science, Department of Neurology, University of Miami Miller School of Medicine, Miami, Fl

AWARDS AND OTHER PROFESSIONAL ACTIVITIES:

1982, 1983 Fellowships (2), Smithsonian Tropical Research Institute (STRI). Panama
1986 Fellowship, Fishing and Conservation Trust. Miami, Fl
1989 - present Member of Society for Neuroscience (1989), International Society on Oxygen Transport to Tissues (1996), International Society of Cerebral Blood Flow and Metabolism (1995), American Association for the Advancement of Science (1996) and American Heart Association (2000)
1991 Koczy Fellowship, (Graduate student of the year) for excellence in graduate research and education, Rosenstiel School of Marine and Atmospheric Science, University of Miami, Miami, Fl
1991 Invited speaker at the Society for Experimental Biology in Birmingham, U.K.
2000 – 03 NIH-NINDS BDCN-3 Study Section reviewer
2000 Invited speaker at the Pharmacology of Cerebral Ischemia Symposium. Marburg, Germany.
2002 Grass Traveling Scientist for the Alaska Chapter of the Society for Neuroscience. Society for Neuroscience
2004 – 08 Brain 2 American Heart Association Grant Reviewer
2006 – 10 NIH-NINDS BINP Study Section
2014 NIH-NINDS BINP Study Section Ad-hoc member
2007 – 08 International Stroke Conference Program Committee: Co-Chair–Experimental Mechanisms and Models.
2008 – 10 International Stroke Conference Program Committee: Chair–Experimental Mechanisms and Models.
2009 Associate Editor for the journal: Translational Stroke Research
2010 Assistant Editor for the journal: Stroke
2010 Elected as Fellow of the American Heart Association/American Stroke Association (FAHA)
2012-13 Co-Chair of the Program Committee for the International Society of Cerebral Blood Flow and Metabolism (Brain 13), Shanghai, China
2014 Member of the Program Committee for the International Society of Cerebral Blood Flow and Metabolism (Brain 15), Vancouver, Canada
2016-18 Vice-Chair of the Program Committee for the International Stroke Conference

C. Contribution to Science

1. **My group has been studying mitochondrial dysfunction for approx 20 years. In the late 1990's we carried out several studies that defined the effect of anoxia/ischemia and reperfusion on mitochondrial electron carrier hyperoxidation. We also published simultaneously with the Pak Chan's group in 1999, the first study demonstrating cytochrome c release from mitochondria following cerebral anoxia/ischemia. For the last 15 years, my group has done seminal work on the signaling pathways that lead to mitochondrial dysfunction and apoptosis and on signaling pathways that lead to ischemic neuroprotection.**

a. Morris-Blanco, K. C., Cohan, C. H., Neumann, J. T., Sick, T. J. & Perez-Pinzon, M. A. Protein kinase C epsilon regulates mitochondrial pools of Nampt and NAD following resveratrol and ischemic preconditioning in the rat cortex. *J Cereb Blood Flow Metab* **34**, 1024-1032, (2014). PMID:24667915
b. Thompson, J. W., Dave, K. R., Saul, I., Narayanan, S. V. & Perez-Pinzon, M. A. Epsilon PKC increases brain mitochondrial SIRT1 protein levels via heat shock protein 90 following ischemic preconditioning in rats. *PLoS One* **8**, e75753, (2013). PMID:24058702
c. Dave, K. R., Bhattacharya, S. K., Saul, I., DeFazio, R. A., Dezfulian, C., Lin, H. W., Raval, A. P. & Perez-Pinzon, M. A. Activation of protein kinase C delta following cerebral ischemia leads to release of cytochrome C from the mitochondria via bad pathway. PLoS One 6, e22057, (2011). PMID:21789211
d. Dave, K. R., DeFazio, R. A., Raval, A. P., Torraco, A., Saul, I., Barrientos, A. & Perez-Pinzon, M. A. Ischemic preconditioning targets the respiration of synaptic mitochondria via protein kinase C epsilon. J Neurosci 28, 4172-4182, (2008). PMID:18417696

e. Perez-Pinzon, M. A., Xu, G. P., Born, J., Lorenzo, J., Busto, R., Rosenthal, M. & Sick, T. J. Cytochrome C is released from mitochondria into the cytosol after cerebral anoxia or ischemia. *J Cereb Blood Flow Metab* **19**, 39-43, (1999). PMID:9886353

2. My group has also been a leader in the field of ischemic preconditioning. We have been studying compounds such as resveratrol and certain PKC isoforms to pharmacologically precondition *in vivo* and *in vitro* to lessen ischemia-induced neuronal damage. We sought to identify novel preconditioning pathways to alleviate ischemia, so therapies can be developed based on this mechanistic approach.

a. Neumann, J. T., Thompson, J. W., Raval, A. P., Cohan, C. H., Koronowski, K. B. & Perez-Pinzon, M. A. Increased BDNF protein expression after ischemic or PKC epsilon preconditioning promotes electrophysiologic changes that lead to neuroprotection. J Cereb Blood Flow Metab 35, 121-130, (2015). PMID:25370861
b. Narayanan, S. V., Dave, K. R., Saul, I. & Perez-Pinzon, M. A. Resveratrol Preconditioning Protects Against Cerebral Ischemic Injury via Nuclear Erythroid 2-Related Factor 2. Stroke 46, 1626-1632, (2015). PMID:25908459
c. Lin, H. W., Thompson, J. W., Morris, K. C. & Perez-Pinzon, M. A. Signal transducers and activators of transcription: STATs-mediated mitochondrial neuroprotection. Antioxid Redox Signal 14, 1853-1861, (2011). PMID:20712401
d. DeFazio, R. A., Raval, A. P., Lin, H. W., Dave, K. R., Della-Morte, D. & Perez-Pinzon, M. A. GABA synapses mediate neuroprotection after ischemic and epsilonPKC preconditioning in rat hippocampal slice cultures. J Cereb Blood Flow Metab 29, 375-384, (2009). PMID:18957990
e. Raval, A. P., Dave, K. R., Mochly-Rosen, D., Sick, T. J. & Perez-Pinzon, M. A. Epsilon PKC is required for the induction of tolerance by ischemic and NMDA-mediated preconditioning in the organotypic hippocampal slice. J Neurosci 23, 384-391, (2003). PMID:12533598

3. Another major area of research in my group is to define the pathological mechanisms in the brain that ensue following cardiac arrest. We have targeted multiple aspects of the pathology that include synaptic dysfunction, cognitive impairments and cerebral blood flow derangements. We have shown that PKCε activation provides neuroprotection while activation of δPKC is detrimental to the ischemic brain. Overall, my studies provide a potential pathway of ischemia-mediated neuroprotection by the regulation of cerebral blood flow from evaluating blood flow dynamics, neuroprotection, and functional neuronal outcomes/firing properties based on electrophysiological studies.

a. Cohan, C. H., Neumann, J. T., Dave, K. R., Alekseyenko, A., Binkert, M., Stransky, K., Lin, H. W., Barnes, C. A., Wright, C. B. & Perez-Pinzon, M. A. Effect of cardiac arrest on cognitive impairment and hippocampal plasticity in middle-aged rats. PLoS One 10, e0124918, (2015). PMID:25933411
b. Lin, H. W., Gresia, V. L., Stradecki, H. M., Alekseyenko, A., Dezfulian, C., Neumann, J. T., Dave, K. R. & Perez-Pinzon, M. A. Protein kinase C delta modulates endothelial nitric oxide synthase after cardiac arrest. J Cereb Blood Flow Metab 34, 613-620, (2014). PMID:24447953
c. Dezfulian, C., Alekseyenko, A., Dave, K. R., Raval, A. P., Do, R., Kim, F. & Perez-Pinzon, M. A. Nitrite therapy is neuroprotective and safe in cardiac arrest survivors. Nitric Oxide 26, 241-250, (2012). PMID:22484664
d. Lin, H. W., Defazio, R. A., Della-Morte, D., Thompson, J. W., Narayanan, S. V., Raval, A. P., Saul, I., Dave, K. R. & Perez-Pinzon, M. A. Derangements of post-ischemic cerebral blood flow by protein kinase C delta. Neuroscience 171, 566-576, (2010). PMID:20813167
e. Raval, A. P., Dave, K. R., Prado, R., Katz, L. M., Busto, R., Sick, T. J., Ginsberg, M. D., Mochly-Rosen, D. & Perez-Pinzon, M. A. Protein kinase C delta cleavage initiates an aberrant signal transduction pathway after cardiac arrest and oxygen glucose deprivation. J Cereb Blood Flow Metab 25, 730-741, (2005). PMID:15716854

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/miguel.perez-pinzon.1/bibliograpahy/40678659/public/?sort=date&direction=ascending

D. Research Support.

Active

R01 NS45676-08 **Perez-Pinzon (PI)** 6/1/07-5/31/15
NIH/NINDS
Mechanisms of Neuroprotection against Cardiac Arrest
The major goal of this project is to study the mechanisms of synaptic and vascular dysfunction and putative neuroprotective agents following cardiac arrest.
Non-cost extension

R01 NS34773-15 **Perez-Pinzon (PI)** 6/1/15-5/31/20
NIH/NINDS
Ischemic Preconditioning: Mechanisms of Neuroprotection
The major goal of this project is to study the signaling pathways that lead to ischemic preconditioning neuroprotection

American Heart Association/ASA-Bugher Foundation (14BFSC17690007). Sacco R. (PI) 4/1/14-3/31/18
Physical and Cognitive Training to Enhance Post-Stroke Outcomes. **Project 2 (PI – Perez-Pinzon)**: Enriched Environment, Exercise And Neurotherapeutics To Enhance Functional Recovery Following A Stroke

1R21NS098896-01 **Perez-Pinzon (PI)** 7/1/16-6/30/18
NIH/NINDS
Decellularized Extracellular Matrix Biomaterials As Therapy To Ameliorate Cerebral Ischemia Damage
The goals of the project are for the University of Miami to help build stroke research capabilities at INDICASAT AIP, Panama which will ultimately help foster stronger collaboration between the two institutes and to evaluate therapeutic potential of decellularized extracellular matrix biomaterials against cerebral ischemic damage.

5R01NS073779-04
Dave, Kunjan (PI) 3/1/12-12/1/16
Increased cerebral ischemic injury by repeated hypoglycemic episodes in diabetes.
The long-term goal of this project is to improve neurological health of diabetics by decreasing the severity and incidence of cerebral ischemia in diabetics.

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: Milena Pinto

eRA COMMONS USER NAME (credential, e.g., agency login): Pintom1n

POSITION TITLE: Research Assistant 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	Completion Date MM/YYYY	FIELD OF STUDY
Universita' degli studi di Trieste, Italy	Ms.D.	04/2005	Medical Biotechnology
International School for Advanced Studies (SISSA) Trieste, Italy	Ph.D.	11/2009	Neurobiology

A. Personal Statement

I have more than ten years of research experience on neurodegenerative disorders, in particular on Parkinson's and Alzheimer's disease. During my Masters and PhD studies, I extensively worked on drug-induced and genetically modified animal models of Parkinson's disease as well as on cellular models of dopaminergic neurons. Since I joined Dr. Moraes lab in 2010 for my postdoctoral training, I have been involved in understanding the possible neuronal-specific role of mitochondrial dysfunctions and mitochondrial DNA deletions and depletion in mouse models of neurodegenerative disorders, in particular of Parkinson's and Alzheimer's diseases.
My PhD background and my recent experience confer me a specific and deep knowledge in both fields of neurology and mitochondria metabolism. I recently accepted a position as research assistant professor at the University of Miami.

B. Positions and Honors.

PROFESSIONAL APPOINTMENTS

present Research Assistant Professor at Neurology department, (position in progress with faculty affairs) University of Miami
Apr 2015-Jul 2016 Sr. Research Associate at Neurology department, University of Miami
Apr 2010-Apr 2015 Postdoctoral Associate at Neurology department, University of Miami
Nov 2009-Apr 2010 Temporary Research Fellow, SISSA, Trieste, Italy

HONORS

Nov-2014 ISSNAF Award for young Investigators, Special Mention, Bio-Medicine and Cognitive Sciences
April-2013 UMDF, Mitochondrial Medicine 2013 Abstract Cash Award
March-2013 Medical Faculty Association Travel Award from the Margaret Whelan fundation

C. Contribution to Science

1. I became involved in the study of neurodegenerative diseases during my Ph.D. at the International School for Advanced Studies (SISSA) in Trieste, Italy, under the supervision of Dr. Stefano Gustincich. In my first years I was involved in the study of the role of PARK7/DJ-1 gene, whose mutations are associated to autosomal recessive early onset forms of Parkinson's disease (PD). We studied two DJ-1 missense mutations that cause misfolding of the protein, degradation or accumulation into insoluble cytoplasmic aggregates. By yeast-two hybrid screening, we identified two novel DJ-1 interactors (TRAF6 and TTRAP) that bound more strongly the mutated forms than the wild type form of DJ1, and we analyzed in vitro their role in physiologic and pathologic conditions.
   Moreover, we discovered that both the proteins were present in the Lewy Bodies (neuropathological hallmarks of PD) of post mortem brains of PD patients, identifying them as new players not only in rare genetic cases of PD but also in the more common sporadic cases.

   A. Zucchelli S, Vilotti S, Calligaris R, Lavina ZS, Biagioli M, Foti R, De Maso L, **Pinto M**, Gorza M, Speretta E, Casseler C, Tell G, Del Sal G, Gustincich S.
      Aggresome-forming TTRAP mediates pro-apoptotic properties of Parkinson's disease-associated DJ-1 missense mutations.
      Cell Death and Differetiation 2009 Mar;16(3):428-38 [PMID 19023331]
   B. Zucchelli S., Codrich M, Marcuzzi F, **Pinto M**, Vilotti S., Biagioli M, Ferrer I, Gustincich S.
      TRAF6 promotes atypical ubiquitination of mutant DJ-1 and alpha-synuclein and is localized to Lewy bodies in sporadic Parkinson's disease brains.
      Hum Mol Genet. 2010 Jul 14 [PMID: 20634198]
   C. Vilotti S, Codrich M, Dal Ferro M, **Pinto M**, Ferrer I, Collavin L, Gustincich S, Zucchelli S.
      Parkinson's disease DJ-1 L166P alters rRNA biogenesis by exclusion of TTRAP from the nucleolus and sequestration into cytoplasmic aggregates via TRAF6.
      PLoS One. 2012;7(4):e35051 [PMID: 22532838]

2. During my PhD I also studied the expression profile of A9 neurons of *substantia nigra*, a subpopulation of dopaminergic neurons that degenerate in patients affected by Parkinson's disease. This research project led to the discovery that these particular neurons express alpha and beta chains of hemoglobin, a well-known protein with essential role in binding and delivering oxygen, carbon dioxide and nitric oxide. This particular finding opened a new line of research since hemoglobin has a non-oxygen-carrying function as an antioxidant and a regulator of iron metabolism, both essential mechanisms involved in the pathogenesis of Parkinson's disease. These findings helped other researchers to look into the role of this protein in brain metabolism, finding correlations with Alzheimer's disease, Parkinson's disease and dementia with Lewy bodies. Moreover, Hemoglobin-derived peptides have been studied as novel type of bioactive signaling molecules.
   We also discovered that 46% of genes that encode for subunits of mitochondrial complex I-V were induced in stable cell lines overexpressing hemoglobin chains, suggesting a link between hemoglobin expression and mitochondrial biogenesis/function.

   A. **Milena Pinto**(*), Marta Biagioli (*), Daniela Cesselli, Marta Zaninello, Dejan Lazarevic, Roberto Simone, Christina Vlachouli, Charles Plessy, Nicolas Bertin, Antonio Beltrami, Kazuto Kobayashi,

Vittorio Gallo, Isidro Ferrer, Claudio Santoro, Stefano Rivella, Carlo Alberto Beltrami, Piero Carninci, Elio Raviola and Stefano Gustincich. (*) co-authorship
Unexpected expression of α- and β-globin in mesencephalic dopaminergic neurons and glial cells PNAS, 2009 Sep. vol.106 no.36 [PMID: 19717439]

3. As a result of this work in Italy, I was recruited to join the Neurology Department of the University of Miami, Miller School of Medicine as a Postdoctoral Associate. I joined Dr. Carlos Moraes laboratory to expand my knowledge and research in the study of the role of mitochondria in neurodegenerative diseases.
   Neuronal OXPHOS deficiency, in fact, has been associated with a variety of late-onset progressive neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease.
   Almost all the animal models of PD available at that time were created by knocking out or knocking in mutated forms of the genes involved in the rare genetic forms of PD. In order to create a model resembling the more common sporadic forms of PD, we decided to induce mitochondrial defects in different neuronal subpopulations, mimicking the mitochondrial function decline that occurs naturally with aging.
   We induced OXPHOS deficiency in neurons by inducing mitochondrial DNA depletion, or by knocking out mitochondrial Complex IV, one of the complexes that is deficient in PD patients. By inducing mtDNA depletion in neurons we discovered that the striatum is particularly sensitive to defects in OXPHOS and these results helped explain how mitochondrial dysfunctions alone can lead to a preferential elimination of certain neuronal populations *in vivo*. We then created and compared two different mouse models of PD, one mimicking the pathology slow progression that occurs in sporadic PD cases, the other more similar to late stages of the disease.
   Because mitochondrial dysfunctions have been closely associated with PD, the creation of this new mouse models provided important clues to the pathophysiology of the disease. The PD mouse models have been widely received and accepted in the field and can provide also a valuable tool to test new mitochondrial therapies in the treatment of this disease.

   A. Alicia Pickrell, Hirokazu Fukui, Xiao Wang, **Milena Pinto**, and Carlos Moraes
      The Striatum is Highly Susceptible to Mitochondrial Oxidative Phosphorylation Dysfunctions
      J Neurosci. 2011 Jul 6;31(27):9895-904 [PMID: 21734281]
   B. **Milena Pinto(*)**, Alicia Pickrell(*), Aline Hida, Carlos Moraes **(*) co-authorship**
      Striatal dysfunctions associated with mtDNA damage in dopaminergic neurons of a mouse model of PD
      J Neurosci. 2011 Nov 30;31(48):17649-58 [PMID: 22131425]
   C. **Pinto M**, Nissanka N, Peralta S, Brambilla R, Diaz F, Moraes CT.
      Pioglitazone ameliorates the phenotype of a novel Parkinson's disease mouse model by reducing neuroinflammation.
      Mol Neurodegener. 2016 Apr 2;11(1):25 [PMID: 27038906]

4. Even though my main line of research is focused on neurodegenerative disorders, my contribution has also been essential in other fields where mitochondrial dysfunctions play an important role, like aging, age-related cachexia, and mitochondrial diseases (Leber's hereditary optic neuropathy plus dystonia), as shown in recent publications in Human Molecular Genetics, Nature Medicine, and Cell Death and Differentiation.

