BrightFocus
Alzheimer’s Fast Track®

Co-chairs:  Sharyn Rossi, PhD
            Frank LaFerla, PhD
            Cynthia Lemere, PhD
            Harry W. M. Steinbusch, PhD

December 1-3, 2021
Virtual Workshop

www.brightfocus.org/AFT2021

#AlzFastTrack
Welcome To the BrightFocus Alzheimer’s Fast Track® 2021 Workshop!

As a longtime supporter of early-career scientists, BrightFocus Foundation is proud to organize and sponsor this immersive opportunity for emerging researchers to learn from, and interact with, leaders in this field.

At BrightFocus, our mission is clear: harness the power of science to end the conditions we fear most – loss of sight and loss of mind. Through our support of research on Alzheimer’s, glaucoma, and macular degeneration, we serve as an umbrella for scientific innovation in neurodegenerative disease research, uniquely positioned for experts to share discoveries about one disease to inform another.

Thank you for joining us this week for the first ever virtual Alzheimer’s FastTrack meeting. While we regretfully cannot meet in person, we have made every effort to translate the immersive, networking workshop experience into the virtual setting. I hope that your time at Alzheimer’s Fast Track is meaningful and rewarding, accelerating your path toward scientific discovery.

Please remember that your journey doesn’t stop at the end of this workshop. As alumni of the BrightFocus Alzheimer’s Fast Track, please keep in touch with each other and with BrightFocus. We hope this experience sparks collaboration for years to come.

Sincerely,

Diane Bovenkamp, PhD
Vice President of Scientific Affairs
Table of Contents

Workshop Schedule and Program .............................................................. 4
Social Media | #AlzFastTrack ........................................................................ 4
BrightFocus Alzheimer’s Fast Track Session Schedule ............................ 5
About the Co-Chairs and Speakers............................................................. 13
Additional BrightFocus Staff ......................................................................... 36
About the Students ........................................................................................ 38

BrightFocus is the world’s premier source of funding and support for research into glaucoma, macular degeneration, and Alzheimer’s. We seek to find the cures for the devastating conditions we all fear most: loss of sight and loss of mind.

We fund cutting-edge ideas from scientists all over the world who are dedicated to making groundbreaking discoveries. Since our beginning, we have invested more than $200 million in bold, innovative scientific research.

51%
BASIC RESEARCH GRANTS

18%
CLINICAL RESEARCH GRANTS

31%
TRANSLATIONAL RESEARCH GRANTS

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Workshop Schedule and Program

Workshop Goals
The Alzheimer’s disease research field continues to grow in size and scope. For people entering such a prolific environment, acquiring an initial understanding of the disease becomes more difficult each year. The goal of this workshop is to offer graduate students and postdocs an immersive opportunity to learn and discuss some of the latest trends in Alzheimer’s disease research through close interaction with established leaders in the field. By the end of this workshop, participants will have:

- Connected with preeminent Alzheimer’s disease experts and fellow early-stage researchers based in the U.S. and around the world
- Participated in interactive workgroups and breakout sessions
- Engaged in scientific debates
- Competed with fellow participants in group “mock” grant proposal presentations

Acknowledgments
BrightFocus would like to give special thanks to the co-chairs, Frank LaFerla, PhD, Cynthia Lemere, PhD, and Harry W.M. Steinbusch, PhD for their advice and leadership in the planning of the workshop and speaker invitations.

To the project management team at Special D Events and the creative and production team at Creative Day Technologies, thank you for your guidance and assistance in pulling off the first ever virtual Alzheimer’s FastTrack.

Thanks to the rest of the BrightFocus team who worked on this project - Diane Bovenkamp, Kara Summers, Adrian Macareg, Riza Decena, Sean Decena, Sarah DiSandro, and Rachel Jacobs. Teamwork makes the dream work!

www.brightfocus.org/AFT2021

Social Media | #AlzFastTrack
Help generate some buzz around BrightFocus Alzheimer’s Fast Track by telling us about your research projects. Please prepare one or two descriptions of your work in 280 characters or less using the #AlzFastTrack hashtag.

Please post your messages directly to Twitter, or email them to Rachel Jacobs, rjacobs@brightfocus.org.
# BrightFocus Alzheimer's Fast Track Session Schedule (all times EST)

## Day 1: Wednesday, December 1, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
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| 11:00am – 11:15pm | **INTRODUCTIONS**             | Stacy Haller, President and CEO, BrightFocus Foundation  
Diane Bovenkamp, PhD, Vice President of Scientific Affairs  
Sharyn Rossi, PhD, Director of Neuroscience Programs  
**Alzheimer’s FastTrack Co-Chairs**  
Harry Steinbusch, PhD, Professor, Maastricht University, The Netherlands  
Cynthia Lemere, PhD, Professor, Brigham and Women’s Hospital  
Frank LaFerla, PhD, Dean, University of California, Irvine |
| 11:15am – 1:00pm | **ELEVATOR PITCHES**          | Participants discuss their research interests – 1 minute each          |
| 1:00pm – 1:30pm | **LUNCH**                     | Collaborate/interact on SpotME platform                                 |
| 1:30pm – 2:00pm | **KEYNOTE ADDRESS**           | Can We ACE Alzheimer’s Disease whilst Negotiating Some Curious Links with COVID-19  
Patrick Kehoe, PhD, Professor, University of Bristol, United Kingdom |
| 2:00pm – 2:30pm | **LIVE DISCUSSION**           | **NEUROLOGICAL EFFECTS OF COVID-19**  
Harry Steinbusch, PhD, Professor, Maastricht University, The Netherlands  
Patrick Kehoe, PhD, Professor, University of Bristol, United Kingdom  
**Risks and Therapeutic Opportunities in the Age of COVID-19: Targeting Soluble TNF-dependent Chronic Inflammation**  
Malú Tansey, PhD, Norman and Susan Fixel Professor of Neuroscience and Neurology, University of Florida |

### Day 1, Wednesday, December 1 (continued):

#### 2:30pm – 3:00pm

**LIVE DISCUSSION**  
**Moderator:** Harry Steinbusch, PhD, Professor, Maastricht University, The Netherlands  
**Speakers:**
- *Aging is the Major Risk Factor for a Majority of Chronic Diseases*
  Julie Andersen, PhD, Professor, Buck Institute
- *The Influence of the Gut Microbiome on Alzheimer’s Disease*
  Laura Cox, PhD, Associate Professor, Neurology, Brigham and Women’s Hospital and Harvard Medical School
- *Multidomain Interventions for Risk Reduction and Prevention of Alzheimer’s Disease and Dementia*
  Francesca Mangialasche, MD, PhD, Assistant Professor, Karolinska Institute, Sweden

#### 3:00pm – 3:05pm  
**Bio Break**

#### 3:05pm – 3:30pm

**LIVE DISCUSSION**  
**Moderator:** Cynthia Lemere, PhD, Professor, Brigham and Women’s Hospital and Harvard Medical School  
**Speakers:**
- *Network Abnormalities and Interneuron Dysfunction in Alzheimer’s Disease*
  Jorge Palop, PhD, Associate Professor, Gladstone Institute of Neurological Disease and Associate Professor of Neurology, University of California, San Francisco
- *Glial Contributions to Alzheimer’s Disease in People with Down Syndrome*
  Elizabeth Head, PhD, Professor, Vice Chair for Research, Professor of Pathology and Laboratory Medicine, University of California, Irvine
- *The Role of Astrocytes in Alzheimer’s Disease*
  Ksenia Kastanenka, PhD, Assistant Professor, Massachusetts General Hospital and Harvard Medical School
- *White Matter loss in Alzheimer’s Disease: Towards keeping the Alzheimer’s brain wired*
  Arthur Butt, PhD, Professor of Cellular Neurophysiology, University of Portsmouth, United Kingdom

#### 3:30pm – 4:00pm

**LIVE PRESENTATION**  
**Speaker:** Bri McWhorter; Founder and CEO, Activate to Captivate
**Day 2, Thursday, December 2:**

### 11:00am – 11:30am

**KEYNOTE ADDRESS**  
**AT(N) Biomarkers for MCI and Alzheimer’s Disease among Mexican Americans: The HABS-HD Study.**  
*Sid O’Bryant,* Graduate School of Biomedical Sciences Member, Institute for Healthy Aging Professor and Executive Director, Institute for Translational Research Professor, Pharmacology & Neuroscience  

**Moderator:**  
*Cynthia Lemere, PhD,* Professor, Brigham and Women’s Hospital and Harvard Medical School

### 11:30am – 12:00pm

**LIVE DISCUSSION**  
**RACIAL AND SEX DISPARITIES**  
*Sid O’Bryant,* Graduate School of Biomedical Sciences Member, Institute for Healthy Aging Professor and Executive Director, Institute for Translational Research Professor, Pharmacology & Neuroscience, The University of North Texas  

**Speakers:**  
*Sex Differences in Cognitive Decline and Resilience to Alzheimer’s Disease*  
*Rachel Buckley, PhD,* Assistant Professor of Neurology, Massachusetts General Hospital and Harvard Medical School  

*Thinking About Sex and Gender Differences in Alzheimer’s Disease and Related Dementias*  
*Michelle Mielke, PhD,* Professor of Neurology and Epidemiology, Mayo Clinic Rochester

### 12:00pm – 12:30pm

**LIVE DISCUSSION**  
**MODEL SYSTEMS**  
*Frank LaFerla, PhD,* Chancellor’s Professor and Dean, University of California, Irvine  

**Moderator:**  
*Frank LaFerla, PhD,* Chancellor’s Professor and Dean, University of California, Irvine  

**Speakers:**  
*Direct Neuronal Reprogramming to Study Aging and Disease*  
*Jerome Mertens, PhD,* Assistant Professor, Neural Aging Laboratory, University of Innsbruck, Austria  

*Mouse Models for Studying Alzheimer’s Disease*  
*Joanna Jankowsky, PhD,* Professor, Neuroscience, Baylor College of Medicine  

*Using Human Microglia and Chimeric Mice to Study the Genetics of Alzheimer’s Disease*  
*Mathew Blurton-Jones, PhD,* Professor, Neurobiology and Behavior, University of California, Irvine
Day 2, Thursday, December 2 (continued):

### 12:30pm – 1:00pm

**LIVE DISCUSSION**

**THERAPEUTIC STRATEGIES**

**Session Moderator:**
Frank LaFerla, PhD, Chancellor’s Professor and Dean
University of California, Irvine

**Speakers:**

- **TMS of the Default Mode Network in Alzheimer’s Disease - a Novel Therapeutic Approach**
  Giacomo Koch, MD, PhD, Professor in Neurology and Physiology,
  University of Ferrara Italy and Santa Lucia Foundation, Rome, Italy

- **Stem Cell Therapies for Alzheimer’s Disease**
  Kevin Chen, MD, Clinical Assistant Professor, Neurosurgery and Neurology, University of Michigan

- **Alzheimer’s Disease: Promise and challenges for Antibody/Immune/Gene Therapy Based Strategies**
  David Holtzman, MD, Professor of Neurology,
  Washington University School of Medicine

### 1:00pm – 1:30pm

**LUNCH**
Collaborate/interact on SpotME platform

### 1:30pm – 3:30pm

**BREAKOUTS**

**NEUROLOGICAL EFFECTS OF COVID-19**

**MODERATORS:**
PAT KEHOE, PhD
MALÚ TANSEY, PhD

**LIFESTYLE INTERVENTIONS**

**MODERATORS:**
JULIE ANDERSEN, PhD
LAURA COX, PhD
FRANCESCA MANGIALASCHE, PhD

**ROLE OF NEUROGLIA**

**MODERATORS:**
JORGE PALOP, PhD
ELIZABETH HEAD, MA, PhD
KSENIA KASTANENKA, PhD
ARTHUR BUTT, PhD
### Day 2, Thursday, December 2 (continued):

#### 1:30pm – 3:30pm

<table>
<thead>
<tr>
<th>BREAKOUTS (CONT.)</th>
<th>RACIAL AND SEX DISPARITIES</th>
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<tbody>
<tr>
<td>MODERATORS:</td>
<td>SID O’BRYANT, PhD</td>
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<td></td>
<td>RACHEL FRANCES BUCKLEY, PhD</td>
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<td>MICHELLE MIELKE, PhD</td>
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<tr>
<td>MODEL SYSTEMS</td>
<td>JEROME MERTENS, PhD</td>
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<td>MODERATORS:</td>
<td>JOANNA LOUISA JANKOWKSY, PhD</td>
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<td>MATHEW BLURTON-JONES, PhD</td>
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<td>THERAPEUTIC INTERVENTIONS</td>
<td>GIACOMO KOCH, MD, PhD</td>
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<td>MODERATORS:</td>
<td>KEVIN CHEN, MD</td>
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<td>DAVID HOLTZMAN, MD</td>
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### Day 3, Friday, December 3:

#### 11:00am – 12:30pm

**STUDENT PRESENTATIONS**

**Neurological effects of COVID-19**
Akinsola Akinyemi | Sarah Biber | Claudio Gouveia Roque
Gillian Coughlan | Irma Cisneros | Elizabeth Fisher | Pravin Marathe
Omonigho Bubu | Özge Güzel | Paula Aduen

**Discussion**

**Lifestyle Interventions**
Karina Alviná | Joshua Babalola | Praveen Bathini | Allison Birnbaum
Amanda Boyd | Rory Boyle | Jessy Etienne | Caroline Wasen
Adam Willis | Emily Willroth

**Discussion**

**Role of Neuroglia in Alzheimer’s disease**
Farzaneh Atrian | Ahmed Bahrani | Andre Batista | David Begelman
Simone Crivelli | Marco Antônio De Bastiani | Patricia Kelly
Daniel Moreira-Silva | Shuai Wang | Melike Yuksel
### Day 3, Friday, December 3 (continued):

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>12:15pm</td>
<td>Discussion</td>
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<td>12:30pm - 1:15pm</td>
<td>LUNCH</td>
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<td>1:15pm – 3:30pm</td>
<td>MORE STUDENT PRESENTATIONS</td>
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<td>Mary Ellen Koran</td>
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<td>Jessica Nicosia</td>
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<td>Lorena Sordo</td>
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<tr>
<td>1:30pm</td>
<td>Discussion</td>
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<td>1:45pm</td>
<td><strong>Model Systems</strong></td>
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<td>Derek Archer</td>
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<td>Ruben Gomez Gutierrez</td>
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<td>Silvia Cecilia Pelucchi</td>
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<td>Ellen Wang</td>
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<td>2:00pm</td>
<td>Discussion</td>
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<td>2:15pm</td>
<td><strong>Therapeutic Interventions</strong></td>
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<td>Mercedes Beyna</td>
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<td>2:30pm</td>
<td>Discussion</td>
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<td>2:45pm – 3:15pm</td>
<td>BREAK - COMMITTEE REVIEW AND DELIBERATION</td>
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<tr>
<td>3:15pm – 4:00pm</td>
<td>AWARD CEREMONY AND PRESENTATION FEEDBACK</td>
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Participant ‘Elevator Pitch’/Ice-Breaker Guidelines

All participants will give their pitch at the start of the meeting so that everyone can introduce themselves, feel more comfortable engaging in the program, and receive feedback on their presentation style. To prepare for your pitch, watch the on demand video where Bri McWhorter, speech and communications coach, provides tips for a successful elevator pitch.

Each participant will have one (1) minute maximum (moderator will have a stopwatch!) to give your verbal pitch. There are no slides permitted. Please state your name, institution/program, and state “What compels you to pursue Alzheimer’s disease research?” or another topic you feel relevant to share with the group.

Participant Group Assignments: “Mock” Grant Proposal Presentation

Each assigned group will prepare an innovative research proposal plan based on their assigned topic. (6 groups with 10 people and one team generated proposal per group). Please watch “Writing Successful Grant Applications” for further tips and instructions. Your presentations should include the following information:

- Description of the research question and hypothesis
- Background and significance
- Specific aims/benchmark achievements
- Experimental design/methodologies
- Preliminary studies/expected results
- Innovative aspects of proposed research
- Relevance of proposed research to Alzheimer’s and related dementias
- Detailed budget and justification/facilities and environment/key personnel

Your group will make a 15 minute presentation with a maximum of 15 slides, followed by 15 minutes of questions from the ‘judging’ panel composed of the BrightFocus Alzheimer’s Fast Track workshop presenters and experts. Only one of the six proposals will successfully receive “mock” funding, after deliberation by judges.

Assignment “Request For Proposals”

Grant proposals for innovative projects to the BrightFocus Alzheimer’s Fast Track Award program* should be for a maximum of $300,000 USD for a term of 3 years (maximum $100,000 per year).* (*Legal disclaimer: this is a hypothetical awarding of funds from a hypothetical program.) Please feel free to visit BrightFocus’ website (including the “Guidelines for Applicants” and “FAQs” pages) for background information and guidance on what is included in a typical application to BrightFocus.
**Research Topics**

Topics to choose from:

1. Long term implications of COVID on brain function
2. Lifestyle Interventions for Alzheimer’s Disease
3. Role of Neuroglia in Alzheimer’s Disease
4. Racial and Sex Disparities in Alzheimer’s Disease
5. Model Systems In Alzheimer’s Disease
6. Therapeutic Strategies for Alzheimer’s Disease

**Tips:**

- Identify and clarify an urgent problem or issue in basic, translational, and/or clinical research—feel free to discuss options with workshop speakers.
- Design an innovative study.
- Identify a clear research question and formulate a clear and testable hypothesis.
- Describe the specific aims (methodology, timing, budget, key personnel, etc.)
- Show/describe the feasibility of the study.
- Describe the relevance for the field (e.g., how does it help patients in the near future?)
- Let your imagination go wild!
- Each person should be prepared to answer questions from the ‘judges’ on the spot about your group ‘application,’ like you all are part of the key personnel on the award.
About the Co-Chairs and Speakers

Sharyn Rossi, PhD - Co-Chair
BrightFocus Foundation
United States
srossi@brightfocus.org

Sharyn Rossi received her Ph.D. in anatomy and neurobiology from the University of California, Irvine, where she studied stem cell replacement therapies for the treatment of spinal cord injury. She continued her post-doctoral work at A.I. duPont Hospital for Children studying spinal muscular atrophy, and Johns Hopkins University, using optogenetics to investigate how transplanted stem cells integrate into brain circuitry after traumatic brain injury. Prior to coming to BrightFocus Foundation, Sharyn was a senior research scientist at the National Institute on Aging, using neuroimaging, light-sheet microscopy, and novel interventions to investigate changes in the brain during normal cognitive aging. Her multi-disciplinary background in systems neuroscience brings a comprehensive perspective and holistic approach to the Alzheimer’s disease program at BrightFocus. When she is not immersed in groundbreaking science, Sharyn can be found cooking, gardening, doing yoga, and playing with her three children.
Frank LaFerla, PhD - Co-Chair
University of California, Irvine
United States
laferla@uci.edu

Dr. Frank LaFerla is a Chancellor’s Professor and Dean of the School of Biological Sciences at the University of California, Irvine. He is past Director of the Institute for Memory Impairments and Neurological Disorders, and is also a Fellow of the Center for the Neurobiology of Learning and Memory. Dr. LaFerla received his BS in Biology from St. Joseph’s University in Philadelphia. His graduate training was completed at the University of Minnesota where he earned his PhD in the field of virology in 1990. Dr. LaFerla’s research is focused on understanding the pathogenesis of Alzheimer disease, the most common form of dementia among the elderly. His laboratory has developed several transgenic mouse models of neurodegenerative disorders including the first transgenic mouse model of Alzheimer disease that recapitulates the two major neuropathological lesions, plaques and tangles. This mouse model, referred to as the 3xTg-AD mice, has been widely distributed to researchers throughout the USA and over 20 countries throughout the world. His laboratory has used this model to understand the relationship between plaques and tangles and how each affects the development of the other, and more significantly, this model has proven to be invaluable for the pre-clinical evaluation of novel therapeutic compounds.
Cynthia A. Lemere, PhD, is Scientist in the Ann Romney Center for Neurologic Diseases at Brigham & Women’s Hospital and an Associate Professor of Neurology at Harvard Medical School in Boston. Dr. Lemere focuses on translational research for understanding, preventing and treating Alzheimer’s disease. Dr. Lemere earned a bachelor’s degree in Psychology and Education from Mount Holyoke College and a master’s in Neurobiology from SUNY Albany. Dr. Lemere examined Alzheimer’s-related brain changes in people with Down syndrome in the Selkoe Laboratory at Brigham and Women’s Hospital while pursuing her doctorate in Pathology at Boston University School of Medicine. After receiving her PhD, she remained at the Center as a Postdoctoral Research Fellow, Instructor, Assistant Professor and is currently an Associate Professor in the Department of Neurology. Her current research involves preclinical studies of antibody treatments to reduce a disease-relevant form of the amyloid-beta protein that accumulates and forms plaques in the Alzheimer’s brain, the role of the body’s immune host-defense system (e.g., complement) in Alzheimer’s disease progression, and the effects of deep space galactic cosmic radiation on brain aging and the risk of Alzheimer’s in preparation for NASA’s first manned mission to Mars in the 2030s. Dr. Lemere participates in local and national mentoring programs for underrepresented minorities including high school, undergraduate and medical students. Dr. Lemere serves on several national and international scientific advisory boards, including the National Alzheimer’s Association Medical and Scientific Advisory Council, the Dominantly Inherited Alzheimer’s Network Therapeutic Unit (DIAN-TU) Therapeutic Evaluation Committee, the International Alzheimer’s Disease/Parkinson’s Disease (ADPD) Conference Scientific Advisory Council, the BrightFocus Foundation Scientific Review Council and the Down Syndrome Achieves Biobank Governing Board of Directors. In addition, she serves as a scientific advisor for several companies.
Harry W. M. Steinbusch, PhD - Co-Chair
Maastricht University
The Netherlands
h.steinbusch@maastrichtuniversity.nl

Prof. Harry Steinbusch is appointed as Professor in Cellular Neuroscience at Maastricht University in the Netherlands. He is involved as Advisor Strategy Internationalization Research at Maastricht University in particular in relation to China / Asia. He took recently the Chairmanship of the Dutch - China University Network, including 12 Universities in both countries. He is Past President of the Neurotoxicity Society. He is Founding Director of the European Graduate School of Neuroscience, a gathering of 8 universities in the EUregio. He has been involved for 13 years as Director of the School for Mental Health and Neuroscience at Maastricht University. He is Founding Director of NENS - Network of European Neuroscience Schools. He is Founding Editor-in-Chief of the Journal of Chemical Neuroanatomy, current i.f. 2.2. He is affiliated with the DGIST in Daegu, Korea; University Of Colombo, Sri Lanka; University of Sao Paulo, Brazil and Capital National University, Beijing, China.

His research interest is focused on neurodevelopmental influences towards depression and neurodegenerative diseases studied in animal models approaches to start and prevent neurodegenerative processes. This implies combining a broad range of techniques, i.e. molecular neurobiology, quantitative neuromorphology, animal behavior and epigenetics. He has thus far guided 96 Ph.D. students. He has gathered a total of 495 papers. He has been twice coordinating a Marie Curie Early Stage Training site. He was coordinator of an Erasmus Mundus + program between 4 Euron universities and 3 universities in Japan. He is affiliated on 27 editorial board and member of 8 International review committees. His current Hirsch factor is 93, citations without self-citations: 34,538 and his M-factor is 2.1.
Julie K. Andersen, PhD
Professor, Buck Institute for Research on Aging
United States
jandersen@buckinstitute.org

Aging is the Major Risk Factor for a Majority of Chronic Diseases

The Andersen lab concentrates on understanding the underlying age-related processes driving neurodegenerative diseases in order to identify novel therapeutics that slow or prevent them from occurring. These include small molecules that boost the cell’s own ability to remove damaged proteins and other cellular components through a process called autophagy or those capable of removing cells which can inflict damage on healthy neighbors via a process called cellular senescence. We collaborate with other laboratories in order to understand the mechanisms involved and to screen and test novel compounds in various preclinical models of disease, including human induced pluripotent stem cells (iPSCs), C. elegans, and mice.

Abstract

“Geroscience” is a concept that unites research on normal aging processes with research on chronic progressive disorders such as Alzheimer’s disease (AD). Integral to the Geroscience approach is the view that aging itself is a likely cause of multiple chronic human diseases. It follows that interventions that target aging will provide novel therapeutic avenues for distinct diseases including AD and related disorders. Scores of chemical compounds that extend the lifespan of the nematode C. elegans have been shown by ourselves and others to counteract cellular processes known to go awry during normal aging and to suppress aspects of neurological disease in mammalian disease models. These include agents which enhance protein homeostasis and repress cellular senescence. These findings have aided not only in development of a better understanding of the relationship between normal aging and AD, but also to the development of new potential therapeutic targets. By undertaking such a “Geroscience approach”, we aim to develop new methods to targeting the very earliest cellular changes that that lead to AD.
Mathew Blurton-Jones, PhD
Professor, Neurobiology and Behavior, UC Irvine
United States
mblurton@uci.edu

Using Human Microglia and Chimeric Mice to Study the Genetics of Alzheimer’s Disease

Dr. Matt Blurton-Jones is a professor in the Department of Neurobiology and Behavior at the University of California, Irvine and director of the UCI ADRC iPS cell core and the UCI Stem Cell CRISPR core. His current research utilizes human induced pluripotent stem (iPS) cells and chimeric mouse models to examine the underlying molecular mechanisms that drive the development and progression of Alzheimer’s disease (AD). His earlier studies were among the first to show that neural stem cells can improve cognitive and motor function in transgenic models of neurodegeneration by elevating levels of brain-derived neurotrophic factor (BDNF) and enhancing plasticity. His lab also demonstrated that the adaptive immune system restrains the development of AD pathology by modulating microglial activation states. More recently, his group developed one of the leading approaches to differentiate patient-derived iPS cells into microglia (Abud et al., Neuron, 2017) and generated chimeric models to study human microglial function in vivo (Hasselmann et. al., Neuron, 2019). Ongoing work in the Blurton-Jones lab is now combining iPS cells, CRISPR gene editing, and chimeric modeling to examine the impact of AD-associated genes on human microglial function (McQuade et al., Nat Comm, 2020).

