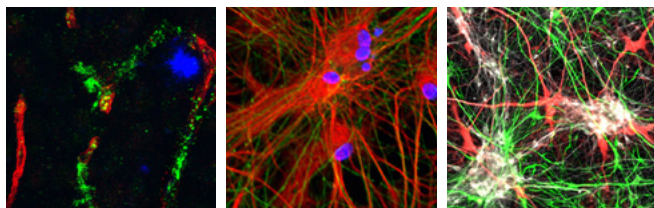


# This Is How.

Projects Inspiring Promise



**Current Alzheimer's  
Disease Research  
Projects**

As of December 2020



**BrightFocus®  
Foundation**

**Alzheimer's  
Disease  
Research**

Alzheimer's Disease Research, a BrightFocus Foundation Program

# We're funding 132 projects worldwide this year in research.

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### Cover photos, left to right:

*Reducing the excitability of brain neurons with a repurposed drug may reduce amyloid-beta deposits in Alzheimer's (nerve cells in green, blood cells in red and amyloid plaques in blue). (Courtesy of Shannon Macauley, PhD, Wake Forest University)*

*Long-term co-culture of iPSC-derived human astrocytes (red) and cortical neurons (green) stained for nuclei in blue. (Courtesy of Dominik Paquet, PhD, Ludwig Maximilian University of Munich, Germany)*

*In another "dish" experiment, neurons grown from stem cells (white) interact with astrocytes (red and green). (Courtesy of Dominik Paquet, PhD, Ludwig Maximilian University of Munich, Germany)*

There is scarcely a person alive today who has not seen or felt the impact of Alzheimer's disease (AD). AD ranks sixth among the leading causes of death in the United States. By disrupting memories, cognition, personality, and more, AD is extremely stressful for family members, friends and caregivers. Alzheimer's disease will claim a greater toll as our population ages—*unless something more is done.*

With generous donor support, the Alzheimer's Disease Research (ADR) program, which began in 1985, has funded nearly \$140 million in research to understand and cure this disease. With our grants, scientists around the world have developed and tested thousands of hypotheses about how the disease destroys brain function over time. As part of this, they are investigating hundreds of ideas to diagnose, treat and cure dementia.

This yearbook provides an overview of BrightFocus' current ADR grant projects. BrightFocus Foundation does not direct funding to specific techniques or categories of research. Applications from scientists for funding can be on any aspect of understanding and curing dementia. Each year, the proposals are evaluated by a Scientific Review Committee (SRC) made up of expert scientists from around the world. Our SRC recommends projects that are the most cutting-edge and innovative. The generosity of our donors helps make this possible.

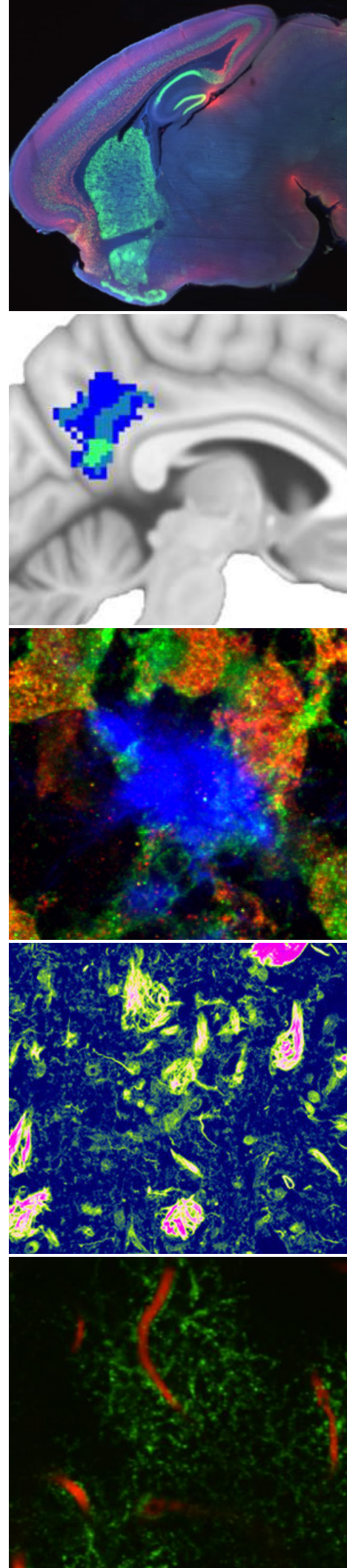
The current portfolio of 132 ADR grants is expansive. In this yearbook, our active projects have been arranged in categories according to the Common Alzheimer's Disease Research Ontology classification system, which is used by research funding agencies around the world, and also used by national and international authorities to track progress towards meeting Alzheimer's research goals.