   A. Bacman SR, Williams SL, **Pinto M**, Peralta S, Moraes CT.

Specific elimination of mutant mitochondrial genomes in patient-derived cells by mitoTALENs. Nat Med. 2013 Sep;19(9) [PMID: 23913125]

B. Wang X, Pickrell AM, Rossi SG, **Pinto M**, Dillon LM, Hida A, Rotundo RL, Moraes CT.
Transient systemic mtDNA damage leads to muscle wasting by reducing the satellite cell pool.
Hum Mol Genet. 2013 Oct 1;22(19):3976-86 [PMID: 23760083]

C. **Milena Pinto(*)**, Alicia M Pickrell(*), Xiao Wang(*), Sandra R Bacman, Aixin Yu, Aline Hida, Lloye M Dillon, Paul D Morton,Thomas R Malek, Siôn L Williams and Carlos T Moraes **(*) co-authorship.**
Transient mitochondrial DNA double strand breaks in mice cause accelerated aging phenotypes in a ROS-dependent but p53/p21-independent manner.
Cell Death and Differentiation 2016, December 2; doi: 10.1038/cdd.2016.123

5. Since mtDNA damage and the generation of reactive oxygen species have been associated with and implicated in the development and progression of Alzheimer's disease, we studied how mtDNA damage affects reactive oxygen species and amyloid beta pathology in vivo. We generated an Alzheimer's disease mouse model expressing an inducible mitochondrial-targeted endonuclease (Mito-PstI) in the central nervous system that cleaves mtDNA causing mtDNA depletion, which leads to a partial oxidative phosphorylation defect when expressed during a short period in adulthood. We found that a mild mitochondrial dysfunction in adult neurons decreased plaque pathology by altering the cleavage pathway of amyloid precursor protein without increasing oxidative stress in the brain. These data suggest that mtDNA damage is not a primary cause of Ab accumulation.

   A. **Pinto M**, Pickrell AM, Fukui H, Moraes CT.
   Mitochondrial DNA damage in a mouse model of Alzheimer's disease decreases amyloid beta plaque formation.
   Neurobiol Aging. 2013 Oct;34(10):2399-407 [PMID: 23702344]

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/milena.pinto.1/bibliography/50578890/public/?sort=date&direction=ascending.

D. Research Support

Post-doctoral fellowships:

Parkinson's Disease Foundation
"The role of Parkin in the clearance of defective mitochondria with deleted mtDNA. A new mouse model of Parkinson's disease."
July/2013 – July/2014

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: **Alberto R. Ramos, MD, MSPH, FAASM**

eRA COMMONS USER NAME (credential, e.g., agency login): ARAMOS1

POSITION TITLE: Associate Professor of Neurology

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 Puerto Rico, Rio Piedras, Puerto Rico	BS	05/1999	Natural Sciences
Universidad Central del Caribe, PR. **CUM LAUDE**	MD	05/2003	Medical Doctor
Jackson Memorial Hospital-U. of Miami	Residency	06/2007	Neurology
Miami VA Health Care System-U. of Miami	Fellowship	06/2008	Sleep Medicine
University of Miami, Miller School of Medicine	MSPH	08/2012	Epidemiology

A. Personal Statement

I am an early stage investigator in the Department of Neurology and Sleep Medicine, at the Miller School of Medicine, University of Miami. Miami, FL. My research is aimed at investigating the sleep health disparities that affect minorities, specifically Hispanic/Latino populations. Of particular interest is the intersection between sleep disorders and neurocognitive aging in population based studies. My work started with the multi-ethnic cohort of the Northern Manhattan study (NOMAS). I completed a diversity supplement grant from the NIH/NINDS, aimed to determine the sleep disorders associated to stroke risk factors and cognitive decline in NOMAS. While I maintain a collaboration with the NOMAS's investigators, my current efforts are with the Hispanic Community Health Study/Study of Latinos; where I serve as a co-investigator and primary consultant for Sleep Research.
I am also the Miami site-Principal investigator of the *Sueño study: Sleep Patterns as a Risk Factor for Disease in the Hispanic Community Health Study* – Field Center at the University of Miami. This NHLBI ancillary study evaluated the determinants of abnormal sleep patterns with actigraphy and their effect on cardiometabolic diseases. I am also the principal investigator of an HCHS/SOL ancillary study evaluating sleep apnea and cerebral hemodynamics as an early marker of cerebrovascular risk at the Miami field site. This study was supported by a K12 mentored award from the Clinical Translational Research Institute at the Miller School of Medicine. My involvement with HCHS/SOL and interest in neurocognitive aging initiated a successful collaboration with Dr. Hector Gonzalez (PI-SOL INCA) and Dr. Wassim Tarraf from the HCHS/SOL neurocognitive reading center. Along with Dr. Susan Redline (PI-Sleep HCHS/SOL), we developed a line of research in sleep and neurocognitive aging, published several manuscripts. Currently, Dr. Noam Alperin and I want to extent my work on sleep apnea by using cutting-edge measures with Magnetic Resonance Imaging.

B. Positions and Honors

Positions

2006-07 Administrative Chief Resident-Neurology, University of Miami/Jackson Memorial Hos., Miami, FL
2007-09 Staff Physician; Neurology Service, Miami VA Healthcare System, Miami, FL
2008-09 Instructor, Miller School of Medicine, University of Miami, Miami, FL
2009 -16 Assistant Professor of Clinical Neurology, Miller School of Medicine, Miami, FL
2010- Co-Director, Sleep Medicine Program, Miller School of Medicine, Miami, FL
2016- Associate Professor of Clinical Neurology, Miller School of Medicine, Miami, FL

Honors

2003 Alpha Omega Alpha. Universidad Central Del Caribe, School of Medicine, PR
2007 Clinical Neuroscience Prize, Neurology Residency program, U. of Miami. Miami, FL
2008 Faculty Development Award-American Neurological Association
2010-14 Who's who in America
2010-14 America's Top Physician, Consumer's Research Council of America
2011 Distinguished Judge. Department of Otolaryngology, Miller School of Medicine. Miami, FL.
2012 NIH/American Academy of Sleep Medicine Young Investigators forum award
2013 Scholar, Program to Increase Diversity among Individuals Engaged in Health-Related Research (PRIDE), NHLBI-New York University, NY
2013 Fellow, American Academy of Sleep Medicine
2015 Diversity Leadership Development Program-American Academy of Neurology, Minneapolis, MN
2015 Peer Mentor, Programs to increase Diversity among individuals Engaged in Health Related Research (PRIDE), NHLBI-New York University, NY.
2015 Award, U13 Conference Series: Sleep, Circadian Rhythms, and Aging: Supported by the National Institutes of Aging and the American Geriatric Society.

C. Contribution to Science

1. Sleep and neurocognitive aging

My research program evaluates sleep as a determinant of health disparities in neurocognitive aging and cerebrovascular risk in minority populations; particularly Hispanic/Latinos, who are at higher risk for Alzheimer's disease, cerebrovascular disease and have a large burden of sleep apnea and other sleep disorders. We published various manuscripts evaluating sleep symptoms and disorders and neurocognitive function in the Northern Manhattan study (NOMAS) and the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). We initially observed a cross-sectional association between long sleep duration and worse global cognitive function in NOMAS. This study was followed by our recent cross-sectional findings from HCHS/SOL Visit 1 ($n \approx$ 8,000). In this study, sleep apnea was associated with worse neurocognitive function, particularly among women, in the domains of memory, language and executive function. The association was stronger in younger (45-54 years), rather than older females (65-74 years). We also performed a cross-sectional evaluation of sleep duration and neurocognitive function in HCHS/SOL. We found curvilinear (inverted U-shaped) associations between self-reports of sleep duration and neurocognitive function. That is, participants with average (7.8 hours ± 1.7 hours) self-reported sleep duration had better neurocognitive scores, compared to the extremes of sleep duration. These innovative findings provided strong rationale to follow the HCHS/SOL cohort and better understand the midlife sleep phenotypes related to neurocognitive decline and mild cognitive impairment/Alzheimer's disease (Aim 1 and Aim 3). Sleep apnea is a risk factor for stroke with strong links to cardiometabolic diseases (i.e. diabetes), which are highly prevalent in Hispanic/Latinos. Therefore we plan to determine if sleep apnea mediates associations between vascular disorders and neurocognitive aging (Aim 2). The HCHS/SOL cohort and its investigators provides the opportunity to evaluate objective and systematic measures of sleep apnea-hypoxemia and sleep habits (duration, quality and fragmentation) in a vulnerable population burdened with Alzheimer's disease.

a) Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, **Ramos A,** Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglus ML. Sleep Disordered Breathing in Hispanic/Latino Individuals of Diverse Backgrounds: The Hispanic Community Health Study/Study of Latinos. Am J Respir Crit Care Med 2014; 189:335-44. PMID:24392863

b) **Ramos AR,** Dong C, Elkind MSV, Boden-Albala B, Sacco RL, Rundek T, Wright CB**.** Association between Sleep Duration and the Mini-Mental Score: The Northern Manhattan Study. J Clin Sleep Med 2013 15; 9:669-673. PMID: 23853560

c) **Ramos AR**, Tarraf W, Rundek T, Redline S, Wohlgemuth WK, Loredo JS, Sacco RL, Lee DJ, Arens R, Lazalde P, Choca JP, Mosely T, Gonzalez, HM. Obstructive Sleep Apnea and Neurocognitive Function among Hispanics/Latinos. Neurology 2015;84:391-398.PMID:2554030

d) **Ramos AR,** Tarraf W, Daviglus M, Davis S, Gallo LC, Mossavar-Rahmani Y, Penedo FJ, Redline S, Rundek T, Sacco RL, Sotres-Alvarez D, Wright CB, Zee PC, González HM. Sleep Duration and Neurocognitive Function in the Hispanic Community Health Study/Study of Latinos. Sleep. 2016 Jul 19. pii: sp-00405-15. [Epub ahead of print] PMID: 27450689

e) **Ramos AR**, Gardener H, Rundek T, Elkind MS, Boden-Albala B, Dong C, Cheung YK, Stern Y, Sacco RL, Wright CB. Sleep disturbances and cognitive decline in the Northern Manhattan Study. Neurology. 2016 Sep 2. [Epub ahead of print] PMID:27590286

2. **Sleep disorders and sub-clinical vascular disease**

My research in this area started while evaluating sleep symptoms and subclinical vascular disease in the Northern Manhattan study. We also evaluated subclinical vascular diseases and vascular risk factors in the Hispanic Community Health Study/Study of Latinos (N=16,415). Collectively, my body of research shows that sleep apnea symptoms and sleep duration is strongly associated with sub-clinical vascular disease, particularly measures of cerebral small vessel disease, which are often adversely related to neurocognitive aging and neurocognitive decline.

f) **Ramos-Sepulveda A**, Wohlgemuth W, Gardener H, Lorenzo D, Dib S, Wallace DM, Nolan B, Boden-Albala B, Elkind MS, Sacco RL, Rundek T. Snoring and insomnia are not associated with subclinical atherosclerosis in the Northern Manhattan Study. Int J Stroke. 2010; 5:264-8. PMID:20636708

g) **Ramos AR**, Cabral D, Lee DJ, Sacco RL, Rundek T. Cerebrovascular Pulsatility in Patients with Sleep Disordered Breathing. Sleep Breath 2013; 17:723-6. PMID: 22773271

h) **Ramos AR,** Jin A, Rundek T, Russo C, Homma S, Elkind M, Sacco RL, Di Tullio MR. Relation between Long Sleep and Left Ventricular Mass from a Multi-Ethnic Elderly Cohort. Am J Cardiol 2013; 112:599-603. PMID: 2371181

i) **Ramos AR**, Dong C, Rundek T, Elkind ESV, Boden-Albala B, Sacco RL, Wrigth CB. Sleep Duration is associated with White Matter Hyperintensity Volume in Older Adults: The Northern Manhattan Study. J Sleep Res 2014; 23:524-30. PMID: 25040435

j) Shah N, Allison M, Teng V, Wassertheil-Smoller S, Sotres-Alvarez D, **Ramos AR**, Zee P, Criqui M, Yaggi H, Gallo L, Redline S, Kaplan R. Sleep Apnea is Independently Associated with Peripheral Arterial Disease in the Hispanic Community Health Study/Study of Latinos. Arterioscler Thromb Vasc Biol. 2015 PMID:25657310

3. **Sleep disorders and health disparities**

The long term goal of my research program is to alleviate the sleep health disparities and improve health outcomes in minority populations. I aimed to determine the factors associated to health disparities in Hispanic/Latinos and non-Hispanic blacks. This line of research presents a unique opportunity to understand and reduce seemingly intractable stroke and cardiovascular disparity among non-Hispanic blacks and Hispanic/Latinos. There is limited awareness, knowledge and screening opportunities for sleep disorders in minorities. Our recent work showed that Hispanic/Latinos have greater frequency of sleep symptoms, compared to non-Hispanic whites; and these sleep symptoms may precede ischemic stroke diagnosis.

k) **Ramos AR**, Wohlgemuth WK, Dong C, et al. Race-ethnic differences of sleep symptoms in an elderly multi-ethnic cohort:The Northern Manhattan Study. Neuroepidemiology 2011; 37:210-5. PMID:22123526

l) Dib S, **Ramos A**, Wallace D, Rundek T.Sleep and Stroke. Periodicum Biologorum 2013;114:369-75

m) **Ramos AR**, Azizi A, Dib SI. Obstructive sleep apnea and stroke: links to health disparities. Sleep Health: Journal of the National Sleep Foundation 2015; 1: 244-248

n) **Ramos AR**, Guilliam D, Dib SI, Koch S. Race/ethnic differences in obstructive sleep apnea risk in patients with acute ischemic strokes in south Florida. Sleep Breath. 2014;18:165-8.PMID 23771345

o) **Ramos AR,** Wallace DM, Pandi-Perumal SR, Williams NJ, Castor C, Sevick MA, Mcfarlane SI, Jean-Louis G Associations between sleep disturbances and diabetes mellitus among blacks with metabolic syndrome: Results from the Metabolic Syndrome Outcome Study (MetSO). Ann Med. 2015;47(3):233-7. PMID: 25856540

Link to complete list of publications:

https://www.ncbi.nlm.nih.gov/sites/myncbi/alberto.ramos.1/bibliography/46171108/public/?sort=date&direction=ascending

D. Research Support

1. KL2TR000461-02 Sacco (PI) 7/2016-6/2016
Sleep apnea and cerebral hemodynamics: The Hispanic Community Health Study. The goal of this study is to evaluate the cerebral hemodynamics as an early marker of cerebrovascular risk in participants with sleep apnea and controls. National Institutes of Health, Clinical Translational Institute at the Miller School of Medicine, University of Miami, Miami, FL. Mentored Translational Research Scholars Program (K12).
Role: Scholar, 75% effort time.

2. Loan Repayment Program 08/2014-07/2016
National Institutes of Health/National Institute of Minority Health and Health Disparities.
Amount: $40,000

3. R37 (Javits Award): 2R01 (NS 29993), Sacco (PI) 06/2009-05/2012
Stroke Incidence and Risk Factors in a Tri-Ethnic Region Agency. The goal of the study was to investigate the associations between sleep symptoms and sub-clinical vascular disease in a prospective cohort of 3298 community subjects in the Northern Manhattan Study. Supplements to Promote Diversity in Health-Related Research. Role: Scholar, 50% effort time.

4. RO1: HL098297 Patel (PI) 07/2011-04/2014
Sueño: Sleep patterns as a risk factor in the Hispanic Community Health Study. The goal of the study was to determine the cardiovascular consequences of abnormal sleep patterns with actigraphy in Hispanic/Latinos.
Role: Site PI/Co-investigator, 10% effort time.

5. Loan Repayment Program, one year extension 08/2013-07/2014
National Institutes of Health/National Institute of Minority Health and Health Disparities
Amount: $35,000

6. Loan Repayment Program, one year extension 08/2012-07/2013
National Institutes of Health/National Institute of Minority Health and Health Disparities
Amount: $35,000

7. Loan Repayment Program 08/2010- 07/2012
National Institutes of Health/National Institute of Minority Health and Health Disparities
Amount: $75,000

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: **Ami P. Raval**

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

POSITION TITLE: **Assistant Professor (Research)**

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
M.S. University of Baroda, India	B. Sc	1989	Zoology, Botany, Chemistry
M.S. University of Baroda, India	M.Sc	1991	Zoology
M.S. University of Baroda, India	Ph.D	1995	Zoology (Physiology of reproduction)
University of Miami, USA	Post-doc	2000-2003	Neurophysiology
University of Miami, USA	MSPH	2010-2012	Epidemiology

A. Personal Statement

I have numerous years of experience in the field of cerebral ischemia. My ongoing research focuses on elucidating the mechanism(s) by which the female sex hormone- estrogen - decreases the risk of cerebral ischemia in females utilizing *in* vivo and *in vitro* cerebral ischemia models in rats, and analysis of mitochondrial function. While working to earn my PhD, I studied the effects of endogenous variations of female sex hormones on non-reproductive tissues; this knowledge helped me design studies to understand the mechanism of ischemic brain protection by estrogen. My post-doctoral training with Dr. Miguel A. Perez-Pinzon, a prominent neuroscientist and a pioneer in field of ischemic preconditioning and PI of present application, laid a strong foundation for me in the basics essential for understanding ischemic neurodegeneration. Dr. Bramlett is CO-PI on current project and a collaborator for more than 10 years. We have published a number of co-author papers that were generated as an outcome of our collaborative funding.

I continued to study the mechanism of neuronal death following cerebral ischemia that is a consequence of cardiac arrest or stroke, and I am well versed in various *in vivo* and *in vitro* models of cerebral ischemia as well as in imaging, electrophysiology, and behavior and molecular biology techniques. I have also succesfully trained and supervised post-doctoral fellows, students, and technicians to perform ischemia models and the aforementioned techniques. I am also part of the University of Miami's undergraduate neuroscience program, and I am involved in the education of premedical and medical students.

B. Positions and Honors:

Professional Experience:

- Lecturer: Zoology, M. S. University of Baroda, Gujarat, India. 07/1994 to 11/2000
- Assistant scientist: University of Miami, U.S.A. 9/1/2003 – 12/31/2006
- Research Assistant Professor: University of Miami, U.S.A. 2/1/2006 - Present
- American Heart Association- Innovative grant study section reviewer Fall 2014 - Present
- American Heart Association- Brain 2 study section reviewer Spring 2015 - Present

- Animal resource committee member 2009- present
- Institutional Animal care and use committee reviewer 2012- present
- Institutional Scientific advisory committee grants Ad-hoc reviewer 2012-Present
- Facilitator for MD-MPH Problem base learning at University of Miami 2013-Present

Honors, Awards, and Professional Societies:

- Fellowship awarded by Gujarat Government of India for Ph.D. studies from 1991 to 1994.
- Awarded Young Scientist award on "Effect of sex hormones on Salivary gland" by ICMR, New Delhi.
- Awarded American Heart Association (Florida/Puerto Rico) Post-doctoral Fellowship 7/2002 to 6/2004. (AHA identification number- 0225227B)
- Best poster 2009 at Celebrating Excellence in Women's Health Research, University of Miami, Miami
- Member of the Society for Neuroscience.
- Member of the Society for Cerebral Blood Flow & Metabolism.

C. Contribution to Science:

1. Mitochondrial dysfunction is a major factor involved in ischemic neuronal death. My early publications directly addressed the fact that protein kinase C subtype epsilon (PKCε) translocates to mitochondria following sub-lethal ischemic insult, and improved mitochondrial function and resistance to cerebral ischemic damage. My work also demonstrated that the activation of PKCε agonist phosphorylates the mitochondrial K^+_{ATP} channel subunit Kir6.2, which is involved in opening of potassium channels. The neuroprotection conferred by ischemic preconditioning was lost in the presence of K^+_{ATP} - channel antagonists. Overall, my work provided initial evidence that PKCε activation and its interaction with mitochondrial targets confer stability to mitochondrial functions during subsequent ischemic stress, thus reducing ischemic damage.

a. **Raval AP**, Dave KR, Mochly-Rosen D, Sick TJ, Perez-Pinzon MA. εPKC is required for the induction of tolerance by ischemic and NMDA – mediated preconditioning in the organotypic hippocampal slice. J Neuroscience. 2003; 23(2): 384-91.
b. **Raval AP****, Dave KR, DeFazio RA, Perez-Pinzon MA. EpsilonPKC phosphorylates the mitochondrial K(+) (ATP) channel during induction of ischemic preconditioning in the rat hippocampus. Brain Res. 2007; 1184:345-53. (PMCID: 2577914)
c. Dave KR, DeFazio RA, **Raval AP**, Torraco A, Saul I, Barrientos A, Perez-Pinzon MA. Ischemic preconditioning targets the respiration of synaptic mitochondria via protein kinase C epsilon. J Neurosci. 2008; 28(16):4172-82. (PMCID: 2678917)
d. Pérez-Pinzón MA, Dave KR, **Raval AP**. Role of reactive oxygen species and protein kinase C in ischemic tolerance in brain. Antioxidants and redox signaling 2005; Vol 7(9 & 10): 1150-57.