Abstract
iPSC-derived microglia offer a powerful new tool to study the influence of Alzheimer’s Disease (AD) risk genes on human microglial function. Yet, microglia are highly sensitive to their environment, exhibiting transcriptomic deficiencies when kept in isolation from the brain. To address this challenge, we developed an approach to study human microglia within a surrogate murine brain environment. Transplantation of iPSC-derived hematopoietic-progenitors into the brain of hCSF1 immune-deficient mice results in context-dependent differentiation into microglia, acquisition of an ex vivo human microglial gene signature, and responsiveness to both acute and chronic insults. Notably, transplanted microglia also exhibit robust transcriptional responses to Ab-plaques that only partially overlap with that of murine microglia, revealing new, human-specific Ab-responsive genes. By combining this new model with CRISPR-edited iPSCs, we have begun to examine the impact of AD risk genes on human microglial function. Taken together, our findings suggest that mutations and polymorphisms associated with increased AD risk lead to impaired induction off a disease-associate microglial (DAM) state. Ongoing studies seek to further define the mechanisms by which these genes alter this important microglial response and whether Neurofibrillary Tangle pathology elicits a similar or differing transcriptomic program.
Rachel Frances Buckley, PhD
Assistant Professor of Neurology, Massachusetts General Hospital, United States
rfbuckley@mgh.harvard.edu

Sex Differences in Cognitive Decline and Resilience to Alzheimer’s Disease

I am an Assistant Professor of Neurology at Massachusetts General Hospital and a recipient of an NIH-NIA K99/R00 Pathway to Independence award. My field of expertise is in the investigation of sex differences in Alzheimer’s disease (AD) biomarkers in preclinical AD. Specifically, my interest is in what sex biological mechanisms might explain female vulnerability to tauopathy.

Abstract
My area of expertise is in sex differences of Alzheimer’s disease (AD) pathology in preclinical AD. Specifically, I’m interested in understanding why women seem to exhibit vulnerability to the disease, particularly with regard to levels of tauopathy. I am also interested in resilience to the disease, and how basic science, genomic and observational studies seem to suggest that women exhibit greater resilience than men to the disease, at least at the preclinical stages. As such, I plan on pushing forward these areas of research by tackling two strands of investigation. The first strand focuses on what might drive higher levels of tauopathy in women – could it be due to sex hormones or sex chromosomes? Here, I am actively investigating sex hormone levels (estrogens, progesterone, testosterone) in middle aged and older women and men in association with their levels of amyloid and tau as measured with positron emission tomography (PET). I have also recently submitted a grant that proposes to do a deep dive on the X chromosome and how dosage disequilibrium from women with escaped X-inactivation might increase risk (or protection) for amyloid and tau levels relative to men. For my second strand of investigation, I am very interested in building predictive models to identify resilience (performing optimally in the face of significant disease burden) and resistance (never exhibiting biomarkers of disease even when possessing risk factors) and differentiating this from normative disease progression. This research track runs in parallel to the first, as I believe that sex differences will inherently underlie some of the resilience and resistance factors that moderate disease risk.
Arthur Butt, PhD
Professor of Cellular Neurophysiology, University of Portsmouth
United Kingdom
arthur.butt@port.ac.uk

White Matter Loss in Alzheimer’s Disease: Towards Keeping the Alzheimer’s Brain Wired

Professor Arthur Butt is an internationally recognised glial cell biologist for over 25 years. He received his PhD from King’s College London in 1986, working with Joan Abbott, a leader in blood-brain barrier research. After a postdoctoral position in North Carolina with Ed Lieberman, he was awarded a Grass Fellowship to work at the Wood’s Hole Marine Biology Laboratories. Next, he moved to Yale University to work with Bruce Ransom, where he began his work on optic nerve glia, a line of research he has pursued ever since. On return to the UK, Arthur Butt first worked again with Joan Abbott in King’s College London and on a Royal Society Fellowship at the Marine Laboratories in Plymouth, UK, before obtaining his first independent position at Guy’s and St Thomas’ Hospitals in 1990. During this time, Arthur Butt worked closely with Professor Martin Berry, a leader in CNS regeneration studies. After gaining a personal Chair at King’s College in 2000, he moved to the University of Portsmouth in 2005, where he was Director of the Institute of Biomedical and Biomolecular Sciences.

Much of Arthur Butt’s work has focused on oligodendrocyte cell biology and the factors that regulate their regeneration, with a particular relevance to Multiple Sclerosis. He was editor on the first special issue on NG2-glia, enigmatic cells that serve as a pool of oligodendrocyte precursor cells. Currently, the focus of Arthur Butt’s research is to learn of new ways to target these cells to promote repair of the brain, in particular in Multiple Sclerosis. Arthur Butt is co-founder of the company GliaGenesis.
**Kevin Chen, MD**  
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**Stem Cell Therapies for Alzheimer’s Disease**

Dr. Chen is a clinically practicing neurosurgeon with sub-specialty training in stereotactic/functional neurosurgery, which utilizes techniques to precisely target specific areas in the brain. His overarching goal is to use his clinical experience with patients to inform his research, and in turn bring discoveries from the laboratory to patients in the form of new and innovative therapies. Dr. Chen is interested in stem cells, and in particular induced pluripotent stem cells (iPSCs). In particular, he seeks to understand pathology related to inhibitory interneurons in neurodegenerative diseases like Alzheimer’s Disease and ALS. With this understanding, he seeks to also explore approaches by which iPSCs and engineered stem cells can be utilized as novel treatments. This understanding could eventually also be applied to other neurologic disorders, such as Parkinson’s disease, epilepsy, stroke, chronic pain, and psychiatric diseases.
Dr. Laura Cox is an Instructor in Neurology at the Ann Romney Center for Neurologic Diseases at Harvard Medical School and BWH Hospital. She was originally trained as a clinical microbiologist, identifying infectious agents. She then obtained her PhD in the lab of Dr. Martin Blaser, where she found that early-life antibiotics lead to lasting metabolic consequences. To gain experience with models of neurologic disease, she then pursued postdoctoral training in the lab of Dr. Howard Weiner. She is currently investigating the role of the microbiome in neurologic diseases, including Alzheimer’s disease, multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson’s disease. She has recently discovered that bacteria that change during aging can contribute to amyloid plaques in experimental models of Alzheimer’s disease. She is now investigating mechanistic pathways by which the gut microbiota bacteria can influence AD in the hopes of finding ways to intervene to prevent and treat AD.

Abstract

Alzheimer’s disease (AD) affects an estimated 5.8 million Americans, and advanced age is the greatest risk factor. AD patients have been found to have altered intestinal microbiota and age-related changes in the microbiota contribute to immunologic and physiologic decline. We investigated the changes in gut microbiota in Tg2576 mice, a model of amyloid-beta deposition, and found that female Tg2576 mice have more substantial age-related microbiome changes compared to wildtype (WT) mice or compared to male mice, including an increase in Bacteroides. Elevated Bacteroides has been observed in aging humans and in AD patients compared to healthy controls. In the gut, we also found that Tg2576 female mice had an enhanced intestinal inflammatory transcriptional profile. We then found that administering a calorie-restricted diet controlled changes in the microbiome and in the intestine and prevented the accumulation of Aβ plaque, which was specific to female mice. These results suggest that long-term calorie-restriction may alter the gut environment in a sex-specific manner and prevent the expansion of microbes that contribute to age-related cognitive decline. We then administered Bacteroides to another model of cerebral amyloidosis (the APP/PS1 mouse) and found that it increased Aβ deposition. This was linked to altered gene expression of Aβ processing enzymes in the brain and altered immune responses, which we identify as two potential mechanisms by which the microbiota may affect Alzheimer’s disease.
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Glial Contributions to Alzheimer's Disease in People with Down Syndrome

Dr. Head received a Masters in Psychology and a Ph.D. in Neuroscience from the University of Toronto, Canada. She received postdoctoral training at the Institute for Memory Impairments and Neurological Disorders at the University of California Irvine. Dr. Head moved to the University of Kentucky in January of 2009 and was a Professor and Associate Director of Education at the Sanders-Brown Center on Aging. After returning to the University of California at Irvine in 2019, she is now a Professor and Vice Chair for Research in the Department of Pathology & Laboratory Medicine. Dr. Head has published over 190 peer reviewed papers, over 30 review papers and book chapters. She is active in mentoring and education and serves on the NIH Alzheimer disease research center Research Education Component Executive Committee. Dr. Head has dedicated over 25 years to the study of aging and Alzheimer disease with a focus on people with Down syndrome using multidisciplinary and translational approaches.
David Holtzman, MD
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Alzheimer’s Disease: Promise and Challenges for Antibody/Immune/Gene Therapy Based Strategies

David M. Holtzman received his BS and MD, Northwestern University followed by Neurology residency at UCSF. Following post-doctoral research, he moved to Washington University in 1994 and is currently Professor of Neurology and director of the Hope Center for Neurological Disorders. Some accomplishments include showing in part how APOE contributes to Alzheimer disease (AD), development of biomarkers for AD, demonstration that synaptic activity and sleep affect Aβ and tau levels in vivo, describing the effects of APOE, TREM2, and microglia on tau-mediated neurodegeneration, and development of several antibodies that are in clinical trials in humans to try to prevent/treat AD.

Abstract
I am a neurologist and neuroscientist, and I have focused much of my efforts over the last 27 years on trying to better understand mechanisms underlying neurodegeneration, particularly as they are relevant to Alzheimer’s disease (AD). My lab has published extensively on the neurobiology of apoE and its receptors, apoE and TREM2 effects on the innate immune system, how apoE, Aβ binding molecules, and other factors such as neuronal activity and sleep influence Aβ and tau metabolism, their accumulation, and their effects. In studying tau metabolism and tau-mediated brain injury, we found that apoE, particularly apoE4, strongly influences tau-mediated neurodegeneration via the brain’s innate immune response. Over the last 8 years, we studied how microglia and specific microglial genes such as TREM2 as well as apoE (produced by astrocytes and microglia) influence neurodegeneration in the setting of Aβ and tau pathology as well as Aβ-induced tau seeding/spreading. From the therapeutic perspective, we have shown that certain anti-Aβ and anti-tau antibodies have therapeutic potential in animal models. The use of one of the anti-Aβ antibodies we studied for potential therapeutic and diagnostic purposes was licensed by Washington University (WU) to Eli Lilly in 2001 and subsequently humanized. It is in a secondary prevention trial in preclinical AD (A4). Some of the anti-tau antibodies were licensed to AbbVie and one went through phase 2 clinical trials in AD and PSP. We also developed an anti-apoE antibody (HAE-4) that only binds non-lipidated apoE that clears amyloid plaques and decreases CAA and CAA-associated vascular dysfunction. We have developed 2 techniques to allow us to better study metabolism of Aβ, tau, apoE, and other proteins in the CNS including: a protein microdialysis method used to assess proteins as frequently as every 30 minutes in the brain interstitial fluid of awake rodents and humans, and a metabolic labeling technique using 13C-labeled amino acids following by sampling of human CSF or rodent brain to measure rates of protein synthesis and clearance in the CNS. In humans, we worked extensively on the development of antecedent biomarkers of AD. In my 27 years at WU, I trained/mentored ~70 graduate students, postdoctoral fellows, and physician-scientists, many who are in successful careers in academia and industry.
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Mouse Models for Studying Alzheimer's Disease

Joanna Jankowsky holds the Vivian L. Smith Endowed Chair in Neuroscience at Baylor College of Medicine. Dr. Jankowsky’s research focuses on understanding factors such as genes and aging that influence Alzheimer’s risk, and testing experimental approaches for treatment including gene therapy. Her work uses genetically engineered mouse models for AD as a testbed for these studies and she is recognized for helping to create and characterize several transgenic models of AD. She serves on the Alzheimer’s Association International Research Grant Program Council and the BrightFocus Foundation Scientific Review Committee, and currently chairs the NIH CMND study section. At her home institution, she teaches extensively and is the Associate Director graduate studies in neuroscience. She has received multiple awards for her research, including the NARSAD Young Investigator Award, the NIH Director’s New Innovator Award, and most recently the Alzheimer’s Association Zenith Fellows Award.
Ksenia Kastanenka, PhD
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The Role of Astrocytes in Alzheimer’s Disease

Ksenia Kastanenka is an Assistant Professor at Massachusetts General Hospital and Harvard Medical School, where she runs a research laboratory with emphasis on neurodegeneration and Alzheimer’s disease. Her laboratory focuses on circuitry disruption during the disease progression and mechanisms of action of Alzheimer’s therapeutics. Ksenia has over 15 years of experience studying neuronal circuits. During her PhD work at Case Western Reserve University under the mentorship of Lynn Landmesser, she used state of the art laboratory techniques, including optogenetics, to study the assembly of spinal circuits during development. 10 years ago, Dr. Kastanenka extended her expertise into the field of Alzheimer’s disease to work with Brian Bacskai. At Massachusetts General Hospital and Harvard Medical School, she has developed a line of work applying optogenetics and multiphoton microscopy to dissect the role that oscillatory activity, particularly slow oscillations, plays in the etiology and progression of Alzheimer’s disease.
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Can We ACE Alzheimer’s Disease Whilst Negotiating Some Curious Links with COVID-19"

Professor Pat Kehoe is the Gestetner Professor of Translational Dementia Research and Faculty Research Director of the Faculty of Health Sciences, University of Bristol, UK. He is a leading international name in the role of the classical renin angiotensin system (cRAS) in AD. Some of his research examines the imbalance in the activity of ACE1, relative to ACE2, and their combined contribution to net levels of angiotensin II. This has a bearing not only on suggested hypertension associations in AD, but also mediates non-blood pressure-related effects that influence several damaging mechanisms known in AD. More recently, this same pathway has moved to the centre stage in the cause of COVID-19. His previous laboratory-based research focussed on the impact of over-production of angiotensin II, which he has translated through to the Phase II RADAR trial. More recently his group uncovered how ACE2 is reduced in AD patients and how enhancement of ACE2, as an alternative way of reducing angiotensin II, may prove to be an even more valuable route to intervention in AD. Notably, the role of ACE2 has also been shown to be pivotal in the transmission of the COVID-19-causing SARS-CoV-2 virus but also in relation to patient responses to COVID-19. Research findings from both the dementia and COVID-19 communities continue to reveal some curious overlapping themes between initially different diseases that may pave the way for greater understanding of the function of angiotensins in the brain and in turn their role as mediators or protective factors against dementia risk and outcomes.
Giacomo Koch, MD, PhD
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TMS of the Default Mode Network in Alzheimer’s Disease - a Novel Therapeutic Approach

Giacomo Koch is a neurologist and neuroscientist leading the non-invasive brain stimulation lab at the Santa Lucia Foundation in Rome. The main goals of his research are to understand mechanisms underlying cortical plasticity and cortical connectivity in the healthy human brain, in order to develop novel therapeutic approaches to promote recovery of neurological functions through methods of non-invasive brain stimulation. He developed novel methods based on multifocal TMS approaches to investigate in real-time the task related activation of parieto-frontal cortical circuits and to study the local mechanisms of cortico-cortical plasticity. Dr. Koch performed several clinical trials evaluating the therapeutic efficacy of rTMS in different neurological disorders. For instance, he used rTMS to treat motor symptoms in Parkinson’s disease, progressive supranuclear paralysis, and focal dystonia. Moreover he conducted clinical studies using rTMS to promote recovery of language and spatial deficits in patients suffering from ischemic stroke. Dr. Koch is also actively investigating the mechanisms of cortical plasticity in patients with Alzheimer’s disease. He was among the first to demonstrate the impairment of long term potentiation (LTP) in this neurological condition and show how dopaminergic therapy could potentially restore such abnormalities. His research is aimed at verifying the potential effects of rTMS applied over the default mode network in patients with early Alzheimer’s disease, in order to improve memory through a consistent variation in functional and structural brain connectivity.

Abstract
Giacomo Koch is a neurologist and neuroscientist leading the non-invasive brain stimulation lab at the Santa Lucia Foundation in Rome. He is also Full Professor of Physiology at the University of Ferrara, Italy.

The main goals of his research are to explore the mechanisms of cortical plasticity and cortical connectivity in the healthy human brain, in order to develop novel therapeutic approaches to promote recovery of neurological functions through methods of non-invasive brain stimulation.

Dr. Koch has a long-lasting experience in the field of clinical neurophysiology of cognitive functions. His main expertise is in the application of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), mainly used in combination with structural and functional magnetic resonance imaging (MRI) and with electroencephalography (EEG).

In the last years his research has been oriented to clarifying the mechanisms of cortical plasticity in patients with Alzheimer’s Disease (AD) and in testing new therapeutic approaches in people with dementia in phase II/III clinical trials, using either drugs acting on synaptic activity or repetitive transcranial magnetic stimulation (rTMS).

Dr. Koch has published more than 250 papers in peer-reviewed journals with an H-index of 58.
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Multidomain Interventions for Risk Reduction and Prevention of Alzheimer’s Disease and Dementia

I am Assistant Professor in Clinical Geriatric Epidemiology at Karolinska Institute, and senior Geriatrician at Karolinska University Hospital (Stockholm, Sweden). My training and work experience are in the field of Geriatric Medicine and Geriatric Epidemiology, with focus on observational and intervention studies in dementia and Alzheimer’s disease (AD).

I am Chief Scientific Officer of the Nordic Brain Network (NBN) at Karolinska Institutet, an international and multidisciplinary research group led by Prof. Miia Kivipelto. The NBN group focuses on clinical and translational research on prevention and treatment of cognitive impairment, dementia and AD. I am part of the Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability (FINGER) research team, and Scientific coordinator for FINGER studies on blood-markers. I am also scientific coordinator of the World-Wide FINGERS Network (40+ countries) and the WW-FINGERS-SARS-CoV2 project, within the WW-FINGERS Scientific Helpdesk. I am scientific coordinator of the EURO-FINGERS Consortium, and member of the WHO Neurology and COVID-19 forum.

I contribute to the NBN multidisciplinary group with expertise in geriatric medicine, clinical trials and epidemiology, and biological knowledge. I work as study physician in projects and studies on brain aging and dementia prevention done at the Memory Clinic of Karolinska University Hospital, campus Solna, and I am Co-PI of the MET-FINGER trial.
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Bri McWhorter is the Founder and CEO of Activate to Captivate, where she teaches communication techniques from an actor’s point of view. She specializes in public speaking, scientific communications, interview skills, and interpersonal communications. She has taught workshops at Fortune 500 companies, privately coached CEOs at nonprofits, and led certificate programs at top universities. She is the creator of W.A.V.E.®, a program where she teaches speakers how to overcome nerves, use body language, and rely on their voice to tell an engaging story. She has coached speakers for academic symposiums at various institutions including the UC Office of the President, UC Irvine, and Chapman University. She has an MFA in Acting from University of California, Irvine and a BA in Theater and Performance Studies from University of California, Berkeley.

Abstract
I help academics and industry professionals distill highly complex research into concise and compelling pitches and presentations. Whether it's talking to a colleague, a patient, or the public, I help professionals craft a message that is memorable and repeatable.
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Direct Neuronal Reprogramming to Study Aging and Disease

Jerome is Assistant Professor at the University of Innsbruck in Tyrol, Austria, and Staff Scientist at the Salk Institute in La Jolla, CA. His research focus is to better understand the interface between the biology of aging and neurodegeneration. His patient-centric approach combines human cell reprogramming technologies such as iPSC differentiation, direct neuronal conversion (iN), and 3D culture models with unbiased multi-omics technologies and functional neuroscience. Jerome completed his PhD in the lab of Oliver Brüstle (University of Bonn) and Philipp Koch, and his postdoc in Rusty Gage’s lab.

Abstract
Jerome Mertens is a cell biologist and head of the Neural Aging Lab at the University of Innsbruck, Austria. His research focus is on modeling brain aging and age-related neurodegenerative and psychiatric diseases using patient-specific cellular reprogramming models. He obtained his PhD at the University of Bonn working on iPSC models for Alzheimer’s Disease, and continued his research as a postdoc at the Salk Institute for Biological Studies in San Diego. Jerome is Assistant Professor at the Institute for Molecular Biology of the University of Innsbruck in Austria, and Assistant Adjunct Professor at the Salk Institute in San Diego. His ERC-funded lab in Austria is focused on using direct conversion of human donor fibroblasts into induced neurons (iNs) for studying human cells, and the interface between aging, dementia, and psychiatric disorders. The lab also combines iN and iPSC differentiation technologies to investigate effects of epigenetic rejuvenation and adult neuronal identity, and to build new multi-cellular model systems. To dissect their human patient-based reprogramming models, the Neural Aging Lab uses multi-omics strategies to complement functional genetic and cell biological approaches. The ultimate goal is to better understand age-related disorders via elucidating the interface between aging and disease.
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Thinking About Sex and Gender Differences in Alzheimer’s Disease and Related Dementias

Michelle M. Mielke, Ph.D. is currently Professor of Epidemiology and Professor of Neurology at the Mayo Clinic. She is also the Associate Chair of Faculty Development and Academic Affairs in the Department of Quantitative Health Sciences. Dr. Mielke works as a translational epidemiologist to further understanding of the etiology and epidemiology of neurodegenerative and other aging-related diseases. One focus of her research is the identification of fluid biomarkers for the diagnosis, prediction, and progression of Alzheimer’s disease and other neurodegenerative diseases. Another focus of Dr. Mielke’s research is on understanding sex and gender differences in the development and progression of Alzheimer’s disease and of other aging-related conditions. She directs the Mayo Clinic Specialized Center of Research Excellence (SCORE) on Sex Differences. Dr. Mielke is co-Chair of the Sex and Gender Diversity Significant Interest Group for the Alzheimer’s Association Professional Interest Area. She received the John R. Raymond Mentor Award from the Women Scholars Initiative. She is the PI of several NIH- and Foundation-funded clinical- and epidemiological-based grants and has published over 330 manuscripts.
Sid O’Bryant, PhD
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AT(N) Biomarkers for MCI and Alzheimer’s Disease Among Mexican Americans: The HABS-HD Study

As the population of those aged 65 and over continues to grow, so does the diversity of the U.S. population. In fact, by 2060 approximately 27.5% of the population will be Hispanic and 15% African American. Dr. Sid O’Bryant is the principal investigator of the Health & Aging Brain Study – Health Disparities (HABS-HD), which is the most comprehensive study of Alzheimer’s disease among the three largest racial/ethnic groups in the U.S. ever conducted – African Americans, Mexican Americans, non-Hispanic whites. The goal of the HABS-HD program is to understand the life course factors, including biological, sociocultural, environmental, and behavioral, that impact risk for Alzheimer’s disease in late life. This work will ultimately lead to population-specific precision medicine approaches to treating and preventing Alzheimer’s disease (i.e., “treating your Alzheimer’s disease”). In addition to being a global leader in Mexican American cognitive aging, Dr. O’Bryant is a global expert in precision medicine approaches to novel diagnostic and therapeutic strategies for Alzheimer’s disease, Parkinson’s disease, Dementia with Lewy Bodies and Alzheimer’s disease among adults with Down Syndrome.
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Network Abnormalities and Interneuron Dysfunction in Alzheimer’s Disease

Jorge J. Palop is an associate investigator at the Gladstone Institutes. He is also an associate professor of neurology at UC San Francisco (UCSF). Palop has received numerous competitive honors and awards, including predoctoral and postdoctoral fellowships from the Spanish Ministry of Education and Science, the Fulbright program, the Hillblom Center for the Biology of Aging, and the Memory and Aging Center at UCSF, as well as the Ramon y Cajal and the S.D. Bechtel Young Investigator Awards. He has published his findings and reviews in many prestigious scientific journals, including Cell, Nature, Science, Nature Medicine, Neuron, Nature Neuroscience, PNAS, and The Journal of Neuroscience. He regularly serves as a scientific reviewer for many of these journals and other organizations. He is a reviewing editor of eNeuro, the open-access online journal of the Society of Neuroscience. Palop earned a PhD in neuroscience (summa cum laude) from the University of Valencia, Spain. He did his postdoctoral training at UCSF and in the laboratory of Lennart Mucke at Gladstone.
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Risks and Therapeutic Opportunities in the Age of COVID-19:  
Targeting Soluble TNF-Dependent Chronic Inflammation

Dr. Malú Gámez Tansey earned her BS/MS from Stanford University, her PhD from UT Southwestern and did post-doctoral work at Washington University on GDNF/Ret signaling. She spent 2 years at Xencor where she co-invented dominant-negative soluble TNF inhibitors currently in clinical trials for Alzheimer’s disease and COVID19. Today, she is the Norman and Susan Fixel Chair in Neuroscience and Neurology and Co-Director of the Center for Translational Research in Neurodegenerative Disease at the University of Florida College of Medicine in Gainesville. Her lab focuses on the role of inflammation and immune system responses in brain health and mechanisms underlying development of neurodegenerative diseases. The long-term goal of her laboratory is to enable earlier diagnoses and better therapies to prevent and/or delay these diseases. Dr. Tansey is a fierce advocate for women and other under-represented groups in STEM and has earned several mentoring awards from students and faculty for these efforts.