*Images to right, top to bottom:*

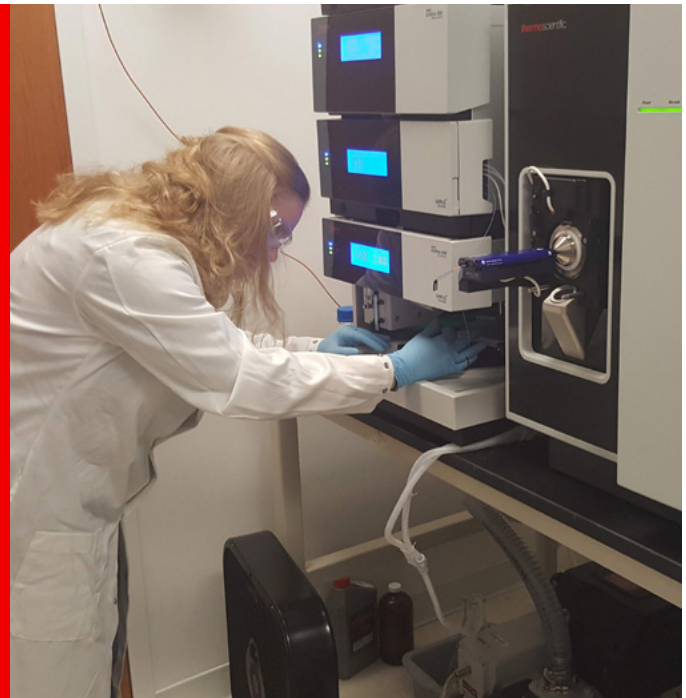
*Courtesy of Alexandre Bonnin, PhD, University of Southern California, Los Angeles, CA; Courtesy of Ryan Darby, MD, Vanderbilt University, Nashville, TN; Courtesy of Christel Claes, PhD, University of California, Irvine; Courtesy of Edward Lee, MD, PhD, Assistant Professor of Pathology and Laboratory Medicine at the Perelman School of Medicine, the University of Pennsylvania; Courtesy of Gustavo Rodriguez, PhD, Columbia University Irving Medical Center, New York, NY.*

*The scientific images at right were furnished by current ADR grantees and show various aspects of their work. Look inside for more information, including a brief description of what's depicted in each image along with the grantee and lab that provided it.*

*Co-principal investigator and fellowship mentor institutions are listed if different than the PI.*



# Battling Amyloid Beta



There are many versions of amyloid protein in the human body, and most serve a useful role. Amyloid beta ( $A\beta$ ) is a type of amyloid that is prone to molecular changes that create fragments that accumulate in the brain. A healthy brain is able to break down  $A\beta$  and eliminate it, but in Alzheimer's disease (AD),  $A\beta$  forms hard, insoluble plaques that are toxic to neurons and are sometimes (not always) associated with AD-related memory loss and other changes. Once only seen after autopsy,

new technologies have made it possible to measure  $A\beta$  plaques and learn which parts of the brain are most affected. Anti-amyloid drugs are being tested in clinical trials, with the hope of preventing formation of  $A\beta$  plaques in the future.

*Above: Dr. Zakaria loads a mass spectrometer, a machine capable of measuring components of blood and other tissues at the molecular level. (Courtesy of Justyna Dobrowolska Zakaria, PhD, Northwestern University)*



**Rita Batista, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*University of Massachusetts Medical School, Worcester, MA*

Fellowship Mentor: Miguel Esteves, PhD

Fellowship Co-Mentor: Guangping Gao, PhD

## **The Effect of the TTR Protein on Alzheimer's Disease**

Our goal is to answer conclusively whether transthyretin (over)expression in a post-developmental setting is an effective approach to either prevent or change the course of disease progression in Alzheimer's and assess the potential of AAV gene therapy approach for translation into human clinical trials.