2. Another focus of my research is investigating the mechanism by which female sex hormone(s) provide ischemic brain protection. Studies from my lab demonstrate that either a single bolus or repetitive periodic 17β-estradiol treatments prior to ischemic episode reduces ischemic brain damage in ovariectomized rats. Periodic E_2 pretreatment protects hippocampal neurons through the activation of estrogen receptor subtype beta (ER-β) and silencing of hippocampal ER-β ameliorated 17β-estradiol-induced ischemic protection. My study also demonstrated that the activation of ER-β regulates mitochondrial function in the brain, and maintains mitochondrial function after cerebral ischemia. My research underscores that ER-β activation is a key mechanism to prevent ischemic neuronal death. My study was the first one to show that the silencing of hippocampal ER-β lowers protein levels of mitochondria-encoded complex IV subunits; it also implicates a role for ER-β in protein expression of the mitochondrial oxidative phosphorylation system.

a. **Raval AP****, Dave KR, Saul I, Gonzalez GJ, Diaz F. Synergistic inhibitory effect of nicotine plus oral contraceptive on mitochondrial complex-IV is mediated by estrogen receptor-β in female rats. J Neurochemistry 2012; 121(1):157-67.
b. **Raval AP****, Borges-Garcia R, Moreno WJ, Perez-Pinzon MA and Bramlett H.Periodic 17β-estradiol pretreatment protects rat brain from cerebral ischemic damage via estrogen receptor-β. Plos One 2013;8(4):e60716

c. **Raval AP****, Saul I, Dave KR, DeFazio1 RA, Perez-Pinzon MA, Bramlett H. Pretreatment with a single estradiol-17β bolus activates CREB and protects CA1 neurons against global cerebral ischemia. Neuroscience. 2009; 160:307–18. (PMCID: 2711690)
d. **Raval AP****, Bramlett H, Perez-Pinzon MA. Estrogen preconditioning protects the hippocampal CA1 against ischemia. Neuroscience. 2006; 141(4):1721-30.

3. Studies form my laboratory simulating the conditions of nicotine exposure produced by cigarette smoking and the oral contraceptive (OC) regimen of women in female rats provides evidence that the severity of ischemic hippocampal damage is far greater in female rats simultaneously exposed to OC than to nicotine alone. These studies also demonstrated that the concurrent exposure of OC and nicotine reduces endogenous 17β-estradiol levels and inhibits ER-β signaling in the brains of female rats. My study demonstrated that concurrent exposure to nicotine and OC impaired ER-β-mediate mitochondrial respiration at the complex-IV level due to lower protein levels of its catalytic subunits in the hippocampus of female rats.

a. **Raval AP****, Borges-Garcia R, Diaz F, Sick TJ and Bramlett H. Oral contraceptives and nicotine synergistically exacerbate cerebral ischemic injury in the female brain. Translational Stroke Research 2013 4:402–412
b. **Raval AP****, Sick JT, Gonzalez GJ, Defazio RA, Dong C and Sick TJ. Chronic nicotine exposure inhibits estrogen-mediated synaptic functions in hippocampus of female rats. Neuroscience Letters 2012; 517(1):41-6
c. **Raval AP****, Hirsch N, Dave KR, Yavagal DR, Bramlett H, Saul I. Nicotine and estrogen synergistically exacerbate cerebral ischemic injury. Neuroscience 2011; 181:216-25.
d. **Raval AP****. Nicotine addiction causes unique detrimental effects on female brain. Journal of Addictive Diseases. Review. 2011; 30:149–158

4. It is known that cerebral ischemia activates the innate immune response, and a key component of the innate immune response is the inflammasome. Recent study from my laboratory demonstranted that the ER-β activation regulates inflammasome activation and protects the brain from global ischemic damage in reproductively senescent female rats.

a. de Rivero Vaccari JP, Patel HH, Brand III FJ, Perez-Pinzon MA, Bramlett H and **Raval AP**. Estrogen receptor beta signaling alters cellular inflammasomes activity after global cerebral ischemia in reproductively senescence female rats. J Neurochemistry 2015; In press

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=raval+ap

D. Active Support

American Heart Association- Grant-in-aid
AHA # 16GRNT31300011 07/1/16- 6/30/2018
Nicotine alters brain oxidative metabolism and exacerbates ischemic brain damage
The major goal of this project was to study the effects of chronic nicotine usage on synaptic functions in female rats.
Role: PI, 20% efforts

NIH/NINDS
Grant #3R01NS034773-16S1 07/1/16- 6/30/2017
Ischemic Preconditioning: Mechanisms of Neuroprotection
This project is an administrative supplement for research on sex/gender differences in ischemic preconditioning.
PI: Dr. Miguel A. Perez-Pinzon
Role: Co-investigator, 10% efforts

Department of Neurology's 2016 Pilot Research Support Program 01/1/16-12/31/16
Mechanism of neuroprotection against cerebral ischemia
Role: PI, no % efforts

United Mitochondrial Disease Foundation 07/1/14-6/30/16
Modulation of GSK3 activity and enhancement of glycolysis to maintain neuronal survival in complex IV deficient mice
PI: Dr. Francisca Diaz
Role: Co-investigator (5% effort)

Completed Research Support (past 3 years):

Florida Department of Heath#09KN-14 07/1/11-06/30/14
Intra-arterial mesenchymal stem cell delivery in a canine model of acute ischemic stroke.
Principal Investigator: Dr. Dileep Yavagal
Role: Co-investigator (5% effort)

American Heart Association- Grant-in-aid
AHA # 11GRNT7370069 7/1/11- 6/30/2013
Nicotine inhibits estrogen-mediated synaptic plasticity after cerebral ischemia in female rat.
The major goal of this project is to study the effects of chronic nicotine usage on synaptic functions in female rats. There is no scientific/ financial overlap between NIH-R01 application under consideration and the funded AHA-grant-in-aid.
Role: Dr. Raval, PI, % efforts 25%

University of Miami Specialized Center Of Research on Addiction & Health in Women, Children & Adolescents (UM-SCOR) 10/1/2011-3/31/2013
Nicotine inhibits estrogen-mediated synaptic plasticity after cerebral ischemia in female rat
Role: PI, no % efforts

University of Miami, Stanley J. Glaser Foundation Award
UM 700852 6/1/11 - 12/31/12
Nicotine impairs hippocampal mitochondrial function in female rat.
This is a seed funding from University of Miami to generate pilot data for future federal funding. The major goal of this project is to study the effects of chronic nicotine exposure on mitochondrial function in hippocampus of female rats.
Role: Dr. Raval, PI, no % efforts

American Heart Association- Scientist Development Grant (National center)
AHA # 0730089N 1/1/11-12/31/11
Estrous cyclicity and mechanism of neuroprotection after cerebral ischemia.
The major goal of this project was to study the effects of endogenous estrogen fluctuations on neuroprotection against cerebral ischemia in normal cyclic rats.
Role: Dr. Raval, PI, % efforts 39%

Florida Department of Heath
#07KN-10 7/1/07-6/30/10
Inhibitory effects of nicotine on estrogen-induced natural hippocampal neuroprotection against ischemia
The major goal of this project was to study the effects of chronic nicotine usage and female sex hormones on cerebral ischemic outcomes.
Role: Dr. Raval, PI, % efforts 50%

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: **Tatjana Rundek, MD PhD**

eRA COMMONS USER NAME (credential, e.g., agency login): **TR89XX**

POSITION TITLE: **Professor of Neurology and Public Health Sciences, Director of Clinical Translational Research Division, University of Miami Miller School of Medicine**

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 Zagreb, Croatia	B.S.	1979-1983	Applied Mathematics
Medical School University of Zagreb, Croatia	M.D.	1984-1989	Medicine
Medical School University of Zagreb, Croatia	M.S.	1989-1991	Epidemiology/Bioinformatics
Ludwig-Maximillian University, Munich, Germany	Ph.D.	1991-1995	Neuroscience
Medical School University of Zagreb, Croatia	Residency	1991-1994	Neurology
Grossharden Spital Munich, Germany	Fellowship	1994-1995	Stroke
Columbia University, New York, NY	Fellowship/MS	1998-2000	Stroke/Neuroepidemiology

A. Personal Statement

As of Nov 1, 2016, I serve as an interim Scientific Director of the McKnight Brain Institute at the University of Miami (UM). Since my relocation from Columbia University to UM, I have been dedicated to the educational and research mission of the McKnight Institute. As a Vice Chair of Clinical Research and Director of the Clinical Translational Research Division in Neurology, and a PI of NIH/NINDS R01 grants and Co-I of several R01s I have been providing research environment and research training in neuroscience, vascular neurology and epidemiology for many graduate and post-graduate trainees over the course of my career. I am also a program Director of Miller School of Medicine MS in Clinical Translational Investigations. I am a Training Director of the NINDS StrokeNet and NeuroNEXT (1 trainee/year) and Miami AHA Bugher Stroke Center (2 trainees/year). I was awarded a NINDS K24 training grant that provided me with the protected time for research and mentorship. In addition, I am a director of the Neurology Residents and Fellows Clinician Researcher Program, a 3-year program aimed to provide research and career development mentorship. In the past 10 years, I have mentored over 20 trainees at various stages of their career, 14 completed their MD, PhD, MS or MPH degrees during my mentorship and obtained NIH grants or other awards. I have been a productive investigator with over 300 publications with extensive collaborations with various national and international research teams, such as investigators from Columbia University on large NIH-funded population based studies (NOMAS, INVEST, CABLE, PHPT, eMERGE) and Albert Einstein in the Bornx on Einstein Aging Study. I am a collaborator and site investigator of the large international stroke genetic and atherosclerosis projects and consortia (NINDS SiGN, ISGC, PROG-IMT, ELSA). I was recently awarded a 3-year AHA Mentor grant to mentor 3 trainees nationally for 3 years. I received the AHA Cor Vitae for Stroke Neurologist Award in 2015.

These peer-reviewed publications highlight my experience and qualifications:

1. Luca CC, **Rundek** T. Parkinsonism, small vessel disease, and white matter disease: Is there a link? Neurology. 2015;85(18):1532-3.
2. Tietjen GE, **Rundek** T. Migraine and cryptogenic stroke: The clot thickens. Neurology.2015;85(17):1436-7.
3. Gardener H, Wright CB, **Rundek** T, Sacco RL. Brain health and shared risk factors for dementia and stroke. Nat Rev Neurol. 2015;11(11):651-7.
4. **Rundek T.** Sacco RL. Comment: New models of successful academic mentoring. Neurology 2011; 77(7):688.
5. **Rundek T**, Bennett DA. Cognitive leisure activities, but not watching TV, for future brain benefits. Neurology 2006; 66(6): 794-5.

B. Positions and Honors

POSITIONS AND EMPLOYMENT

Academic Appointments:

1994-96	Assistant Professor of Neurology	Dept. of Neurology, University of Zagreb, Croatia
1996-98	Associate Professor of Neurology	Dept. of Neurology, University of Zagreb, Croatia
2002-07	Assistant Professor of Neurology	Columbia University, New York, NY
2007-11	Associate Professor of Neurology	Miller School of Medicine, Univ. of Miami, Miami, FL
2011-	Professor of Neurology (with tenure)	Miller School of Medicine, Univ. of Miami, Miami, FL

Hospital Appointments:

1994-00	Stroke Attending	Department of Neurology, University of Zagreb, Croatia
2002-07	Director&Attending,Vascular Laboratory	Columbia University Medical Center, New York, NY
2007-	Director, Clinical Translational Division	Miller School of Medicine, Univ. of Miami, Miami, FL
2010-	Vice Chair, Clinical Translational	Miller School of Medicine, Univ. of Miami, Miami, FL
2014-	Director, MS Clinical Translational	Miller School of Medicine, Univ. of Miami, Miami, FL

Honors

1995	Humbolt Award, Neurosonology Laboratory, University of Ulm, Germany
1996	George Soros Scholarship, Neurology Seminars, University of Krems, Austria
1997-99	Fulbright Award and Scholarship, Neurological Institute, Columbia University, New York, NY
2006	Nassau Women Physicians Foundation Award for Stroke Research in Women; Long Island, NY
2009-14	President, the Neurosonology Community of Practice, American Institute of Ultrasound in Medicine
2012-	Member, the Board of the Directors, Intersocietal Accreditation Committee (IAC)-Vascular
2012-	Consulting Editor of *Stroke*
2013-	Editorial Board Member of *Neurology, Cerebrovascular Disease, Journal of Ultrasound in Medicine*
2014-	Member, the Clinical Standards Committee, American Institute of Ultrasound in Medicine (AIUM)
2015-	Secretary, the Executive Committee, Intersocietal Accreditation Committee (IAC)-Vascular
2015-	Reviewer, NIH section ZHL1 CT-K (C1)1 – LRP
2015	The American Heart Association Core Vitae Award for Stroke

C. Contribution to science

C.1. Epidemiology of stroke and atherosclerosis. Over the past 20 years I have pursued research in stroke epidemiology. The central findings from this research include the discovery of novel stroke risk factors (e.g., insulin resistance, sleep duration, homocysteine, adiponectin, oral infection). Some of these reports were among the first in the literature. We conducted the largest investigation of the role of PFO in stroke and migraine. Our group was the first to report that atorvastatin reduces the serum coenzyme Q10 levels linking it to muscle pain. More recently I have been investigating neurocognitive functions in large longitudinal studies including HCHS-SOL. I am a strong believer in team science and many of my research products are the results of multiple collaborations between various national and international research teams and institutions.

1. **Rundek T**, Gardener H, Xu Q, Goldberg R, Wright C, Boden-Albala B, Disla N, Paik M, Elkind MSV, Sacco RL. Insulin Resistance and Risk of Ischemic Stroke in NOMAS. **Arch Neurol.** 2010;67:1195-200.
2. **Rundek T**, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, Homma S. Patent Foramen Ovale and Migraine. A Cross-Sectional Study from the Northern Manhattan Study. **Circulation**. 2008;118:1419-24.
3. **Rundek T**, Sacco RL. Prognosis after stoke (Chapter 16). In: Stroke- Pathophysiology, Diagnosis, and Management. Mohr JP, Grotta, Alberts GW, Broderick JP, asner SE, Lo EH, Mendelow D, Sacco RL, Wong LKS (Eds); Sixth edition, Elsevier Inc., 2016; 234-252.
4. **Rundek T**, Naini A, Sacco RL, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol. 2004; 61:889-892.
5. Ramos AR, Tarraf W, **Rundek T**, Redline S, Wohlgemuth WK, Loredo JS, Sacco RL, Lee DJ, Arens R, Lazalde P, Choca JP, Mosley T Jr, González HM. Obstructive sleep apnea and neurocognitive function in a Hispanic/Latino population. Neurology. 2015;84(4):391-8.

C.2. Extracranial and intracranial imaging markers of carotid disease. Vascular imaging has been my primary tool to investigate atherosclerosis. I have been in the field of ultrasound for over 25 years. I was trained in ultrasound technologies by the inventor of transcranial Doppler (TCD) Dr. Rune Aaslid in early 80's and have been a part of an international brain hemodynamic research group since. I coauthored the first consensus document on carotid ultrasound imaging. I have been a part of large international collaborations on the

progression of subclinical atherosclerosis (PROG-IMT, USE-IMT). I have applied arterial vessel wall principles to improve arterial compliance using a new technique of integrated power Doppler and changes of vessel wall diameter during cardiac cycle. In addition, I have helped advancing the field of brain circulation investigations using TCD to vascular cognitive impairment, memory loss and dementia. I have been an active member of IAC (Intersocietal Accreditation Committee) Board of Directors, the largest US accreditation body that sets the standards for performance of clinical ultrasound, CT/MRI and cardiac Echo. I have been an advocate for advancing quality and access to clinical ultrasound in medicine for vascular and cognitive disorders.

1. **Rundek T**, Blanton SH, Bartels S, Dong C, Raval A, Demmer RT, Cabral D, Elkind MS, Sacco RL, Desvarieux M. Traditional risk factors are not major contributors to the variance in carotid intima-media thickness. **Stroke**. 2013;44:2101-8. PMC3738011
2. **Rundek T**, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RLS. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. **Neurology** 2008; 70:1200-7. PMC2831775
3. Ramos AR, Tarraf W, **Rundek T**, Redline S, Wohlgemuth WK, Loredo JS, Sacco RL, Lee DJ, Arens R, Lazalde P, Choca JP, Mosley T Jr, González HM. Obstructive sleep apnea and neurocognitive function in a Hispanic/Latino population. Neurology. 2015;84(4):391-8.
4. Suemoto CK, Santos IS, Bittencourt MS, Pereira AC, Goulart AC, **Rundek T**, Passos VM, Lotufo P, Benseñor IM. Subclinical carotid artery atherosclerosis and performance on cognitive tests in middle-aged adults: Baseline results from the ELSA-Brasil. Atherosclerosis. 2015;243(2):510-5.
5. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, **Rundek T**, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012;308(8):796-803. PMC4523149

C.3. Genetic contribution to atherosclerosis and stroke. I have been investigating genetic contribution to carotid disease for the past 10 years as PI of 2 NINDS R01 grants and a NINDS K24 award, co-PI of family study of atherosclerosis and site PI of the NINDS SiGN (ischemic Stroke Genetic Network). In one of my investigations I have take the approach of extreme phenotypes by investigating genetic profile of individuals with a lot of risk factors but less atherosclerosis than expected as well as those with little to no risk factors but a lot of atherosclerosis. These investigations are now contributing novel findings on genetic and environmental determinants of atherosclerosis and stroke for targeted vascular therapies and prevention of CVD and stroke. I have also investigated family of sirtuin genes that are playing a central role in aging and caloric restriction that can be targets for anti-aging medical interventions.

1. **Rundek T**, Elkind MS, Pittman J, Boden-Albala B, Martin S, Humphries SE, Hank Juo SH, Sacco RL. Carotid Intima-Media Thickness is Associated with Allelic Variants of Stromelysin-1, Interleukin-6 and Hepatic Lipase Genes: The Northern Manhattan Prospective Cohort Study. **Stroke** 2002, 333:1420-3.
2. Dong C, Della-Morte D, Beecham A, Wang L, Cabral D, Blanton SH, Sacco RL, **Rundek T**. Genetic variants in LEKR1 and GALNT10 modulate sex-difference in carotid intima-media thickness: A genome-wide interaction study. Atherosclerosis. 2015;240(2):462-7.
3. Traylor M, Zhang CR, Adib-Samii P, Devan WJ, Parsons OE, Lanfranconi S, Gregory S, Cloonan L, Falcone GJ, Radmanesh F, Fitzpatrick K, Kanakis A, Barrick TR, Moynihan B, Lewis CM, Boncoraglio GB, Lemmens R, Thijs V, Sudlow C, Wardlaw J, Rothwell PM, Meschia JF, Worrall BB, Levi C, Bevan S, Furie KL, Dichgans M, Rosand J, Markus HS, **Rundek T**, Rost N; International Stroke Genetics Consortium. Genome-wide meta-analysis of cerebral white matter hyperintensities in patients with stroke. Neurology. 2016;86(2):146-53.
4. Della-Morte D, Ricordi C, **Rundek T**. The fountain of youth: role of sirtuins in aging and regenerative medicine. Regen Med. 2013;8(6):681-3.
5. Della-Morte D, Dong C, Beecham A, Wang L, Cabral D, Markert MS, Blanton SH, Sacco RL, **Rundek T**. Relationship between sirtuin and mitochondrial uncoupling protein genes and carotid artery stiffness. Transl Res. 2015;165(2):358-9.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=rundek
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40707409/?sort=date&direction=ascending

D. Research Support
List of selected ongoing and completed research projects for the past three years:

Ongoing Research Support

Novel Factors for Unexplained Phenotypes of Subclinical Carotid Atherosclerosis
NIH/NINDS R01 NS 065114 (no cost extension)
PI: T. Rundek 07.01.10-06.30.17
This is a selective genotype study of the extreme phenotypes of subclinical atherosclerosis among individuals with high burden of atherosclerosis and no risk factors (RF) and high burden of RF but no atherosclerosis.