Abstract
The role of microglia in brain development and neuronal survival is now well established. As brain-resident immune cells, microglia perform a myriad of important functions required to maintain a healthy brain, including removal of debris, production of neurotrophic factors, and surveillance of the neuronal environment to protect against invasion of pathogens. Due to increased human longevity, immune cells in the brain as well as in the periphery experience chronic antigenic load and, along with immunosenescence and inflamm-ageing, their chronic activation may create the set of conditions in the brain that can promote neurodegeneration. Moreover, how microglia cells communicate with peripheral immune cells to recruit their entry into the CNS under normal conditions and during aging is still largely unknown. Specifically, the extent to which the destruction of neurons in the brain is solely a result of chronic microglia dysregulation versus a collaborative activity with infiltrating macrophages has yet to be determined. Identification of the role of key inflammatory regulators of innate and adaptive immune cells in the brain and in the periphery will reveal opportunities for intervention to delay or slow down progression of neurodegeneration without the need for immunosuppression. Innovative thinking will be needed to uncover new therapeutic avenues that can mitigate chronic neuroinflammation in individuals with Long-COVID19 to reduce the risk for neurodegenerative conditions later in life  without immunosuppressing individuals. Ultimately, although mitigation of inflammation may be achievable by targeting soluble TNF even in late stages of neurodegenerative diseases, there is likely to be a narrow window of opportunity for timely intervention in order to achieve neuroprotection and disease-modifying effects. A summary of these studies and lessons learned from ongoing clinical trials in Alzheimer’s disease and COVID19 will be presented to stimulate discussion and debate about the potential use of immunomodulatory biologics to mitigate chronic inflammation centrally and peripherally to reduce risk for age-related neurological disorders and dementia.
Additional BrightFocus Staff

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BrightFocus President and CEO Stacy Pagos Haller has significantly expanded the foundation’s stature as a premier source of private funding and support for research on Alzheimer’s, macular degeneration, and glaucoma. Under her tenure, the Maryland-based nonprofit has nearly tripled its financial commitment to innovative, high-risk research that spans scientific disciplines and national borders. Ms. Haller regularly appears on panels for scientific, health care, and philanthropic audiences and represents BrightFocus among public and private sector leaders in efforts to increase and diversify sources of research funding. Her honors and recognitions include Disruptive Women in Health Care naming her to its list of Disruptive Women to Watch and the thought leader Ideagen presenting her with their Global Leadership Award. Prior to assuming the leadership of BrightFocus in 2010, Ms. Haller served as the Executive Director of CureSearch National Childhood Cancer Foundation, the world’s largest children’s cancer research organization. Additionally, she co-created the first Outcomes Measurement Training in the Mid-Atlantic region to improve nonprofit performance. Ms. Haller, whose board service includes America’s Charities, is a graduate of Mount Holyoke College.
Diane Bovenkamp, PhD, Vice President of Scientific Affairs, oversees the global scientific operations for BrightFocus and serves as the scientific liaison for the organization in local, national, and international forums. Dr. Bovenkamp obtained her PhD in Biochemistry from Queen’s University in Kingston, Ontario, Canada, discovering and studying Eph receptors in angiogenesis and neural development in zebrafish and mice. She completed a Postdoctoral Fellowship in the Vascular Biology Program at Boston Children’s Hospital/Harvard Medical School, isolating and characterizing zebrafish neuropilins. Dr. Bovenkamp conducted further research at the Johns Hopkins University Bayview Proteomics Center in the Division of Cardiology at Johns Hopkins School of Medicine in Baltimore, Maryland, using proteomic techniques for biomarker detection in human serum. Prior to assuming her current position, Dr. Bovenkamp served as the Scientific Program Officer and Science Communications Specialist at BrightFocus, and as Director of Science Information and Programs at Foundation Fighting Blindness.

Kara Summers is the Scientific Program Grants Manager, managing all administrative aspects of the BrightFocus core research grant program. She works closely with the scientific community and BrightFocus review committee members to keep the annual grant cycle on track and on schedule. Kara began working part time at BrightFocus in 2004. In her part-time capacity she gained experience in several departments throughout the company, including cage and data entry, development, and donor services. In 2009 she transitioned to the Department of Scientific Affairs. Kara graduated from NC State University. She lived in North Carolina, Virginia and Kansas prior to settling in Maryland in 2002.
Abstract
Prevalence rates of Alzheimer’s disease and related dementias (ADRD) are greater among older Latinos and African Americans compared to their White-Caucasian counterparts. While it is well established that older age and family history are risk factors for ADRD and accelerated aging, there has been increasing interest in identifying potentially modifiable lifestyle factors to mitigate risk among vulnerable populations. It is well established that greater lifetime stress exposure is associated with increased risk for an array of mental and physical health outcomes that can lead to biological aging and premature mortality. Further, psychological stress can impact cognition both transiently, through depletion of attentional resources that are important for efficient processing in the moment, and long-term. Studies have consistently linked chronic life stress to poorer long-term cognitive functioning, accelerated cognitive decline, and increased risk for dementia through posited mechanisms of allostatic load or physiological “wear and tear.” Cognitive domains of executive functioning and episodic memory appear to be particularly sensitive to stress-related changes. Studies have demonstrated greater exposure to chronic and acute stress in minorities compared to non-Hispanic Whites. Given several psychosocial factors associated with immigration- and acculturation-related stress, it is unsurprising that Latino immigrants are particularly at risk for adverse health consequences from chronic stress. As such, investigating whether chronic stress impacts cognitive decline, and overall risk for ADRD in older Latinos is pivotal to improve prevention, early detection, and development of novel treatments and interventions for this critically underserved and understudied population. To our knowledge, this will be the first study to examine chronic stress, through a multi-pronged assessment approach utilizing both psychological (chronic stress exposure, perceived stress, and cognitive appraisals of stress) and biological measures of stress, as a risk factor for cognitive decline in older Latinos. Analysis of cortisol in scalp hair, a relatively novel method, has been proposed to be an apt endocrine biomarker of chronic psychological stress, as it can assess cumulative cortisol exposure over prolonged periods of time (~3 months). Characterization of the impact of chronic stress on cognitive decline and AD risk in Latinos may help refine detection, prevention, and development of interventions in this critically underrepresented population.

Biosketch
I am a bilingual, bicultural clinical neuropsychologist who specializes in the evaluation, diagnosis, and care of multicultural adult patients, including Spanish-speaking individuals, presenting with cognitive concerns. Following completion of my post-doctoral fellowship in the Harvard Partners Consortium in Clinical Neuropsychology (MGH/BWH) in Fall 2020, I joined the faculty at the MGH Department of Psychiatry and HMS, where I provide clinical care, supervise trainees, and conduct research on risk factors associated with increased dementia risk in the Latino population. I serve as Assistant Director of the Multicultural Assessment and Research Center (MARC), alongside my mentor Dr. Yakeel Quiroz. We have fully approved Multicultural Neuropsychology Fellowship and Practicum Programs, both of which I am the Co-Director. I have dedicated most of my research career to examining the relationship between cognition, behavior, and functional outcomes in neurological disorders. As a graduate student at the University of Virginia my work focused on exploring the neuroscience of Attention-Deficit/Hyperactivity Disorder (ADHD). As my clinical focus shifted to the diagnosis and characterization of Alzheimer’s disease, so did my areas of scientific inquiry. I began to make this transition to the field of cognitive aging and dementia through work with the Multicultural Alzheimer’s Prevention Program. Recently, I was awarded the MGH/ECOR CDI Clinician-Teacher Development Award, which provides me with funding to investigate the mechanisms by which cumulative stress impacts cognition in older adult Latinos.
Abstract
Alzheimer’s disease is a prevalent, slowly progressive neurodegenerative condition marked by brain shrinkage, gradual loss of memory and clinical symptoms of cognitive decline in the elderly population. Its pathogenesis has been attributed to extracellular aggregates of amyloid β (Aβ) plaques and intracellular neurofibrillary tangles made of hyperphosphorylated tau-protein in cortical and limbic areas of the human brain. Despite significant progress in the research into Alzheimer’s disease, its etiology is still unclear, and no cure is available at present, hence, it poses a significant social and economic burden, with a huge impact on the close family of the patients. Many variables, including age, genetic variation, and environmental factors, have been demonstrated to have a role in the progression of Alzheimer’s disease. More importantly, RNA binding proteins, the key regulators of gene expression at several levels of RNA metabolism, have been implicated in the pathogenesis of Alzheimer’s disease. Nevertheless, there is a paucity of details about the mechanism of action of these proteins and how they ultimately contribute to the pathophysiology of Alzheimer’s disease. Our recent findings show that ELAVL4, a glutamatergic neuron-specific RNA-binding protein, is upregulated early in mutant microtubule-associated protein tau (MAPT) iPSC-derived cerebral organoids (tau-V337M). Moreover, glutamatergic dysfunction and ultimately neuronal loss are phenotypes observed in the MAPT mutated tau-V337M 3D organoids, compared to the isogenic tau-V337V controls (Bowles et al., 2021; PMID: 34314701). This finding may be relevant to the pathophysiology of Alzheimer’s disease, owing to the progressive tau and p–tau accumulation phenotypes observed in tau-V337M organoids. We propose that in mutant tau-V337M neurons, ELAVL4 binds an altered set of mRNAs and that it interacts with different proteins, and together these contribute to abnormal glutamatergic neuron differentiation, hyperexcitability, and subsequent cell death. Hence, this study aims to provide insight into the mechanisms by which the early upregulation of ELAVL4 is initiated and how ELAVL4 biology contributes to the consequent loss of glutamatergic tau-V337M neurons, by exploring possible its mRNA targets and protein interactions.

Biosketch
I obtained my Bachelor of Science and Master of Science Degrees in Anatomy from Olabisi Onabanjo University and the University of Ibadan, respectively. Following my outstanding academic records at both undergraduate and master levels, along with my early career contribution to the field of basic medical sciences research, I was employed as a Faculty member at the University of Medical Sciences, Ondo. I taught medical students in neuroanatomy/neurophysiology, developmental anatomy, and gross anatomy. Later, I got the Chinese Academy of Sciences and The World’s Academy of Sciences President’s Fellowship (CASTWAS) Scholarship to pursue my Doctorate at the University of Science and Technology of China, (USTC) Hefei, China, and bagged my Doctor of Natural Science in Biology, (Ph.D. Neurobiology). While in USTC, I explored the role of RNA-binding proteins (RBPs) in cognitive function, synaptic plasticity, and lipid metabolism (PMID: 33727124; PMID: 34258925). My postdoctoral training is aimed at using my knowledge of molecular/cellular/behavioral neuroscience to dissect the role of RNA-binding proteins in neurodegenerative diseases. My mentor Dr. Sally Temple is a recognized expert in the field of neuroscience, with a long history of training postdoctoral fellows. Her lab has a strong focus on neurodegenerative disease, being one of the greatest challenges in current healthcare, and one I am passionate about contributing to. I will study the neuronal RNA-binding protein ELAVL4, following the recent discovery that it upregulates early in a tauopathy 3D organoid model, in a study led by Dr. Temple.
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The Myokine Irisin as Mediator of Exercise-Induced Improvement of Cognitive Function in Alzheimer’s Disease (AD)

Abstract
AD continues to rise as our population ages and despite significant efforts, there is currently no effective treatment. These limitations increase the urgency for prevention measures such as exercise. Indeed, exercise improves overall health and brain function. Exercise can increase blood flow to the hippocampus, brain area involved in memory and severely affected in AD. However, while neuroprotective effects of exercise are gaining acceptance, a substantial knowledge gap remains regarding the specific mechanisms whereby exercise improves cognition and might help in AD.

Myokines (hormones released by skeletal muscles), are one possible mediator. Specifically, the myokine Irisin that is released into circulation during exercise. Irisin induces a brain-derived neurotrophic factor (BDNF)-mediated neuroprotective pathway in the hippocampus. Reducing Irisin impairs hippocampal long-term synaptic plasticity and memory in mice, and such deficits are reversed by restoring Irisin brain levels. Moreover, Irisin is reduced in AD patients and animal models. While these data suggest that Irisin may mediate exercise-induced neuroprotection, the effects of Irisin on cellular function as well as on cellular resistance to AD pathology remain unknown. Thus, our long-term goal is to determine how exercise confers neuroprotection and to provide insights into therapeutic targets in AD. Our specific objectives are to determine how Irisin affects hippocampal cell and synaptic function in normal and transgenic models of AD (TgCRN8 mouse). Our specific aims (SA) are: SA1. Determine how Irisin alters cellular and synaptic function in hippocampal granule cells. Using slice electrophysiology recordings, we will directly examine the effect of Irisin on intrinsic properties and synaptic transmission onto hippocampal granule cells in TgCRND8 mice. SA2. Test the hypothesis that exercise-induced Irisin maintains normal synaptic function in the hippocampus of tgCRND8 mice. First, we will use repeated exercise (swimming) to induce the physiological release of Irisin from skeletal muscles and slice electrophysiology to compare hippocampal synaptic function between sedentary and swimmer AD mice. Second, we will use adeno-associated virus (AAV) technology to directly manipulate Irisin levels in the hippocampus of sedentary tgCRND8 mice mimicking exercise.

Biosketch
I am a neuroscientist studying neural mechanisms altered by environmental factors such as stress, diet and exercise. I am particularly focused on uncovering how these mechanisms can sometimes lead to unhealthy cognitive aging and neurodegenerative disorders such as Alzheimer’s disease. The motivation to continue studying mechanisms underlying these conditions is deeply personal as I have first hand experience watching close family members being affected by devastating neurodegenerative diseases.

I am also a junior faculty passionate about mentoring trainees that will be the future of science. As a Latinx woman in science I am well aware of the challenges and obstacles. However, I am determined to contribute not only by being a productive researcher but also by ensuring that everyone feels appreciated and welcome in the lab, especially those coming from communities heavily underrepresented in academia.

I am looking forward to participate in this workshop and to integrate myself into a scientific community that is so well structured and defined as the AD research community.
Derek, Archer, PhD
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Abstract
While reductions in medial temporal lobe (MTL) white matter tract microstructure have been suggested to have a role in longitudinal cognitive decline in aging and Alzheimer’s disease (AD), it is unknown what genetic factors drive these reductions. The objective of this LRP proposal is to use MTL white matter tract templates in conjunction with genome-wide analyses to identify the genetic drivers of white matter tract microstructure. This proposal will leverage several aging datasets to conduct all analyses (n=2,509 participants) and validation will be conducted using UK Biobank data. The central hypothesis is that MTL white matter tract microstructure is driven by genes and pathways related to myelination, axonal transport, and neuroinflammation in aging and AD. The primary aims of this proposal will take a multi-level approach to understand which genes and pathways lead to MTL white matter microstructural decline by using candidate gene, genome-wide, and gene expression approaches. The complementary training plan will equip me with the skills necessary to transition to an independent career focused on imaging genetics by emphasizing the following training objectives: (a) expand expertise in computational genetics, (b) acquire a practical understanding of the pathophysiology and clinical manifestation of AD, and (c) enhance my skillset in data harmonization and big data analytical techniques. Importantly, this project has recently been funded by the NIA as a K01 award (K01-AG073584).

My K01 mentoring team is made up of experts in each training area, and their training will be augmented through interdisciplinary training at the Vanderbilt Memory & Alzheimer’s Center and cutting-edge computational and genomic resources available at the Vanderbilt University Medical Center. Together, these resources provide the ideal training environment, and these resources will allow me to dedicate 100% protected effort to focus on research and career development.

Biosketch
Dr. Derek Archer is a neuroscientist and a Research Assistant Professor of Neurology at Vanderbilt University Medical Center. Dr. Archer’s research interests focus on computational neurogenomics with the goal of identifying novel in vivo neuroimaging and genetic biomarkers in neurodegenerative disease. Specifically, he is determining how vascular risk, genetic susceptibility to white matter decline, and Alzheimer’s disease pathology lead to reductions in white matter integrity. Dr. Archer is a collaborator of the Vanderbilt Memory and Aging Project, the Vanderbilt Memory and Alzheimer’s Center Computational Neurogenomics Team, and an investigator in the Vanderbilt Alzheimer’s Disease Research Center.

Dr. Archer completed his doctoral degree in biobehavioral science at University of Florida and a postdoctoral fellowship in diffusion magnetic resonance imaging with funding from the Parkinson’s Foundation. He joined the Vanderbilt faculty in 2019.
Martina Assogna, MD
Santa Lucia Foundation IRCCS, Rome, Italy
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Abstract
My research is focused on clinical experimentation in the field of neurodegenerative disorders and in clinical neurophysiology of cognitive functions.

In particular I am interested in investigating the pathophysiology of Alzheimer’s disease and to find early biomarkers of disease progression, through the use of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS), mainly in combination with electroencephalography (EEG).

I am also involved in clinical trial using therapeutic rTMS in patients with early Alzheimer’s disease, in order to improve memory through a consistent variation in functional and structural brain connectivity.

Biosketch
Martina Assogna is a neurologist and a neuroscientist working at the Non-invasive Brain Stimulation Unit, Santa Lucia Foundation IRCCS (Rome, Italy) lead by Giacomo Koch. She graduated in Medicine and Surgery in la Sapienza University (Rome, Italy) in 2015. She completed the Residency in Neurology in November 2020 at Tor Vergata University (Rome, Italy). In 2019 she attended as research fellow the Berenson Allen Center for Non-Invasive Brain Stimulation, Beth Israel Deaconess Medical Center (BIDMC), Harvard University (Boston, Massachusetts) under the supervision of Emiliano Santarnecchi where she was actively involved in clinical trials on brain stimulation in Alzheimer’s disease patients. She has an expertise in the field of neurodegenerative disorders. In particular, she is currently involved in healthcare, research and clinical experimentation in Alzheimer’s disease and frontotemporal dementia patients. In particular, her research activity is focused on the application of non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), mainly used in combination with electroencephalography (EEG), to investigate the pathophysiology of these disorders an the response to interventions.
Investigating Circular RNA-Mediated Neurotoxicity in Tauopathies

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Abstract
Circular RNAs (circRNA) are a subclass of non-coding RNAs with a covalently closed loop structure that are formed via non-canonical splicing. CircRNAs are specifically enriched in the brain among different species and further accumulate in the brain as a function of physiological aging. CircRNAs biogenesis is directly associated with N6-methyladenosine (m6A), a post transcription modification of RNA molecule. An increase in circRNAs and abnormal m6A modification significantly correlate with clinical diagnosis and development of Alzheimer’s disease, respectively. Alzheimer’s disease and related “tauopathies” are pathologically defined by various forms of tau aggregates in the brains of affected individuals. We have previously reported that tau-induced dysfunction of lamin, a nuclear scaffold protein, causes nuclear polymorphisms including invaginations and blebs in tauopathies. We have also found that polyA RNA accumulates within nuclear invaginations in the context of tauopathy and that genetic and pharmacologic reduction of RNA export reduce RNA accumulation within invaginations and suppresses tau neurotoxicity. While dysfunction of the nuclear envelope and consequent aberrant RNA export mediate tau-induced neurotoxicity, the identity of the RNAs that accumulate within nuclear blebs, the role of posttranslational modifications (m6A) in circRNA accumulation, and their relationship with aging and tauopathy are currently unknown. Based on the association between nuclear polymorphism and RNA export, alongside the global enrichment of circRNAs and disrupted RNA methylation during aging, I hypothesize that an m6A-dependent accumulation of circRNA in tauopathies sequester complementary RNAs and RNA binding proteins into large inclusions that trigger RNA export via nuclear blebbing. I find that circRNA accumulates in brains of Drosophila model of tauopathy and RNAi-mediated reduction of mbl, which is particularly enriched in its circular form in the brain, significantly suppresses tau-induced neurotoxicity at day ten of adulthood. RNAi-mediated reduction of m6A writer and reader significantly reduces circMbl biogenesis and neuronal death in adult Drosophila. I observed increased presence of nuclear blebs with large inclusions in brains of tau transgenic Drosophila compared to the control and that circMbl and m6A lining these nuclear buds, suggesting a potential role of nuclear blebs in circRNA nuclear export.

Biosketch
Farzaneh Atrian is a postdoctoral fellow at Sam and Ann Barshop Institute for Longevity and Aging Studies at San Antonio, TX. Farzaneh earned her PhD in cancer biology from Purdue University where she studied the role of nuclear mechanics in the context of chemoresistance in cancer cells. She continues to pursue her interest in identifying the role of nuclear architecture in mediating cell fate decisions during aging as a postdoctoral fellow in the laboratory of Dr. Bess Frost, who is a pioneer in the field of brain aging and neurodegeneration. Currently she is investigating the causes and consequences of nuclear envelope polymorphisms in the context of aging and tau-induced neurodegeneration. She received the T32 Biology of Aging Training Grant for two years and she has co-authorships on manuscripts published in Nature Aging and ACS journals. Her long-term career goal is to lead an academic lab that focuses on Alzheimer’s disease and aging-related neurodegeneration.
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Effects of Diet and Post Translational Modification of Aβ Peptides on Alzheimer’s Pathology and Pathophysiology

Abstract
Amyloid beta (Aβ) peptides which accumulate in brains of Alzheimer’s disease (AD) patients are heterogeneous at the N-terminus. The N-terminus of Aβ is cleaved by β-secretase at position aspartat1 (β-cleavage) and to a much lesser extent at glutamat11 (β-cleavage). More importantly, the glutamates are cyclized to pyroglutamatic acid (pGlu) in truncated peptides starting at position 3 or 11. Peptides containing N-terminal pGlu e.g., pGlu3-Aβ (3-40/42) are the major Aβ peptide fragments within the core of neuritic plaques. These peptides can account for about 50% of the whole Aβ deposited in plaques. It was shown that these peptides are more neurotoxic and that they aggregate more rapidly than full length isoforms. In brain fractions of AD patients, a significantly higher amount of N-terminally truncated, pGlu-modified Aβ peptides was detected. Type-2 diabetes mellitus (T2DM) is a known risk factor for AD. Compelling evidence supports the notion that insulin deficiency and insulin resistance are involved in AD-type neurodegeneration. Extensive epidemiologic evidence indicates that individuals with T2D are at higher risk of developing AD. Genetic predispositions to T2D implicate the fundamental insulin signaling pathways including insulin resistance and insulin receptor expression. Till date there is no study on effect or probable correlation between high fat/western diet modelling type 2 diabetes phenotype and post translational modification of N-terminal Aβ peptides on the progression of AD and other vascular dementia. We intend to investigate the effects of diet and post translational modification of N-terminal Aβ peptides on AD pathophysiology and potential disease modifying therapies.

Biosketch
Joshua Babalola is a third-year doctoral student of the doctoral programme in Metabolic and Cardiovascular Disease, Medical University of Graz. His primary affiliation is with D & F Institute of Pathology, Medical University of Graz, Austria. For his doctoral thesis, he is investigating the effect of blood brain barrier dysfunction and diets on the pathophysiology of Alzheimer’s disease and potential disease modifying therapies.
Ahmed Bahrani, PhD
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Abstract
MarkVCID is the premier National Institute of Neurologic Diseases and Stroke consortium tasked with developing and validating novel biomarkers that will facilitate clinical trial development in the area of vascular cognitive impairment and dementia. Seven imaging protocols were selected for further development including our novel longitudinal white matter hyperintensity (WMH) Growth/Regression protocol that allows for the determination of within-subject change in WMH volumes over periods as short as one year, ideal for future clinical trial use. This protocol expands on our previous work demonstrating that WMH volumes due to cerebrovascular risk factors demonstrate admixtures of focal growth, stability, and regression that define disease progression. Instrumental validation of this protocol within the MarkVCID consortium is presented. MRI 3D T2-weighted acquisitions were collected from the MarkVCID database: 14 subjects (75.6 ± 7.8 years) for the Inter-rater reliability and Inter-site reproducibility, and 18 subjects (73.1 ± 11.0 years) for the test-retest repeatability that underwent repeat baseline scans within seven days and one follow-up visit (or vice versa). The consortium sites are the University of Kentucky (the kit lead site), John Hopkins University, Rush University, University of California Davis/San Francisco, University of New Mexico, University of South California, and University of Texas Health San Antonio. The WMH growth/regression kit was built inside a Singularity Container to be unified. ICC values of WMH growth/regression of Test-retest repeatability were 0.969/0.937, and for Inter-rater/Inter-site validation were 0.992/0.961, respectively. The novel WMH growth/regression protocol developed by our team at the UK is robust and reproducible. It represents the first validated method for measuring discrete, neuroanatomic, within-subject change in WMH volumes over practical clinical trial timelines as short as one year. As such, the protocol is well positioned to take on national and international importance as the first validated longitudinal biomarker for tracking cerebrovascular disease and response to therapies in the MarkVCID biomarker portfolio. Further work biological validation are underway in the national MarkVCID consortium.