[www.brightfocus.org/grant/A2019468F](http://www.brightfocus.org/grant/A2019468F)



**Lucía Chávez-Gutiérrez, PhD** (9/1/20 – 8/30/23)  
*Vlaams Institute Voor Biotechnologie (VIB), Flanders, Belgium*

### **Nanobodies Stabilizing Fragile Molecular Machines to Lower the Production of Toxic Amyloid-B in Alzheimer's Disease**

The molecular machinery that produces harmful material (amyloid beta) in the brain of people affected with Alzheimer's disease is well known. Our research has recently shown that this molecular machinery (called gamma-secretase) is fragile and prone to malfunctioning, but fortunately the use of 'stabilizing' molecular bricks can stop its malfunction and prevent the production of toxic, Alzheimer's-causing material. In this project we will generate novel stabilizing nanobricks (called nanobodies) to stabilize gamma-secretase and thus prevent the production of toxic amyloid beta. The novel nanobody stabilizers could pave the way for Alzheimer's therapy.

[www.brightfocus.org/grant/A20201828S](http://www.brightfocus.org/grant/A20201828S)

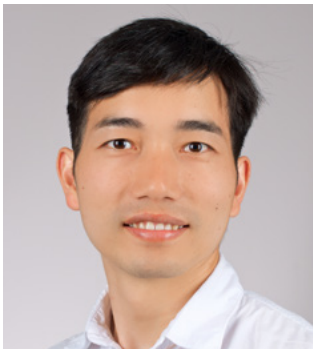


**Congcong He, PhD** (7/1/18 - 6/30/21)  
*Northwestern University, Chicago, IL*

### **How Autophagy Recognizes & Degrades Alzheimer's Disease-Causing Amyloids in the Brain**

The goal is to understand how autophagy, a protein degradation pathway, regulates A $\beta$  metabolism and prevents neuronal inflammation in the Alzheimer's brain.

[www.brightfocus.org/grant/A2018100S](http://www.brightfocus.org/grant/A2018100S)



**Jinghui Luo, PhD** (9/1/20 – 8/30/21)  
*Paul Scherrer Institute (PSI), Villigen, Switzerland*

### **A New Method to Determine Alzheimer's and Parkinson's Toxins in the Lipid-Rich Environment**

In diseases such as Alzheimer's and Parkinson's, toxic proteins accumulate and form holes in the nerve cells. Accumulated proteins are dynamic and take on different conformational shapes, making it difficult to study the features and functions of the protein. These proteins can be stabilized with experimental protein/lipid scaffolds in order to determine their structure with x-ray analysis. Understanding the structure of these accumulated toxic proteins will give insight into mechanisms of toxicity.

[www.brightfocus.org/grant/A20201759S](http://www.brightfocus.org/grant/A20201759S)



**Masato Maesako, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*Massachusetts General Hospital & Harvard Medical School), Boston, MA*

Fellowship Mentor: Oksana Berezovska, PhD

### **A New Method to Visualize Amyloid Beta Generation**

This project will identify which cells, and where within cells, amyloid beta is produced using a new kind of biosensor that will allow for visualization of the protein in living cells.

[www.brightfocus.org/grant/A2019056F](http://www.brightfocus.org/grant/A2019056F)



**Bryndon Oleson, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*University of Michigan, Ann Arbor, MI*

Fellowship Mentor: Ursula Jakob, PhD

### **Understanding the Function of the Biomolecule Polyphosphate During Aging and Alzheimer's Disease**

The highly-conserved polymer polyphosphate was recently found to protect cells and organisms from the toxic effects of amyloidogenic proteins, such as amyloid beta. The goal of this project is to characterize how polyphosphate changes with age, modifies amyloid beta toxicity, and influences susceptibility to Alzheimer's disease.