Genetic Determinants of Extreme Phenotypes of Subclinical Atherosclerosis
NIH/NINDS K24 NS 062737 (no cost extension)
PI: T. Rundek 09.30.09-08.31.17
This is a award to train young investigators in patient-oriented research, perform research on genetic factors of extreme phenotypes of subclinical atherosclerosis, and enhance career development in genetic epidemiology.

Stroke Incidence and Risk Factors in a Tri-Ethnic Region
NIH/NINDS R37 NS 029993-11
PI: RL. Sacco; T. Rundek, Co-Investigator 02.01.03-01.31.20
The major goals of this project are to determine the effect of vascular risk factors on cognitive impairment and subclinical MRI findings in a prospective cohort study from 3 race-ethnic groups from Northern Manhattan.

Family Study of Stroke Risk and Carotid Atherosclerosis
NIH/NINDS R01 NS 40807
PI: RL. Sacco; T. Rundek, Co-Investigator 05.01.02-09.30.17
The major goal of this study is to evaluate heritability and genetic linkage of novel vascular risk factors such as carotid intima-media thickness among the families of high-risk Caribbean Hispanics.

University of Miami: Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT)
NIH/NINDS U10 NS 077423
PI: M. Benatar, R.L. Sacco; T. Rundek, Co-Investigator 09.30.11-08.31.18
The goals of this proposal are to enhance quality and efficiency of NIH trial implementation at the University of Miami and to leverage existing institutional strengths to enhance NeuroNEXT consortium activities.

The Albert Einstein Study Program Project in Aging
NIH/NIA 2P01 AG003949-26
PIs: Lipton, Derby; Albert Einstein, NY; T. Rundek, PI of TCD Core Laboratory 07.1.11-06.30.20
This is a Cerebral Hemodynamics Study of Aging of the AES program project aimed to study the vascular mechanisms of normal aging, MCI and dementia using TCD challenge test.

Oral Infections, Carotid Atherosclerosis and Stroke (INVEST)
NIH/NIDCR R01 DE 13094
PI: M. Desvarieux; T. Rundek, Co-Investigator 06.15.06-05.31.17
This cohort study will examine the effect of chronic periodontal disease and inflammation as a risk factor for stroke and carotid atheroma progression.

Stroke Prevention/Intervention Research Program in Hispanics
NIH/NINDS U54 NINDS SPIRP U54NS081763
PI: RL Sacco; T. Rundek, PI of Core C and PI of Supplement- Stroke Outcome in Women 01.01.13-12.31.17
The goal is to develop high-impact stroke disparities interventions with the ability to reduce stroke disparities in distinct Hispanic groups in Miami and Puerto Rico using effective and culturally appropriate methods

Miami Regional Coordinating Center for NINDS Stroke Trials Network
NIH/NINDS U10 NS086528
PI: J Romano; T. Rundek, Co-Investigator 09.30.13-07.31.18
The major goal of this award is to function effectively as a Regional Coordinating Center for the NINDS stroke trials and to enhance quality and efficiency of NINDS stroke trial implementation at the Miami site.

Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD)
NIH/NINDS R01 NS084288-01A1
PI: J Romano; T. Rundek, Co-Investigator 04.01.14-03.31.19
The objective of this proposal is to determine the mechanisms and predictors of stroke in patients with symptomatic Intracranial Atherosclerotic Disease.

Hispanic Community Health Study-Study of Latinos (HCHS-SOL) Miami Field Center
NIH/NHLBI N01-HC65234
PI: N. Schneiderman; T. Rundek, Adjudication Core investigator 06.01.14-05.31.19
The HCHS/SOL is a multi-center epidemiologic study designed to determine the role of acculturation in disease prevalence and to identify health risk factors in Hispanics/Latinos.

AHA-ASA/Bugher Foundation Center of Excellence in Stroke Collaborative Research
AHA14BFSC17690000
PI: RL. Sacco; T. Rundek, Training Director 04.01.14-03.31.18
This initiative supports a collaboration of basic, clinical and population research and training in stroke prevention and recovery after a stroke including the areas of repair, regeneration, and rehabilitation.

NCRP Winter 2015 Mentor / AHA Mentee Award
AHA 15MM26340000
PI: T. Rundek, Mentor 07.01.15-06.30.18
This awards supports Dr. Rundek's mentorship activities for 2 AHA fellows (from John Hopkins & UT Huston).

Prior Research Support (prior 5 years)
Ischemic Stroke Genetics
NIH/NINDS U01 The NINDS International Stroke Genetics Consortium Study
PI: S. Kittner, U Maryland; T. Rundek, Site PI 04.01.10-3.31.16
This was a GWAS, which will greatly advance the field of ischemic stroke genetics by establishing a large 11-study collaboration of unique scale to bring together the world's leading clinician-scientists in stroke genetics.

FGF-23 and the Risk of Stroke and Cognitive Decline
NIH/NHLBI R01 HL108623-01A1
PI: C. Wright; T. Rundek, Co-Investigator 12.01.12-11.30.16
This was an epidemiology project on FGF23 and risk of stroke and cognitive decline that set the stage for novel randomized controlled trials.

Genetic Determinants of Subclinical Carotid Disease; NIH/NINDS R01 NS 047655
PI: T. Rundek 01.01.04-12.31.11
This was a cross-sectional study evaluating potential candidate genes related to carotid IMT and distensibility in the Northern Manhattan Study cohort.

Gene-Smoking Interactions and Atherosclerosis; KN01 James & King Biomedical Research
PI: C. Dong; T. Rundek, Co-Investigator 09.01.11-08.31.14
The major goal of this project was to identify genetic variants that modify the effect of smoking on the development of atherosclerosis and the risk of clinical vascular diseases.

Primary Hyperparathyroidism: Non-Classical Manifestations; NIH/NIDK R01 DK 66329
PI: S. Silverberg; T. Rundek, Co-Investigator 7.01.05-06.30.11
The main objective of this study was to determine whether there was structural and functional evidence of increased vascular stiffness or cardiovascular calcification in patients with mild asymptomatic PHPT.

Aortic, Cardiovascular Disease and Silent Brain Infarcts; NIH/NINDS R01 NS 36286
PI: M. Di Tullio; T. Rundek: Co-Investigator 7.01.05-06.30.11
The objective of this study was to investigate cardiac sources of silent brain infarcts and cerebral white matter disease.

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: **Ralph Lewis Sacco, MD MS**

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

POSITION TITLE: **Chairman and Professor of Neurology, Public Health Sciences, Human Genetics, and Neurosurgery**

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
Cornell University, College of Engineering	B.S. distinction	1975-79	BioElectrical Engineering
Boston University, School of Medicine	M.D. cum laude	1979-83	Medicine
Columbia University, School of Public Health	M.S.	1987-89	Epidemiology
Neurological Institute, Presbyterian Hospital	Residency	1984-87	Neurology
Columbia College of Physicians & Surgeons	Fellow	1987-89	Cerebrovascular Disease

A. Personal Statement

I serve as Executive Director for the Evelyn F. McKnight Brain Institute at the University of Miami. I am currently Professor and Chairman of Neurology at the Miller School of Medicine, Director of the UM-Clinical Translational Science Institute, and Senior Associate Dean for Clinical and Translation Science. I am fully committed to a clinical translational research agenda within my department and institution and have enhanced this mission through recruitment of academic faculty and support of research infrastructure for training the next generation of translational scientists. My clinical translational research interests include epidemiology, diagnosis, prevention, genetic, and treatment studies of stroke, cognitive impairment, and other cardiovascular conditions. I have an extensive research track record in stroke clinical trials and disparities research. I have successfully applied and managed large collaborative research programs at Columbia University and the University of Miami. For the past 24 years, I have been the PI of the Northern Manhattan Study, consisting of a collaborative, multi-disciplinary research team across three institutions (UMiami, Columbia, and Mt Sinai. This NINDS-funded community-based, epidemiologic cohort study is designed to evaluate the determinants of stroke and cognitive impairment among an elderly, multi-ethnic, urban population living in northern Manhattan. This study has provided essential data on stroke disparities, describing the greater incidence of stroke among Hispanics and the increased burden of hypertension and diabetes in this ethnic group. We have also published on the impact of novel risk factors including inflammatory biomarkers and infectious burden, and as the study cohort ages, our focus has expanded beyond stroke towards studies of the vascular contributions to cognitive aging and functional impairment. I also continue to lead and engage in large preventive trials and national and international consortia sponsored by industry and NIH. I am dedicated to improving efficiency in the design and implementation of randomized trials as co-PI for our Neuro-NEXT and Stroke-NET regional coordinating centers for NINDS trials. I have published extensively with over 600 peer-reviewed articles and over 120 invited articles in the areas of stroke prevention, treatment, epidemiology, risk factors, vascular cognitive impairment, and human genetics. I have been honored with several awards including the World Stroke Organization, Global Leadership Award, the Feinberg Award of Excellence in Clinical Stroke, the Wepfer Award, the Chairman's Award from the American Heart Association, and the NINDS Javits Award in Neuroscience, and I have lectured extensively at national and international conferences. I have helped train numerous fellows in stroke and epidemiology and was co-director of a T32 entitled Neuro-epidemiology Training Program to train neurologists in epidemiology, as well as to mentor MD, PhD, and graduate students. As former president of the American Heart Association and president-elect of the American Academy of Neurology, I have been and continue to be fully committed to advancing scientific collaborations and building partnerships for translational research.

These four peer reviewed publications highlight my experience and qualifications for this project:

1. **Sacco RL**, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. **Stroke**. 2001; 32:1725-31.
2. **Sacco RL**, DeRosa JT, Haley EC Jr, Levin B, Ordronneau P, Phillips SJ, Rundek T, Snipes RG, Thompson JL; Glycine Antagonist in Neuroprotection Americas Investigators. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. **JAMA**. 2001; 285:1719-28.
3. **Sacco RL**, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T; American Heart Association/American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke

Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. **Circulation**. 2006; 113:e409-49.

4. **Sacco RL**. Achieving ideal cardiovascular and brain health: opportunity amid crisis: Presidential Address at the American Heart Association 2010 Scientific Sessions. **Circulation**. 2011; 123:2653-7.

B. Positions and Honors

Academic Appointments:

89-97	Assistant Professor of Neurology & Public Health (Epidemiology) in the Sergievsky Center
97-02	Associate Professor of Neurology & Public Health (Epidemiology) (with tenure)
03-07	Professor of Neurology & Epidemiology, Columbia University, College of Physicians and Surgeons, Mailman School of Public Health, and the Sergievsky Center (with tenure)
07-	Olemberg Family Chair in Neurological Disorders, Miller Professor of Neurology, Public Health Sciences, Neurosurgery, and Human Genetics (with tenure) and Chairman of Neurology, Miller School of Medicine, University of Miami
16-	Senior Associate Dean for Clinical and Translation Science

Honors**:**

1982	Alpha Omega Alpha	1998	American Neurological Association
2001	Fellow of the American Heart Association	2004	Fellow of the American Academy of Neurology
2006	AHA/ASA William Feinberg Award	2007	AHA Chairman's Award
2008	NINDS Jacob Javits Award in the Neurosciences	2008	American Association of Physicians
2015	AHA, Gold Heart Award	2015	The Johann Jacob Wepfer Award of the ESC
2015	UM Provost's Award for Scholarly Activity	2016	World Stroke Organization, Global Leadership

Other Professional Experience

1997-03	NINDS, Performance Safety & Monitoring Committee, VISP Trial
2004-06	NINDS Neurosciences Training Grant Review Group, Member
2013-16	NINDS, National Advisory Neurological Disorders and Stroke Council
2002-03	NIH, Center for Scientific Review, EDC-3
2003-07	FDA, Peripheral and Central Nervous System Drug Advisory Panel
2005-08	AHA, National Board of Directors; ASA, Chair Stroke Advisory Committee
2010-11	AHA, President, National Board of Directors
1999-05	American Academy of Neurology, Clinical Research Subcommittee, Chair
2005-09	American Academy of Neurology, Board of Directors
2013-15	AAN, Vice President
2015-17	AAN, President-elect

C. Contribution to Science

C.1. Health Disparities As Principal Investigator for both a 24-year old community-based, epidemiologic study designed to determine stroke incidence, risk factors, and prognosis in an elderly, multi-ethnic, urban population, as well as a more recent stroke registry, we have been gathering and reviewing essential data on stroke disparities. Through these studies, we have been able to document the greater incidence of stroke among Hispanics and the increased burden of hypertension and diabetes in this ethnic group. My work in the area aims to develop and implement high-impact, culturally-appropriate interventions and prevention programs aimed at minority racial/ethnic groups, as well as those who are socioeconomically disadvantaged.

1. **Sacco RL**, Boden-Albala B, Gan R, Kargman DE, Paik M, Shea S, Hauser WA, and the Northern Manhattan Stroke Study Collaborators. Stroke incidence among white, black and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. **Am J Epidemiol** 1998; 147:259-268
2. **Sacco RL**, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors: The Northern Manhattan Stroke Study. **Stroke** 2001; 32:1725-1731
3. Dong C, Rundek T, Wright CB, Anwar Z, Elkind MS, **Sacco RL**. Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks, and Hispanics: the northern Manhattan study. **Circulation**. 2012; 125:2975-84. PMCID: PMC3396556
4. **Sacco, RL**, Gardener H, Wang K, Dong C, Ciliberti-Vargas MA, Gutierrez CM, Asdaghi N, Burgin WS, Carrasquillo O, Garcia-Rivera EJ, Nobo U, Oluwole S, Rose DZ, Waters MF, Zevallos JC, Robichaux M, Waddy SP, Romano JG, Rundek T for the FL-PR CReSD Investigators and Collaborators*. Race-Ethnic Disparities in Acute Stroke Care in the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities Study. **JAHA** in press.

C.2. Randomized Clinical Trials – I have been involved in the design and conduct of numerous NIH and industry sponsored randomized clinical trials on stroke treatment and prevention. These include serving as PI, co-PI, co-I or on

the executive or steering committees of international multi-center trials. Some have included innovative designs and answered important evidence treatment gaps.

1. **Sacco RL**, DeRosa JT, Haley EC Jr, Levin B, Ordronneau P, Phillips SJ, Rundek T, Snipes RG, Thompson JL. Glycine Antagonist in Neuroprotection Americas Investigators. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. **JAMA**. 2001; 285:1719-28.
2. Mohr JP, Thompson JL, Lazar RM, Levin B, **Sacco RL**, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. .**N Engl J Med.** 2001;15;345:1444-51.
3. Homma S, **Sacco RL**, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. **Circulation**. 2002; 105:2625-31.
4. **Sacco RL**, Diener HC, Yusuf S, Cotton D, Ôunpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW; PRoFESS Study Group.. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. **N Engl J Med**. 2008; 359:1238-1251. PMCID: PMC2714259.

C.3. Vascular Determinants of Cognitive Aging. Through the 24-year-old Northern Manhattan Study, which maintains an aging cohort, I have led our multi-disciplinary team towards research which considers a broader definition of brain health. Some resulting studies have focused on characterizing vascular risk factors and their involvement as brain health determinants.

1. Warsch JR, Rundek T, Paik MC, Elkind MS, **Sacco RL**, Wright CB. Association between northern Manhattan study global vascular risk score and successful aging. **J Am Geriatr Soc** 2013 Apr;61(4):519-24. Epub 2013 Mar 25. PMID: 23527874; PMCID: PMC3628415
2. Katan M, Moon YP, Paik MC, **Sacco RL**, Wright CB, Elkind MS. Infectious burden and cognitive function The Northern Manhattan Study. **Neurology**. 2013 Mar 26;80(13):1209-15.
3. **Sacco RL**. Evolution from Stroke Risk Factors to Brain Health Determinants. **Cerebrovascular Diseases**. 2015 Jul 18;40(3-4):102-13.
4. Gardener H, Wright CB, Dong C, Cheung K, DeRosa J, Nannery M, Stern Y, Elkind MS, **Sacco RL**. Ideal cardiovascular health and cognitive aging in the Northern Manhattan Study. **JAHA**. 2016 Mar 1;5(3):e002731.

C.4. Epidemiology of stroke. Over the past 31 years we have pursued research in stroke epidemiology. The central findings from this research include the elucidation of novel risk stroke factors (e.g., patent foramen ovale, carotid plaque, ideal cardiovascular health, homocysteine, HDL, alcohol, inflammation and infectious burden in stroke prevention) particularly in minority populations. Some of these reports were among the first in the literature.

1. **Sacco RL**, Elkind M, Boden-Albala B, Lin I-F, Kargman DE, Hauser WA, Shea S, Paik M. The protective effect of moderate alcohol consumption on ischemic stroke. **JAMA** 1999;281:53-60
2. **Sacco RL**, Benson RT, Kargman DE, Boden-Albala B, Tuck C, Lin I-F, Cheng JF, Paik MC, Shea S, Berglund L. High-density lipoprotein cholesterol and ischemic stroke in the elderly. **JAMA** 2001;285:2729-35
3. **Sacco RL**, Anand K, Lee HS, Boden-Albala B, Stabler S, Allen R, Paik MC. Homocysteine and the Risk of Ischemic Stroke in a Triethnic Cohort. The Northern Manhattan Study. **Stroke** 2004;35:2263-9
4. **Sacco RL**, Khatri M, Rundek T, Xu Q PhD, Gardener H, Boden-Albala B, Di Tullio M, Homma S, Elkind MSV, Paik MC. Improving Global Vascular Risk Prediction with Behavioral and Anthropometric Factors: The Multi-ethnic Northern Manhattan Cohort Study. **J Am Coll Cardiol** 2009;54:2303-11 PMCID: PMC2812026

C.5. Evidence-based Treatment Recommendations, Scientific Statements and Honorary Lectures – I have participated as lead author or collaborator on numerous highly-cited evidence-based recommendations from the AHA/ASA NSA, and IOM, as well as Scientific Statements that have been important to the field of stroke and cardiovascular diseases. I have also been a collaborator on numerous consortium including the Global Burden of Disease reports, Stroke Genetics Consortia, CHARGE, and other meta-analyses.

1. **Sacco RL**, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. **Stroke**. 2006 Feb 37(2):577-617 PMID: 16432246 and **Circulation**. 2006; 113:e409-49.
2. **Sacco RL**. The 2006 William Feinberg lecture: shifting the paradigm from stroke to global vascular risk estimation. **Stroke**. 2007; 38:1980-7.
3. **Sacco RL**. Achieving ideal cardiovascular and brain health: opportunity amid crisis: Presidential Address at the American Heart Association 2010 Scientific Sessions. **Circulation**. 2011;123:2653-7.
4. **Sacco RL**, Frieden TR, Blakeman DE, Jauch EC, Mohl S. What the million hearts initiative means for stroke: a presidential advisory from the American Heart Association/American Stroke Association. **Stroke**. 2012; 43:924-8.