Biosketch
I earned a Ph.D. in biomedical Engineering in 2020 from the University of Kentucky, focusing on biophotonics technology and MRI neuroimaging post-processing. My work mainly was on developing and improving the diffuse correlation spectroscopy technology and MRI neuroimaging protocols to quantify white matter lesions and cerebral blood flow in the aging population. Currently, I am a postdoc scholar at the Sander-Brown Center on Aging. I have several publications in biophotonics and neuroimaging.
Praveen Bathini, PhD  
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Abstract
N-terminally-truncated and modified amyloid-beta peptides are abundant in cerebral amyloid deposits in Alzheimer’s disease (AD). Pyroglutamate3 Aβ (pyroGlu3 Aβ) is generated upon N-terminal truncation of Aβ followed by cyclization by glutaminyl cyclase to convert glutamic acid at residue 3 to pyroGlu3 Aβ, which aggregates quickly, resists degradation, and is neurotoxic. AD progression appears to correlate with the presence of pyroGlu3 Aβ peptide aggregates in brain. Growing evidence, including our own, indicates that pyroGlu3 Aβ acts as a seed for Aβ deposition and accelerates inflammation, neurodegeneration and cognitive decline; therefore, targeted removal of this toxic species by immunotherapy will reduce Aβ deposition, inflammation and neuritic dystrophy, and protect cognition. We have demonstrated that targeted removal of pathogenic pyroGlu3 Aβ by immunotherapy using an anti-pyroGlu3 Aβ IgG1 mAb (07/1) in a prevention study and the IgG2a version of the same antibody (07/2a) in a therapeutic study, reduced pyroGlu3 Aβ and general (non-pyroGlu3) Aβ suggesting that pyroGlu3 Aβ acts as a seed for Aβ deposition. Furthermore, the anti- pyroGlu3 Aβ mAbs protected cognition. Together with Probiodrug AG, we have developed a CDC-mutant (K332A) version of the 07/2a mAb (07/2a-k) to avoid vascular inflammation observed in clinical trials using plaque binding Aβ antibodies. Here, I am working on the following hypotheses: 1. 07/2a-k, a novel murine anti- pyroGlu3 IgG2a CDC-mutant antibody, will effectively reduce plaques and protect cognition while avoiding potential inflammatory vascular side effects in APP/E4 mice that are prone to vascular amyloid and microhemorrhages; 2. Microglia will have a less inflammatory response to 07/2a-k exposure. 3. 07/2a-k antibody will neutralize the toxic effects of pyroGlu3 Aβ on neurons (in vitro). The goal is to determine whether passive immunotherapy with the novel CDC-mutant anti-pyroGlu3 Aβ mAb (07/2a-k) is safe and effective in a relevant pre-clinical animal model as a prelude to a clinical trial for AD.

Biosketch
Dr. Praveen Bathini has 7 years of experience in neuroscience research, with a particular focus on molecular mechanisms underlying neurodegeneration in protein malnutrition, ischemic stroke, and Alzheimer’s disease. He utilizes molecular and Omics technologies applied both to the rodent and human brain, central and peripheral biofluids, animal behaviors and histology. He secured a competitive Swiss excellence fellowship from the confederation to pursue his doctoral studies. As EKSAS fellow of the University of Fribourg, he worked on Alzheimer’s disease research, particularly exploring the molecular mechanisms of peripheral inflammation in sporadic dementia and investigating non-invasive diagnostic biomarkers for early detection of Alzheimer’s disease. His work has been featured in UNIFR and communicated to the public through social media and Youtube. Before joining the laboratory of Dr. Lavinia Alberi at SICHH, Praveen worked as a research assistant at the National Brain Research Centre. Presently, he is working as a research fellow in the laboratory of Dr. Cynthia Lemere at Brigham and Women’s Hospital, Harvard Medical School. Currently, he is working on passive immunotherapy with the novel CDC-mutant anti-pyroGlu3 Aβ mAb (07/2a-k) in an AD mouse model.
Abstract
Complement component C3, an innate immune molecule, is important for removing pathogens and in synapse elimination during brain development, aging and Alzheimer’s disease. The classical complement cascade is a complex process leading to the elimination of dead cells, debris, or pathogens. Upon activation, complement initiating protein C1q binds to and coats dead cells, debris, or pathogens, triggering a protease cascade leading to the activation of complement protein C3, the central component, which opsonizes material for elimination by triggering phagocytosis of microglia or by forming the membrane attack complex (MAC), causing cell lysis. Previously, our lab has found that C3-deficiency protected against synapse loss during normal aging in hippocampal CA3 of WT mice neuroprotective in aged, plaque-rich APP/PS1dE9 mice. However, it remains unknown whether suppressing complement C3 signaling during early stages of AD pathogenesis, when relevant therapeutic interventions might be considered, would confer neuroprotection later in life. To address this question, we generated the first-ever C3 floxed mouse line with our Collaborator, Dr. Carroll, and then crossbred the C3fl/fl mice with an inducible, global Cre line, Rosa26-Cre-ERT2+/-, to generate our novel inducible C3 conditional knockout mouse line, C3fl/fl; Rosa-Cre-ERT2+/-; (C3iKO) mice. First, 4–5-month-old male and female C3iKO mice were i.p. injected with tamoxifen (TAM) or corn oil (CO; control) daily for 5 days. Tamoxifen treatment of C3iKO mice led to a sustained ~95% lowering of serum C3 levels. Behavioral testing for hippocampal-dependent spatial memory, object memory, and object location was performed when TAM-treated and CO-treated mice reached 16-17 months of age. C3iKO+TAM mice performed significantly better than C3iKO+CO-treated mice in these behavioral tasks, indicating that C3 lowering after brain development protected mice from age-related cognitive decline. In another study, mice were treated with TAM or CO at 3–4 months of age and electrophysiological recording of long-term potentiation (LTP) was conducted 3 months later in hippocampal slices incubated with neurotoxic Aβ S26 dimers. Remarkably, C3 lowering protected hippocampal synapses from Aβ S26 dimer-mediated LTP impairment. In conclusion, global C3 lowering in young adult mice protected against hippocampal dysfunction, suggesting that targeting C3 may be an effective therapeutic strategy for AD.

Biosketch
I have been working since 2010 with the intriguing connection between Alzheimer’s disease (AD) and diabetes, and the molecular mechanisms linking these diseases have just recently started to be unraveled. In this line, neuroinflammation appears to be one of these mechanisms which could be rationed with both disorders. I have been working as a postdoc with Dr. Cynthia Lemere (Harvard Medical School and Brigham Women’s Hospital, Boston, USA) since 2019. I have experience with neurobiology cellular and biochemistry with an emphasis in neuroinflammation, synaptic plasticity, tau pathology, diabetes, and mitochondrial dysfunction, and complement system dysfunction.
Abstract

Vitamin D has been observed to improve protein homeostasis and decrease the risk of age-related chronic diseases, including Alzheimer’s disease (AD). Vitamin D deficiency has epidemiologically been linked to AD, leading to a rising medical concern that individuals may be self-medicating prophylactically to avoid the risk of the disease, resulting in the consumption of large dosages for which the potential negative consequences are currently unknown. In this study, we utilized a triple transgenic AD mouse model (3xTg) to determine the effects of a megadose Vitamin D supplementation (10,000 IU/kg) on the neuropathology and progression of AD. Our results suggest that a megadose Vitamin D supplementation can drive 3xTg mice into a diabetes-like state as indicated by increased weight gain and fat mass, reduced glucose tolerance, and altered respiration compared to 3xTg mice fed normal Vitamin D levels (1500 IU/kg). The gut microbiome has been increasingly recognized for contributing to metabolic and inflammatory changes. In 3xTg mice supplemented with megadose Vitamin D, we observe an increase in bacteria that may impact both gut barrier integrity and its inflammatory state, specifically an increase in the phylum Firmicutes and a decrease in the phylum Bacteroidetes, which may alter metabolic homeostasis contributing to the insulin-resistant state. Our findings demonstrate that Vitamin D megadosing may potentially have detrimental effects on patients predisposed for AD, driving individuals into pre-diabetes, a major known risk factor for the disorder.

Biosketch

David’s undergraduate work focused on understanding how toxic aggregated proteins exacerbate neurodegenerative diseases and applying biochemical methods to characterize Alzheimer’s disease mouse models. After graduating from the University of Minnesota Twin Cities with a bachelor’s degree in neuroscience, David joined Dr. Julie Andersen’s laboratory in 2018 at the Buck Institute for Research on Aging as a SENS Research Foundation post-baccalaureate scholar. At the Buck Institute, David utilized microscopy and computational methods to explore the cellular mechanisms underlying brain region vulnerability to neurodegenerative and age-related disease. His recent efforts have focused on the pathological implications of the gut, microbiome, and immune systems in neurodegenerative diseases. David has also been engaged with Dr. Martin Brand’s laboratory exploring the mitochondrial involvement in age-related diseases. In the Brand laboratory, David is currently developing a gene therapy technique in vivo for rescuing damage within the mitochondria that appears in age-related metabolic and neurodegenerative disorders.
Suet Theng Beh, PhD
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Human Autopsy-Derived Scalp Fibroblasts and Postmortem Human Scalp-Derived Precursors for Neural Cell Differentiation: Biobanking for Age-Related Neurodegenerative Disease Research

Abstract
The Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute (BSHRI) annually receives tissues from 60-90 autopsy cases who were non-demented elderly or had neurological disorders. The Human Cells Core for Translational Research (HCCTR), established since 2018, takes advantage of the BBDP tissue resource to build a human fibroblasts banking program using postmortem scalp tissues. Fibroblasts are widely used for inducible pluripotent stem cells reprogramming and differentiation. The purpose of banking postmortem fibroblasts from clinically and neuropathologically characterized patients is to provide human cells to academic and pharmaceutical communities to facilitate translational research and drug development for age-related diseases that are currently without cure. Since HCCTR has built a sustainable program for banking human autopsy-derived scalp fibroblasts from neuropathologically characterized donors, we are currently working on human skin-derived precursors (hSKPs) isolating and direct reprogramming human fibroblasts and hSKPs into neurons from our banked human autopsy-derived scalp fibroblasts. This makes banked hSKPs and neurons derived from patient-specific fibroblasts a good candidate to facilitate progress in human cell-based basic and translational research. Our initial effort will be focusing to provide a source of primary and differentiated disease-relevant cells. The differentiation of these disease-relevant cell types will provide a valuable tool to model specific molecular phenotypes of age-related neurodegenerative disease.

Biosketch
I joined the Human Cells Core for Translational Research (HCCTR) in October of 2019 as a post-doctoral fellow and I have recently been promoted to staff scientist. The HCCTR is a new core added to the Banner Sun Health Research Institute (BSHRI) in August of 2018. The goal of the HCCTR is to bank cryoprotected human cells isolated in neuropathologically confirmed neurodegenerative disease cases and to provide the cells to research scientists all over the world to facilitate translational research. This cell banking program will result in a valuable human cell resource to use for a better understanding of normal aging and age-related neurodegenerative diseases. In the next phase of my career, I will be worked to reprogram our banked human autopsy-derived scalp fibroblasts from neuropathologically characterized donors into neurons and human skin-derived precursors (hSKPs). The neurons and hSKPs reprogramming and banking potential from well-characterized primary dermal fibroblasts are easily accessible and could be expanded to include several different types of stem cells produced and maintained in HCCTR. This makes banked cells a good candidate to facilitate progress in human cell-based basic and translational research. Our initial effort will be focusing to provide a source of primary and differentiated disease-relevant cells. The differentiation of these disease-relevant cell types will provide a valuable tool to model specific molecular phenotypes of age-related neurodegenerative disease.
Abstract
Alzheimer’s disease (AD), the most prevalent form of dementia worldwide, affects a growing proportion of the elderly and poses a significant societal burden. Pathological hallmarks include the appearance of misfolded proteins in the brain. This is evidenced by the deposition of amyloid-β (Aβ) plaques and tau-containing neurofibrillary tangles leading to neuronal loss.

Age is the single most important factor that leads to the expression of the dementia associated with AD. Additionally, a number of molecular factors underlie the severity and/or age of onset. APOE-ε4 is one of the strongest genetic risk-factors for AD. Very subtle changes in the gene lead to three common variants: APOE-ε4, APOE-ε3, and APOE-ε2. In terms of AD, APOE-ε4 is considered disease promoting, APOE-ε3 is neutral, and APOE-ε2 is protective. ApoE is involved in numerous functions in the brain including cholesterol homeostasis and has significant roles in clearance of Aβ. Functional complexity is increased as apoE is primarily synthesized and secreted from astrocytes while neuronal expression has also been identified in certain contexts. This raises questions regarding which cell source and what fundamental functions of APOE modulate AD progression. Is there a glia-neuron disease modifying interaction and/or a neuron-autonomous impact of APOE?

I will compare isogenic cell lines in which the genome is engineered to carry different APOE alleles. I aim to interrogate the impact of the various genotypes on neuronal differentiation, neuronal structure and/or function, and neuronal vulnerability to diseased-associated insults. These approaches will allow me to better define the cellular and molecular interactions that underpin the modulation of disease progression by apoE.

References:

Biosketch
Mercedes Beyna, a research scientist at Biogen, focuses on Drug Development mainly in the area of neurodegeneration. Captivated by neuroscience, she has worked in the field for over a decade, in both academic and industrial laboratory settings. Mercedes earned her undergraduate degree in Biology at Binghamton University and Master’s Degree in Biology from New York University. Mercedes is privileged to be pursuing her PhD in neuroscience while working fulltime and expects to graduate in 2022! As an active member of the Biochemical Pharmacology Discussion Group at the New York Academy of Sciences since 2010, she enjoys developing interesting and educational symposia. Mercedes is highly motivated about encouraging young women, especially those of underrepresented minorities, to join STEM fields.
Sarah Biber, PhD
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Abstract
I am thrilled to be stepping into a new role as the Program Director for the National Alzheimer’s Coordinating Center (NACC) based at University of Washington. I am trained as a PhD scientist in molecular and cellular biology with a focus on molecular neuroscience but I have been away from the bench since 2014. Over the past seven years, I have been focused on facilitating and advancing healthcare research and innovation in variety of roles. I am eager to jump into the Alzheimer’s field as I take on this new role at NACC but have never specifically studied Alzheimer’s. The Alzheimer’s Fast Track workshop will be the perfect opportunity to get up to speed on the latest Alzheimer’s research which will be invaluable to me in my new role. I am happy to see that one focus of the workshop is on racial and sex disparities as addressing this is something I will be focused on early on.

Biosketch
Sarah Biber, PhD, is the new Program Director for the National Alzheimer’s Coordinating Center which is focused on facilitating collaboration to advance Alzheimer’s research and innovation. She most recently led the Surgical Innovation Program and OHSU Invent-a-thon at Oregon Health and Science University and has been actively engaged in advancing healthcare innovation over the past seven years both working directly with startup companies and as an intrapreneur. She previously served as the Assistant Director for NIH’s National Center for Data to Health (CD2H), where she focused on facilitating informatics innovation, data sharing, software development, and collaboration across the Clinical Translational Science Awards Program. Prior to her CD2H role, she was Entrepreneurial Program Director at the Oregon Bioscience Incubator where she helped grow the incubator three-fold and spearheaded statewide programs and partnerships to support entrepreneurs and startups. During this time she also served as chair of the Startup Resource Workgroup for the Portland Innovation Quadrant and co-founded Accelerate Biotech and Digital Health PDX. Dr. Biber received her PhD in Molecular and Cellular Biology from Brandeis University in 2014.
Abstract

Neuroinflammation is a hallmark of Alzheimer’s Disease (AD), and the transition of glia to a chronic pro-inflammatory state is thought to be a pre-clinical indicator of AD onset. Exercise has well documented neuroprotective effects in the AD central nervous system (CNS) by promoting neuronal plasticity, stimulating adult neurogenesis and enhancing cognitive function. Exercise also promotes powerful systemic and CNS anti-inflammatory effects which inhibit neuroinflammation both in healthy aging systems and in models of AD. However, the ability to perform exercise remains largely inaccessible to the elderly populations most at risk for developing AD. Skeletal muscle autophagy is highly activated during exercise, and secretes cytokines into circulation in response to physical activity that can have potent CNS beneficial effects. We have recently derived transgenic mice that moderately overexpress Transcription Factor EB (TFEB), a lysosome biogenesis promoter, in skeletal muscle (cTFEB;HSA-Cre mice), which resulted in enhanced muscle proteostasis, similar to what is observed with long-term exercise regimens. Surprisingly, we observed amelioration of proteotoxicity and a promotion of neurogenesis in the aging CNS of muscle enhanced animals, suggesting that our TFEB;HSA-Cre model acts as a potential exercise mimetic. Additionally we see reduced levels of inflammatory cytokine transcriptional activation and fewer amyloid-beta aggregates in the hippocampus of 5XFAD;TFEB;HSA-Cre transgenic animals compared to their 5XFAD littermates, suggesting muscle TFEB-regulated pathways may serve as potential therapeutic targets against neurodegenerative disease progression. Currently, I am investigating the effects of muscle TFEB-induced circulating factors on regulation of astrocyte activation, a key feature present during AD pathogenesis. I will perform medium-throughput Nanostring analysis to identify transcriptional changes in neuroinflammatory signaling associated with skeletal muscle TFEB overexpression, and identify TFEB-activated secretory factors that may serve as direct CNS-targeting cytokines. Using these methods, we can identify essential exercise-associated cytokines that can reduce AD-associated neuroinflammation and prevent disease progression, as well as establish skeletal muscle TFEB-overexpression as a therapeutic exercise mimetic.

Biosketch

I am a Postdoctoral Fellow in the lab of Dr. Constanza Cortes at the University of Alabama at Birmingham. I am interested in understanding the interaction between glia and neurons and how this communication is impacted during aging and neurodegenerative disease progression. My current research focuses on the identification of circulatory factors that get upregulated with exercise and play a role in modulating astrocyte-associated neuroinflammation in Alzheimer’s disease in order to develop a novel therapeutic method to treat AD. This research is funded by the Alzheimer’s Association Research Fellowship. My goal is to become a leader in AD research and serve as a mentor for incoming scientists interested in investigating neurological dysfunction and intercellular communication. In my free time, I enjoy playing volleyball and doing pub trivia.
Amanda Boyd, PhD
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Abstract
Alzheimer’s disease and related dementias (ADRD) affects 5.5 million Americans. The number of people in the US with ADRD is expected to increase to 16 million by 2050 unless preventive interventions and effective treatments are developed. Despite advances in ADRD research among non-Hispanic Whites, little is known about the prevalence and risk factors for ADRD in American Indian and Alaska Native (AI/AN) populations. This is in part due to low participation of AI/ANs in ADRD research. Numerous organizations have issued calls for an increase in minority participation in clinical trials. However, success has been evasive in efforts to recruit AI/AN populations into ADRD clinical studies. The internet is a primary method for providing information about ADRD and recruiting participants into clinical studies. AI/ANs frequently use the internet for health information but also report that the websites they access lack cultural sensitivity. To increase AI/AN participation in ADRD research, it is critical to understand how AI/ANs consume and process online information. This information can be used to create effective communication and recruitment material for ADRD clinical studies. In this study, we will apply a multi-method approach to assess how AI/ANs process and consume online material. Using this information, we will create culturally tailored online content to educate AI/ANs about ADRD to promote their enrollment into ADRD research. Our Specific Aims are to: 1) conduct psychophysiology testing and semi-structured interviews to characterize visual website search patterns, objectively measured cognitive and emotional responses, knowledge about ADRD and research, and preferences for accessing health information online; and 2) create a culturally tailored educational ADRD website for AI/ANs that offers research opportunities and conduct a pilot study to demonstrate feasibility of a future randomized controlled trial. Given the increasing use of the internet for health-related information seeking, improving the availability and cultural relevance of online AD information resources may help expand AI representation in AD research. Our cutting-edge methods and materials can be adapted and used with other conditions with the ultimate goal of finding ways to prevent or treat AD and dementia among all people.

Biosketch
Dr. Amanda Boyd is faculty in the Edward R. Murrow College of Communication and the Institute for Research and Education to Advance Community Health, both at Washington State University. She is a member of the MvÈ¬tis Nation (Indigenous person of Canada) from Treaty 8 territory in Alberta. Her research focuses on health communication with Indigenous populations and draws from an interdisciplinary education, which includes communication, Indigenous studies, and rural sociology. Dr. Boyd’s K01 Career Development Award funded by the National Institute on Aging, aims to advance knowledge about Alzheimer’s disease communication and recruitment science among American Indians and Alaska Natives. Ultimately, her research program aims to develop the tools and theory needed to improve the communication of health risks to Indigenous populations in the United States and Canada.
Rory Boyle, PhD
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Abstract
My research aims to understand why, and how, some people are resilient to cognitive decline despite significant neurodegeneration or high levels of neuropathology.

As part of the Harvard Aging Brain Study, I will be directly involved in the analysis of neuropsychological and neuroimaging data from a longitudinal observational study of a preclinical older adult cohort.

I will analyze tau and amyloid PET imaging data in order to understand why some individuals at risk of Alzheimer's disease are resilient to cognitive decline despite significant tau and/or amyloid burdens. I will further investigate the extent to which sex differences in resilience may moderate the association between tau burden and cognitive decline, and between amyloid burden and cognitive decline.

I will use machine learning models (connectome-based predictive modeling, gaussian process regression, elastic net regression) to analyse neuroimaging data in order to develop objective measures of resilience to tau and amyloid burdens. These methods will enable the generalizability of the models to be assessed via their external validation on separate independent datasets (such as the Alzheimer's Disease Neuroimaging Initiative cohort).

Biosketch
I completed my PhD in the Whelan Lab in Trinity College Dublin. I am now working in Massachusetts General Hospital, as a Postdoctoral Fellow under the supervision of Dr. Rachel Buckley, as part of the Harvard Aging Brain Study. My work focuses on the development and validation of neuroimaging measures of cognitive reserve and resilience. I am also greatly interested in sex differences in cognitive reserve and resilience to cognitive decline. Ultimately, I hope to apply my research to improve outcomes for people living with, or at risk of, dementia.
Abstract

Introduction: We examined the association of obstructive sleep apnea (OSA) severity with plasma levels of Aβ42/Aβ40, and determined whether the combination of plasma Aβ42/Aβ40 and OSA-severity improved diagnosed brain amyloidosis and tau pathology.

Methods: Cross-sectional analysis of baseline data from 120 community-dwelling cognitively normal older-adults, selected from ongoing NYU longitudinal studies on memory, sleep and aging. Of the 120 participants, 70 had baseline CSF-Aβ42, and CSF-PTau (measured using ELISA), dichotomized using data driven approach to quantify brain amyloidosis (CSF-Aβ42 ≤375pg/ml) and tau pathology (CSF-PTau ≥53.7pg/ml). OSA-severity was defined using AHI4% ([5<AHI4% <=15 [mild], 15<AHI4% <=30 [moderate], AHI4% >30 [severe]] vs AHI4% <5[control]). Levels of plasma Aβ42/Aβ40 were assayed using SIMOA technology. Associations of OSA-severity and plasma Aβ42/Aβ40 (n=120) were assessed using regression and correlation analyses. Receiver operating characteristic (ROC) analyses were performed to evaluate the ability of plasma Aβ42/Aβ40 and OSA to diagnose CSF brain amyloidosis and tau pathology (n=70) and were implemented with PROC LOGISTIC. Analyses controlled for age, sex, BMI, education and APOE4.

Results: Of the 120 participants, 80 (67%) were women. Mean (SD) age was 69.1 (7.2) years. Mean (SD) AHI was 14.3/hr (16.3). Forty-eight subjects (40%) had AHI <5, 30 (25%) had AHI: 5 to ≤ 15, 18 had AHI: 15 to ≤30 and 22 had AHI >30. Among individuals with a negative CSF-Aβ42 status, relative to controls, OSA severity was associated with higher levels of plasma Aβ42/Aβ40 (Mean Difference (d) (SD) 0.009 (0.0032), 95%CI: 0.003, 0.016; d (SD) 0.010 (0.0036) 95%C: 0.005, 0.019; d (SD) 0.008 (0.0037) 95%C: 0.004, 0.017. P-value <.05 for mild, moderate and severe OSA respectively). Plasma Aβ42/Aβ40 had a low correspondence with CSF-amyloid status (receiver operating characteristic area under the curve [AUC] 0.54 (95% CI=0.45 - 0.62) and CSF-PTau (AUC 0.51 (95% CI=0.41 - 0.60). The combination of plasma Aβ42/Aβ40, and OSA severity significantly improved correspondence with CSF-amyloid status (AUC 0.78 (95% CI=0.67 - 0.90) and CSF-PTau status (AUC 0.71 (95% CI=0.61 - 0.84).

Conclusion: In cognitively normal older-adults, together with AHI indices, plasma Aβ42/Aβ40 may represent a minimal-invasive reliable and cost-effective blood test that can potentially power large clinical OSA-AD trials.