[www.brightfocus.org/grant/A2019250F](http://www.brightfocus.org/grant/A2019250F)



**Angèle Parent, PhD**

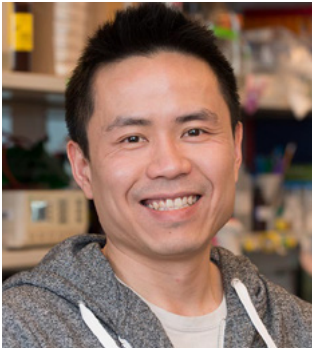
(7/1/17 - 6/30/20)

*University of Chicago, Chicago, Illinois*

### **Targeting APP Intracellular Fragment to Improve Memory and Reduce Amyloid Beta Burden in Alzheimer's Disease**

This research tests the hypothesis, using mouse models of AD, that production of an intracellular fragment originating from amyloid precursor protein (APP) could initiate signaling events that benefit memory process and reduce amyloid beta generation when delivered through modified viral vectors.

[www.brightfocus.org/grant/A2017443S](http://www.brightfocus.org/grant/A2017443S)



**Eitan Wong, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

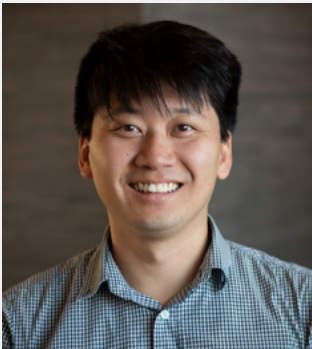
*Memorial Sloan-Kettering Cancer Center, New York, NY*

Fellowship Mentor: Yueming Li, PhD

### **Relationship Between Biological Clock and $\gamma$ -Secretase, the Enzyme Responsible for Generating Senile Plaques in Alzheimer's Disease**

Although the cause of Alzheimer's disease (AD) is poorly understood, the disease progression is associated with amyloid beta peptide senile plaques and sleeping disorder, suggesting malfunction in internal biological clock and alteration of circadian rhythm. Interestingly, our initial data discovered that  $\gamma$ -secretase activity, the enzyme responsible for  $A\beta$  plaques generation, also exhibits a daily circadian oscillation. This project will reveal the molecular interaction between circadian function,  $\gamma$ -secretase activity and the connection to AD.

[www.brightfocus.org/grant/A2019356F](http://www.brightfocus.org/grant/A2019356F)



**Hyunjun Yang, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of California, San Francisco*

Fellowship Mentor: William DeGrado, PhD

Fellowship Co-Mentor: Carlo Condello, PhD

### **Fingerprinting In Vivo and In Vitro Prion Strains**

Alzheimer's Disease (AD) is associated with the misfolding of tau and  $A\beta$  proteins. AD shares important molecular characteristics with classical PrP prion diseases, including the induced misfolding of soluble proteins in an autocatalytic manner and the accumulation of insoluble amyloids. Different conformational strains of PrP give rise to different neurodegenerative diseases. Conformation sensitive dyes are used to rapidly screen and fingerprint these conformational strains of prion proteins.

[www.brightfocus.org/grant/A2020039F](http://www.brightfocus.org/grant/A2020039F)



**Justyna Dobrowolska Zakaria, PhD** (7/1/19 - 6/30/22)

*Northwestern University, Chicago, IL*

Co-Principal Investigator: Robert J Vassar, PhD

### **A New Method to Separate Sub-groups of Alzheimer's Disease by Measuring sAPP $\beta$ in Human Cerebrospinal Fluid**

The goal of this project is to measure how quickly an Alzheimer's patient's brain makes a protein known as sAPP $\beta$ , and compare this to a healthy patient's brain, to determine if in Alzheimer's disease (AD) there is more sAPP $\beta$  being made than normal. Also, there is increasing evidence that not every patient's AD has the same cause. So additionally, we want to use sAPP $\beta$ , and other proteins such as sAPP $\alpha$  and  $A\beta$ , to determine if there are subgroups within AD patients that might respond in different ways to drugs that target AD.