Complete List of Published Work in My Bibliography: http://www.ncbi.nlm.nih.gov/pubmed/?term=sacco rl

D. Current Research Support

Stroke Incidence and Risk Factors in a Tri-Ethnic Region

Role: PI; Agency: NIH/NINDS; Type: R37 (formerly 2R01) (NS 29993); Period: 01.01.93-07.31.20

Aims: To determine the effects of risk factors including subclinical carotid and brain disease on the risk of stroke, MI, and vascular death in a prospective cohort of 3299 stroke-free community subjects from Northern Manhattan.

Family Study of Stroke Risk and Carotid Atherosclerosis

Role: PI; Agency: NIH/NINDS; Type: 1R01 (NS 240807); Period: 05.01.02-08.30.17

Aims: The major goals of this project are to determine the genetic determinants of carotid IMT and plaque among high-risk Caribbean Hispanic families of the NOMAS.

Clinical and Translational Science Award

Role: PI; CTSA Executive Committee; Agency: NIH/NCRR/NIMHD; Type UL1TR000460 Period: 06.27.12-05.31.17;

Aims: The goal of this CTSI is to facilitate translational research at UM

Hispanic Stroke Prevention Intervention Research Program

Role: PI; Agency: NIH/NINDS; Type: U54 (NS 081763); Period: 01.01.13-12.31.17

Aims: The major goals of this project are to create the Florida Puerto Rico Stroke Registry to identify and reduce stroke disparities in acute stroke and secondary prevention

AHA/ASA Bugher Center Foundation Center of Excellence in Stroke Award

Role: Center Director; Agency: AHA Period: 04.01.14-03.31.18

Aims: To conduct two projects evaluating the effects of physical activity and cognitive training on animals and stroke survivors on cognitive recovery.

Miami Regional Coordinating Center for NINDS Stroke-NET

Role: Co-PI Agency: NIH/NINDS; Type U10 NS086528 (Romano) Period: 09.01.13-08.31.18

Aims: The goals of the Miami RCC are to implement high-quality research clinical trials that address acute stroke treatment, prevention and recovery.

NSTN National Clinical Coordinating Center Stroke NET

Role: Prevention, Co-chair, Co-I; Agency: NIH/NINDS: Type: 1U01NS086872 (Broderick) Period: 10.01.13-09.30.18

Aims: The goals for the National Clinical Coordinating Center for the NINDS Stroke Network are to coordinate NINDS-funded trials in stroke prevention, acute therapy, and rehabilitation.

University of Miami: Network of Excellence in Neuroscience Clinical Trials (NEXT)

Role: PI (dual); Agency: NIH/NINDS; Type: U10 (NS077423); Period: 09.30.2011-08.31.2018

Aims: The goals of this proposal are to function effectively as a Neuro-NEXT NINDS consortium trial site

Clinical and Translational Science Award

Role: Co-I; PI: JSzapocznik; Agency: NIH/NCRR/NIMHD; Type: UL1TR000460; Period: 07/01/12-6/30/17

Aim: To build research capacity and facilitate translational research at University of Miami.

Hispanic Secondary Stroke Prevention Initiative (HISSPI)

Role: Co-I; PI: Carrasquillo; Agency: NIH/NIMD; Type: R01MD009164; Period: 07.10.14-03.31.19

Aim: To reduce the risk for a recurrent stroke among Latinos at high risk for a second and potentially much debilitating stroke.

Prevalence and predictors of asymptomatic atrial fibrillation in the community

Role: Co-I; PI: di Tullio; Agency: NIH/NIMD; Type: R01NS083784; Period: 04.01.14-01.31.19

Aim: To expand knowledge of atrial fibrillation/other arrhythmias in the elderly and their relationship with stroke and other vascular events in addition to identifying high risk candidates for arrhythmia development whom might best benefit from intervention.

Curriculum Vitae
Xiaoyan Sun, MD, PhD
Dept of Neurology
University of Miami Miller School of Medicine
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ACADEMIC TRAINING:

1996 Ph.D.	Neuroscience, Gunma University School of Medicine, Japan
1984 M.D.	Xi'an Medical College (Present name: School of Medicine, Xi'an Jiaotong University), China

POSTDOCTORAL TRAINING:

2012-2014	Clinical fellow in Cognitive/Behavioral Neurology, Boston VA Medical Center, Boston, MA
2009-2012	Resident in Neurology, Medical University of South Carolina, SC
2008-2009	Intern in Neurology, Medical University of South Carolina, SC
2004-2008	Clinical Research Fellow, Dept Psychiatry, Tufts Medical Center and School of Nutrition Science and Policy, Boston, MA
2002-2004	Postdoctoral Fellow, Dept of Neurology and Center for Neurologic Disease, Brigham and Woman's Hospital, Harvard Medical School, Boston, MA
1996-1998	Postdoctoral Fellow, Dept Medicine, UCLA, CA
1983-1984	Intern, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China

ACADEMIC APPOINTMENTS:

2014-present	Assistant Professor, Department of Neurology, University of Miami Miller School of Medicine
2013-2014	Assistant Professor, Department of Neurology, Boston University
1998-2002	Staff Scientist, Brain Science Institute of RIKEN, Japan

HOSPITAL APPOINTMENTS:

1989-1990	Attending, Dept Neurology, Qinghai Provincial People's Hospital, China

HONORS:

2010	Best Case Presentation Award, Dept Neuroscience, Medical University of South Carolina
1996-1997	Staff Incentive Award For Exceptional Performance And Valuable Contribution, Dept Medicine, UCLA
1996.8	Travel award 5th International Alzheimer's disease Conference, Japan
1992-1996	Japanese Government Scholarship for Ph.D course, Japan
1990-1991	Clinical fellowship of Neurology, Sasakawa Foundation, Japan
1987-1987	Clinical fellowship, The Iodine Deficient Disorder (IDD) Project between China and Australia

LICENSES AND CERTIFICATION:

2014-present	Florida Medical License # ME121152
2012-present	Board Certified Neurology

2012-present	South Carolina Medical License # 30195
2012-present	Massachusetts Medical License # 251388
1987	Psychometrics certificate, Macquarie University, Australia

TEACHING EXPERIENCE AND RESPONSIBILITIES:

2014.10-present	Education director, McKnight Brain Institute, University of Miami
2013-2014	Faculty Member of Educational Program (From Synapses to Systems), Harvard South Shore Psychiatry Residency Program
2012-2014	Supervise resident at General Neurology clinic
2012	Neurological examination for medical student in Medical University of South Carolina

OTHER PROFESSIONAL ACTIVITIES:

PROFESSIONAL SOCIETIES: MEMBERSHIPS, OFFICES, AND COMMITTEE ASSIGNMENTS

2010-present	Member of American Academy of Neurology

INVITED JOURNAL REVIEWER

2008	Biological Psychiatry
2008	Journal of Affective Disorder
2008	American Journal of Psychiatry
2012	American Journal of Alzheimer's disease and other dementia
2013	Neuroscience Letter
2015	Neurology
2015	Alzheimer's & dementia

Past Other Support:

1998-2000	Chinese Natural Science Foundation
2002-2003	Sabbatical Program In Drug Discovery, HCNR of Harvard Medical School

Bibliography

ORIGINAL, PEER REVIEWED ARTICLES:

1 Okamoto K., Hirai S., Yamazaki T., **Sun X.,** and Nakazato Y. New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with ALS. Neurosci Lett 1991, 129:233-236

2 Tanaka M., Kondo S., Hirai S., **Sun X.**, Yamagishi T., Okamoto K.. Cerebral blood flow and oxygen metabolism in progressive dementia associated with amyotrophic lateral sclerosis. J Neurol Sci. 1993; 120:22-28

3 Kondo S., Tanaka M., **Sun X.**, Saka Y., Hirai S. Study of patients with spinocerebellar degeneration using positron emission tomography Clin. Neurol., 1993; 33:1039-1049

4 **Sun X**, Tanaka T., Kondo S., Hirai S., Ishihara T.. Reduced cerebellar blood flow and oxygen metabolism in spinocerebellar degeneration: a combined PET and MRI study J Neurol. 1994; 241:295-300

5 Yamaguchi H., Yamazaki T., Kawarabayashi T., **Sun X.**, Sakai Y, Hirai S.. Localization of Alzheimer amyloid beta protein precursor and its relation to senile plaque amyloid Geronto.l 1994; 40(Suppl. 2): 36-

6 Yamaguchi H., Ishigoro K., Sugihara S., Nakazato Y., Kawarabayashi T., **Sun X.** and Hirai S.. Presence of apolipoprotein E on extracellular neurofibrillary tangles and on meningeal blood vessels precedes the Alzheimer beta-amyloid deposition. Acta. Neurpathologica. 1994;8:413-419

7 **Sun X.**, Tashiro T., Hirai S. and Yamaguchi H.. Identification of 5.8 kDa C-terminal fragments of Alzheimer amyloid generated in the lysosomal system. Amyloid: Int.J.Exp.Clin.Invest. 1994;1:100-106

8 Kondo S., Tanaka M., **Sun X.**, Okamoto K., and Hirai S.. Cerebral blood flow and oxygen metabolism in atients with pure akinesia and progressive supranuclear palsy Clin. Neurol. 1994; 34:531-537

9 Tanaka M., Uesugi M., Igeda Y, Kondo S., **Sun X.** and Hirai S.. Luxury perfusion phenomenon in acute herpes simplex virus encephalitis. Annals of Nuclear Medicine 1995; 9:43-45

10 **Sun X.**, Tashiro T., Hirai S., Yamamoto H., Miyamoto E., and Komiya Y.. Preparation of tau from the peripheral nerve: Presence of insoluble low molecular weight tau with high phosphorylation Biochem. Biophy. Res. Comm. 1995; 210:338-344

11 Tashiro T., **Sun X.**, Tusda M., Komiya Y. Differential axonal transport of soluble and insoluble tau in the rat sciatic nerve J. Neurochem 1996; 67(4):1566-74

12 Yang F., **Sun X.**, Beech W., Teter B., Wu S., Sigel J., Frautschy S. and Cole GM. Detection of actin cleavage at an apoptosis related site in vitro and in Alzheimer's disease Am J Pathol 1998; 158:379-389

13 **Sun X.**, Tanaka M., Kondo S., Okamoto K, Hirai S. Clinical significance of reduced cerebral metabolism in multiple sclerosis: A combined PET and MRI study Annals of Nuclear Medicine 1998 12(2): 89-94

14 Tanaka M., Hirai S., Kondo S, **Sun X.**, Nakagawa T., Tanaka S., Hayashi K., Okamoto. Cerebral hypoperfusion and hypometabolism with altered striatal signal intensity in chorea-acanthocytosis: a combined PET and MRI study. Mov Disord. 1998 13(1):100-7

15 Murayama O., Murayama M., Honda T., **Sun X**, Nihonmatus N. and Takashima A. Twenty-nine missense mutations linked with familial Alzheimer's disease alter the processing of presenilin 1 Prog Neuro-Psychopharmacol & Biol Psychiat 1999 23: 905-913

16 Murayama O., Tomita T., Nihomatsu N., Murayama M., Sun X., Honda T., Iwatsubo T., Takashima A. Enhancement of amyloid beta 42 secretion by 28 different presenilin 1 mutations of familial Alzheime's disease. Neurosci Lett 199 265(1):61-3

17 Murayama M., Tanaka S., Palacino J., Murayama O, Honda T., **Sun X.**, Yasutake K., Nihonmatue-Kikuchi N., Wolozin B, and Takashima A.. Direct association of presenilin-1 with beta-catenin FEBS Lett. 1998; 433:73-77

18 Tanemura K., Akagi T., Murayama M. , Kikuchi N., Murayama O., Hashikawa T., Yoshiike Y., Park J-M., Matsuda K., Nakao K., **Sun X.**, Sato S., Yamaguchi H, and Takashima A. Neurobiol. of Diseasees 2001; 8:1036-1045

19 Murayama M., **Sun X.**, Takashima A.. Synthesis of the His6-tagged recombinant protein APPC99 and His-Ps1 Using the RTS 500 Biochemica 2001, 4:24-26

20 Yoshiike Y., Tanemura K., Murayama O., Akagi T., Murayama M., Sato S., **Sun X.**, Tanaka N., and Takashima A. New insights on how metals disrupt amyloid beta-aggregation and their effects on amyloid-

beta cytotoxicity J Bio Chem 2001; 276(34):32293-9

21 **Sun X.**, Cole GM,, Chu T., Xia W., Galasko D., Yamaguchi H., Frautschy SA., and Takashima A.. Intracellular A-beta is increased by okadic acid exposure in the transfected neuronal and non-neuronal cell lines Neurobiol. of Aging 2002; 23:195-203

22 **Sun X.**, Sato S., , Murayama O., Murayama M., Park J.-M., Yamaguchi H., and Takashima A. Lithium inhibits amyloid secretion in the cells transfected with amyloid precursor protein C100 Neurosci Lett 2002; 321:61-64

23 Xia X., Wang P., **Sun X.**, .Soriano S., Shum W.-K., Yamaguchi H., Trumbauer ME., Takashima A., Koo EH., and Zheng H. The Aspartate 257 of presenilin 1 is indispensable for mouse development and Abeta production through beta-catenin independent Mechanisms Proc. Natl.Acad.Sci.USA 2002; 99:8760-8765

24. Sato S, Tatebayashi Y, Akagi T, Chui DH, Murayama M, Miyasaka T, Planel E, Tanemura K, **Sun** X, Hashikawa T, Yoshioka K, Ishiguro K, Takashima A. Aberrant tau phosphorylation by glycogen synthase kinase-3beta and JNK3 induces oligomeric tau fibrils in COS-7 cells. J Biol Chem. 2002 Nov 1;277(44):42060-5.

25 Leissring M.A., Farris W., Chang A.Y., Walsh D.M., Wu X., **Sun X.**, Frosch M.P., Selkoe D.J. Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. Neuron. 2003 Dec 18;40(6):1087-93

26 Beglopoulos V*, **Sun X.***, Saura R., Kim R., and Shen J. Reduced amyloid production and increased inflammatory responses in presenilin conditional knockout mic. J Biol Chem. 2004 Nov 5; 279 (45): 46907-14 (*equal contribution)

27 Zhang L., Lee J., Song L., **Sun X.**, Shen J., Terracina G., Parker E.M.. Characterization of the Reconstituted gamma-Secretase Complex from Sf9 Cells Co-Expressing Presenilin 1, Nacastrin, aph-1a, and pen-2. Biochemistry. 2005 Mar 22;44(11):4450-7.

28 **Sun X. ***, Beglopoulos V*,., Mattson M, Shen J.. Hippocampal Spatial Memory Impairments Caused by the Familial Alzheimer's Disease-linked Presenilin 1 M146V Mutation Neurodegenerative Dis 2005; 2:6-15

29 Cruz J.C., Kim D., Moy L.Y., Dobbin M.M., **Sun X.**, Bronson RT, and Tsai L.-H.. p25/cyclin-dependent kinase 5 induces production and intraneuronal accumulation of amyloid β in vivo. J. of Neurosci, October 11, 2006, 26(41):10536-10541

30 Qiu W.Q., Price L.L., Hibber P., Beull J., Collins L., Leins D., Mwamburi D.M., Rosenberg I., Smaldone B.A., Scott T.M., Siegel R.D., Summergrad P., **Sun X.**, Wagner C., Wan L., Yee J., Tucker K. and Folstein M.. Executive Dysfunction in Homebound Elderly with Diabetes J Ameri Geria Soci 2006; 54: 456-501.

31 Qiu W.Q., *, **Sun X., ***, Selkoe D.J., Mwamburi D.M., Huang T. , Bhadela R., Bergethon P., Scott T.M., Summergrad P., Wang L., Rosenberg I., and Folstein M. . Depression is Associated with Low Plasma Ab42 Independently of Cardiovascular Disease in the Homebound Elderly. Int J. Ger Psych, Nov. 6, 2006 (*equal contribution)

32 **Sun X.,** Selkoe D.J., Mwamburi D.M., Bungay K., Prasad J., Yee J., Lin Y. , Liu T.C., Summergrad P., Folstein M. , and Qiu W.Q. . Depression, antidepressants and plasma Ab peptides in those elderly who do not have cardiovascular disease. Biological Psychiatry, 2007 Jun. 1;

33 Farris W., Schütz S.G., Cirrito J. R., Shankar G. M., **Sun X.**, George A., Leissring M., Walsh D. M., Qiu W.Q., Holtzman D. M., Selkoe D. J.. Loss of neprilysin function promotes amyloid plaque formation and precipitates cerebral amyloid angiopathy. American Journal ofominic Pathology, 2007, 171(1):241-251.

34 **Sun X.**, Steffens D.C., AU R., Folstein M., Summergrad P., Yee J., Rosenberg I., Mwamburi D.M., Qiu W.Q.. Amyloid-associated depression: a prodromal depression of Alzheimer disease? Arch Gen Psych 2008, 65: 542-50

35 Okereke O.I., Xia W., Irizarry M.C., **Sun X.**, Qiu W.Q., Fagan A.M., Mehta P.D., Hyman B.T., Selkoe D.J., Grodstein F.. Performance of characteristics of plasma amyloid-beta 40 and 42 assays. J Alzheimers Dis. 2009;16(2):277-85.

36 Shankar G.M., Leissring M.A., Adame A., **Sun X.**, Spooner E., Masliah E., Selkoe D, J,, Lemere C,A,, Walsh D,M,. Biochemical and immunohistochemical analysis of an Alzheimer's disease mouse model reveals the presence of multiple cerebral Abeta assembly forms throughout life. Neurobiol Dis. 2009 Nov;36(2):293-302

37 **Sun X.,** Chiu C.C., Liebson E., Crivello N.A., Wang L., Folstein M., Rosenberg I., Mwamburi D.M. , Peter I., and Qiu W.Q. Depression and plasma Amyloid β peptides in the elderly with and without apolipoprotein E4 allele. Alzheimer Dis Assoc Disord. 2009 Jul-Sep;23(3):238-44.

38 Qiu W.Q., **Sun X.,** Mwamburi, D.M., Haker J., Lisle D., Rizal A., Lin Y., Qiao L., Summergrad P., Wang L., Folstein M., and Rosenberg I.. Plasma Amyloid-β and Homocysteine in Depression in the Homebound Elderly. North American Journal of Medicine and Science, 2010 Vol 61-67

39 **Sun X**, Bhadelia R, Liebson E, Bergethon P, Folstein M, Zhu JJ, Mwamburi DM, Patz S, Qiu WQ. The relationship between plasma amyloid-β peptides and the medial temporal lobe in the homebound elderly. Int J Geriatr Psychiatry. 2011 Jun; 26(6):593-601

40 **Sun X.,** Nicholas J., Walker A., Wagner M., and Bachman D. APOE genotype in the diagnosis of Alzheimer's disease in the patients with cognitive impairment. American Journal of Alzheimer's disease and other dementia. 2012 Aug; 27(5):315-20.

41 **Sun X.**, Salat D, Upchurch K, Deason R, Kowall N, Budson A; Alzheumer's Disease Neuroimaging Initiative. Destruction of white matter integrity in patients with mild cognitive impairment and Alzheimer disease. J Investig Med. 2014 Oct;62(7):927-33.

42 Ravenscroft T., Pottier C., Murray M, Baker M., Christopher E., Levitch D., Brown P., Barker W., Duara R., Greig-Custo M., Betancourt A., English M., **Sun X.,** Ertekin-Tane N., Graff-Radford N., Dickson D., Rademakers R. The presenilin Gly206Ala mutation is a frequent cause of early-onset Alzheimer's disease in Hispanics in Florida. Am J Neurodegener Dis 2016;5(1):94-101

43 **Sun X.;** Dong C. Levin B., Crocco E., Loewenstein D., Zetterberg H., Blennow K., Wright C. APOE ε4 carriers may undergo synaptic damage conferring risk of Alzheimer's disease. Alzheimers & Dement. 2016 Jun 16

44 **Sun X** and Rundek T Does Increased Arterial Stiffness Herald Cognitive Impairment? Stroke. 2016 Sep;47(9):2171-2.