Funding: NIH/NIA/NHLBI (K23AG068534, L30-AG064670, CIRAD P30AG059303 Pilot, NYU ADRC P30AG066512 Developmental Grant, AASM 231-BS-20, R25HL105444 SRG, T32HL129953, R01HL118624, R21AG049348, R21AG055002, R01AG056301, R01AG022374, R21AG059179, R01AG056682, R01AG056531, K07AG05268503)

Biosketch

Dr. Bubu was recently supported as a postdoctoral fellow at NYUSoM Department of Population Health under a T32 funding mechanism. Dr. Bubu has graduate, internship, and fellowship-level clinical and research training in neurology, neuro-epidemiology and public health. His research examines how age-related and age-dependent sleep changes, and vascular risk, impact cognitive decline and AD risk, and how they drive AD related disparities. He has received various grants to fund his research, such as the American Academy of Sleep Medicine (AASM) Bridge Award for Early Career Investigators, NYU Alzheimer’s Disease Research Center Developmental Grant, and Columbia Center for Interdisciplinary Research on Alzheimer’s disease Disparities Pilot Grant. Dr. Bubu recently received a mentored NIA K23 award “The mediating role of Slow Wave Sleep and Vascular Risk Factors on Alzheimer Disease related disparity between African-Americans and non–Hispanic Whites.” The K23 award will provide Dr. Bubu the opportunity for training in sleep neurobiology, health disparities and MRI/PET data analysis of Alzheimer’s disease biomarker and neuroimaging data.
Abstract
The progressive accumulation of amyloid beta (Aβ) and tau neurofibrillary tangles, accompanied by cognitive impairment leading to dementia, are recognized hallmarks of Alzheimer’s disease (AD). Until recently, the postmortem observation of Aβ and tau neuropathology has been sufficient for a definitive diagnosis of AD. Observations of resilient cases exhibiting Alzheimer’s-associated pathology but no dementia have challenged this concept. Understanding the molecular mechanisms of resilience can provide a powerful suite of targets for therapeutic interventions to enhance neuroprotection. With the aim of determining molecular signatures of resilience, we used levels of plaques and tangles as a first dimension, and presence/absence of cognitive impairment as a second dimension, to classify individuals from the Religious Order Study and Memory and Aging Project (ROSMAP) into AD, Resilience, and Control groups. Building upon our studies of bulk transcriptional signatures of AD resilience in brain, and in order to identify cell-specific markers of resilience, we have leveraged single nuclei RNA-seq data from ROSMAP (n = 48) and performed differential gene expression analyses to identify cell-tropic resilience expression. Among the cell-specific differences observed, we noticed patterns where cells from the resilience group had an opposing direction of expression in comparison to the AD group and normal controls, suggesting protective events, or even resistance to the presence of AD neuropathology. For example, in excitatory neurons, we identified 1,615 and 142 differentially expressed genes (DEGs) between resilience and controls and between AD and resilience, respectively. CAMK2N1 showed significantly decreased expression in resilient subjects compared to AD and controls. It codes for an inhibitor of CaMKII, a pivotal synaptic protein for learning and memory processes, with a role in long-term memory. In contrast, in microglia, where we identified 4 DEGs between resilience and AD and 1 DEG between resilience and controls, SRGN exhibited increased expression in resilience compared to AD and controls. It codes Serglycin, involved in compound storage in secretory vesicles and involved in inflammation. We are validating markers of resilience that we have identified and building predictive models that can be applied in the identification of resilient cells and for sample and cell categorization.

Biosketch
I am a Postdoctoral Research Fellow at Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School, with a background in biology, neuroscience and genomics. I did my PhD at the University of Exeter, United Kingdom, where I was recruited as the top-ranked student for the Exeter Alzheimer’s Society Doctoral Training Centre. During my PhD I investigated changes in gene regulation associated with AD neuropathology in mouse models, which resulted in my first scientific publication as first author in Cell Reports in 2020. I already have recognizable contributions to the AD field and achieved considerable success in my short academic career, with highlights including two publications as first author in Cell Reports, two publications as second author (one currently in press), and one book chapter; pilot grants to conduct some of the experiments during my PhD; several conference travel awards to attend national and international conferences; a British Neuroscience Association award for public engagement in neuroscience; and I was selected as the ISTAART Student Volunteer Lead awardee for the Alzheimer’s Association International Conference 2018, as recognition of my leadership aptitude as an ISTAART student volunteer in 2017. I have presented my research at national and international conferences, including as invited speaker. In my current research I am investigating protective mechanisms of resilience and resistance to AD and other dementias, particularly at the single cell level, that can be used as foundations for therapeutical strategies.
Abstract
Neuropsychiatric and neurodegenerative diseases are a delayed response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) central nervous system (CNS) infections affecting ~75% of patients 6 month after hospitalization. Among neurodegenerative diseases that share common neuropathology with coronavirus disease (Covid)-19 is Alzheimer’s Disease (AD). Dysregulation of critical pathways by SARS-CoV2 may underlie maladaptive changes in the CNS that exacerbate the development of AD including the prospect of the kynurenine (KYN) pathway (KP), a major regulator of serotonergic and glutamatergic systems, which are dysregulated during AD and Covid-19. The amino acid l-tryptophan (TRP) is essential for the biosynthesis of serotonin. The kynurenine pathway is a major route of degradation of ingested l-tryptophan, during which the bioactive compound kynurenic acid (KYNA) is produced. It is possible the KP is impacting the development of Covid-19 neurological sequelae and exacerbating the onset and severity of AD given that the KP is activated in patients with Covid-19 and imbalances in KP, such as increased KYN/TRP ratios are found in blood and CSF of AD patients. These findings implicate KP dysregulation in the development of AD pathology following Covid-19.

Biosketch
The overarching goal of the Cisneros Lab is to understand the mechanisms dictating interactions between the immune system and nervous system during substance use disorders and neuroinfectious diseases. Increasing evidence demonstrates that the immune system plays a critical role in both normal and pathological processes in the central nervous system. A particular interest is on immunocompetent cells of the CNS, including astrocytes and microglia, and their innate immune responses, both inflammatory and antiviral during substance use disorders and CNS viral infections. Using in vivo, ex vivo and in vitro models, we focus on neuroimmune interactions in addiction and viral-mediated neurodegeneration.
Elisia Clark, PhD, MSTR  
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Abstract
The autophagy-lysosomal pathway is essential for cell homeostasis in both healthy and diseased neurons, and it’s implicated as a primary pathway for clearance of pathological proteins in neurodegenerative diseases. TMEM106B is a transmembrane lysosomal protein identified as a genetic risk factor for Frontotemporal Dementia. TMEM106B overexpression results in increased autophagosome – lysosome fusion, an essential step in the autophagy pathway mediated by SNARE protein VAMP8. It is not understood how VAMP8 is recruited to lysosomes. Our preliminary data shows TMEM106B directly interacts with VAMP8 and when TMEM106B-lysosome binding motif mutation is expressed, VAMP8 redistributes away from lysosomes. Thus, we hypothesize that TMEM106B is necessary for VAMP8 recruitment to lysosomes. This will further be examined by identifying structural domains necessary for TMEM106B and VAMP8 interaction and examining autophagosome-lysosome fusion and lysosome vacuolization in a CRISPR -TMEM106B -/- induced pluripotent stem cell (iPSC) neuronal cell line.

Defects in the autophagy-lysosomal pathway can lead to proteinopathies, the hallmarks of many neurodegenerative diseases such as Alzheimer’s disease and Lewy Body Dementias. I will also investigate how the effect of TMEM106B on autophagy-lysosomal pathway integrity affects degradation and internalization of misfolded proteins. Our lab has successfully utilized Alexa Fluor-tagged alpha synuclein preformed fibrils (PFF) to examine internalization in iPSC-neurons. I hypothesize that loss of TMEM106B will result in increased PFF internalization by impeding autophagosome-lysosome fusion. This will be examined by tracking exogenous PFF transmission and internalization over time across compartmentalized cell populations. This will provide understanding of how the autophagy-lysosomal pathway can be targeted and modified to mitigate cell-to-cell transmission that can be applied to other neurodegenerative diseases with misfolded proteins as pathological hallmarks, including Alzheimer’s disease.

Biosketch
Dr. Elisia Clark is an African American Woman, daughter of Southern Virginia natives with no college degree, enthusiastic about solving problems using atypical approaches, and aspiring Independent Research Scientist dedicated to increasing Diversity in Science by means of VISIBILITY and OPPORTUNITY. Her journey began as a Meyerhoff and HHMI Scholar at University of Maryland, Baltimore County. Her research interests intersect molecular biology and tissue engineering to examine molecular mechanisms of neurodegeneration using 3D scaffolds. Significant contributions to science include identifying how disease-associated mutations alter protein processing and mitochondria function in Friedreich’s ataxia, and successfully demonstrating how a tissue-engineered 3D nigrostriatal pathway encased in a tubular hydrogel can be used as a testbed for evaluating axonal pathophysiology in Parkinson’s disease. Her current work contributes new insight into the interaction of the frontotemporal dementia-associated protein TMEM106B with VAMP8 in lysosome-autophagosome fusion, which are currently being extended in iPSC neurons using CRISPR technology to understand the role of TMEM106B in autophagy-lysosomal pathway integrity. Seeing as how this serves as primary pathway for clearance of pathological proteins in neurodegenerative diseases, her long-term overarching objective is to understand and explore modifiers of the autophagy-lysosomal pathway to gain understanding of how neurons evade the native mechanisms intended to protect them from death, relevant to all neurodegenerative diseases.
Gillian Coughlan, PhD
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Abstract
My future research aims to understand the importance of sex differences in risk for Alzheimer’s disease (AD). This research will include: 1a) examining the association between menopause status, hormone replacement therapy and amyloid and tau, and 1b) the moderating effect of the menopause on the relationship between tau and cognitive changes. These aims will be completed using the Wisconsin Registry for Alzheimer’s Prevention dataset 2) Pursue my interest in digital technology testing of cognition in relation to genetic risk for AD, with the aim of investigating the influence of APOE4 on frequent testing of cognition using a smartphone app administered in the Australian Healthy Brain Project. 3) Improve the sensitivity of spatial navigation paradigms in AD, by investigating how well navigation performance tracks spread of AD in the brain, and work towards developing a novel spatial navigation paradigm for use in pre-dementia research populations.

Biosketch
Gillian received a PhD in Biomedical Science from Norwich Medical School (2016-2020), where she studied the behavioural and neural characteristics of spatial navigation impairments in preclinical Alzheimer’s disease. She completed postdoctoral training at the Rotman Research Institute where she continued her work on refining early cognitive and biological markers of Alzheimer’s disease (2020-2021). She is now joining the MGH/Harvard Medical School as a postdoctoral research fellow, under the primary supervision of Dr Rachel Buckley, where she will examine the associations between menopause status, hormone replacement therapy, amyloid and tau, and cognitive changes.
Simone Crivelli, PhD
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FTY720 Decreases Ceramides Levels in the Brain and Prevents Memory Impairments in a Mouse Model of Familial Alzheimer’s Disease Expressing APOE4

Abstract
Background and Purpose: A metabolic shift favoring ceramide (Cer) production over sphingosine-1-phosphate (S1P), contributes to amyloid-β (Aβ) formation, inflammation and neurodegeneration in Alzheimer’s disease (AD). The drug FTY720 mimics S1P bioactivity, once phosphorylated in vivo. However, it is unclear if FTY720 can counterbalance S1P downregulation and prevent memory impairment.

Experimental approach: Two doses of FTY720 (0.1 mg / kg and 0.5 mg / kg daily) were given by oral gavage for 15 weeks to transgenic mouse models of familial AD carrying human apolipoprotein E (APOE) APOE3 (E3FAD) or APOE4 (E4FAD). After 12 weeks of treatment, animals were subjected to behavioral tests for memory, locomotion, and anxiety. Blood was withdrawn at different time points and brains were collected for sphingolipids analysis by mass spectrometry, gene expression by RT-PCR and Aβ quantification by ELISA.

Key Results: Sphingosine kinase 1 was downregulated in E3FAD, while S1P lyase was upregulated in E4FAD. In the cortex of E3FAD and E4FAD, Cer d18:1/16:0 and Cer d18:1/22:0 levels were elevated compared to littermate controls. Low levels of S1P in the plasma were associated with a higher probability of failing the memory test. FTY720 increased the likelihood of E4FAD mice to succeed in the memory test by 1.8-fold and reduced anxious behavior in APOE4 mice. Furthermore, FTY720 reduced Cer levels, inflammation, and Aβ concentration in cortex of E4FAD.

Conclusions & Implications: Our data indicates S1P plasma levels predict cognitive decline and that FTY720 improves memory and anxious behavior by reducing inflammation, Aβ, and Cer levels in the cortex.

Biosketch
I took my bachelor in Pharmacy at the University of Turin (Italy). For my PhD training, I moved to Maastricht University (the Netherlands), where I defended my thesis in neuroscience in 2019. My PhD focused on pharmacological modulation of lipid bioactivity and transgenic mouse models of Alzheimer’s disease (AD). In my thesis, we investigated the role of a family of lipids, known as sphingolipids, in AD pathophysiology and treatment. The specific aims of my research were to identify new biomarkers and develop interventional strategies that target the sphingolipid pathway. The dedication and hard work invested in these exciting years of my PhD were recognized by the Alzheimer’s Drug Discovery Foundation as I received an Outstanding Young Investigator Award in 2017. After finishing my PhD thesis, with the support of a travel award offered by the Alzheimer Nederland Foundation, I relocated to the laboratory of Professor Dr. Erhard Bieberich to continue my scientific interest in understanding neurodegeneration and the potential of lipids as therapeutic modalities. During my postdoctoral years, I was funded by the National Institute on Aging to investigate if lipid changes in synaptic mitochondria isolated from brain of AD patients by using the AD biobank at the Sanders-Brown Center on Aging in Lexington. Later, I was funded for two years by the BrightFocus Foundation to study a pharmacological approach for controlling lipid production in mitochondria as a treatment for AD.
**Abstract**

My future research aims to understand the importance of sex differences in risk for Alzheimer's disease (AD). This research will include: 1a) examining the association between menopause status, hormone replacement therapy and amyloid and tau, and 1b) the moderating effect of the menopause on the relationship between tau and cognitive changes. These aims will be completed using the Wisconsin Registry for Alzheimer’s Prevention dataset 2) Pursue my interest in digital technology testing of cognition in relation to genetic risk for AD, with the aim of investigating the influence of APOE4 on frequent testing of cognition using a smartphone app administered in the Australian Healthy Brain Project. 3) Improve the sensitivity of spatial navigation paradigms in AD, by investigating how well navigation performance tracks spread of AD in the brain, and work towards developing a novel spatial navigation paradigm for use in pre-dementia research populations.

**Biosketch**

I am a South African postdoctoral researcher at the University of Copenhagen’s Department of Public Health. My main interest is to better understand the molecular underpinnings of non-communicable diseases and how intervention strategies can be better tailored to target the molecular and not just the phenotypic aspects of diseases. My previous research has focused on the use of -omics data in predicting the risk of cardio-metabolic diseases. Prior to my Ph.D. I was performing largely laboratory-based research in the context of genetics and cardiovascular disease. This evolved to large-scale -omics during my Ph.D., where I performed epigenome-wide investigations in a population-based cohort in South Africa. I am currently involved in two proteomics investigations, one where I investigate plasma proteomics in relation to diabetes, and the other focusing on tissue-based proteomics in the context of non-alcoholic fatty liver disease fibrosis. I recently received funding from the Alzheimer’s Association to commence the next phase of my research career. For the next three years, I will be leading a plasma proteomics project within the SPRINT-MIND study, where I will investigate plasma proteomic profiles associated with future risk of all-cause dementia, cognitive decline, and vascular and atrophic brain abnormalities. In addition, I will investigate the ability of baseline proteomic profiles to predict the efficacy of blood pressure treatment regimens to delay incident cognitive impairment.
Abstract
My main research interests involve the application of systems biology, bioinformatics and omics technologies to tackle and solve biological problems. I believe that a systems view of biology using these novel technological tools can enable more reliable and robust representations of biological reality. As a Master of Science student, my research focused on the search for biomarkers of diseases using transcriptomics, and I gained expertise in R and Python programming languages, microarray and RNA-seq bioinformatics analyses and multivariable analyses. My PhD relied on systems biology approaches in lung cancer, which required me to further develop skill in network biology, systems pharmacology and omics data exploration, analyses and integration. My current research interest in Alzheimer’s disease involves the application of omics and systems biology approaches to study molecular and functional aspects of the disease and to develop new therapeutic and diagnostic strategies. I am leading three main projects. One involves comparing transcriptomic profiles of animal models with human pathology to highlight and prioritize the most appropriate for a given research question. The second is a neuroinformatic project in which we are developing a strategy to integrate neuroimaging and transcriptomics through groups of genes. In a third project, we explored molecular features of astrocytes sorted by cell cytometry of two animal models to better identify the effect of Aβ and tau neuropathological markers of AD in these cells.

Biosketch
My name is Marco Antônio De Bastiani. I am a postdoctoral fellow at Zimmer Lab in Universidade Federal do Rio Grande do Sul (UFRGS), Brazil. I finished my PhD in 2019, during which I studied molecular drivers and master regulators controlling the development and initiation of lung cancer. My research interests involve the application of systems biology, bioinformatics and omics technologies to tackle and solve biological problems. During my PhD, I also participated in collaborations aiming to explore systems biology strategies in Alzheimer’s disease (AD) development and treatment. In fact, I noticed that the usage of such approaches in AD is lagging when compared to cancer research. I also realized the great potential that could be unearthed by exploring omics, network biology and systems thinking in this field.
Abstract
Alzheimer’s disease (AD) is not part of the normal aging process. Age-associated changes in brain lipids are exacerbated in AD but the precise role of lipid metabolism dysregulation in AD remains uncertain. My project will better characterize AD-associated changes in brain lipids and whether increased levels of lipid-derived aldehydes produced by persistent oxidative stress are sufficient to cause AD-associated defects. I will use both AD Human cells and mice carrying a mutation in the aldehyde dehydrogenase 2, the primary enzyme that detoxifies from the accumulation of aldehydes.

Biosketch
Jessy Etienne is a fourth-year postdoctoral researcher in Pr. Daria Mochly-Rosen laboratory (Chemical and Systems Biology, Stanford). He entered the research on Alzheimer’s disease (AD), investigating the role of aldehyde dehydrogenase (ALDH) 2 in the disease development and progression. Before that, he had three years of postdoctoral training in Pr. Irina Conboy’s laboratory (Bioengineering, UC Berkeley). He studied the role of age-accumulated systemic factors on tissue aging and assessed rejuvenation strategies that remove them in the circulation of older mice. Finally, Dr. Etienne earned his Ph.D. from the Sorbonne University (Paris, France), where he characterized skeletal muscle progenitors expressing ALDH in health, aging, and disease. His pioneered work was the first step to target ALDH with small molecules to boost skeletal muscle regeneration.
Elizabeth Fisher, PhD
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Abstract
Recent studies highlight a role for inflammation and blood brain barrier (BBB) breakdown in progression of Alzheimer's Disease (AD). While significant work examining interactions between microglia and astrocytes, and astrocytes and endothelial cells (ECs) has been done, relatively few studies have examined how microglia influence vasculature directly, and their potential to impact vascular inflammation, BBB function and permeability. The pro-inflammatory cytokine IL1β, released actively from diseased microglia, is elevated in AD. The IL1b receptor and its obligate co-receptor, Interleukin receptor 1 associated protein (IL1RAP), are expressed on both microglia and ECs. An IL1RAP gene variant has been associated with more rapid AD progression, reduced microglial activation, and increased amyloid accumulation. The goal of this study is to test the overarching hypothesis that targeting IL1RAP on both microglia and ECs will dampen the inflammatory interaction between these two key cell types and prevent damage to blood vessel integrity which exacerbates AD progression. Utilizing human induced pluripotent stem cell (iPSC)-derived cells, I will examine the consequences of overexpression and knockdown of IL1RAP in microglia and ECs. In Aim 1, using isolated cells of each type, I will 1) examine the AD-relevant inflammatory profile of microglia using markers as well as cytokine release profiles, and assess their ability to phagocytose Aβ, 2) examine the effects of IL1RAP levels on barrier permeability of ECs and their inflammatory cytokine release. In Aim 2, I will utilize co-culture combinations to assess how microglia and IL1RAP levels interact with EC monolayers to impact barrier function, inflammation, and cytotoxicity. As there has been correlation between APOE44 and IL1β levels in patients with AD, I will perform all these studies in APOE33 and APOE44 genetic backgrounds using an established collection of isogenic iPSC lines. The proposed experiments will provide foundational studies on microglial-EC interactions, and further mechanistic insights into the development of vascular breakdown in AD, and rich datasets to build upon in my independent research lab. My long-term goal is to establish an independent research lab focused on understanding the molecular mechanisms and sequence of events contributing to inflammatory processes driving breakdown of the BBB.

Biosketch
Elizabeth (Liz) Fisher is a postdoctoral fellow in the laboratory of Dr. Sally Temple at the Neural Stem Cell Institute in Rensselaer, NY. She obtained her PhD in the laboratory of Dr. James Lechleiter, where her focus was on glutamate metabolism in astrocytes following stroke and oxidative stress. Her current work is on examining immune cells which infiltrate the spinal cord following injury, for which she has a fellowship funded through New York State’s Spinal Cord Injury Research Board. She is also starting new research on examining the interactions between microglia and endothelial cells in induced pluripotent stem cell models.
Abstract
Mild Cognitive Impairment (MCI) is the pre-dementia stage characterized by early cognitive and behavioral changes preceding Alzheimer’s disease dementia. Although the development of efficacious treatments has been hampered by variability in the neurocognitive presentation of MCI, repetitive transcranial magnetic stimulation (TMS) has emerged as a promising treatment for transdomain cognitive impairment. TMS is thought to exert its therapeutic effects through stimulation of local neuronal tissue influencing the interactions between connected brain regions. There is preliminary evidence of TMS-related cognitive benefits in MCI, but the underlying functional brain changes are not well-understood. My current work aims to characterize alterations in resting-state functional connectivity and cognition following TMS treatment in MCI. Individuals with amnestic MCI will receive high-dose accelerated intermittent theta burst repetitive TMS targeting the left dlPFC, a primary region of the frontoparietal network (FPN) which is highly implicated in executive function and hypoactive in MCI. We hypothesize that excitatory stimulation of the left dlPFC may bolster cognitive abilities that facilitate compensation for MCI-related deficits by altering network interactions. My primary aim is to examine alterations in functional networks known to be altered in MCI following TMS treatment, with hypothesized greater local effects (i.e., within the FPN) than distributed effects (i.e., between the FPN and default mode, limbic, and dorsal attention networks). I will also assess changes in cognition secondary to TMS treatment, with hypothesized greater focal improvements in executive function and smaller benefits for episodic memory. Lastly, I will employ an innovative, data-driven approach, using machine learning to identify whole-brain functional networks associated with cognitive change following TMS treatment. This project will provide a clearer understanding of TMS-induced changes to distributed neurocircuitry, which is a critical step in advancing cutting-edge neuromodulation for MCI. The results will directly inform future randomized controlled trials, aiding in the development of more personalized approaches to stimulation targeting and establishing the optimal dose of TMS therapy for cognitive rehabilitation in MCI, ultimately promoting translation to the clinic.

Biosketch
I am a postdoctoral fellow of clinical neuropsychology in the Department of Neurology at the Medical University of South Carolina. My long-term career goal is to become an independent investigator conducting clinical trials that mitigate the risk and progression of Alzheimer’s disease and related dementias (ADRD). I completed my doctoral training in clinical psychology at Ohio State University with a concentration in health psychology and neuropsychology, during which time I developed expertise in cognitive aging. My graduate work focused on investigating normal age-related changes in cognition and brain function and testing behavioral interventions for promoting healthy cognitive aging. I developed strong skills in research design and advanced neuroimaging analysis through collecting and analyzing complex neuropsychological and functional MRI data from both cross-sectional and longitudinal studies. During my postdoctoral fellowship, I am furthering my clinical and research training in aging and ADRD. I provide outpatient neuropsychological evaluations for patients seen in the Department of Neurology, many of whom have MCI or ADRD. I am currently using data from an NIA-funded longitudinal study to investigate how specific neuropsychological measures and brain functional connectivity can be used to detect preclinical AD. I am advancing my program of research by acquiring new training in brain stimulation therapies for MCI and AD.
Abstract
Evidence indicates that health and wellness factors such as exercise, diet, and management of vascular risk factors can impact cognition and functional independence during the aging process. However, the neuroprotective effects of these factors are not fully understood. We aim to examine the biological underpinnings of health and wellness factors using neuroimaging and biomarkers in order to inform prevention and treatment efforts for neurodegenerative disease processes such as Alzheimer’s Disease using the Vanderbilt Memory and Aging Project longitudinal samples.

Biosketch
Marissa Gogniat is a postdoctoral fellow in Neuropsychology at the Vanderbilt Memory and Alzheimer’s Center under the mentorship of Dr. Angela Jefferson. She graduated summa cum laude from Emory University with bachelor’s degrees in Neuroscience & Behavioral Biology and Psychology. She earned a doctorate in Clinical Psychology with a concentration in Neuropsychology from the University of Georgia. Prior to joining VMAC, she completed a doctoral internship at the VA Maryland Health Care System/University of Maryland School of Medicine Psychology Internship Consortium in the VA Neuropsychology Track.