[www.brightfocus.org/grant/A2019520S](http://www.brightfocus.org/grant/A2019520S)

# Biology of Fats and Proteins (APOE)



Initially recognized for its role in cardiovascular disease, the APOE gene also plays a role in Alzheimer's disease. Its primary function is to regulate a class of proteins involved in the metabolism of fats (lipids) in the body. However, APOE has several common variants (or "alleles") whose effects vary. The e4 allele, in particular, is the most prevalent genetic factor associated with late-onset Alzheimer's disease, and may cause an increased risk and/or earlier onset. Its impact varies depending on whether the mutation appears on one or both chromosomes, as well as a person's race and ethnicity (ie, risk is not

increased uniformly across all ethnic groups). Scientists are still trying to find out the reasons why. Some clues may lie with APOE's interactions with the immune system, where it influences inflammation and a type of cellular damage known as oxidation. Also, while the APOE gene influences the breakdown of amyloid beta protein located in and around neurons, its e4 variant is less effective at doing so.

*Above: Dr. Fan prepares tissue samples in the lab. (Courtesy of Weiwei Fan, PhD, The Salk Institute for Biological Studies, La Jolla, CA)*



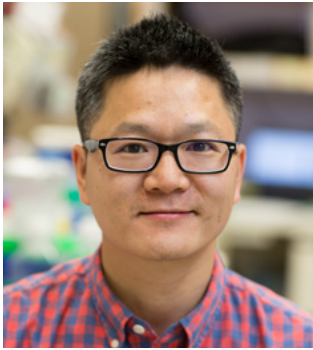
**Joseph Castellano, PhD** (7/1/18 - 6/30/21)  
Icahn School of Medicine at Mount Sinai, New York, NY

## **ApoE4's Effects on Blood Proteins and Brain Function in Alzheimer's Disease**

The researchers will directly investigate how manipulating proteins in the blood influences the ability of the risky APOE4 gene to influence development of Alzheimer's disease and the extent to which it can be rescued with more neutral forms of the gene.

[www.brightfocus.org/grant/A2018213S](http://www.brightfocus.org/grant/A2018213S)





**Weiwei Fan, PhD**

(7/1/18 – 09/18/20)

*Salk Institute for Biological Studies, La Jolla, CA*

### **Developing a New Drug for Alzheimer's Disease by Improving Lipid Metabolism in the Brain**

PPAR $\delta$  is a protein that is present in the brain. It is suggested to have important functions in brain. This proposal will help us understand its exact functions in brain. I will also test whether we can target PPAR $\delta$  to treat AD.

[www.brightfocus.org/grant/A2018325S](http://www.brightfocus.org/grant/A2018325S)



**Carl Frieden, PhD**

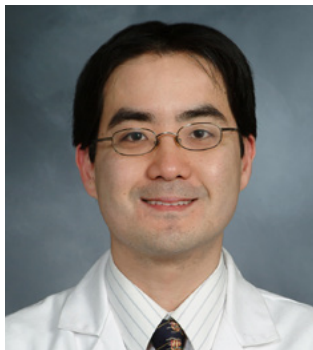
(9/1/20 – 8/30/23)

*Washington University School of Medicine, St. Louis, MO*

### **Understanding ApoE**

Over 5.6 million people in the United States have Alzheimer's disease (AD). Among these individuals, about 50 percent have a mutant protein called apoE4 which is considered to be the major risk factor for developing late onset AD. The current project investigates the properties of this protein.

[www.brightfocus.org/grant/A2020382S](http://www.brightfocus.org/grant/A2020382S)



**Makoto Ishii, MD, PhD**

(9/1/20 – 8/30/23)

*Weill Cornell Medicine, New York, NY*

### **The Role of Signaling Factors that Modulate Immune and Metabolic Function In Alzheimer's Disease**

Irreversible loss of brain cells and brain function may already exist by the time patients start developing memory loss due to Alzheimer's disease. Therefore, it is imperative to identify the earliest changes occurring in Alzheimer's disease, as they may yield new ways to intervene before irreversible brain damage has occurred. During the very early stages of Alzheimer's disease, when the memory remains relatively intact, there are significant changes in immune and metabolic function that contribute to Alzheimer's disease; however, the underlying cause of these changes remains unclear. The goal of this project is to identify the circulating factors that affect immune and metabolic function early in Alzheimer's disease before the memory loss and determine how they are involved in the overall disease process.