45 David A. Loewenstein, Rosie E. Curiel,, Clinton Wright, **Xiaoyan Sun**, Noam Alperin, Elzabeth Crocco, Sara J Czaja, Arlene Raffo, Ailyn Penate, Jose Melo, Kimberly Capp, and Ranjan Duara, Recovery from Proactive Semantic Interference in MCI and Normal Aging: Relationship to Atrophy in Brain Regions Vulnerable to Alzheimer's disease. 2016 in submission

46 Alison Headley, Andres De Leon-Benedetti, Chuanhui Dong, Bonnie Levin, David Loewenstein, Christian Camargo, Tatjana Rundek, Henrik Zetterberg, Kaj Blennow, Clinton B. Wright, **Xiaoyan Sun**, and the Alzheimer's Disease Neuroimaging Initiative.

CASE REPORTS, REVIEWS, CHAPTERS AND EDITORIALS

Proceedings of Meetings

1 Yamaguchi H., Yamazaki T., Ishiguro K., Sakai Y., **Sun X.**, Ebara K. Ultrastructural localization of amyloid beta protein precursor with Kunitz-type protease inhibitor domain in the human brain. Ann. Rep. Coll. Med. Care Technol. Gunma Univ. 1994;14:175-180

2 Tanaka M. Kondo S., **Sun X.**, Hirai S. Cerebral blood flow and oxygen metabolism in patients with Parkinsonism. Research Reports on Dementia (Ministry of Health and Welfare of Japan) 1994; pp.234-237

3 Tashiro T., **Sun X.**, Komiya Y. Microtubule-binding tau protein in the axon Neurochemistry 1994; 33: 494-495

4 Tashiro T., **Sun X.**, Komiya Y.. Biochemical characterization and axonal transport of microtubule-associated protein tau in the peripheral nerve J. Neurochem. 1995; 65: S216

5 Takashima A., Murayama O., Honda T, **Sun X.** Mechanism of neuron death in Alzheimer's disease Neuroscientific Basis of Dementia 1999; pp 201-207

6 **Sun X.,** Sato S., Murayama O., Takashima A. Presenilin 1 directly regulates the alpha-pathway of amyloid precursor protein processing in CHO cells and PS1 knock-out fibroblasts Neurobio of Aging 23 (19):829 Supp. 1 Jul-Aug 2002

Editorials and Critical Reviews

1 Planel E., **Sun X.**, Takashima A. Role of GSK-3beta in Alzheimer's disease pathology. Drug Development Reseach 56:491-510 2002

Book Chapters:

1 **Sun X.** and Takashima A. Regulation of amyloid by lithium. In Amyloid precursor protein: A practical approach 2005; pp. 145-154.

Case Reports:

1 **Sun X.**, Tanaka M., Morita M., Hirai S., T. Shibasaki. A giant aneurysm of the internal carotid artery delineated by positron emission tomography Neurological Medicine 1991, 35:225-226

2 **Sun X**., Cianfonia A., Nozaki K., Nolte J., Wagner MT. and David L. Pritchard P., Bachman A case report of Creutzfldt-Jakob disease presenting with severe peripheral polyneuropathy Research Day in Neuroscience 2010

Research grant and clinical trials

Current projects:

Research and clinical grant:

Novel Detection of Early Cognitive and Functional Impairment in the Elderly
PI: Dr. David Lowenstein; 2015-present
Role: investigator

Florida Memory disorder clinic
PI: Dr. Elizabeth Crocco
Co-director

Clinical trials:

1. Toyama Trial Role: Sub-investigator
2. Biogen 221AD301/221AD302 Study(s) Role: Sub-investigator
3. Eli Lilly 18D-MC-AZET Role: Sub-investigator

Past projects:

1. Boston University Alzheimer's Disease Center Pilot grant Dr. Neil Kowall (PI), Xiaoyan Sun (Investigator) 2012-2013
   Hippocampal and white matter abnormalities in older veterans with post-traumatic stress disorder or dementia: a pilot imaging study

2. Identification of novel AD genes and disease associated pathways through FPADS: a Florida Presenile Alzheimer's Disease Subjects registry
   PI: Dr. Rosa Rademakers; 2015-present

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: Wang, Jianhua

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

POSITION TITLE: Tenured Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Zhejiang Medical University, Hangzhou, Zhejiang	MD	07/1988	Medicine
University of Waterloo, Waterloo, ON	MS	06/2000	Vision Science
University of Waterloo, Waterloo, ON	PHD	07/2003	Vision Science

A. Personal Statement

I have a broad background in vision research and electronic engineering, especially on advanced ophthalmic imaging and human studies. As an assistant professor at the University of Rochester, I have learnt optics and prototyped time domain optical coherence tomography devices through the join work with OCT experts. After I moved to Miami, I have been working with other researchers to develop many other prototypes of spectral domain OCT devices. They are ultra-high resolution OCT, ultra-long scan depth OCT, dual-channel OCT, magnetomotive OCT and CMOS camera based ultra-high speed OCT. In recent 5 years, I have worked on vascular imaging of the eye and developed the methods and hardware to image microvasculature on the conjunctiva and retina. Working with a group of clinicians, I focus on microvasculature in the retina as a window of the cerebral vasculature in multiple sclerosis and dementia. As the PI or co-Investigator on many previous industrial- and NIH-funded grants, I worked out the proposed research and published more than 100 papers in top journals. Currently, I am the co-director of scientific experimental imaging laboratory at the Bascom Palmer Eye Institute and managing my own lab. In summary, I have a good record of successful research projects in the area of ophthalmic imaging. My expertise and experience make me well equipped and qualified for working in this proposed project.

1. Jiang H, Delgado S, Tan J, Liu C, Rammohan KW, DeBuc DC, Lam BL, Feuer WJ, Wang J. Impaired retinal microcirculation in multiple sclerosis. Mult Scler. 2016 Feb 22;PubMed PMID: 26903007.
2. Jiang H, Delgado S, Liu C, Rammohan KW, DeBuc DC, Lam BL, Wang J. In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis. Ophthalmology. 2016 Feb;123(2):437-8. PubMed PMID: 26299696; PubMed Central PMCID: PMC4724448.
3. Jiang H, Zhong J, DeBuc DC, Tao A, Xu Z, Lam BL, Liu C, Wang J. Functional slit lamp biomicroscopy for imaging bulbar conjunctival microvasculature in contact lens wearers. Microvasc Res. 2014 Mar;92:62-71. PubMed PMID: 24444784; PubMed Central PMCID: PMC3960300.
4. Jiang H, Debuc DC, Rundek T, Lam BL, Wright CB, Shen M, Tao A, Wang J. Automated segmentation and fractal analysis of high-resolution non-invasive capillary perfusion maps of the human retina. Microvasc Res. 2013 Sep;89:172-5. PubMed PMID: 23806780; PubMed Central PMCID: PMC3773708.

B. Positions and Honors

Positions and Employment

1988 - 1990 Resident, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou
1991 - 1995 Ophthalmologist, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou
1996 - 1999 Professional Affairs Manager, Johnson & Johnson Vision Products, China, Shanghai
2001 - 2001 Research Associate, University of Waterloo, Waterloo, ON

2003 - 2006	Research Assistant Professor, University of Rochester, Department of Ophthalmology, Rochester, NY
2006 - 2010	Assistant Professor, Bascom Plamer Eye Institute, University of Miami, Miami, FL
2008 -	Assistant Professor, Department of Electrical and Computer Engineering, University of Miami, Miami, FL
2009 -	Scientific Co-director of Experimental Imaging Laboratory, Bascom Plamer Eye Institute, University of Miami, Miami, FL
2010 - 2012	Associate Professor, Bascom Plamer Eye Institute, University of Miami, Miami, FL
2012 -	Associate Professor (Tenured), Bascom Plamer Eye Institute, University of Miami, Miami, FL

Other Experience and Professional Memberships

1999 -	Member, Association for Research in Vision and Ophthalmology (ARVO)
2001 -	Fellow, American Association of Optometry (FAAO)
2001 -	Member, American Association of Ophthalmology (AAO)
2002 -	Member, Contact Lens Association of Ophthalmologists (CLAO)
2003 -	Fellow, International Association of Contact Lens Research (IACLE)
2005 -	Member, International Society of Contact Lens Research (ISCLR)

Honors

2000	Irvin M. & Beatrice Borish Student Travel Fellowship Award, American Academy of Optometry
2001	Travel award, International Society of Contact Lens Research
2003	Best Paper in Session, American Society of Cataract & Refractive Surgery
2003	Travel award, International Society of Contact Lens Research
2004	Pearson Medal for Creative Research, University of Waterloo

C. Contribution to Science

1. Through my more than 15 years of career development, I significantly contribute the development of optical coherence tomography prototypes for clinical research, especially in the field of anterior segment imaging. Worked with OCT experts, high speed time-domain OCT was developed for imaging tear film and tear dynamics in contact lens wearers and patients with dry eye syndrome. Collaborated with clinicians and engineers, ultra-high resolution OCT devices for imaging the anterior segments were developed for imaging the tear film, epithelium and ocular tumor by conducting clinic research.

    a. Shao Y, Tao A, Jiang H, Mao X, Zhong J, Shen M, Lu F, Xu Z, Karp CL, Wang J. Age-related changes in the anterior segment biometry during accommodation. Invest Ophthalmol Vis Sci. 2015 Jun;56(6):3522-30. PubMed PMID: 26030106; PubMed Central PMCID: PMC4464043.

    b. Zhu D, Shen M, Jiang H, Li M, Wang MR, Wang Y, Ge L, Qu J, Wang J. Broadband superluminescent diode-based ultrahigh resolution optical coherence tomography for ophthalmic imaging. J Biomed Opt. 2011 Dec;16(12):126006. PubMed PMID: 22191923; PubMed Central PMCID: PMC3247935.

    c. Chen Q, Wang J, Shen M, Cui L, Cai C, Li M, Li K, Lu F. Tear menisci and ocular discomfort during daily contact lens wear in symptomatic wearers. Invest Ophthalmol Vis Sci. 2011 Apr 6;52(5):2175-80. PubMed PMID: 21051728.

    d. Palakuru JR, Wang J, Aquavella JV. Effect of blinking on tear dynamics. Invest Ophthalmol Vis Sci. 2007 Jul;48(7):3032-7. PubMed PMID: 17591869.

2. Worked with optics experts, I contributed significantly to long scan depth OCT for imaging the full eyes in studying accommodation and full eye biometry. A unique system consists of two spectral domain OCT devices equipped with wavefront sensor was developed.

    a. Du C, Shen M, Li M, Zhu D, Wang MR, Wang J. Anterior segment biometry during accommodation imaged with ultralong scan depth optical coherence tomography. Ophthalmology. 2012 Dec;119(12):2479-85. PubMed PMID: 22902211; PubMed Central PMCID: PMC3505244.

b. He JC, Wang J. Measurement of wavefront aberrations and lens deformation in the accommodated eye with optical coherence tomography-equipped wavefront system. Opt Express. 2014 Apr 21;22(8):9764-73. PubMed PMID: 24787861; PubMed Central PMCID: PMC4083049.

c. Shao Y, Tao A, Jiang H, Mao X, Zhong J, Shen M, Lu F, Xu Z, Karp CL, Wang J. Age-related changes in the anterior segment biometry during accommodation. Invest Ophthalmol Vis Sci. 2015 Jun;56(6):3522-30. PubMed PMID: 26030106; PubMed Central PMCID: PMC4464043.

3. I contribute significantly to image microvasculature on the ocular surface and retina. A system called functional slit-lamp biomicroscope (FSLB) was developed and a patent of single shot for generating conjunctival microvascular network map was filled. This novel system enables easily imaging the conjunctival microvascular network and small vessel blood flow velocity, which can be used to study microvascular response to contact lens wear and changes in dry eye.Worked with vascular experts in neuro-ophthalmology, we developed automatic segmentation of retinal microvascular network obtained using Retinal Function Imager (RFI) for studying retinal microvascular changes in multiple sclerosis, AD, diabetics and cerebral small vessel diseases. In addition, we developed ultra-high resolution OCT for imaging the retina and our segmentation software can segment 9 retinal sub-layers. Recent development of segmentation software enables automatic segmentation of 6 maps of retinal sub-layers. Furthermore, I adapted the RFI for the first time for imaging the conjunctiva by designing a optical adapter.

   a. Jiang H, Delgado S, Tan J, Liu C, Rammohan KW, DeBuc DC, Lam BL, Feuer WJ, Wang J. Impaired retinal microcirculation in multiple sclerosis. Mult Scler. 2016 Feb 22;PubMed PMID: 26903007.

   b. Xu Z, Jiang H, Tao A, Wu S, Yan W, Yuan J, Liu C, DeBuc DC, Wang J. Measurement variability of the bulbar conjunctival microvasculature in healthy subjects using functional slit lamp biomicroscopy (FSLB). Microvasc Res. 2015 Sep;101:15-9. PubMed PMID: 26092682; PubMed Central PMCID: PMC4537817.

   c. Jiang H, Zhong J, DeBuc DC, Tao A, Xu Z, Lam BL, Liu C, Wang J. Functional slit lamp biomicroscopy for imaging bulbar conjunctival microvasculature in contact lens wearers. Microvasc Res. 2014 Mar;92:62-71. PubMed PMID: 24444784; PubMed Central PMCID: PMC3960300.

   d. Jiang H, Debuc DC, Rundek T, Lam BL, Wright CB, Shen M, Tao A, Wang J. Automated segmentation and fractal analysis of high-resolution non-invasive capillary perfusion maps of the human retina. Microvasc Res. 2013 Sep;89:172-5. PubMed PMID: 23806780; PubMed Central PMCID: PMC3773708.

4. I am also the first person who applied molecular imaging in ophthalmic research by using multimodal imaging modalities. Working with biologists, I developed a strategy to use novel spectroscopic and magnetomotive OCT approaches for in vivo detecting cochlin (a protein) in glaucomatous mice. This approached significantly improve our ability to detect and quantify proteins that are predictors of susceptibility (and/or progression or efficacy of treatments) in specific local tissue prior to clinical detection. The breakthrough will be immensely helpful to control various disease states.

   a. Wang J, Wang MR, Jiang H, Shen M, Cui L, Bhattacharya SK. Detection of magnetic particles in live DBA/2J mouse eyes using magnetomotive optical coherence tomography. Eye Contact Lens. 2010 Nov;36(6):346-51. PubMed PMID: 21060257; PubMed Central PMCID: PMC3401487.

   b. Goel M, Sienkiewicz AE, Picciani R, Wang J, Lee RK, Bhattacharya SK. Cochlin, intraocular pressure regulation and mechanosensing. PLoS One. 2012;7(4):e34309. PubMed PMID: 22496787; PubMed Central PMCID: PMC3319572.

   c. Wang J, Aljohani A, Carreon T, Gregori G, Bhattacharya SK. In vivo quantification of cochlin in glaucomatous DBA/2J mice using optical coherence tomography. Sci Rep. 2015 Jun 5;5:11092. PubMed PMID: 26047051; PubMed Central PMCID: PMC4457137.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Sun 1, Sun Yat-sen University collaboration award
Wang, Jianhua (PI)

10/01/15-09/30/20
Clinical applications of advanced ophthalmic imaging
Role: PI

NMSS, National Multiple Sclerosis Society
Hong Jiang (PI)
04/01/16-03/31/19
The Role of retinal microvascular impairment on Neurodegeneration in Multiple Sclerosis
Role: Co-Investigator

JJVC, Johnson & Johnson Vision Product
Hong Jiang (PI)
12/01/14-12/31/16
Conjunctival microvascular characterization of contact lens wear
The purpose is to characterize conjunctiva microvascular in contact lens wearer
Role: Co-Investigator

UM SAC 2015-27R1 , University of Miami
Jianhua Wang (PI)
01/01/15-06/30/16
Conjunctival Microvasculature and its association with tear protein biomarkers in dry eye syndrome
The purpose is to characterize conjunctival microvasculature in dry eye
Role: PI

NANOS, North American Neuro-Ophthalmology Society
Hong Jiang (PI)
04/15/15-10/15/16
Retinal microvascular alteration as a possible biomarker in Alzheimerâ disease
The purpose of this project is to characterize the retinal microvascular dysfunction and optical properties of Retinal nerve fiber layer in AD patients.
Role: Co-Investigator

Imaging Research, Bausch & Lomb, CooperVision and Allergan
Jianhua Wang (PI)
01/01/06-12/31/20
Advanced ophthalmic imaging research
Unrestricted grants from Bausch & Lomb, CooperVision and Allergan for developing advanced ophthalmology imaging lab and clinical research.
Role: PI

Completed Research Support

R21 EY021012-01
WANG, JIANHUA (PI)
08/05/10-07/31/12
Magnetomotive optical coherence tomography for molecular imaging of the eye
The purpose of this project is to develop magnetomotive OCT for molecular imaging of the eye.
Role: PI

R03 EY016420-02
WANG, JIANHUA (PI)
09/30/05-08/31/08
Characterization of Tear Dynamics
The purpose of this project is to characterize human tear dynamics using custom built optical coherence tomography
Role: PI

Allergan UM Contract, Allergan
Jianhua Wang (PI)
07/25/11-12/31/15
Tear dynamics after Restasis treatment in dry eye patients
This project is a clinical trial for further studying tear dynamics after treatment with Restasis in dry eye patients.
Role: PI

R21EY021336-01A1, National Eye Institute (NEI)
He, Jichang (PI)
12/01/11-12/01/14
Optical coherence tomography equipped wavefront system for studying accommodation
The purpose of this project is to develop optical coherence tomography equipped wavefront system for studying accommodation
Role: Co-Investigator

1R21 EY019742-01A2, National Eye Institute (NEI)
Wang, Michael (PI)
08/01/10-07/31/12
Optical reflectometry for tear film measurement
The purpose of this project is to develop a novel method called optical reflectometry for measuring human tear film in a nanometer scale.
Role: Co-Investigator

R03 EY016420-03
WANG, JIANHUA (PI)
09/30/05-08/31/08
Characterization of Tear Dynamics
Role: PI

R03 EY016420-01
WANG, JIANHUA (PI)
09/30/05-06/30/06
Characterization of Tear Dynamics
Role: PI

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: Juan I. Young

eRA COMMONS USER NAME (credential, e.g., agency login): JIYOUNG1

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
School of Exact and Natural Sciences, University of Buenos Aires, Argentina	M.Sc.	11/1992	Biological Science
University of Buenos Aires, Argentina	Ph.D.	08/1998	Molecular genetics

A. Personal Statement

I have over 15 years of experience in molecular biology, biochemistry and mouse genetics. I have a long standing interest in epigenetic mechanisms of gene regulation in general and in understanding the role of DNA methylation in particular. My work includes the determination of DNA methylation dynamics in an *in vitro* model of cellular aging, functional studies of the epigenetic regulators methyl-CpG binding protein 2 (MeCP2, mutated in Rett Syndrome), and methyl-CpG binding domain protein 5 (MBD5, mutated in 2q23.1 deletion syndrome). Recently we have embarked in the identification of brain DNA methylation patterns induced by exposure to drugs of abuse (methamphetamine). I have been involved with the Parkinson Udall Center at the Miller School of Medicine, University of Miami (UM) for the last two years as a project co-PI to study epigenetics of Parkinson Disease.
Thus, our laboratory has extensive experience in the investigation of epigenetic mechanisms underlying physiological and pathological processes. The lab has been performing mouse work, as well as *in vitro* and *ex vivo* experimental work for a number of years and is currently very well versed in mouse genetics, phenotyping and epigenetic methodologies.