Dr. Gogniat’s research focuses on the neuroprotective effects of health and wellness factors in aging using neuroimaging techniques and neuropsychological assessment.
Abstract

Lakmal Gonawalaa,c,d, Maheehsa Madhumalia, Priyani Paranagamab Harry WM Steinbusch, K Ranil D. de Silva,a,d*Interdisciplinary Centre for Innovations in Biotechnology and Neuroscience, University of Sri Jayewardenepura, Nugegoda, Sri Lanka; bDepartment of Chemistry, University of Kelaniya, Kelaniya, Sri Lanka; cDepartment of Cellular Neuroscience, Faculty of Health, Medicine & Life Sciences, Maastricht University, Maastricht, The Netherlands; dInstitute for Combinatorial Advanced Research and Education (KDU-CARE), General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka.

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Background – A neuropathological study guided by the corresponding author, (1) performed across two countries in South Asia; Sri Lanka (n =50) and India (n = 32) with a mean age 72.1yrs ± 7.8, mean ± SD. and mean age 65.9yrs ± 9.3 respectively, aging cytoskeletal pathologies were comparatively higher in elderly Sri Lankans compared to Indians. (2) age, education, and genetic factors (APOE, MTHFR T allele ) were associated with AD-related neuropathological changes in 76 Sri Lankan elderly subjects (≥50 years), possibly resulting due to their genetic, dietary and/or environmental variations.

Cinnamon, an ancient spice which has generated increased interest in the treatment of Alzheimer’s disease due to its activity in inhibiting Aß aggregation, therefore reduces Aß toxicity. Thus opened a biologic means to study neuroprotective role of Ceylon cinnamon. In this study explored the antioxidant, anti-inflammatory properties of extracts of bark and leaf of seven indigenous cinnamon species grown in Sri Lanka namely, Cinnamomum zeylanicum (C. zeylanicum), C. dubium, C. Rivulorum, C. sinharajaense, C. cappuru, Sri Gemunu and Sri Vijaya.

Methodology – The cinnamon bark and leaf essential oil, methanol and Hexane extracts were extracted. Anti-oxidant (ABTS, DPPH) and anti-inflammatory (HRBC membrane-stability) assays were performed on essential oil, methanol and Hexane extracts.

Results - According to the lowest IC50 Values we determined that the bark of C. rivulorum (0.18), Sri vijaya (15.01) and the leaf of C. sinharajaense (0.05), Sri Vijaya (2.76) have the most significant antioxidant properties. The bark of C. Rivulorum (80.53), Sri Vijaya (102.9) and the leaf of Sri Vijaya(35.33) and C.

Cont. on next page
Lakmal Gonawala, MSc, cont.

Zeylanicum (63.74) have the most significant anti-inflammatory properties.

Conclusion - The leaf and bark essential oil of all seven indigenous cinnamon species showed different ranges of chemical compositions among them with different levels of antioxidant and anti-inflammatory properties. The data obtained in this study opened another dimension of therapeutic potential of Ceylon Cinnamon in neurodegenerative diseases including AD leading to nutraceutical and drug development. Blending the authenticated pure Cinnamomum varieties with the synergistic approach according to their individual medicinal properties will be the next generation holistic medicine.

Biosketch

I am a Ph.D. candidate, researching on role of clinical genetics, proteomics and metabolomics in patients with Trinucleotide Repeat Disorders (TRDs). I have successful in creating, 1. South Asia’s one of the most comprehensive and largest biomaterial collection in TRDs which comprise of, • clinical data, DNA, serum samples of over 90 Huntington’s disease (HD) and 253 Spinocerebellar ataxias (SCA) patients • 03 villages in Sri Lanka with common ancestry with high prevalence of SCA type 1 • SCA and HD (48%) patients’ who are genetically negative for common mutations could be analyzing for rare/ novel mutations. 2. Sri Lanka’s • 1st ever state sector free of charge molecular diagnostic service as a service to the nation which aim to provide possible Antisense Oligonucleotide based clinical trials. • pioneers in establishing mobile clinics across the country increasing its access to the inherited neurological disease community Succeeded in identifying novel protein-based biomarkers in SCA by analyzing 1300 proteins in patient serum (Unpublished) in collaboration with University of Houston, USA. I have co-authored 05 Research Papers published in PubMed Indexed Journals including Lancet neurology and 01 book chapter Published with Springer. I have 1st author research publication on Cinnamon and book chapter in Elsevier which are under review. I have secured a total of 10 international “Full Travel Awards and Training Fellowships” which enabled me to obtain advanced training in neuroscience techniques from Universities/ Research Centers in Netherlands, Japan, Singapore, China, and India.
Abstract

Objective: In clinical studies administering certain anti-beta-amyloid antibodies, vascular inflammatory adverse events have been reported. These events are observed as amyloid-related imaging abnormalities (ARIA). The frequency of ARIA events is higher among apolipoprotein (APOE) E4 allele carriers compared to non-carriers. With the intent of improving preclinical modeling of patients with Alzheimer’s disease who are most at risk for vascular complications of anti-beta-amyloid immunotherapy, we selected a recently developed mouse model: APP/PS1dE9 mice crossbred with human APOE E4 targeted replacement mice. The model has yet to be characterized at multiple ages. To evaluate face validity of the mouse model, we are conducting a battery of histological and biochemical tests.

Methods: To examine age-related pathological changes, we euthanized male and female APP/E4 mice across 3 ages: 8-, 12- and 16-months. Immunohistochemical methods and immunofluorescent staining are being used to evaluate beta-amyloid plaque deposition, cerebral amyloid angiopathy, blood-brain barrier leakiness, neuritic dystrophy, and microhemorrhages. Additionally, we implemented immunoassays to quantify levels of beta-amyloid and APOE.

Results: ELISA of brain insoluble homogenates revealed significantly higher beta-amyloid40 and beta-amyloid42 levels in 16-month mice compared to 8- and 12-month mice. Furthermore, 16-month females showed significantly higher beta-amyloid40 levels than age-matched males. A significantly lower beta-amyloid (42/40) ratio was exhibited in 16-month mice compared to 8- and 12-month mice. Further analyses are underway.

Conclusions: Sex- and age-dependent increases in beta-amyloid deposition were observed in the APP/E4 mouse model. Upcoming analyses will better define the APP/E4 as a model for future preclinical anti-amyloid immunotherapy studies.

Funding: NIH RF1 AG058657 (CAL)

Biosketch

I am a graduate student studying Cognitive and Clinical Neuroscience with specialization in Drug Development and Neurohealth at Maastricht University in the Netherlands. During my undergraduate degree in Neuroscience at the University of Guelph, Canada, I supported the characterization of attention and visual-spatial learning in three of the most used transgenic mouse models of Alzheimer’s disease: APP/PS1, 5xFAD, and 3xTG. We used touchscreen equipped operant chambers to assess behaviour, using the 5-choice serial reaction time and paired associate learning tasks. For my graduate degree, I am conducting my thesis research in Dr Cynthia A. Lemere’s lab at Brigham and Women’s Hospital, Boston MA. We are preclinically testing a novel CDC-mutant anti-pyroglutamate-3 Aβ- antibody for Alzheimer’s disease treatment in a transgenic mouse model. My enthusiasm for our research stems from my desire to translate molecular, genetic and mechanistic data into the development of novel disease-modifying treatments for Alzheimer’s disease.
Ruben Gomez Gutierrez, MSc and PhD
Baylor College of Medicine, Houston, Texas
Ruben.GomezGutierrez@bcm.edu

Abstract

Background: Current clinical PET imaging relies on translocator protein (TSPO) to detect neuroinflammation in brain disorders including degenerative conditions such as AD, however this marker lacks cell type-specificity and offers no information on what type of insult is causing the reaction. An ideal PET tracer would detect both the rise in pro-inflammatory and loss of anti-inflammatory glial responses and would discriminate cellular responses to amyloid-beta from tau. We investigated whether a pair of glial purinergic receptors would provide a better measure of inflammatory status in mouse models of AD than the current standard TSPO.

Methods: We studied the expression of P2X7, P2Y12, and TSPO in 5xFAD and PS19 transgenic mice at early and late stages of pathology using quantitative immunohistochemistry. Co-staining with microglial (Iba1) and astroglial (GFAP) markers was used to identify cell types expressing each receptor.

Results: Expression of P2Y12 decreased significantly with the onset of both Aβ and tau pathology. TSPO increased in 5xFAD mice with amyloid pathology, but not in PS19 mice with tau pathology. We observed the opposite pattern in P2X7 signal, which increased in PS19 mice with tau pathology, but less in 5xFAD mice with amyloid plaques.

Conclusions: Our findings suggest there may be distinct neuroinflammatory responses to Aβ and tau with increased TSPO around amyloid but not tau, and a reciprocal increase in P2X7 around tau but not amyloid. We found that P2Y12 and P2X7 serve as complementary markers reflecting the loss of homeostatic microglia and the rise of a reactive phenotype. Our results support continued investigation of P2Y12 and P2X7 as potential biomarkers of distinct neuroinflammatory responses which may be used in conjunction with TSPO to distinguish AD pathologies in clinical settings.

Biosketch

Ruben Gomez Gutierrez graduated with MSc in Cellular in Molecular Biology from the University of Málaga (Spain) and is currently undergoing PhD graduation from the same institution. Most of his PhD work was performed at University of Texas Health Science Center and later joined Dr. Joanna Jankowsky lab at Baylor College of Medicine. His research focuses on two main areas: basic mechanisms of neurodegeneration and tools for imaging neuroinflammation. Specifically, he is working to uncover the biological significance of TMEM106B in the context of neurodegeneration using novel genetically-engineered mouse models. Concurrently, he is working with collaborators to study whether microglial purinergic receptors may be appropriate targets for new PET tracers to study inflammation in the brain. This work is being funded through the Alzheimer’s Association and the Baylor College of Medicine Center for Alzheimer’s and Neurodegenerative Diseases.
Abstract
I have come to think of Alzheimer’s disease (AD) also as a disorder of the genome. Many studies have now conclusively shown that significant gene expression changes develop over the years in the brains of those affected by the condition, and we are beginning to understand how different brain regions and cell types are affected by AD pathology. This implies an overall failure of transcriptional regulatory mechanisms to maintain network homeostasis. However, the molecular players behind these complex disease-associated transcriptional mechanisms and the signaling pathways that modulate their activation remain mostly unknown, limiting our understanding of the range of biological processes that contribute to this neurodegenerative condition. As I approach the final stages of my postdoctoral training with Prof. Ulrich Hengst, I look enthusiastically into these questions both for their disease relevance and as a fascinating biological problem. Indeed, my time with him has given me a profound appreciation for the complexity – and inherent beauty – of genome biology and its contribute to disease. My future independent research program aims at elucidating how transcriptional misregulation arises during the course of AD and the cell type-specific components driving these changes.

Biosketch
I am approaching the final stages of my postdoctoral training with Prof. Ulrich Hengst at Columbia University, where I have been dissecting how brain gene expression changes come about in Alzheimer’s disease. I received my PhD from University of Coimbra, Portugal, for my work on axon guidance mechanisms in the visual system with Professor Christine Holt at University of Cambridge. Looking further back, I studied Pharmaceutical Sciences as an undergraduate, having obtained a MPharm degree from University of Coimbra in 2009. My research has been supported by the Alzheimer’s Association since 2017.
 Özge Güzel, PhD
University of Bristol, Bristol, United Kingdom
ozge.guzel@bristol.ac.uk

Abstract
Renin angiotensin system (RAS) involvement is becoming increasingly recognised as a biochemical pathway that is likely to give rise to the development and progression of Alzheimer’s disease (AD) and quite likely Vascular dementia (VaD). RAS involvement has been reported to be linked via recurring genetic associations and a recent GWAS with AD and increasingly likelihood of classical hallmarks of AD pathology.

The main aim of my study is to investigate the genetic associations between RAS function and increased risk of AD and to identify the underlying pathophysiological process that are responsible, in a well-characterised cohort of post-mortem brain tissue. More specially, it will explore the impact of genetic variation in ACE1, ACE2, and AGT, key regulators of RAS function, and how these impact their role and role of other proteolytic regulatory enzymes, signalling peptides, and related receptors in RAS pathways. It will investigate the effect of ACE1, ACE2, and AGT variations on gene expression, protein levels of key mediators of RAS function, and disease pathology including Aβ, tau, and CAA pathology in AD, Mixed, and VaD post-mortem human brain tissue.

Biosketch
Ozge Guzel is a second year PhD student in Clinical Neuroscience at University of Bristol. Her research interests centre the role of the renin angiotensin system in Alzheimer’s Disease. She received her bachelor’s degree in Bioengineering from Marmara University. She earned her first master’s degree in Biotechnology at Izmir Institute of Technology and second master’s degree in Molecular Neuroscience at University of Bristol. She was awarded Higher and Overseas Education Scholarship by Republic of Turkey to undertake postgraduate education in the UK. In her free time, she could be found chatting with friends, hiking, and playing tennis.
Abstract
Mild Cognitive Impairment (MCI) seen in early stages of age-related dementia, such as in Alzheimer’s Disease (AD), have severe impacts on health economy and overall human well-being. Although clinical symptoms and hallmark anatomical signs for the late dementia, such as amyloid beta plaques and tau tangles, are well described, alterations in brain structure that lead to early behavioral symptoms are unknown. Triple Transgenic mice (3xTg) that express all three mutations described in AD patients, develop amyloid and tau pathologies, as well as neuronal death, similar to those found in human AD patients. These pathologies make them the ideal model to study AD progression. 3xTg mice begin showing cognitive impairment in spatial memory assays as early as postnatal month four (PM4), with no apparent plaques or tangles evident in the brain. This suggests there are other, not yet identified, neuropathologies involved in the onset of MCI in early age 3xTg animals. A candidate for early neuropathological changes in 3xTg mice was encountered in a recent preliminary electron microscopy (EM) study in our lab. We observed widespread structural alteration that involved ectopic outfolding of oligodendrocyte membranes. A quantifiable occurrence of this oligodendrocyte-induced neuronal damage (OIND) pathologies, multilamellar bodies, was found in the Mossy fiber terminals in the CA3 region of the hippocampus in 3xTg mice by PM3. Based on the role of CA3 in episodic and spatial memory, we reason that OIND could be the underlying mechanism of early cognitive decline in 3xTg animals. It is important to identify these alterations to have a better understanding of the anatomical and molecular basis of MCI.

Biosketch
I graduated Magna Cum Laude with a B.S. in neuroscience and a minor in psychology from George Mason University. During my time at Mason I was awarded Black Scholar of the Year 2018 as well as Outstanding Neuroscience Senior. I am now currently a third year Phd Student at UVA in their sensory and behavioral Neuroscience program, working under Álev Erisir in her neuroanatomy lab. My lab specializes in utilizing Electron Microscopy to study sensory systems, as well as neurodegeneration resulting from disease and injury.
Hao Hu, PhD
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Abstract
There are increasing evidence showing the altered immunological responses occurred during the progression of Alzheimer’s disease (AD). My planned research on AD focused on how the microglia cells acquired this disease associated gene signatures and whether the disease associated microglia (DAM) can potentially induce the non-specific damage to the neuronal cells in AD mouse model. My previous research related to autoimmune diabetes shows that islet macrophages become activated via interferon gamma signaling and can directly induce beta cell death via nitric oxide. It has been shown that in AD mouse model, at later stage of disease progression, a subset of microglia expressed high levels of Interferon related genes. It would be interesting to know whether this subset of microglia can contribute to AD related dementia.

Biosketch
My name is Hao Hu. I received my Ph.D. degree in immunology at Washington University School of Medicine. My Ph.D. work focused on the immunological regulation of T cells and macrophages in islets during autoimmune diabetes development under the supervision of Dr. Emil Unanue. After graduation in Aug 2021, I joined Dr. David Holtzman’s lab to work on brain immunology under the context of AD progression in Nov 2021.
Abstract

6.2 million Americans are living with Alzheimer’s disease (AD), experiencing reduced quality of life and irreversible deterioration of cognitive function. AD development is likely driven by inflammation in the central nervous system (CNS), yet there remain no broadly effective therapies. We propose that AD pathology may be, in part, caused by circadian dysregulation of CNS immune function. The circadian clock is a critical regulator of biological processes, generating ~24 h rhythms in gene expression, hormone release, and behavior, but its efficacy in various cells and tissues deteriorates with age. Up to 70% of individuals with AD experience circadian disruption and sleep-wake disturbances, which often present years before clinical diagnosis. Circadian dysregulation is therefore a potential biomarker and signal for early intervention in AD-related pathology. The immune system is tightly regulated by the circadian clock, generating daily cycles of high and low immune reactivity. During AD, the CNS immune system gradually shifts from a balance between pro- and anti-inflammatory function towards a more reactive inflammatory state, with detrimental consequences for cognition. Thus, we hypothesize that circadian rhythms in CNS immune function are disrupted in AD, leading to cognitive and behavioral changes. We will address the following specific aims: First, establish the role of circadian dysregulation of CNS immune function and cognitive decline during AD by quantifying immune parameters (e.g., microglial activation, expression of pro-migratory molecules, and adaptive immune cell numbers) in the CNS of 3xTg-AD mice and age-matched controls at different times of day; second, determine if disruption of molecular clocks in key CNS-immune interface cells expedites cognitive decline leading to AD-like pathology, using transgenic approaches to selectively ablate a critical clock element in microglia and CNS-immune interfaces and measuring the impact upon cognitive behavior and neuroinflammatory pathology; and third, reveal whether boosting circadian rhythms via time-restricted feeding ameliorates AD-induced pathology and improves cognition in the 3xTg-AD model. We expect that our results will identify a novel role for biological rhythms in regulating neuroinflammatory pathology and cognition, highlighting novel therapeutic avenues to target cognitive decline and behavioral changes in AD and AD-related dementia.

Biosketch

I am a postdoctoral research associate at the University of Texas at Austin, developing a research program in biological rhythms in neuroimmune function. I completed my PhD in the UK, investigating circadian rhythms in glucocorticoid actions and their influence on pulmonary inflammation. I then moved to Germany for a postdoc, applying my knowledge of rhythmic immunity to the adaptive immune system. There, I developed key skills in flow cytometry and imaging, and generated critical data showing that migration of antigen presenting cells (APC) to lymph nodes follows a diurnal rhythm. I stayed with the lab during a relocation to Switzerland and moved into a more senior position to drive my research program focused on time-of-day effects upon vaccination efficacy. I am now building upon my background in rhythmic immunity and cell migration, combining it with behavioral neuroimmunology, to determine the influence of biological rhythms upon immune cell trafficking and neuroimmune function during aging and neurodegeneration.
Abstract
Presence of TDP-43 is shown to enhance neurodegeneration in the late stages of Alzheimer’s disease (AD). For my postdoctoral training, I am researching the synergistic interactions between TDP-43 and tau pathologies. This intensive study will be conducted using various model systems such as C. elegans, mouse models and human brain samples with numerous molecular and biochemical techniques along with transcriptomics approaches. I will be mentored by Drs. Brian Kraemer and Nicole Liachko in their laboratories at the University of Washington, Seattle. During this training, I envision to develop an independent research career in the field of Alzheimer’s research. My long-term goal is to identify effective targets for therapeutics and gain in depth understanding of the cellular and molecular events in AD for better diagnosis.

Biosketch
EDUCATION/TRAINING
2007-2010  B.Sc. (Bachelor of Science) Biotechnology, University of Pune, India
2010-2012  M.Sc. (Master of Science) Biotechnology, University of Pune, India
2015-2021  PhD, Medical Neuroscience, Indiana University School of Medicine, Indianapolis, IN
2021-present  Postdoctoral scholar, University of Washington, Seattle, WA

PEER-REVIEWED PUBLICATIONS
Patricia Kelly, PhD  
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Cell-Wide Calcium Dysfunction in Astrocytes Throughout Cortex of Awake APP/PS1 Mice

Abstract

Aims
Astrocytes are predominant glial cells that exhibit spontaneous intra- and intercellular calcium dynamics that strongly modulate synaptic activity, vascular dynamics, neurovascular coupling and sleep, which are affected by Alzheimer’s disease (AD). Advancing our understanding towards pharmacological protection and/or restoration of astrocytic calcium dynamics is an exciting research avenue towards astrocyte-targeting therapies. We tested the hypothesis that amyloid plaques disrupt all spontaneous calcium dynamics throughout all cellular compartments of cortical astrocytes (somata, primary processes and endfeet) in the awake mouse brain.

Methods
APP/PS1 transgenic mice and age-matched non-transgenic littermates (12-17 months old; n=10) were anesthetized during surgical intracortical injection of our genetically encoded calcium indicator, gfa2.yc3.60, into both hemispheres of the somatosensory cortex followed by ~ 6 mm cranial window over both injection sites and a head-post secured to the skull to permit habituation to awake multiphoton imaging. Cortical volumes containing astrocytes and high magnification time-lapses at 2.3 Hz were acquired for 300 seconds. Custom-written MATLAB scripts were used to quantify all spontaneous intra- and intercellular calcium dynamics in awake mice.

Results
Cortical astrocytes have cell-wide elevated resting calcium both near and far from plaques and remain in the cortex over many months despite very high levels of somatic intracellular calcium. Astrocytic intracellular calcium events are compartmentalized within processes and pathologically impacted by amyloid plaques. Spontaneous intercellular calcium events involve vascular endfeet and propagate at ~33 microns/second throughout the cortex of awake mice. Spontaneous calcium events occurred with greater amplitude within somata.

Conclusions
Astrocytic spontaneous intra- and intercellular calcium events are heterogeneous and dysfunctional throughout all cellular compartments (somata, primary processes, fine processes and endfeet). Astrocyte-targeting therapeutic strategies should consider compartmentalization and heterogenous cell-wide dysfunction.

Biosketch
Patricia Kelly PhD, is currently a Post-doctoral Research Fellow within the laboratory of Prof. Brian J. Bacskai at Massachusetts General Hospital (MGH)/Harvard Medical School, Boston, USA. Dr Kelly uses two-photon microscopy to quantify astrocyte physiology in the brain of awake transgenic mouse models of Alzheimer’s disease (AD) to advance current understanding of astrocyte physiology towards astrocyte-targeting therapies for AD.
Mary Ellen Koran, MD, PhD  
Vanderbilt University, Nashville, Tennessee  
m.e.koran@vumc.org

Abstract
As a new member of the Vanderbilt Memory and Alzheimer’s Center (VMAC), I will be developing a research program that integrates innovative positron emission tomography (PET) and magnetic resonance imaging (MRI) methods for Alzheimer’s disease (AD) to address the major unmet need for PET biomarkers of AD and related dementias. I am interested in the clinical use of amyloid and tau PET and methodological PET development. I will help implement tau PET in the Vanderbilt Memory and Aging Project (VMAP) cohort, and use this cohort with existing PET databases and cohorts. I plan to use these tau PET cohorts to showcase that we can clinically read and stage tau PET more finely than binary staging to predict cognitive change, for clinical trial selection, and to monitor treatment response. Furthermore, I am interested in developing artificial intelligence algorithms as an accurate method for screening possible clinical trial participants that does not require labor-intensive image quantification or patient access to a participating center with these capabilities. For methodological PET development, I am interested in the translation between tracers so that large cohorts can be harmonized. I will also work on methods to optimize PET-CT protocols so that multiple radiotracers can be used in one appointment, decreasing patient appointment burden and increasing clinic throughput. Lastly, I am interested in using these cohorts to analyze the relationship between a person’s brain-age, estimated by their amyloid- and tau- PET scans and MRI, and their whole body “phenotypic” age, to determine if there are genetic effects on this relationship and if changes in modifiable lifestyle factors known to contribute to phenotypic age (such as BMI, glucose, creatinine) effect change on brain age as well.

Biosketch
Mary Ellen grew up in Annapolis, Maryland. She attended Duke University, where she was a Pratt research fellow in Biomedical Engineering. After graduating with honors, Mary Ellen moved to Nashville, Tennessee to pursue a joint MD/PhD in Vanderbilt’s Medical Scientist Training Program. She completed her PhD in Human Genetics in the laboratory of Dr. Tricia Thornton-Wells, where she studied the radiogenomics of Alzheimer’s Disease. She was inducted into the Alpha Omega Alpha medical honor society, was active as a Student Advisor for the MSTP, and graduated as valedictorian of her medical school class. She matched into Stanford’s radiology residency program, where she was served as chief resident and pursued a dual board pathway in Diagnostic Radiology and Nuclear Medicine. While at Stanford she received the Etta Kalin Moskowitz Fund Research Award and the RSNA Trainee Research Prize.

She will join the faculty at Vanderbilt in November 2021 as an Assistant Professor of Radiology in the nuclear medicine division on the physician scientist tenure track. As a member of the Vanderbilt Memory and Alzheimer’s Center (VMAC), she will be developing a research program that integrates innovative magnetic resonance imaging (MRI) and positron emission tomography (PET) methods for Alzheimer’s disease to address the major unmet need for PET biomarkers of Alzheimer’s disease and related dementias.

Outside of work, Mary Ellen enjoys swimming with the local Masters’ team and exploring Nashville with her husband, Cody, and their dogs.
Ana Sabsil Lopez Rocha, MD
Karolinska Institute, Stockholm, Sweden
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Dementia Risk Reduction and Prevention in the Era of the Sustainable Development Goals: the World-Wide FINGERS Network

Abstract
BACKGROUND: Dementia is the main cause of disability in older adults, and its prevention has been set as a global health priority (WHO, 2012). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER trial) showed that a multidomain intervention ameliorating simultaneously several vascular, metabolic and lifestyle-related risk factors can benefit cognition and reduce dementia risk in older adults, but needs to be validated in different settings and populations.