[www.brightfocus.org/grant/A2020363S](http://www.brightfocus.org/grant/A2020363S)



**Lydia Le Page, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

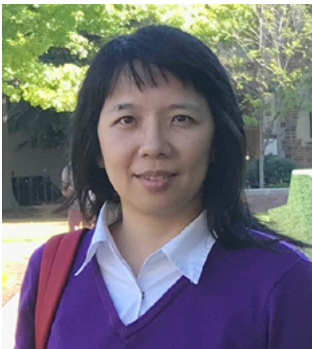
*University of California, San Francisco*

Fellowship Co-Mentors: Myriam Chaumeil, PhD & Ken Nakamura, MD, PhD

### **A New Way to Measure How the Brain Uses Ketones as Fuel in Alzheimer’s Disease.**

The ketogenic diet is thought to provide an alternative fuel for the struggling brain in Alzheimer’s disease (AD) – but is this fuel actually being used to make energy? Currently we have no way of knowing. We will develop a new way of imaging the brain to see if it is using the ketones as fuel, and use the method to discover new insights into brain ketone metabolism in a mouse model of AD.

[www.brightfocus.org/grant/A2020928F](http://www.brightfocus.org/grant/A2020928F)



**Chia-Chen (Jenny) Liu, PhD**

(9/1/20 – 8/30/23)

*Mayo Clinic Jacksonville, FL*

### **Explore the Impacts of APOE Genotype Switching from APOE4 To APOE2 in the Periphery (Liver and Bloodstream) for Alzheimer’s Disease Therapy**

Having apolipoprotein E4 (APOE4) gene increases a person’s risk, whereas having APOE2 is protective for Alzheimer’s disease (AD). Our previous study found that ApoE4 produced in the liver compromises the vascular health and impairs brain function (even though ApoE4 circulating in the bloodstream does not get into the brain). Using our unique mouse model in which ApoE2 is produced in the liver of ApoE4 mice, our studies will for the first time test whether converting harmful ApoE4 to protective ApoE2 in the liver can restore brain functions. In addition, this study will examine whether treating ApoE4 mice with ApoE2 young blood promotes aging-related memory deficits and reduces AD progression. Our findings will provide preclinical evidence for designing future human clinical trials, which may offer individualized treatment strategies based on APOE genotype.

[www.brightfocus.org/grant/A20201542S](http://www.brightfocus.org/grant/A20201542S)



**Edoardo Marcora, PhD**

(7/1/17 - 6/30/21)

*Icahn School of Medicine at Mount Sinai, New York, NY*

Co-Principal Investigator Anne Schaefer, MD, PhD

### **Understanding the Role of Apolipoprotein E in Microglia**

In normal conditions, microglia cells do not make APOE; however, in disease conditions, they sense the brain damage and respond by churning out APOE. The researchers are investigating what happens in mouse models if the APOE gene is removed from microglia.

[www.brightfocus.org/grant/A2017458S](http://www.brightfocus.org/grant/A2017458S)

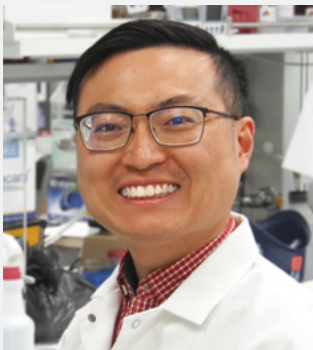


**Henrietta Nielsen, PhD** (7/1/19 - 6/30/22)  
*Stockholm University, Stockholm, Sweden*

**Assessment of Associations Between ApoE4 in the Blood, Behavior and Alzheimer’s Disease Related Changes Inside the Brain**

Alzheimer’s is a disease of the brain for which the risk is partially determined by a heritable factor, APOE4. This project will investigate the potential effects of a specific APOE4-linked liver-generated blood profile on disease-related changes inside the brain. A successful discovery of a factor that can be targeted in the periphery, rather than in the brain, for the cure or prevention of AD would facilitate the development of medication to prevent the disease.