B. Positions and Honors

Positions and Employment

1993-1995 Junior Research Fellowship, National Council of Scientific and Technological Research (CONICET-Argentina)
1995-1997 Senior Research fellowship, National Council of Scientific and Technological Research (CONICET-Argentina)
1997 Visiting Student, Oregon Health Science University, Vollum Institute for Advanced Biomedical Research (OHSU-VIABR)
1998-2001 Postdoctoral Associate, Baylor College of Medicine, Houston, Texas
2001-2004 Postdoctoral Associate, Baylor College of Medicine, Houston, Texas
2005-2009 Assistant Professor, Centro de Estudios Científicos-CECS, Valdivia, Chile
2009 Assistant Professor, Dr. John T. Macdonald Foundation Department of Human Genetics, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida
2010 Director, Division for Epigenetics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida
2013 Co-Director, Center for Human Molecular Genetics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida

2015 Associate Professor (tenure track), Dr. John T. Macdonald Foundation Department of Human Genetics, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida

Other Experience and Professional Memberships

2009 American Society of Human Genetics, Member

Honors

1991 Research Grant for Advanced Students-University of Buenos Aires
1997 Bernardo A. Houssay Award-Argentina
2002 Rett Syndrome Research Foundation (RSRF)- Research Award-USA
2002 Alan P. Wolffe Memorial Fellowship (RSRF)-USA
2004 Extension of the RSRF Research Award-USA
2005 Proyecto Fondecyt Regular-Chile # 1051079
2006 RSRF Research Award-USA

C. Contribution to Science

Tissue specific genome activity

My research career was initiated by studying the genomic elements that command the neuronal expression of the *Pomc* gene. This gene encodes for a precursor protein that produces many biologically active peptides including the melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH) and β-endorphin. In the brain, *Pomc* expression is restricted to a subset of neurons in the hypothalamus and the brainstem. In order to identify the genomic elements necessary for the brain-specific expression of *Pomc*, we resorted to the use of transgenic mice. This work led to the identification of two distal neuron-specific enhancers that spurred several investigations into the evolution of cis-acting DNA regulatory elements and to my realization of the exquisite complexity of gene expression control mechanisms.

-**Young JI**, Otero V., Cerdan M.G., Falzone T.L., Chan E.C., Low M.J., Rubinstein M. Authentic cell-specific and developmentally regulated expression of pro-opiomelanocortin genomic fragments in hypothalamic and hindbrain neurons of transgenic mice. J. Neurosci. Sept 1; **18**: 6631-40, 1998. PMID: 9712635.
-Cerdan M.G., **Young JI**, Zino E., Falzone T.L., Otero V., Torres H.N., Rubinstein M. Accurate spatial and temporal transgene expression driven by a 3.8-kilobase promoter of the bovine beta-casein gene in the lactating mouse mammary gland. Mol. Reprod. Dev. Mar; **49**: 236-45, 1998. PMID: 9491375

Aging as a modulator of genome activity

Although the study of genomic elements directing gene expression is particularly informative for the identification of mechanisms controlling genome activity, an equally important area of study is the dynamics of these control mechanisms. I am particularly interested in delineating plastic changes in genome activity, due to either stochastic defects or a regulated developmental process. Perhaps one of the best examples of accumulation of cellular changes in the context of an inflexible genome is seen in cells aging in culture. Using cultured human primary cells, we found that the interplay between the enzymes telomerase and DNA methyltransferase results in age-related changes in the epigenome that ultimately control gene transcription including expression of senescence-inducing cell cycle inhibitors. These findings greatly contributed to the current "epigenetic hypothesis of cellular aging".

-**Young JI**, Sedivy J.M. and Smith J.R. Telomerase expression in normal human fibroblasts stabilizes DNA 5-methylcytosine transferase I. J. Biol. Chem. May 30;**278**:19904-8, 2003. PMID: 12665523
-**Young JI** and Smith J.R. DNA methyltransferase inhibition in normal human fibroblasts induces a p21-dependent cell cycle withdrawal. J. Biol. Chem. Jun 1; **276**: 19610-6, 2001. PMID: 11259405
-**Young JI** and Smith J.R. Epigenetic aspects of cellular senescence. Exp. Gerontol. Feb; **35**: 23-32, 2000.

Genetic alterations in the mechanisms that regulate genome activity

The idea that epigenetic processes afford the genome the plasticity to respond to developmental and environmental clues has led to one of the main focus of my research laboratory. We seek to determine the functional consequences of genetic alterations in "interpreters" of the epigenetic code, with the overarching goal of identifying processes that play a role in adaptation and disease. In particular, we focus our efforts in two purported DNA methylation "interpreters": MeCP2 and MBD5.

Mutations in MeCP2 cause Rett Syndrome, characterized by loss of motor and communication abilities. By using mouse models we discovered that MeCP2, a protein that binds DNA, preferentially when it is methylated, is a splicing regulator, linking for the first time splicing and epigenetic regulation. In addition, we found that environmental manipulations could alter the course of the disease and that transgenic expression of MeCP2 results in prevention of development of RTT-like phenotypic manifestations in a mouse model lacking *Mecp2,* supporting the possibility of gene therapy in Rett syndrome cases. For this reason, a major goal of my laboratory is to determine whether gene restoration is a putative therapeutic avenue for Rett patients that are not represented by the mouse model lacking *Mecp2* (null model), but are better modeled by mice carrying coding point mutations in this gene. To achieve this goal we are performing "rescuing" experiments in mouse and cellular models carrying mutated, but non-null versions of MeCP2.

-Kerr B, Soto J, Saez M, Abrams A, Walz K, **Young JI**. Transgenic complementation of MeCP2 deficiency: phenotypic rescue of Mecp2-null mice by isoform-specific transgenes. Eur J Hum Genet. 2012 Jan;20(1):69-76. PMCID: PMC3234513
-Alvarez-Saavedra M, Carrasco L, Sura-Trueba S, Demarchi Aiello V, Walz K, Xavier Neto J, **Young JI**. Elevated expression of MeCP2 in cardiac and skeletal tissues is detrimental for normal development. Hum Mol Genet. Jun 1;19(11):2177-90, 2010. PMID: 20203171
-Kerr B, Alvarez-Saavedra M, Sáez MA, Saona A and **Young JI**. Defective body weight regulation and motor control in Mecp2 hypomorphic mice. Human Molecular Genetics, Jun 15;**17**:1707-17, 2008.PMID: 18321865.
-Alvarez-Saavedra M, Sáez MA, Kang D, Zoghbi HY and **Young JI**. Cell-specific expression of wild-type MeCP2 in mouse models of Rett syndrome yields insight about pathogenesis. Human Molecular genetics, Oct 1;**16** :2315-25, 2007. PMID: 17635839
-**Young JI,** Hong E.P., Castle J.C., Crespo-Barreto J., Bowman A.B., Rose M.F., Kang D., Richman R., Johnson J.M., Berget S. and Zoghbi H.Y. Regulation of RNA splicing by the methylation-dependent transcriptional repressor methyl-CpG binding protein 2. Proc Natl Acad Sci U S A. Dec 6;**102**:17551-8, 2005. PMCID: PMC1266160
-**Young JI** and Zoghbi H.Y. X-chromosome inactivation patterns are unbalanced and affect the phenotypic outcome in a mouse model of Rett syndrome. Am. J. Hum. Genet. Mar; **74**:511-20, 2004. PMCID: PMC1182264

Patients with deletions in MBD5 (2q23.1 microdeletion syndrome) are mentally retarded with speech delay and additional abnormalities including short stature, seizures, microcephaly, stereotypic repetitive behavior and coarse facies. We have recently characterized a mouse model of the disease and have observed behavioral phenotypes that are accompanied by alterations in neuronal development. In addition, we discovered that MBD5 acts as a transcriptional activator. Our ongoing studies include the characterization of MBD5 function in neurons by biochemical approaches and the delineation of pathogenesis mechanisms of 2q23.1 microdeletion syndrome.

-Walz K, **Young JI**. The methyl binding domain containing protein MBD5 is a transcriptional regulator responsible for 2q23.1 deletion syndrome. Rare Diseases 2014, 2:1, e967151, DOI: 10.4161/2167549X.2014.967151.
-Camarena V, Cao L, Abad C, Alexander A, Toledo Y, Araki K, Araki M, Walz K, **Young JI**. Disruption of Mbd5 in mice causes neuronal functional deficits and neurobehavioral abnormalities consistent with 2q23.1 Microdeletion Syndrome. EMBO Mol Med. 2014 Jul 7;6(8):1003-15. PMID: 25001218

Environmental disruptions in the regulation of genome activity

Another important goal of my lab is to determine the consequences of exposure to environments capable of eliciting epigenetic plasticity, such as exposure to drugs of abuse, on genome activity. We are studying the effects of methamphetamine exposure not only on the epigenome of mice directly exposed to the drug, but on subsequent generations (*in utero* exposed and unexposed). Our preliminary experiments, performed in collaboration with the laboratory of Dr. Yossef Itzhak, Department of Psychiatry- UMMSM, suggest that exposure of parental mice (F0 generation) to methamphetamine resulted in aberrant behavioral phenotypes in the F1, F2 and F3 generations, that are accompanied by changes in DNA methylation in the hippocampus of the F1 progeny. In addition, through cross-fostering experiments we found that methamphetamine-induced maternal care affect behavioral phenotypes and DNA methylation of the F1 offspring. An immediate next goal is to determine whether DNA methylation changes are also transmitted to the F2 and F3 generations and to check for transcriptional correlates of the altered epigenome that could explain the phenotypic observations. We are also interested in delineating the mode of transmission of these aberrant phenopyes and "epigenotypes".

-Itzhak Y, Ergui I, **Young JI**. Long-term parental methamphetamine exposure of mice influences behavior and hippocampal DNA methylation of the offspring. Mol Psychiatry. 2014 Feb 18. 1-11 PMID: 24535458.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/juan.young.1/bibliography/47446499/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

PC140622 (Zhang F) 09/30/15- 08/31/18
Department of Defense (DoD) Idea-award grant
"An Unknown Role of Arginylation in Prostate Cancer"
The objective of this application is to test whether a down-regulation of Ate1 can be used to predict the metastasis of prostate cancer.
Role: Co-Investigator

R01 NS34773 (Perez-Pinzon) 7/1/2015 – 6/30/2020
NIH/NINDS
"Ischemic Preconditioning: Mechanisms of Neuroprotection"
The major goal of this project is to study the mechanisms by which ischemic preconditioning promotes neuroprotection.
Role: Co-Investigator

2R01DE011931 (Hecht, J; Blanton S) 12/26/12–11/30/17
NIH-NIDCR / University of Texas
"Mapping nonsyndromic cleft lip and palate genetic loci"
Nonsyndromic cleft lip with or without cleft palate (NSCLP) is a common birth defect affecting 4000 newborns in the US and 135,000 worldwide each year. The etiology is poorly understood and currently, only 20% of the NSCLP genetic liability has been identified, limiting our ability to identify at-risk individuals or provide accurate counseling for families. In these studies, we apply the newest technology to identify the genetic variation underlying NSCLP in families with multiple cases, will test the variants for expression and functionality in a fish model and develop ethnic-specific risks. The results of this study will ultimately be utilized to identify and test for potential at-risk genotypes.
Role: Co-I

2P50NS071674 (Vance JM) 09/01/11 -08/31/17
NIH/NINDS *(no-cost extension)*
"Genetics of Parkinsonism" – Morris K. Udall Parkinson's Disease Research Center of Excellence"
Project 2 "Long ncRNAs as Epigenomic Modulators and CSF Biomarkers in Parkinson's Disease"
The overall goal of the center is to identify genes that cause or contribute to an individual's susceptibility to Parkinson Disease (PD). The discovery of PD risk genes will provide insight into the biological and environmental mechanisms that cause PD.
Role: Co-PI Project 2

Completed Research Support

1R01NS081208-01A1 (Wahlestedt, CR) 04/01/13-03/31/15
NIH/NINDS
"Antisense RNA Mediated Epigenetic Regulation of Brain Derived Neurotrophic Factor"
The major goal of this research is to investigate epigenetic regulation of BDNF, both *in vitro* and *in vivo* and to study the potential beneficial effects of BDNF up-regulation on the Rett Syndrome mouse model.
Role: Co-I

1R21AI103547-01A1 (Adkins, R) 04/10/13-3/31/15

NIH
“Genetic and Epigenetic Contributions to the Neonatal Th2 Bias”
This proposal will examine the contribution of selective components of the genome to the poor immunity in newborn animals. This information will provide an important foundation for developing novel approaches to meet the health challenges of pediatric life, such as (a) enhancing vaccine responsiveness, (b) mitigating pediatric-onset asthma, and (c) increasing resistance to pathogenic microorganisms.
Role: Co-I

5 R21MH093876-02 (Young, JI) 04/01/12-11/30/14
NIH
“Modulation of Rett-Like Phenotypes in Mouse Models of Rett Syndrome”
We will use mouse and cellular models of Rett syndrome to test whether the effect of mutations that affect MeCP2’s functionality (but do not eliminate the protein) could be reversed by transgenic restoration of MeCP2.
Role: PI

Jérôme Lejeune Foundation (Walz, K) 07/01/11-09/06/14
“Exploring the reversibility of neuron functional deficiency”
The presence of microdeletions or microduplications in our genome is often related to various diseases. Our studies will uncover whether restoring the appropriate amount of key proteins can prevent or ameliorate the phenotypic consequences related to abnormal gene dosage.
Role: Co-I

Jérôme Lejeune Foundation (Young, JI) 07/01/11-09/06/14
“Modulation of Rett-like phenotypes in mouse models of Rett syndrome”
We will use mouse models of Rett syndrome to test whether the effect of a truncating mutation that affects MeCP2’s functionality could be reversed by transgenic restoration of MeCP2.
Role: PI

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: Zeki Al Hazzouri, Adina

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

POSITION TITLE: Assistant 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
American University of Beirut, Lebanon	B.S.	06/04	Biology
American University of Beirut, Faculty of Health Sciences, Lebanon	MSc	06/06	Epidemiology
University of Michigan School of Public Health, Department of Epidemiology	PhD	06/11	Epidemiology
University of California San Francisco, Department of Epidemiology and Biostatistics		10/13	Post-doctoral fellow (AHA/ASA/AAN Fellow)

A. Personal Statement

I am an epidemiologist and my primary research focus pertains to how psychosocial and cardiovascular risk factors experienced across the life-course influence cognitive function, dementia, stroke and other related health outcomes in old age, with a particular focus on minority populations. I have a 5-year career development award (K01) from the National Institute on Aging to study clinical and subclinical cardiovascular determinants of aging. My ultimate research goal is to employ life-course models to better understand how timing of risk factors (predictors) influences older age outcomes, and how modification of risk factors or their timing may reduce the burden of these outcomes and associated disparities.

Examples of publications that relate to the McKnight mission:

a. **Zeki Al Hazzouri A**, Haan MN, Kalbfleisch J, Galea S, Lisabeth L, Aiello A. Life course socioeconomic position and incidence of dementia and cognitive impairment without dementia in older Mexican Americans: Results from the Sacramento Area Latino Study on Aging. Am J Epidemiol 2011; 173(10):1148-58. PMC3121319.

b. **Zeki Al Hazzouri** A, Elfassy T, Sidney S, Jacobs D, Pérez Stable EJ, Yaffe K. Sustained Economic Hardship and Cognitive Function: The Coronary Artery Risk Development in Young Adults Study. American Journal of Preventive Medicine. 2016 [Epub ahead of print]. PMID 27692543.

c. **Zeki Al Hazzouri A**, Mayeda ER, Elfassy T, Lee A, Odden MC, Thekkethala D, Wright CB, Glymour MM, Haan MN. Perceived Walking Speed, Measured Tandem Walk, Incident Stroke and Mortality in Older Latino Adults: A Prospective Cohort Study. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2016 [Epub ahead of print]. PMID 27549992.

d. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S, **Zeki Al Hazzouri A**. The Impact of Hypertension on Cognitive Function. American Heart Association Scientific Statement. A Scientific Statement for Health Care Professionals from the American Heart Association/American Stroke Association. Hypertension, 2016. *Forthcoming.*

B. Positions and Honors

Positions and Employment

11/2013 – 9/2014	Assistant Professor of Epidemiology, Department of Epidemiology and Biostatistics, University of California San Francisco.
9/2014 – Present	Assistant Professor of Epidemiology, Department of Public Health Sciences, University of Miami.

Honors

2009	Student Dissertation Workshop Award on Epidemiological Methods. 42nd Annual Society for Epidemiologic Research (SER) meeting, June 23, 2009 Anaheim, CA.
2010 – 2011	The Barbour Scholarship for women from the 'Orient' region and who are of high academic and professional caliber. Rackham Graduate School. University of Michigan.
2010	The Harburg Student Award for Excellence in Social Epidemiology. Center for Social Epidemiology and Population Health, School of Public Health. University of Michigan.
2011	RAND Summer Institute award to attend the Mini-Med workshop and the workshop on Aging. RAND Institute, Santa Monica, CA.
2012	Award for "Excellence in Research on Alzheimer's and Related Disorders" from the Alzheimers' Association in Northern California and Northern Nevada.
2012	American Heart Association/American Stroke Association/ American Brain Foundation (AHA/ASA/ABF) Lawrence M. Brass, M.D. Stroke Research Postdoctoral Fellowship.
2017/2018	Elected Co-chairs (Adina Zeki Al Hazzouri/Eileen Crimmins) for the Epidemiology of Aging Interest Group (EAIG) of the Gerontological Society of America.

C. Contributions to Science

1. Early Life and cumulative Social and Psychosocial Determinants of Cognitive Aging and Dementia

Dr. Zeki Al Hazzouri's dissertation research challenged the life-course framework of cognitive aging and dementia in minority populations. Using data from the Sacramento Area Latino Study on Aging, she was among the first to examine life-course socioeconomic determinants of cognitive aging and dementia in Latinos. She evaluated the role of a childhood socioeconomic construct, determined by variables such as sibling mortality and parental education and occupation, along with adult and late-life socioeconomic constructs on cognitive function and dementia incidence. She also evaluated how socioeconomic mobility across the life course (upward or downward mobility) shaped these older age outcomes. Her findings suggested that greater cumulative socioeconomic disadvantage and all-time low or downward socioeconomic mobility were associated with faster cognitive decline and greater dementia incidence, compared with more advantageous life-course socioeconomic trajectories. She also investigated the influence of the neighborhood's social context on trajectories of cognitive decline and the role of individual-level socioeconomic factors in mediating these contextual effects. For her work in this area of research, she received the Harburg Award by the University of Michigan School of Public Health as recognition for outstanding study of psychosocial and biological correlates of health. More recently, she examined how cumulative depressive symptoms over 20 years influenced cognition and dementia risk in very old white women. In her work she continues to focus on long-term and cumulative psychosocial and socioeconomic burden. For example, she has recently examined how cumulative exposure to economic hardship over 25 years, as determined by the federal poverty level, is associated with cognitive function in young and middle-aged adults of the CARDIA (Coronary Artery Risk Development in Young Adults) study. These findings have been recently published in the American Journal of Preventive Medicine. Dr. Zeki Al Hazzouri conducts this work with the goal of better understanding how social and psychosocial exposures from across the life-course influence cognitive health of minority and vulnerable populations.

a. **Zeki Al Hazzouri A**, Haan MN, Kalbfleisch J, Galea S, Lisabeth L, Aiello A. Life course socioeconomic position and incidence of dementia and cognitive impairment without dementia in older Mexican Americans: Results from the Sacramento Area Latino Study on Aging. Am J Epidemiol 2011; 173(10):1148-58. PMC3121319.

b. Haan MN, **Zeki Al Hazzouri A**, Aiello AE. Life course socioeconomic trajectory, nativity and cognitive aging in Mexican Americans: the Sacramento Area Latino Study on Aging. J Gerontol B Psychol Sci Soc Sci 2011; 66 Suppl 1: i102-i110. PMC3132761.

c. **Zeki Al Hazzouri A**, Vittinghoff E, Byers AL, Covinsky K, Blazer D, Diem S, Ensrud K, Yaffe K. Long term depressive symptom burden and risk of cognitive decline and dementia among very old women. The Journals of Gerontology, Series A, Biological Sciences and Medical Sciences, 69(5):595-601, 2014. PMC3991142.

d. **Zeki Al Hazzouri** A, Elfassy T, Sidney S, Jacobs D, Pérez Stable EJ, Yaffe K. Sustained Economic Hardship and Cognitive Function: The Coronary Artery Risk Development in Young Adults Study. American Journal of Preventive Medicine. 2016 [Epub ahead of print]. PMID 27692543.