AIMS: Develop global partnership and collaboration to support SDG implementation and promote healthy ageing on a global scale, within multidomain strategies for dementia prevention.

METHODS: World-Wide FINGERS (WW-FINGERS, https://wwfingers.com/) is the first global network of multidomain intervention trials (RCTs) for dementia risk reduction and prevention. WW-FINGERS includes 40+ countries from different income levels and cultural backgrounds (17 low and middle-income countries, LMICs), in partnership with WHO and Alzheimer Disease International. Methodological pillars of FINGERS trials are: i) use of FINGER-like multidomain interventions to ameliorate lifestyle and vascular factors, adapted to the geographical and cultural context of the country participating; ii) delivery of the interventions utilizing both individual and group sessions; iii) randomization design; iv) prospective harmonization of cognitive and other outcomes.

RESULTS: the WW-FINGERS global network, launched in 2017, has been rapidly growing, and work is ongoing to add new countries, focusing on LMICs. In response to the COVID-19 pandemic, a survey has been launched (30 participating countries, >18000 participants) to assess pandemic effects on mental and physical well-being and lifestyle of adults at-risk of dementia, and thus adapt and successfully deliver preventive interventions in the pandemic and post-pandemic landscape. The network holds meetings twice a year and has developed guidelines to harmonize and adapt the RCTs across various populations and settings and promote data sharing. Within the harmonization guidelines, a plan for promoting the SDG3 and enabling healthy aging and well-being is being developed by the network through global collaboration.

CONCLUSION: Finding effective and feasible dementia prevention strategies is essential for a sustainable society in an aging world, as dementia is growing exponentially, especially in LMICs. WW-FINGERS is a global interdisciplinary network which can directly contribute to SDG3 and 17.

Biosketch
I am a medical doctor trained in Mexico. With a particular interest in non-communicable diseases with a Global Health focus.

I have three years of working experience as a general practitioner and in research in Mexico. Last summer, I graduated from the Master’s program in Global Health at Karolinska Institutet. Currently, I am working at Nordic Brain Network as a Research Assistant and as clinical coordinator for the WW-FINGERS-SARS-CoV-2 project.

I recognize that in our aging world, the prevention of dementia is a global health priority, and urgent actions must be taken, considering the different backgrounds and cultural settings worldwide to tackle the burden of the disease. This is why I aim to pursue a Ph.D. in the area of dementia and Alzheimer’s disease.
Pravin Marathe, PhD  
University of South Florida, Tampa, Florida  
marathe13@usf.edu

Understanding the Role of BIN1 in Alzheimer’s Disease Using Live Cell Super Resolution Microscopy

Abstract

In the recent past, Bridging Integrator 1 gene (BIN1) has been classified as the second most important risk locus for late onset Alzheimer’s disease (LOAD), after apolipoprotein E (APOE). Genome wide association studies (GWAS) have also identified BIN1 gene as potential genetic risk for Alzheimer’s disease. BIN1 is an adaptor protein that binds to diverse cellular proteins including adaptor protein-2, dynamin, c-Myc, clathrin. It is known to influence Alzheimer’s disease risk predominantly by modulating tau pathology along with affecting other cellular processes in limited extent like neuroinflammation, endocytosis, cell and membrane trafficking, actin dynamics, calcium homeostasis, DNA repair, and cell apoptosis. Our study is focused on understanding the functional role of BIN1 in distinct cellular processes like neuroinflammation, endocytosis, cell and membrane trafficking in neurons and glia. Using live cell super-resolution imaging, the role of BIN1 in these cellular processes and its molecular dynamics in live cells can be studied. Live cell super resolution imaging gives us edge over conventional fluorescence microscopy as it allows us to resolve the biomolecules and cellular structures beyond the diffraction-limited resolution (<200 nm) of conventional light microscopy. We expect that understanding the role of BIN1 in these cellular processes using live cell super resolution microscopy might present us with novel targets for effective Alzheimer’s disease therapy.

Acknowledgments: This study is supported by the National Institutes of Health grant.

Biosketch

During my Masters and Ph.D. I gained research experience in molecular biology, biophysical applications, and advanced microscopy. In my Ph.D., I developed improved variants of photoconvertible fluorescent protein mEos3.2 using the directed evolution method. The optimized brighter mEos3.2 protein variants showed augmented utility in live-cell confocal and super-resolution imaging studies. In Thinakaran lab my research interest is focused on understanding the functional roles of BIN1 in neurons and glia. I will apply my experience in fluorescent protein optimization and microscopy to study the localization and function of BIN1 and other proteins that have been identified as GWAS risk factors for late-onset Alzheimer’s disease.
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The Role of Amylin in Tau Pathology: a Critical Link Between Alzheimer’s Disease and Diabetes

Abstract
Amylin is a peptide, which can cross the blood-brain barrier and activate receptors in the brainstem, suppressing food intake. The aggregation of amylin in the pancreas is a pathological hallmark of diabetes. Moreover, amylin oligomers participate in a cross-seeding interaction with β-amyloid aggregates, which are a hallmark of Alzheimer’s disease (AD). The accumulation of hyperphosphorylated tau (p-tau) in the brain is another hallmark of AD that is strongly associated with memory impairments and cell death. Although some shared molecular pathways between β-amyloid and amylin aggregates have been described, less is known about amylin’s influence on AD tau pathology. In vitro studies evidenced that amylin forms hetero-oligomers with tau and that amylin was able to increase p-tau levels in primary neurons. However, it remains unknown whether amylin modulates the tau pathology in vivo. Therefore, we hypothesized that amylin can have a functional interaction with tau, increasing the risk of diabetic individuals developing tau pathology. We aim to investigate whether diabetic conditions induced by streptozotocin (STZ) will worsen AD-related tau pathophysiology, and to test if amylin synergizes with STZ to exacerbate tau pathology in transgenic mice. STZ and amylin were sequentially administered to 3-months-old male human Tau P301S transgenic mice (PS19 line). After the treatment, the motor and cognitive performance of the mice were analyzed, and at 6 months, they were euthanized and the brain and pancreas were harvested for molecular and histological analysis to evaluate the localization and level of expression of markers of tau pathology, gliosis, synaptic density, and amylin amyloid pathology. So far, our data showed that the treatment with STZ resulted in a failure to gain body weight and increased the blood glucose levels of PS19 mice. STZ also worsened the motor performance and increased the retention of fear-conditioned memory of PS19 mice. Amylin synergized with STZ, enhancing the presence of p-tau in the visual cortex of PS19 mice, worsening tau pathology. The successful outcome of this research would contribute to the understanding of how amylin aggregates can affect tau pathology and increase the risk for diabetes patients to develop AD. Acknowledgments: This study is supported by the National Institutes of Health grant AG057290.

Biosketch
I am interested in the interface between cellular changes and behavior. In this sense, my Undergraduate research explored the protective effect of caffeine on endocannabinoid-induced memory impairments. During my Master’s degree, I studied the influence of stress on ethanol addiction and its relation to neurochemical alterations in the mesocorticolicmbic pathway. During my Ph.D., I went deeper to my initial interest in the endocannabinoid system and memory. I developed a project that investigated the neuroprotective effects of the endocannabinoid on cognitive, synaptic, metabolic, cellular and molecular alterations induced by streptozotocin, which is an animal model of sporadic Alzheimer’s disease (AD) based on brain resistance to insulin. In the Thinakaran group, I continue to explore the interface between AD and diabetes, studying the role of amylin on the development of AD-related changes such as cognitive impairment and neuronal dysfunction.
Abstract
Age-related and Alzheimer’s Disease (AD) pathologies are increasingly understood to confer cognitive and mobility risk, but the malleability of functional brain networks may be a mechanism for mobility reserve. In particular, accumulation of white matter hyperintensities (WMH), amyloid beta (Aβ), and tau tangles are strongly associated with declines in cognition, mobility, and are known to alter functional network connectivity. However, there are individuals who, despite increased accumulation of neuropathology, maintain high levels of both cognition and mobility. These individuals, deemed as “resilient”, have been observed to constitute between 20-30% of the general population. Consequently, resilience has been proposed as a key feature of healthy aging, yet little is known about the mechanisms through which resilience acts. In an effort to elucidate these mechanisms, we are leveraging neuroimaging, genetic, demographic, and socioeconomic data from a host of cohorts including the Rush Memory and Aging Project (ROS/MAP), the Alzheimer’s Disease Neuroimaging Initiative (ADNI), and the Vanderbilt Memory and Aging Project (VMAP). We are attempting to develop and generate statistical models of resilience to assist in the exploration of the neural and genetic contributions to resilience in aging and AD. My postdoctoral work revolves around combining neuroimaging data (structural and functional) with our existing resilience residual models to strengthen their accuracy and elucidate new genetic markers of resilience. This is a critical research gap as it is widely accepted that increasing neuropathology and changes in functional connectivity are associated with declines in cognitive and physical function, but there are few studies that include these measures in models of resilience.

Biosketch
I am a neuroscientist trained in neuroimaging and currently being trained in genetics. I graduated from the Wake Forest School of Medicine Neuroscience Graduate program in August 2021 under the training of Dr. Christina Hugenschmidt. I recently began my postdoctoral fellowship at Vanderbilt University Medical Center under Dr. Timothy Hohman in October 2021. My graduate work involved the use of MRI, fMRI, and PET to determine the neural correlates of physical resilience with increased age and Alzheimer’s Disease pathology. Individuals were deemed physically resilient if they maintained healthy levels of mobility (gait speed, leg strength, etc.) despite high accumulation of white matter hyperintensities or amyloid beta. I am primarily interested in differences in functional brain network connectivity between resilient individuals and their counterparts. My postdoctoral training is immersing me in the genetics of Alzheimer’s Disease and resilience to combine my functional network findings with a more targeted molecular approach. Generally, the aim of my work is to develop earlier diagnostic measures for AD as well as methods for the identification of resilient individuals so that treatments and interventions can be developed.
Abstract
Smartphones are increasingly being used to capture subtle changes in cognition associated with preclinical Alzheimer disease (AD). We evaluated the reliability and validity of the Ambulatory Research in Cognition (ARC) app against traditional cognitive measures and AD biomarker burden (CSF and PET amyloid and tau as well as MRI structural measures). ARC is a smartphone-based cognitive battery which uses ecological momentary assessment principles and is designed for unsupervised completion on participants’ personal devices in their everyday natural environments. A sample of 268 clinically normal older adults and 22 individuals with very mild dementia completed at least one ARC “visit” (comprised of 28 sessions, 4 sessions per day for 7 days); a subset additionally underwent traditional cognitive testing, a lumbar puncture, and neuroimaging. Key findings included the following: First, ARC tasks showed good between-person reliability across the 7-day EMA protocol (reliabilities > 0.85) and good test-retest reliabilities at 6-month and 1-year follow-ups (ICCs > 0.85). Second, ARC demonstrated construct validity as evidenced by correlations with the traditional cognitive measures (r = 0.53). Finally, ARC showed comparable predictive validity as the traditional cognitive measures in predicting AD biomarker burden. Overall, the results of the present study suggest that ARC is a reliable and valid tool for measuring subtle cognitive changes associated with earliest stages of AD.

Biosketch
I’m currently a Postdoctoral Research Associate in Dr. Jason Hassenstab’s Cognitive Technology Research Laboratory in the Knight Alzheimer’s Disease Research Center in the Department of Neurology at Washington University in St. Louis School of Medicine. I graduated with my Ph.D. in 2021 from the Department of Psychological and Brain Sciences at Washington University in St. Louis, working with Dr. David Balota. I received my B.A. and M.S. degrees from the University of Michigan in 2016, where I studied with Dr. Cindy Lustig. My research explores attentional control, mind-wandering, and memory as they change with healthy aging and preclinical Alzheimer’s disease.
Abstract
The training program by Lemere lab will provide the opportunity for Maria to complete her Master’s degree study. The research project for Maria’s training is to study the efficacy and safety of the mutant anti-pGIu3-Abeta monoclonal antibody (mAb) in preclinical AD mouse models and explore possible mechanisms of amyloid clearance. The project is funded by Dr. Lemere’s NIH grant titled “AD Immunotherapy with a Novel CDC-Mutant Anti-Pyroglutamate-3 Abeta Antibody to Avoid Vascular Side Effects”. Maria will help immunize aged APP/PS1;APOE4 mice with 2 different amyloid-beta protein antibodies (pyroGlu3 and an N-terminal amyloid-beta mAbs) for 16 weeks. Non-transgenic wildtype mice and human targeted replacement APOE4 mice (without mutant human APP) will be used for behavioral controls. Following immunization, she will participate in mouse behavioral studies and then assist with euthanizing the mice and harvesting brain, blood and other organs. Maria will participate in the brain and blood analyses and perform statistical tests on the data. She will participate in the organization and presentation of the data, including using this data to support her Master’s Thesis. Maria will contribute to the publication of the data on which she will be a co-author.

Biosketch
I have always been fascinated by nature’s complexity and by the time I was a high school student, my inclination to the field of biological sciences was undeniable. That later motivated me to choose the field of my bachelor’s studies. Studying in the Department of Molecular Biology and Genetics gave me the opportunity to expose myself to a range of courses, which sparked my great interest in the function of the brain and neurodegenerative diseases. My passion for Neuroscience was further developed during my Erasmus internship at the laboratory of Molecular Psychiatry and Psychopharmacology at the University of Milan, where I was part of a project with main goal the understanding of molecular mechanisms of psychopathology in mental illnesses such as depression. This internship stimulated my interest in the variability of molecular mechanisms that can lead to the pathological function of the brain, and more specifically how inflammation can be implicated in those mechanisms. Thus, this led me to apply to my current master’s program, in order to acquire the proper background and tailor in more detail my research interests. During this program my interest always came back to the same idea: the therapeutic potential of targeting the inflammatory mechanisms that lead to diseases of the nervous system. This idea came to an agreement with my inclination to further understand neurodegenerative diseases, and especially Alzheimer’s disease. That is why I was very happy to be accepted to conduct my master’s research internship in the Lemere lab, which perfectly reflects my research interests.
Abstract
Mislocalization of protein Tau from axons to neuronal cell bodies is an early event in tauopathies, and is believed to cause a breakdown of the cellular polarity and, as a consequence, disruption of its distal functions. Recently, it has been reported that human iPSC-derived neurons carrying frontotemporal dementia (FTD)-related MAPT gene mutations showed altered microtubule dynamics in the cell bodies. This provokes an increase of sheer forces on the nuclear membrane, and leads to an impairment of nucleocytoplasmic transport (NCT). Further, Tau species can directly bind to Nup98 in neurons from Alzheimer’s disease patients, where they cause impaired nucleocytoplasmic compartmentalization. This interaction further can lead to aggregation and fibrilization of Tau in the cytoplasm, disrupting the nuclear pore complex function. Interestingly, deficits in NCT have not only been associated with neurodegenerative disease, but also become impaired during physiological aging of human neurons. Recent evidence suggests that Tau interacts with DNA and exhibits significant somato-nuclear translocation, and that it directly affects NCT. As a response to acute stress, Tau has been shown to converge at the soma, and further translocate to the nucleus through the nuclear pore complex (NPC). Under persistent cellular stress, as in the context of neurodegenerative diseases, Tau can get hyperphosphorylated and accumulate into the soma where it can impair NCT function and induces nuclear envelope abnormalities.

Taken together, mislocalization of Tau to the structures of the nuclear periphery and nucleus may provide a mechanistic link between aging and disease. However, it remains to be explored to what extent Tau mislocalization is observed in aging human neurons, and such a relationship is further extended towards pathological Tau species. The induced neurons (iNs) system can represent an inclusive in vitro approach that will allow studying Tau nucleocytoplasmic transport dysfunctions in an age-equivalent patient-specific neuronal model. The goal of this study is to develop a platform for exploring how changes in nuclear Tau might contribute to neuronal aging and neurodegeneration, and to assess to what extent changes in nuclear-associated tau might act as a convergence platform for aging and disease.

Biosketch
Silvia is the only postdoctoral fellow in Jerome’s lab. She obtained her PhD in Pharmacological Experimental and Clinical Sciences at the University of Milan, investigating the connection between the alpha secretase ADAM10 and the synaptic structural plasticity in Alzheimer’s disease. She going the lab in Innsbruck to obtain new perspectives, and to learn human cell reprogramming technologies, such as iPSC differentiation and iN. Silvia enjoys a lot to get lost in the nature by herself, but mostly she loves to share good food and good wine with friends.
Abstract
Aggregation of intracellular hyperphosphorylated Tau is a hallmark pathogenic feature of Alzheimer’s disease (AD) and related tauopathies. Bridging integrator 1 (BIN1) is the second most prevalent genetic risk factor identified by GWAS for Late-Onset Alzheimer’s Disease (LOAD). Alternate splicing of BIN1 generates multiple tissue-specific and ubiquitous isoforms that participate in diverse cellular functions, including endocytosis, membrane remodeling, actin cytoskeleton regulation, DNA repair, and apoptosis. However, neuronal BIN1 expression decreases in patients with AD, and the loss of BIN1 affects neuronal excitatory synaptic transmission. Studies from our laboratory have shown that BIN1 regulates excitatory synaptic transmission but does not affect amyloid-beta (A\textsubscript{B}) pathology in vivo. BIN1 is known to bind to Tau in vitro, and BIN1 expression in patients with AD has been correlated with neurofibrillary tangle (NFTs) pathology. Available evidence suggests at least three different modes by which BIN1 might impact Tau pathology: (i) an SH3 domain in BIN1 facilitates direct binding to the proline-rich motif in Tau; (ii) the loss of BIN1 in cultured neurons promotes extracellular Tau uptake and results in greater neuron-to-neuron propagation; and (iii) microglial BIN1 influences the release of Tau in extracellular vesicles. However, BIN1’s role and the mechanism involved in Tau progression in vivo and tau-mediated neurodegeneration has not yet been characterized. To directly link neuronal BIN1 expression and the severity of NFT pathology in AD, my current research focuses on assessing the role of excitatory neuronal BIN1 expression on Tau pathology and Tau seed propagation in vivo. To accomplish this goal, we generated transgenic mice conditional Bin1 knock-out in PS19 Tau transgenic background and analyzing the link between excitatory neuronal BIN1 expression and the severity of Tau pathogenesis.

Biosketch
I am Dr. Moorthi Ponnusamy, currently working as a Post-doctoral Fellow in Prof. Gopal Thinakaran’s Lab, Department of Morsani College of Medicine, University of south Florida, Health Byrd Alzheimer’s Center, Tampa, USA. I am glad to be a neurobiologist for the past 12 years with a passion for finding novel strategies for understanding and treating devastating neurodegenerative disorders such as Alzheimer’s disease (AD). As a master student, I performed my research to reveal the mechanism behinds the aberrant activation of cell cycle regulatory proteins implicated in neurodegenerative diseases. My doctorate research focused on revealing the biochemical mechanisms behind sporadic AD pathogenesis by analyzing AD-related proteins in various brain regions during post-natal-developmental stages to determine the sensitive period and vulnerable brain regions. I completed 7 years of rigorous training in basic biochemical, cell and molecular neurobiology, protein trafficking, and pathological aspects that are essential for understanding pathophysiological mechanisms for AD. Based on my experience, I received an internship to work with Prof. Lawrence Rajendran, and I got a chance to do exciting research on the role of exosomes in AD and investigating the link between Rab11A and LOAD. For my postdoctoral training, I am doing research with Prof. Gopal Thinakaran, we have been characterizing late-onset AD risk factors identified by GWAS efforts using cell-type-specific conditional knock-out and transgenic mice.
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Abstract
Background: Sleep disturbances are common in individuals with Mild Cognitive Impairment (MCI); and sleep disturbances increase the risk of Alzheimer’s disease (AD). Lower ratings of quality of life (QoL) are also found in MCI. We examined the association between sleep disturbances and QoL ratings among participants with MCI.

Methods: Baseline in-home sleep assessments using the WatchPAT (Itamar Medical) and the QoL in AD questionnaire were collected from amnestic MCI (aMCI) participants from the diet intervention trial, Brain Energy for Amyloid Transformation in Alzheimer’s Disease (BEAT-AD) at the Wake Forest ADRC. The WatchPAT assessed sleep time, efficiency, and sleep-related hypoxemia measures including the apnea-hypopnea index (AHI), oxygen desaturation index (ODI) and respiratory disturbance index (RDI), where higher values indicate greater disturbances in sleep. The QoL in AD scale ranged from 13–52 with lower scores indicating poorer QoL ratings. We assessed the association between total sleep time and sleep efficiency with QoL. Pearson correlations and regression models measured the association of sleep metrics with QoL scores.

Results: Forty-two aMCI participants (mean age =69.0 ± 7.4 years; N=23 female; mean BMI =27.6) were studied. Disturbed sleep indicated by the average number of apneas and hypopneas (AHI, mean = 18.6 ± 14.6) and respiratory events or related arousals (RDI, mean = 20.7 ± 14.2) was negatively associated with lower subjective measures of QoL. Higher AHI and RDI scores, indicating greater intermittent hypoxia and respiratory burden, were associated with lower QoL (AHI: r= -0.359, p=0.027; RDI: r= -0.340, p=0.037). There was a trend toward a negative association of ODI and QoL scores (r= -0.309, p=0.059). Regression models including age, sex, and BMI did not significantly predict QoL scores with AHI (F(4,35)=1.95, p>.1) or RDI (F(4,34)=1.76, p>.15), however, AHI and RDI individually added significantly to the prediction of QoL scores (AHI: B=-.136, t=-2.4,P<.05; RDI: B=-.162, t=-2.4, p<.05).

Conclusions: Greater sleep disturbances related to hypoxic and respiratory events were associated with lower self-ratings of QoL in MCI participants. Further research will increase the sample, investigate the impact of hypoxic and respiratory events on brain function, and whether longitudinal changes in diet influence the relationship of sleep-related hypoxemia and QoL.

Biosketch
Ashley H. Sanderlin, PhD is a passionate researcher that investigates modifiable risk factors and early interventions for Alzheimer’s disease. She received a Bachelor’s of Science in Biology from Bowling Green State University where she conducted research as a Ronald E. McNair Scholar. She then went on to attain a PhD in Neuroscience from Michigan State University. There, Dr. Sanderlin worked with Alzheimer’s disease patients and people with mild cognitive impairment as the lead psychometrist in the Department of Neurology. Her doctoral work focused on the interactions of body mass index, mood and behavioral changes, and their relationship with brain structure and function. As research faculty at Wake Forest School of Medicine, Dr. Sanderlin’s research encompasses clinical intervention trials, specifically focused on the relationship of diet intervention on biomarkers for Alzheimer’s disease. Dr. Sanderlin is a recipient of the Alzheimer’s Research Fellowship to Promote Diversity from the Alzheimer’s Association which assesses the impact of a modified Mediterranean ketogenic diet on sleep quality in adults with mild cognitive impairment.
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Abstract
I am in the early stages of studying therapeutic mechanisms in mouse models of Alzheimer’s disease. At this time, I request an exemption from describing my plans. I hope that is acceptable!

Biosketch
I am an Instructor at Harvard Medical School who is new to the field of Alzheimer’s research. I specialize in rodent models of cognition and my research approach combines pharmacological and genetic methods with electrophysiology and sophisticated behavioral tasks to characterize neural mechanisms of attention, motivation, learning & memory.
Abstract
Leptin is a hormone secreted by adipocytes in response to the amount of fat tissue in the body. Circulating leptin can reach different tissues, such as the gastrointestinal system and placenta, amongst others; however, its major site of action is in the brain, specifically in the hypothalamus, where it regulates food intake and energy expenditure.

Leptin is involved in weight control, as high leptin levels in plasma have been correlated with high adipose tissue mass. High circulating leptin levels signal the hypothalamus to reduce food intake and increase energy expenditure; however, pathologically high levels of leptin, which are commonly seen in obesity, may lead to disruption in the signaling to the hypothalamus (i.e., leptin resistance).

Leptin is involved in several other biological functions, such as regulation of blood pressure, glucose utilization, sensitivity to insulin, etc. In the brain, leptin is also believed to modulate the function of hippocampal neurons. Hence, pathologically low levels of leptin or leptin signal disruption may lead to impairment of hippocampal functions, resulting in cognitive decline.

Changes in weight are known to increase the risk of developing Alzheimer’s disease (AD), such as mid-life obesity. Studies in rodents have shown that leptin treatment in early AD decreases β-amyloid and hyperphosphorylated tau deposits, the two major hallmarks of AD. In contrast, low adipose tissue mass and low leptin levels have been associated with worsening of AD pathology, suggesting that leptin may also be involved in AD progression.

Obesity and AD are highly prevalent in people with Down Syndrome (DS). Studies have shown that children with DS have higher circulating leptin levels than non-DS age-matched controls. However, further studies are needed to determine the role of leptin in the development of AD in people with DS. It is plausible that the obesity commonly seen in people with DS leads to high circulating concentrations of plasma, resulting in leptin resistance that could be associated to cognitive decline and the development of AD. If true, implementing low-fat diets and exercise early in life may delay the onset of this devastating disease in the DS population.