[www.brightfocus.org/grant/A2019446S](http://www.brightfocus.org/grant/A2019446S)



**Chao Wang, PhD** (7/1/18 - 12/31/20) FELLOWSHIP  
*Washington University School of Medicine, St. Louis, MO*  
Fellowship Mentor: David M. Holtzman, MD

**A New Approach to Treating Tauopathy by Lowering Apolipoprotein E Level**

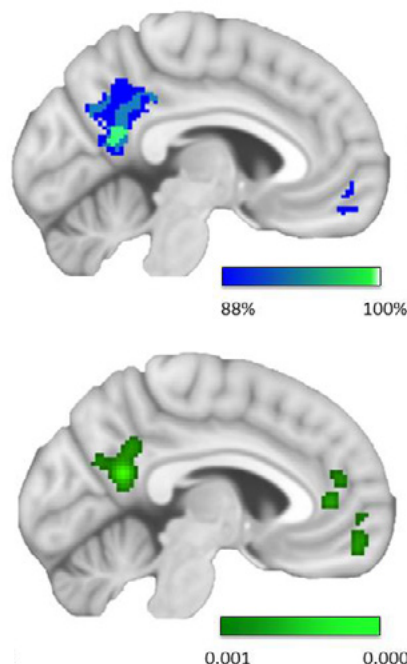
The researchers will determine if decreasing apolipoprotein E (ApoE) levels in the brain can alter tau aggregation and tau-induced neurodegeneration, and we will also try to determine how ApoE exerts its effects on tau.

[www.brightfocus.org/grant/A2018128F](http://www.brightfocus.org/grant/A2018128F)



**5.8 million**  
people live with Alzheimer’s in the United States today and by 2050 there will be close to **15 million.**

# Biomarkers



Biomarkers are early markers of biological changes associated with Alzheimer's disease (AD), which may begin causing gradual changes in the brain some 10-20 years before the onset of symptoms. The best hope of stopping AD is during this phase, and the need for earlier treatment makes the search for biomarkers critically important. Numerous types of biomarkers are in development, including tests to measure elevated amyloid beta ( $A\beta$ ) levels in blood and/or cerebrospinal fluid; use of advanced imaging to detect tiny changes in brain structure; and techniques identifying  $A\beta$  protein deposits in the retina

of the eye that mirror those in the brain. Biomarkers like these can help identify who is most likely to develop AD in the future, and what type, and also provide reliable measures of disease progress. This will help guide treatment decisions in the future, when drugs become available, determining such things as who needs treatment, when to start, and which drugs and treatment strategies are most likely to be successful.

*Above: Results from a neuroimaging study show brain regions and networks involved in hallucinations and delusions in Alzheimer's and related dementias. (Courtesy of Ryan Darby, MD, Vanderbilt University)*



**Iman Aganj, PhD**

(7/1/16 - 9/30/20)

Massachusetts General Hospital & Harvard Medical School, Boston

## **Imaging Biomarkers for Alzheimer's: New Methods to Account for Indirect Brain Connections**

The goal of the proposed project is to develop and validate novel computational methods, such as those accounting for indirect neural pathways, and subsequently derive more accurate AD imaging biomarkers based on brain connectivity with different versions of MRI.

[www.brightfocus.org/grant/A2016172S](http://www.brightfocus.org/grant/A2016172S)

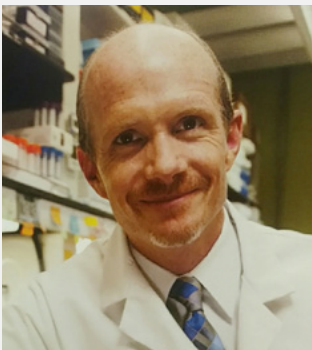


**Ganesh Babulal, PhD** (9/1/20 – 8/30/23)  
*Washington University School of Medicine, St. Louis, MO*

**Using Naturalistic Driving Behavior to Identify Older Adults with Preclinical or Symptomatic Alzheimer’s Disease**

Crashes are a leading cause of injury and deaths among older adults, with as many as 19 older adults killed each day, and crashes are higher among persons with Alzheimer disease (AD). Since 2015, we tested a new way to continuously collect driving behaviors (distances, speeding, hard braking, times of day driving, etc) by plugging a device into people’s cars and recording how they drive. This was termed the “Driving Real-World In-Vehicle Evaluation System” (DRIVES). We will use the DRIVES technology to see if we can sort out those who have early AD from those who do not. We will also look at whether or not other tests of brain abilities, including navigation (finding one’s way around), physical functioning, and sensory functioning (vision, hearing, smell), can help pinpoint individuals with early AD more accurately.