2. Determinants of cardiovascular Disease And Risk Factors, Nativity, and Acculturation

Because of the cultural characteristics of the Latino population and the modifiable nature of cardiovascular disease risk factors, Dr. Zeki Al Hazzouri has been interested in how nativity and acculturation, among other determinants, shape cardiovascular health and consequently cognitive aging. She has led or contributed to research evaluating the association of intergenerational education and acculturation on metabolic syndrome and cardiovascular disease risk factors in Latinos. In addition, using data from the Sacramento Area Latino Study on Aging, she created a cardiovascular risk score that predicted the 10-year risk of cardiovascular disease in Mexican Americans, and evaluated its association with dementia incidence. Her findings suggested that higher 10-year cardiovascular risk score was associated with higher dementia risk, only in individuals with low education level, a marker of low cognitive reserve. Dr. Zeki Al Hazzouri is also leading work on determinants of stroke outcomes in minority populations. For example, she has recently examined whether measures of walking speed are associated with risk of stroke among Mexican Americans, independent of cognitive and physical functions. These findings have been recently published in the Journals of Gerontology: Medical Sciences.

a. Peralta CA, Lee A, Odden M, Lopez L, **Zeki Al Hazzouri A**, Neuhaus J, Haan MN. Association between chronic kidney disease detected using creatinine and cystatin C and death and cardiovascular events in elderly Mexican Americans: the Sacramento Area Latino Study on Aging. J Am Geriatr Soc 2013; 61(1):90-95. PMC3545054.

b. **Zeki Al Hazzouri A,** Haan MN, Neuhaus JM, Pletcher M, Peralta CA, Lopez L, Perez Stable EJ. Cardiovascular risk score, cognitive decline, and dementia in older Mexican Americans: The role of sex and education. J Am Heart Assoc 2013; 2(2). PMC3647277.

c. **Zeki Al Hazzouri A**, Haan MN, Robinson W, Gordon-Larsen P, Clayton E, Aiello A. Associations of intergenerational education with waist circumference, metabolic syndrome, and type-2 diabetes in US Latinos. Obesity, 23(5): 1097-1104, 2015. PMC4414717.

d. **Zeki Al Hazzouri A**, Mayeda ER, Elfassy T, Lee A, Odden MC, Thekkethala D, Wright CB, Glymour MM, Haan MN. Perceived Walking Speed, Measured Tandem Walk, Incident Stroke and Mortality in Older Latino Adults: A Prospective Cohort Study. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2016 [Epub ahead of print]. PMID 27549992.

3. Subclinical and Clinical Cardiovascular Risk Factors of Cognitive Function and Dementia

Dr. Zeki Al Hazzouri leads ongoing work on how subclinical and clinical cardiovascular risk factors contribute to cognitive aging, Alzheimer disease and other dementias. She has led research, jointly funded by the American Heart Association, American Stroke Association and American Brain Foundation, evaluating the associations of biological biomarkers and subclinical cardiovascular disease with cognitive aging in diverse populations. For example, she showed that obesity and leptin, a biomarker of body fat, interacted in their influence on cognitive decline and development of dementia in older adult Hispanics and non-Hispanic whites – and for this work she was granted an award for “Excellence in Research on Alzheimer’s and Related Disorders” from the Bay Area Alzheimers’ Association. Furthermore, she showed that pulse wave velocity and heart rate variability were associated with measures of cognitive function. Recently, using data from the Coronary Artery Risk Development in Young Adults Study, she showed that intima-media thickness, a measure of subclinical vascular disease, was strongly associated with worse cognitive performance at a mean age of 50 years old. In addition, Dr. Zeki Al Hazzouri has recently contributed, as a member of the writing group, to the American Heart Association/American Stroke Association scientific statement on the impact of hypertension on cognitive function (*In Press*). As part of

her K01 Award from the National Institute on Aging, Dr. Zeki Al Hazzouri continues to examine subclinical and clinical cardiovascular risk factors in relation to older age outcomes.

a. **Zeki Al Hazzouri A**, Newman AB, Simonsick E, Sink KM, Tyrrell KS, Watson N, Satterfield S, Harris T, Yaffe K, for the Health ABC study. Pulse Wave Velocity and Cognitive Decline in Elders: The Health, Aging, and Body Composition Study. Stroke 2013; 44(2):388-93. PMC3572783.
b. **Zeki Al Hazzouri A**, Haan MN, Deng Y, Yaffe K. Reduced heart rate variability is associated with worse cognitive performance in elderly Mexican Americans. Hypertension 2014; 63(1):181-7. PMC4045649.
c. **Zeki Al Hazzouri A**, Vittinghoff E, Sidney S, Reis J, Jacobs D, Yaffe K. Intima-Media Thickness and Cognitive Function in Stroke-Free Middle-Aged Adults: Findings From The Coronary Artery Risk Development in Young Adults Study. Stroke, 46(8): 2190-2196, 2015. PMC4519386.
d. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S, **Zeki Al Hazzouri A**. The Impact of Hypertension on Cognitive Function. American Heart Association Scientific Statement. A Scientific Statement for Health Care Professionals from the American Heart Association/American Stroke Association. Hypertension, 2016. *Forthcoming.*

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1-OQdGSK0wU5Q/bibliograpahy/46032250/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

K01AG047273 Zeki Al Hazzouri (PI) 04/14 – 03/19
NIH/NIA
Lifecourse cardiovascular risk, depression and cognition in black & white adults.
The goal of this study is to address the associations between cardiovascular risk factors and outcomes of cognitive function and depressive symptoms. This project will conduct separate analyses in a cohort of young adults and another of older adults.
Role: PI.

Completed Research Support

University of California San Francisco 09/13 – 06/14
Center for Aging in Diverse Communities- Pilot Grant
Race/ethnicity, life course socioeconomic factors, and cognitive performance among non-Hispanic white and African American young to middle-aged adults: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study.
The goal of this grant was to examine the role of life course socioeconomic factors on cognitive performance among black and white middle-aged adults.
Role: PI.

University of California San Francisco 8 KL2 TR000143-08 10/13 – 04/14
(Johnston)
NCATS
Clinical and Translational Science Institute (CTSI)
Effects of race and lifecourse cardiovascular risk on neuropsychiatric outcomes.
The goal of the CTSI KL2 career development award is to increase the number and quality of clinical and translational investigators skilled at leading multidisciplinary research teams. My role was as a KL2 Scholar, for which I receive salary support for 9 calendar months, plus research funds. The goal of my project was to evaluate the associations of cardiovascular risk factors with the risk of neuropsychiatric outcomes.
Role: KL2 scholar.

Lawrence M. Brass, MD Stroke Research Fellowship 01/12 – 10/13

American Heart Association, American Stroke Association, and American Brain Foundation
Cardiovascular risk factors for stroke and consequences of stroke among three racial/ethnic groups.
The goal of this Postdoctoral research fellowship grant was to examine subclinical measures of disease and risk factors for stroke (such as arterial stiffness and heart rate variability) in relation to cognitive function among three racial/ethnic older adult populations: Mexican Americans, African Americans and Non-Hispanic Whites.
Role: PI.

University of California San Francisco 10/11– 06/13
Center for Aging in Diverse Communities- Pilot Grant
Socioeconomic factors, metabolic and inflammatory biomarkers in relation to cognitive status in older Mexican Americans.
The goal of this grant was to examine the interplay between socioeconomic factors, inflammatory and metabolic biomarkers in predicting cognitive outcomes among older adult U.S. Hispanics.
Role: PI.

University of California San Francisco Department of 01/12 – 12/12
Psychiatry- Pilot Grant
Arterial stiffness and depressive symptoms among white and black older adults.
The goal of this grant was to examine whether arterial stiffness was associated with change in depressive symptoms and whether this association was different for whites and blacks.
Role: PI.

Pending Research Support
NIH/NIA R01 (Yaffe/ Zeki AL Hazzouri) 09/2016 – 08/2020
University of California San Francisco/ University of Miami
Healthy Heart, Healthy Brain? A Pooled Life-course Cohort for Dementia Risk Assessment
The goal of this study is to investigate cardiovascular risk factors over the life-course and their association with dementia risk.
Role: Multiple PI.

NIH/NIA R01 (Zeki Al Hazzouri/ Glymour) 04/2017 – 03/2021
University of Miami/ University of California San Francisco
A Binational Study to Understand Dementia Risk and Disparities of Mexican Americans: The Role of Migration and Social Determinants.
The goal of this study is to create a binational study of two nationally representative cohorts from the US and Mexico to study how migration influences dementia risk of Mexican Americans and factors that increase or reduce dementia risk in Mexican Americans.
Role: Multiple PI.

NIH/NIA R01 (Yaffe/ Zeki AL Hazzouri) 07/2017 – 06/2021
University of California San Francisco/ University of Miami
Association Between Depression and Risk of Alzheimer's Disease Across the Lifespan: A Pooled Cohort Approach.
The goal of this study is to investigate the relationship between depression, cognitive decline and dementia risk over the life-course.
Role: Multiple PI.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Clinton Wright	Scientific Director, Evelyn F. McKnight Brain Institute Associate Professor of Neurology, Neuroscience, Public Health Sciences
eRA COMMONS USER NAME (credential, e.g., agency login) WRIGHTCL	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
George Washington University; Washington DC	B.A.	09/90	Psychology
Columbia University College of P&S; New York, NY	M.D.	05/97	Medicine
Columbia University, Mailman School of PH; New York, NY	M.S.	05/03	Epidemiology

A. Personal Statement

My research has focused on vascular disease and its relationship to age-related memory loss and cognitive disorders and the aging brain. I am a board certified vascular neurologist and a dementia specialist, and have been Scientific Director of the McKnight Brain Institute and Chief of the Division of Cognitive Disorders in the Department of Neurology at the University of Miami since 2008. In my role as Scientific Director of the UM MBI, my goal is to create the best infrastructure possible to allow intra- and extra-mural collaboration on science that advances the mission of the Institute. I am also dedicated to creating an ideal mentoring environment to allow trainees at all levels to grow into independent investigators. My approach to vascular cognitive impairment is summarized in the following papers.

1. DeCarli C, Kawas C, Morrison JH, Reuter-Lorenz PA, Sperling RA, **Wright CB**. Session II: Mechanisms of age-related cognitive change and targets for intervention: neural circuits, networks, and plasticity. J Gerontol A Biol Sci Med Sci. 2012 Jun;67:747-53. PMCID: PMC3732094.

2. Gardener H, **Wright CB**, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. Nat Rev Neurol. 2015. PMCID: PMC26481296.

B. Positions and Honors

1997-1998	Intern, Internal Medicine.
1998-2001	Resident, Neurology, New York Presbyterian Hospital; New York, NY
2001-2003	Stroke Fellowship, Columbia University College of Physicians and Surgeons, New York, NY
2001-2003	Neuroepidemiology Fellowship, Columbia University College of Physicians and Surgeons, New York, NY
2001-2003	Neuroepidemiology NIH Training Grant (T32) awardee
2001-2008	Assistant Attending in Neurology, New York Presbyterian Hospital, New York, NY
2003-2008	Assistant Professor of Neurology, Columbia University, New York, NY
2008-present	Adjunct Associate Professor, Department of Neurology, Columbia University, New York, NY

2008-present	Associate Professor of Neurology, Neuroscience, and Epidemiology & Public Health, University of Miami, Miami, FL
2008-present	Scientific Director, Evelyn F. McKnight Brain Institute
2008-present	Chief, Division of Cognitive Disorders, Department of Neurology, University of Miami School of Medicine
2012	Chairman's Award for Teaching Excellence, Department of Neurology, University of Miami School of Medicine
2012-present	Member, Center On Aging, Department of Psychiatry & Behavioral Sciences, University of Miami School of Medicine

C. Contribution to Science

Much of my work has focused on the epidemiology and correlates of subclinical cerebrovascular damage. As a co-investigator in the population-based Northern Manhattan Study, I have been responsible for the MRI subcommittee overseeing the conduct of an imaging substudy in which 1290 clinically stroke-free participants underwent imaging. I have described the prevalence of MRI-defined infarcts, white matter hyperintensities, and other markers of subclinical cerebrovascular disease and have identified links with some of their key risk factors, with an emphasis on novel and potentially modifiable factors as well as inflammation.

1. **Wright CB**, Rundek T, Paik MC, Elkind MSV, Sacco RL. Alcohol intake, carotid plaque, and cognition. Stroke 2006;37:1160-1164. PMCID: PMC1447604
2. **Wright CB**, Moon Y, Paik MC, Brown TR, Rabbani L, Yoshita M, DeCarli C, Sacco R, Elkind MS. Inflammatory biomarkers of vascular risk as correlates of leukoariosis. Stroke. 2009;40:3466-71. PMID: 20531432, PMCID: PMCID: PMC3114944
3. Marcus J, Gardener H, Rundek T, Elkind MSV, Sacco RL, DeCarli C, **Wright CB**. Baseline and longitudinal increases in diastolic blood pressure are associated with greater white matter hyperintensity volume: the Northern Manhattan Study. Stroke 2011;42: 2639-41. PMCID: PMC3189513
4. Willey JZ, Gardener H, Moon YP, Yoshita M, DeCarli C, Cheung YK, Sacco RL, Elkind MS, **Wright CB**. Lipid profile components and subclinical cerebrovascular disease in the northern Manhattan study. Cerebrovasc Dis. 2014;37:423-30. doi: 10.1159/000362920. PMCID: PMC4142052.

5. The links between vascular risk factors, subclinical cerebrovascular damage, and cognition have also been a major focus of my research. I have established connections of silent stroke and white matter lesions with global cognition as well as domain-specific associations, including those with psychomotor speed, executive function, and memory. I am particularly interested in the effects of vascular damage on cognitive phenotypes in relation to age-related processes and Alzheimer disease.

6. **Wright CB**, Festa J, Paik MC, Schmiedigen AP, Brown TR, Yoshita M, DeCarli C, Sacco RL, Stern Y. White Matter Hyperintensities and Subclinical Infarction: Associations with Psychomotor Speed and Cognitive Flexibility. Stroke 2008;39:800-805. PMCID: PMC2267752
7. Khatri M, Nickolas T, Moon Y, Paik MC, Rundek T, Elkind MSV, Sacco RL, **Wright CB**. Chronic Kidney Disease (CKD) associates with Cognitive Decline. *Journal of the American Society of Nephrology* 2009; 20: 2427-2432.PMCID: PMC2799177

8. Siedlecki KL, Stern Y, Reuben A, Sacco RL, Elkind MSV, **Wright CB**. Construct Validity of Cognitive Reserve in a Multi-Ethnic Cohort: the Northern Manhattan Study. Journal of the International Neuropsychological Society 2009;15:558-69. PMCID: PMC2803322
9. Siedlecki K, Rundek T, Elkind MSV, Sacco RL, Stern Y, **Wright CB**. Using contextual analyses to examine the meaning of neuropsychological variables across samples of English-speaking and Spanish-speaking older adults. J Int Neuropsychol Soc. 2012 Mar;18:223-33. PMCID: PMC3370823
10. Vieira JR, Elkind MSV, Moon YP, Rundek T, Boden-Albala B, Paik MC, Sacco RL, **Wright CB.** The Metabolic Syndrome and Cognitive Performance: The Northern Manhattan Study. Neuroepidemiology 2011;37:153-9. PMCID: PMC3214939
11. Katan M, Moon YP, Paik MC, Sacco RL, **Wright CB**, Elkind MS. Infectious burden and cognitive function: The Northern Manhattan Study. Neurology. 2013 Mar 26;80:1209-15. PMCID: PMC3691781
12. Willey JZ, Park Moon Y, Ruder R, Cheung YK, Sacco RL, Elkind MS, **Wright CB**. Physical Activity and Cognition in the Northern Manhattan Study. Neuroepidemiology. 2013; 42:100-106. PMCID: PMC3942085
13. Reitz C, Mayeux R; **Wright CB**. TREM2 and neurodegenerative disease. Alzheimer's Disease Genetics Consortium. N Engl J Med. 2013 Oct 17; 369(16):1564-5.
14. Economos A, **Wright CB** (corresponding), Moon YP, Rundek T, Rabbani L, Paik MC, Sacco RL, Elkind MS. Interleukin 6 plasma concentration associates with cognitive decline: the northern Manhattan study. Neuroepidemiology. 2013;40:253-9. PMCID: PMC3725587

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1zYPdoOWM7D5s/bibliograpahy/48085663/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1 R01 HL108623 **Wright (PI)** 3/16/2012-2/29/2016
NIH/ NHLBI
FGF-23 and the Risk of Stroke and Cognitive Decline
Elevated fibroblast growth factor 23 and serum phosphate are novel risk factors for cerebrovascular disease and cognitive decline. This study takes advantage of an ongoing population-based cohort study that includes Hispanic, black, and white people living in the same community, to examine elevated serum FGF23 and phosphate and the risk for stroke, subclinical small and large vessel injury, and cognitive decline. Elevated serum phosphate is modifiable and the results of this study have therapeutic potential that can be tested in randomized clinical trials.

HHSN268200900048C 9/14/2009-10/2/2018
Wake Forest University (subcontract)/NHLBI
Systolic Blood Pressure Intervention Trial (SPRINT) – MRI Substudy
The purpose of this grant is to examine the effects of tight blood pressure control on brain morphology and relate these findings to cognitive outcomes in the MIND component of the SPRINT trial.

R37 NS029993 **Sacco (PI)** 01/07/1993 - 03/31/15

NIH/NINDS: Subcontract to Columbia University
Stroke Incidence and Risk Factors in a Tri- Ethnic Region
This prospective cohort study (Northern Manhattan Study, NOMAS) investigates risk factors for stroke and other vascular outcomes in a multi-ethnic, urban population. In addition, the study seeks to understand the relationships between these risks factors and cognition and MRI-defined cerebrovascular disease.
Role: Co-investigator

AHA/ASA 14BFSC1759000 Sacco (PI) 04/01/2014 – 03/31/2018
AHA
Bugher Center Foundation Center of Excellence in Stroke Award
This award will conduct two projects evaluating the effects of physical activity and cognitive training on animals and stroke survivors on cognitive recovery.
Role: Co-investigator

Completed Research Support
AHA 0735387N (PI: Wright) 07/01/2008-06/30/2011
AHA
Vascular Risk and Cognition in a Tri- Ethnic Community
The purpose of this grant is to examine vascular risk factors as correlates of cognitive dysfunction in a stroke-free multi-ethnic sample. Aims will focus on the role of both traditional and novel vascular risk factors.

K02 NS 059729-03 (PI: Wright) 09/01/2008 - 11/30/13
NIH/NINDS
Vascular Risk and Cognition in a Multi-ethnic Cohort
The purpose of this grant is to examine vascular risk factors for cognitive dysfunction in a stroke-free multi-ethnic sample. Aims will focus on identification of traditional and novel vascular risk factors for cognitive dysfunction as well as the role of brain imaging markers of vascular damage.