Biosketch
Lorena Sordo graduated from FMVZ UNAM veterinary school in Mexico City in 2006. She practiced as a small animals veterinary clinician for 8 years before moving to Scotland in 2015 to pursue an MSc in Applied Animal Behaviour and Animal Welfare at The University of Edinburgh. She obtained her PhD in 2021 at The Roslin Institute, The University of Edinburgh, where she studied feline cognitive dysfunction syndrome (aka feline dementia) and its similarities to Alzheimer’s disease (AD). She joined Prof Elizabeth Head lab on that same year as a Postdoctoral Scholar. She is interested in all aspects of neuropathology and in translational research by using different animal models for the study of Alzheimer’s disease.
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Abstract
The Tansey lab is largely focused on studying the immune system’s ability to have a substantial impact on the progression of neurodegenerative diseases through mechanisms involving neuroinflammatory responses and genetic risk factors. Within the lab, there are numerous studies utilizing models of Parkinson’s disease, Alzheimer’s disease, and frontotemporal dementia, just to name a few. Over the course of my graduate education, I plan to look at a genetic variant in the phospholipase C gamma 2 (PLCG2) gene, found in microglia and other macrophages, that has been shown to be protective in patients with Alzheimer’s disease. This rare variant, known as P522R, has been shown to slow disease progression. We are primarily going to be looking at this variant’s effect on microglial effector functions, and using this knowledge to try to determine how this variant is providing a protective effect.

Biosketch
I am currently a graduate student working in the lab of Dr. Malú Tansey. Before attending the University of Florida, I received a bachelor’s degree in biology with a minor in chemistry from Georgia Gwinnett College. My current research interests include genetic risk factors associated with Alzheimer’s disease, and how both central and peripheral immune cells affect neuro-inflammation.
Abstract
Large genomics studies have uncovered a wealth of information regarding genetic risk factors for Alzheimer's disease (AD). Despite common assumptions that neurons are key effectors of disease, the most significant risk factors have extremely high expression levels in microglia. Abundant in microglia, BIN1 is the second-most common risk factor for late-onset AD (LOAD).

BIN1 is an adaptor protein with >10 isoforms expressed in the CNS. Alternative splicing of exons within important functional domains dictate BIN1's interactions with other proteins, with myriad functional implications. Our recently-submitted manuscript identified four isoforms expressed in microglia. Notably, the lack of CLathrin and AP-2 binding (CLAP) domain exons suggests endocytosis may not be the principal function mediated by BIN1 in these cells. However via the membrane-interacting BIN-Amphiphysin-RVS (BAR), MYC Binding (MBD) and Src-homology 3 (SH3) domains, BIN1 potentially interacts with and regulate an exhaustive list of signalling proteins. The identification of cellular pathways regulated by BIN1 is imperative for elucidating how BIN1 affects AD risk. The first step towards this goal is to characterise microglial BIN1 in amyloid and Tau pathogenesis.

My project will characterise the pathophysiological role of BIN1, assessing changes in pathology following microglia-specific BIN1 deletion in mice. Behavioural assessment of cognition and motor function will be utilised to monitor the phenotypic development in transgenic mice. Fluorescence immunohistochemistry will be performed on brain sections, allowing assessment of histological phenotypes, as well as changes in gene localisation. RT-qPCR and immunoblot analyses will be used to assess changes in gene regulation from whole-brain samples. Additionally, microglia will be FACS-isolated to assess gene expression in microglia manipulated in vivo.

Our preliminary data suggest that microglial BIN1 deletion accelerates or accentuates amyloid and tau pathologies. The precise neural circuitry affected by microglial BIN1 deletion will be investigated, with important implications for knowledge of AD-related pathogenesis. This project will pave the way for future investigations into inter-cellular signalling mechanisms to identify microglia-neuron signalling during pathology. The necessity for this manner of extracellular signalling implies a key involvement of surface receptors on these cell types; this is a positive indication for lead identification of pharmaceutical agents to target these receptors.

Biosketch
I am currently a postdoc at the USF Byrd Alzheimer’s Institute. My interest in the cellular and molecular mechanisms of Alzheimer’s disease (AD) began prior to my undergraduate education. This has dictated my entire adult education, ultimately leading me to pursue a professional career in neurobiology. I undertook a MSc project with an AD-focussed molecular neurobiology group at King’s College London, and a PhD with a neurogenetics group at Queen Mary University of London.

In my current position I have been working to elucidate the role of late-onset Alzheimer’s Disease (AD) risk gene BIN1, in microglia. Using in vivo (mouse) and in vitro (hiPSC-derived and immortalised microglia) models, I have employed genetic manipulations and endotoxin-induced neuroinflammation to characterise disease-specific roles of microglial BIN1.

Having begun to research microglia, I have become fascinated with the role of cells in neurodegeneration. As both causal agents and potential therapeutic targets, I am convinced that elucidating the cell biology of microglia in AD is imperative for therapeutic development. The expert supervision and cutting-edge technology available to me at the Thinakaran Lab is allowing me maximise my output work quality, with exciting prospects for my future career.
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Abstract
Alzheimer’s disease (AD) is the most common cause of dementia, currently affecting about 6.2 million Americans age 65 and older. However, the relationship between pathological amyloid-beta (Aβ) aggregation, one of the major hallmarks of AD, and cognitive decline is not well understood. There is a clear need to illuminate the mechanism of AD pathogenesis and translate it to effective therapies for the disease. We propose that Aβ, one of the major hallmarks of AD, induces neurons to undergo a senescent-like state, which is defined by irreversible cell cycle arrest and the development of the senescence-associated secretory phenotype (SASP), in which cells secrete deleterious pro-inflammatory and oxidative factors. Since the senescent phenotype persists after the stressor is removed, this may offer an explanation as to why the cognitive decline in AD continues even after antibody-mediated reduction of amyloid-beta plaques. We also propose that lymphocytes such as natural killer (NK) cells, which have been shown to target senescent cells outside of the brain, can infiltrate the AD brain and selectively kill neurons and/or astrocytes exposed to Aβ, further exacerbating AD progression.

To test this hypothesis, we administered amyloid beta oligomers (AβO) to primary human neuron and astrocyte mixed cultures and analyzed senescent marker expression on a single cell basis. Additionally, we treated these cultures with two senolytic drugs (Navitoclax and Quercetin+Dasatinib), which preferentially eliminate senescent cells, to observe whether they eliminate senescent-like neurons/astrocytes in our in-vitro model of AD. Finally, we co-cultured mixed neuron and astrocyte cultures with NK-92 cells, a human NK cell line, to observe whether there was the selective killing of senescent-like cells.

Biosketch
I was raised in Southern California and graduated from Pomona College in spring 2020 with a Bachelor’s degree in Molecular Biology. At Pomona College, I completed a senior thesis project in the Cheney lab on the effect of N-terminal acetylation on GDP Dissociation Inhibitor (GDI), a key player in intracellular vesicle trafficking. Motivated by my personal experiences with Alzheimer’s disease (AD), I am currently working in the Andersen lab at the Buck Institute for Research on Aging, studying senescence in an in-vitro human model of AD. In my free time, I enjoy cooking and reading science fiction.
Abstract
Impaired gene expression lies at the heart of many disorders, including developmental disease, cancer, and neurodegenerative disease. As epigenetic modification of DNA and histone proteins regulates gene expression, N6-methyladenosine (m6A), a modification present in mRNAs and long noncoding RNAs, can be removed by the activity of RNA demethylases, launched the field of epitranscriptomic. Reversible modifications of mRNA control various aspects of mRNA metabolism, including stability, localization, and translation. The m6A modification seems to play an important role in the cellular response to physical and oxidative stress in both the peripheral and central nervous systems. In vivo studies of PNS and CNS regeneration have found that the m6A modification plays a critical role in injury-induced protein synthesis and axon regeneration.

The RNA post-transcriptional modifications are determined and recognized by the activity of writer complexes, eraser proteins and reader proteins. Three main reader proteins have been identified: YTHDF1, YTHDF2, and YTHDF3. YTHDF1 is thought to increase translation efficiency of mRNA transcripts, specifically in response to cellular stress. YTHDF1 could potentially mediate the enhanced translation observed for some AD-relevant m6A transcripts. For instance, the loss of YTHDF1 expression in knockout mice results in reduced ribosome recruitment to transcripts normally bound by YTHDF1. These findings reveal that the m6A modification, in conjunction with YTHDF1, is responsible for actively regulating mRNA translation in response to cellular stress and suggests the possibility that an epitranscriptomic mechanism may underlie the altered levels of protein synthesis observed in response to neuronal stress during the progression of AD.

Our preliminary data shows an overall increase in m6A RNA level in the PS19 mice, suggesting that the m6A profile could be greatly affected by tau pathology in favor of an increase in m6A modification (Thinakaran lab unpublished data). This data supports the idea that levels of m6A modification in transcripts relevant to AD pathogenesis, might be regulated in response to neuronal stress. The project aims to investigate the role of epitranscriptomic in the drastic alterations of protein translation, localization, and aggregation that drive AD progression.

Biosketch
I am working as a Postdoctoral Researcher in the Department of Molecular Medicine, Byrd Alzheimer Center & Research Institute, the University of South Florida in the laboratory of Dr. Gopal Thinakaran. My specific interests are in neuronal mechanisms responsible for amyloid pathology and Alzheimer’s disease-related axonal transport defects, biological pathways, and pathogenic mechanisms regulated by the second most common late-onset Alzheimer’s disease risk factor, BIN1.

Before joining the laboratory of Dr. Gopal Thinakaran, I received my Ph.D. degree from Shanghai Jiao Tong University(SJTU), China. During my study at SJTU, my research focused on epigenetic in learning and memory where I was exposed to the most recent technologies that can model and characterize the mouse model of cognitive deficits in mice. This experience further developed my research interest from cognitive deficits, depression to biomedical research on Alzheimer’s disease.
Abstract
Introduction. Accumulation of amyloid-β (Aβ) peptides in the brain is an early feature of Alzheimer’s disease (AD). Microglia and monocytes aid in the clearance of Aβ and prevent the formation of amyloid plaques. However, this function declines in aging and in Alzheimer’s disease and may be affected by the microbiome since these cells express receptors for microbial secreted substances. We have identified species in the gut microbiota that are associated with Aβ levels in the brain of AD mice. Specifically, bacteria belonging to the Erysipelotrichaceae family were associated with low Aβ and Bacteroides fragilis was associated with higher levels, and AD mice colonized with B. fragilis had more amyloid plaques (Cox et.al. 2019).

Method. Aged wild-type C57BL/6J mice were treated with Erysipelotrichaceae (Faecalibaculum rodentium, Ileibacterium valens, Dubosiella newyorkensis) or B. fragilis by weekly oral gavages. FITC-conjugated Aβ-42 (FITC-Aβ) peptides were injected into the hippocampus and Aβ uptake by microglia and monocytes was assessed by flow cytometry 14-18h later. APP/PS1 transgenic AD mice were treated with B. fragilis weekly starting at 2.5 months of age. The mice were sacrificed at 5 months of age, and the microglia transcriptional signature was analyzed.

Results. Female and male WT mice treated with Erysipelotrichaceae between 14.5-16.5 months of age had a 3.4-fold higher uptake of FITC-Aβ by microglia compared to mice treated with PBS (p=0.048). The Aβ uptake by monocytes was similar in both groups. Male WT mice treated with B. fragilis between 8-10 or 12-14 months of age (pooled) had a 2.4-fold reduction in FITC-Aβ uptake by monocytes (p=0.014), and a similar trend could be seen in microglia (1.7-fold reduction, p=0.097). Treatment with B. fragilis also led to a reduced expression of the Aβ-binding scavenger receptor Scara-1 by monocytes in the spleen (p=0.0049). In APP/PS1 mice, colonization of the gut with B. fragilis suppressed expression of 54 genes and increased expression of 10 genes in microglia. Enriched KEGG pathways included lysosome, the phagosome, protein processing in the endoplasmic reticulum, autophagy, and FcγR-mediated phagocytosis. Among down regulated genes were Psen1, Itm2b, and Itm2c that participate in Aβ processing and aggregation, mutations in Psen1 that cause loss of function have been found in familial AD.

Conclusions. Bacteria belonging to the Erysipelotrichaceae family stimulated Aβ uptake by microglia, indicating that they may have a protective role against plaque formation in AD. B. fragilis inhibited the uptake of Aβ, suppressed cellular pathways involved in the processing, aggregation and degradation of Aβ and may have a detrimental role in amyloid pathology.


Biosketch
I am a postdoctoral research fellow at the Ann Romney Center for Neurological Diseases at Brigham and Women’s Hospital in Boston, MA. I defended my doctoral thesis in immunology in 2019 at the University of Gothenburg, Sweden. Presently, I research how the intestinal microbiota modulates the immune system to aid in the clearance of amyloid beta in Alzheimer’s disease.
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Prevention of Alzheimer’s Disease: Early Recognition of Risk Factors Attributing to Small Vessel Disease

Abstract

Background

A neuropathological study across two South Asian countries; India (n=32) and Sri Lanka (n=50), by the corresponding author showed a significant association (p<0.05) of cerebral small vessel lesions compared to large vessel disease with AD-related neuropathological changes which showed a significant association only with Braak NFT stages ≥I. The study aims to detect the prevalence of vascular risk factor profile of small vessel disease; (1) to understand etiopathological factors leading to small vessel disease, (2) early detection of ischemia-related neuronal loss preventing further progression into AD.

Methodology

A cross-sectional study was carried out from February 2010 to September 2016 at the National Hospital, Colombo, Sri Lanka. 628 ischemic stroke patients, confirmed with neuro-imaging were enrolled and out of 219 (34.87%) patients [male n=136, female n=83], age range from 18 to 95 years were diagnosed as cerebral small vessel disease. Data of sociodemographic and vascular risk factors were evaluated through a standard questionnaire.

Results

Cases of small vessel disease [ n= 219, male- 62%, female-38%, mean age 61±13 years, stroke in adults (age≥45 years), n= 186 (84.9%), under the age 45 years n= 33 (15.1%)]. According to the age specific categories, stroke in young (<45 years) and stroke in adults (45>), the prevalence of hypertension [ 54.5%, 57.5%], dyslipidemia [27.3%, 24.2%,] and diabetes [ 34.4%, 39.4%,] obesity, [9.1%,18.3%.,], overweight [36.4%, 39.2%], positive smoking history of one pack year [18.2%, 25.3%], previous history of stroke [3.0%,11.8%,] respectively. Univariate analysis showed that the risk factors do not show any statistically significant association in age specific manner.

Conclusion

This study shows that the prevalence of risk factors statistically does not vary according to the age of young <45 and adult >45. Recognition of risk factors and early treatment may guide tailored primary and secondary stroke prevention and improve vascular remodeling of the brain, thus ameliorating the development of Alzheimer’s disease.

Biosketch

I am a graduate of MBBS and a M.Phil candidate at Institute for Combinatorial Advanced Research & Education (KDU-CARE),General Sir John Kotelawala Defence University, Sri Lanka, researching on

Cont. on next page
Gayathri Wijeweera, cont.

Investigating into the stroke mechanisms of Small Vessel Disease and cognitive enhancement with dietary Cinnamomum zeylanicum in patients diagnosed with vascular cognitive impairment (VCI)

This study will lead

1. To pooling of stroke DNA samples with genotype data for the South Asian largest Biobank established by Ranil De Silva (Lancet Neurology”, (Wijekoon N, De Silva R.2020) to discover genes that influence stroke and understand the etiopathogenesis (genetic, environmental, and lifestyle) of subtypes of small vessel disease.

2. Detailed risk factor assessment, and neuroimaging is essential to determine to understand variation in small vessel disease subtypes to predict the effects of disease on clinical, physical, and cognitive outcomes and will bridgens the gap of understanding etiopathological mechanism of small vessel disease subtypes in the Sri Lankan population from a South Asian aspect.

3. Dietary Cinnamomum zeylanicum might be a novel therapeutic approach to mitigate the disease progression hence increasing cognitive function in patients diagnosed with vascular cognitive impairment (VCI) and this may lead to value-added nutraceutical development and commercialization of Ceylon cinnamon-based nutraceuticals.

I have submitted my first author publication” Impact of natural products on neuroimmune diseases:Insight for future clinical studies” into the journal Evidence-based complementary and alternative medicine (IF-2.62). I am a Recipient of ALBA –FKNE-YIBRO diversity grant for FENS 2020 virtual forum. (Federation of European Neuroscience Societies)
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Biosketch
I am a masters student in the laboratory of Dr. Arthur Butt with an interest in working in Multiple Sclerosis research. I completed an undergraduate in pharmacology with hopes of going onto completing a PhD program to become a specialist in the MS field. At undergraduate level I studied at the University of Portsmouth, my project was a systematic review on the Tyro3 receptor as a drug target in cancer.
Well-being as a Protective Factor Against Cognitive Decline and Dementia

Abstract
Alzheimer’s Disease and Related Dementias (ADRD) is a rapidly growing public health crisis, with no available disease-modifying treatments. Given the magnitude of the crisis and the absence of effective treatments, prevention is of the utmost importance. Researchers, clinicians, and policymakers have increasingly begun to recognize and embrace a resilience-based approach to ADRD prevention that considers the role of psychosocial factors in protecting against or delaying cognitive decline and ADRD. Psychological and subjective well-being are promising targets for resilience-based prevention approaches, given that they have been associated with ADRD risk, are amenable to intervention, and are critical for building social, intellectual, and physical resources that may ultimately protect against disease. Greater well-being may protect against dementia risk by promoting positive health behaviors, directly influencing physiological processes, and by buffering the harmful effects of stress on these physiological processes. Research linking well-being to ADRD risk has typically involved assessing one type of well-being at one or two timepoints in a single sample, leaving key open questions concerning causality and generalizability across individuals and well-being types. My research addresses these open questions in three ways. First, I am currently using data from a longitudinal epidemiological study to test different types of well-being (i.e., subjective well-being and psychological well-being) as predictors of cognitive resilience to ADRD-related neuropathology. Second, using a multi-study integrated data analysis framework, I am investigating bidirectional associations between well-being and cognitive decline across diverse samples. Third, I am planning a pilot study to test the feasibility of a self-guided online positive emotion regulation program for slowing cognitive decline and increasing well-being in older adults with mild cognitive impairment. Results from these three lines of research will inform our understanding of the specificity versus generalizability of well-being protective factors and will provide strong tests of causality using both observational and experimental methods. Furthermore, results from the planned pilot project will establish the feasibility of a low-cost and easily-administered training program that has the potential to slow or prevent cognitive decline and improve well-being in older adults at a large-scale.

Biosketch
I received my PhD in Social-Personality Psychology from the University of California Berkeley in 2019 and I am currently a Senior Research Associate at Northwestern University. Broadly, I study well-being and health across the lifespan. First, I investigate how well-being changes, both in the short-term from moment-to-moment and in the long-term across the adult lifespan. Second, I apply findings from this research to examine links between well-being and important health outcomes in older adulthood, such as cognitive decline and dementia risk. I apply sophisticated statistical modeling approaches to test these research questions, using longitudinal data, daily diaries and experience sampling, as well as experimental and physiological methods.
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Abstract
BIN1, the second most important risk locus for Late-Onset Alzheimer’s Disease (LOAD) after ApoE, is expressed as more than 10 isoforms in the brain. Previous studies have shown that neuronal-specific BIN1 isoform 1 protein expression is decreased concomitantly with neuronal loss in LOAD cases, whereas the levels of the ubiquitous isoform 9 (BIN1iso9) were elevated. However, how ubiquitous BIN1 is involved in AD progression and how it contributes to amyloid pathology remain enigmatic. Thus, this study aims to investigate the role of BIN1iso9 in neuronal dysfunction and AD neuropathology using mouse models that recapitulates increased expression of BIN1iso9 in specific brain cells. To test whether the overexpression of BIN1iso9 in neurons influences amyloidogenic processing of APP in vivo, we used CaMKII-Cre driver to generate neuronal BIN1 conditional overexpression mice (R26BIN1:CaMKII-Cre). The mice had a significant but modest increase in BIN1 levels in the forebrain as compared with littermate controls. The results of MSD ELISA of Aβ peptides and immunoblotting for APP and BACE1 showed no significant difference between groups. Besides, we also generated R26BIN1 mouse model under Emx-Cre line, which conditionally overexpress human BIN1iso9 in excitatory neurons and glial cells (R26BIN1/+;Emx-Cre/+). Like R26BIN1:CaMKII-Cre, R26BIN1/+;Emx-Cre/+ mice had elevated levels of BIN1 compared to controls. The mice were exposed to long-term potentiation or antidromic action potential analyses to examine whether there are any gross alterations in synaptic transmission response or myelin-dependent physiological processes, respectively. We observed a significant decrease in the successful propagation of antidromic action potential with no apparent impact on hippocampal synaptic transmission in R26BIN1/+;Emx-Cre/+ mice compared to controls. Thus, we conclude that the elevated expression of BIN1iso9 might contribute to AD pathophysiology through myelin integrity rather than amyloid pathology.

Acknowledgments: This study was supported by Cure Alzheimer’s Fund and National Institutes of Health grants AG054223 and AG056061 (G.T.).

Biosketch
I am a postdoctoral researcher with experience contributing to Alzheimer’s disease research since my PhD. After graduating with a bachelor’s degree in Molecular Biology and Genetics at Middle East Technical University in Turkey, I completed my master’s on Microbiology and Biochemistry at Georg-August University, Gottingen in Germany. My thesis focused on the role of long-chain acyl-CoA synthetases in fat metabolism in Arabidopsis. I shifted my research area to Alzheimer’s disease during my PhD, which I completed at Hacettepe University in Turkey. My doctoral dissertation was about therapeutic roles of potential drug candidates on Alzheimer’s disease pathology. During PhD years, I analyzed the effects of phenothiazine compounds on amyloid and tau pathologies using AD-mimicking in vitro and in vivo models. As being potent inhibitors of cholinesterases, our studies showed that they have mitigating effects on both pathologies, suggesting their possible use as a disease-modifying drug for AD treatment. After my PhD, I joined Thinakaran Lab in Byrd Alzheimer’s Institute at the University of South Florida as a postdoctoral researcher. In Thinakaran lab, my research focuses on the role of BIN1 in disease progression. To this end, we generate knock-in or knock-out mouse models of BIN1 in specific brain cells and analyze the cell-specific pathological changes to reveal its role. My experience includes running broad-range laboratory bench studies, writing, and editing scientific papers and reports, budget management of projects as well as teaching and mentoring undergraduate students.
Notes
Notes
Index

Paula Aduen ............................38
Akinsola Akinyemi ....................39
Karina Alviña ..........................40
Julie K. Andersen ......................17
Derek, Archer .......................41
Martina Assogna ......................42
Farzaneh Atrian .......................43
Joshua Babalola .......................44
Ahmed Bahrani .........................45
Praveen Bathini .........................46
Andre Batista ..........................47
David Begelman .......................48
Suet Theng Beh .......................49
Mercedes Beyna .......................50
Sarah Biber ............................51
Allison Birnbaum ......................52
Mathew Blurton-Jones ...............18
Diane Bovenkamp .....................37
Amanda Boyd ..........................53
Rory Boyle .............................54
Rachel Frances Buckley .............19
Arthur Butt .............................20
Isabel Castanho .......................56
Kevin Chen .............................21
Irma Cisneros .........................57
Elisia Clark .............................58
Gillian Coughlan ......................59
Laura Cox ...............................22
Simone Crivelli .......................60
Toinét Cronjé ..........................61
Marco Antônio De Bastiani ..........62
Jessy Etienne ..........................63
Elizabeth Fisher ......................64
Stephanie Fountain-Zaragoza .........65
Marissa Gogniat ......................66
Lakmal Gonawala ......................67
Martine Grenon .......................69
Ruben Gomez Gutierrez .............70
Claudio Gouveia Roque ..........71
Özge Güzel ............................72
Tiana Hairston ........................73
Elizabeth Head .......................23
Stacy Pagos Haller ....................36
David Holtzman .......................24
Hao Hu .................................74
Louise Ince .............................75
Vaishnavi Jadhav .....................76
Joanna Jankowsky ....................25
Ksenia Kastanenka ...................26
Pat Kehoe ...............................27
Patricia Kelly ..........................77
Giacomo Koch ..........................28
Mary Ellen Koran .....................78
Frank LaFerla ..........................14
Cynthia A. Lemere ....................15
Ana Sabsil Lopez Rocha ............79
Francesca Mangialasche ............29
Pravin Marathe .......................80
Bri McWhorter .......................30
Jerome Mertens ......................31
Michelle Mielke ......................32
Daniel Moreira-Silva ...............81
Blake Neyland .........................82
Jessica Nicosia .......................83
Sid O’Bryant ...........................33
Jorge Palop .............................34
Maria Tzousi Papavergi ..........84
Silvia Cecilia Pelucchi .............85
Moorthi Ponnuasamy .................86
Sharyn Rossi .........................13
Ashley Sanderlin .....................87
Felipe Schiffino ......................88
Lorena Sordo .........................89
Hannah Staley .........................90
Harry W. M. Steinbusch ............16
Ari Sudwarts .........................91
Kara Summers .........................37
Malú Gámez Tansey ..................35
Ellen Wang .............................92
Shuai Wang ............................93
Caroline Wasen ......................94
Gayathri Wijeweera ..................95
Adam Willis ...........................97
Emily Willroth .......................98
Melike Yuksel .........................99
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