[www.brightfocus.org/grant/A20201142S](http://www.brightfocus.org/grant/A20201142S)



**Randall Bateman, MD** (7/1/17 - 9/30/20)  
*Washington University School of Medicine, St. Louis, MO*  
Co-Principal Investigators: Norelle C. Wildburger, PhD & Robert Schmidt, MD, PhD

**A New Way to Image Amyloid Plaque Growth in Human Alzheimer’s Disease**

Critical to the development of therapeutics that may treat and even cure AD is an understanding of Aβ dynamics in the human brain. This project uses the most advanced imaging technology to study the rate of plaque pathology in patients.

[www.brightfocus.org/grant/A2017081S](http://www.brightfocus.org/grant/A2017081S)



**David Berron, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
*Lund University, Lund, Sweden*  
Fellowship Mentor: Oskar Hansson, PhD

**Learning About the Early Consequences of Alzheimer’s Disease on our Brain and Cognitive Functions**

With the powerful and novel combination of state-of-the-art positron emission tomography (PET) imaging for amyloid/tau and structural as well as functional ultrahigh-field magnetic resonance imaging (MRI) at 7 Tesla, this project will unravel the early effects of AD pathology on brain functional connectivity and memory task-related functional activity, grey matter loss and specific memory functions.

[www.brightfocus.org/grant/A2019401F](http://www.brightfocus.org/grant/A2019401F)



**Becky Carlyle, PhD**

(7/1/19 - 6/30/22)

*Massachusetts General Hospital (affiliated with Harvard Medical School), Boston, MA*

### **Investigating Neuropeptides as Biomarkers and Novel Therapeutics for Alzheimer’s Disease**

Alzheimer’s disease (AD) is currently defined by the abundance of two insoluble proteins, amyloid beta (A $\beta$ ) and tau, but the amount of these proteins does not accurately predict cognitive problems in people with AD. Recent studies have found that neuropeptides are widely dysregulated in AD, and might play roles in the AD disease process. In this proposal, we investigate whether neuropeptides may be used to more accurately assess AD patients, and whether supplementation with these peptides might eventually prove a new potential therapy for AD.

[www.brightfocus.org/grant/A2019128S](http://www.brightfocus.org/grant/A2019128S)

*This grant is made possible by the support from The Luminescence Foundation, Inc.*



**Carol Yim Lui Cheung, PhD**

(7/1/18 - 6/30/22)

*The Chinese University of Hong Kong, China*

### **Recognizing “Retinal Fingerprint” for Alzheimer’s Disease Using Artificial Intelligence**

In this study, an artificial intelligence will “learn” structural patterns in the eyes of Alzheimer’s patients using deep learning methods to create a “retinal fingerprint” of the disease. This technique only requires a routine eye-check, and represents an inexpensive, non-invasive, efficient and accessible method to screen for Alzheimer’s disease.

[www.brightfocus.org/grant/A2018093S](http://www.brightfocus.org/grant/A2018093S)



**Ryan Darby, MD**

(7/1/17 - 8/30/20)

FELLOWSHIP

*Vanderbilt University, Nashville, TN*

Fellowship Co-Mentors: Daniel Claassen, MD, Bradford Dickerson, MD, Massachusetts General Hospital, Boston, MA, Michael Fox, MD, PhD, Beth Israel Deaconess Medical Center, Boston, MA

### **Neuroimaging and Behavioral Correlates of Delusions and Hallucinations in Alzheimer’s Disease**

Delusions and hallucinations commonly occur in Alzheimer’s disease, causing considerable distress for patients and families. The goal of this research is to determine why these symptoms arise, using different types of brain scans and behavioral tests.

[www.brightfocus.org/grant/A2017226F](http://www.brightfocus.org/grant/A2017226F)



**Jill M. Goldstein, PhD**

(3/30/18 - 3/29/21)

*Massachusetts General Hospital & Harvard University, Boston*

### **Clinical Algorithm to Identify Alzheimer's Disease Risk in Early Midlife**

This project will support the launching of a comprehensive effort (integrating clinical, physiological and brain biology traits) to identify in early midlife biomarkers for Alzheimer's risk informed by sex differences in brain aging and memory decline.

[www.brightfocus.org/grant/CA2018607](http://www.brightfocus.org/grant/CA2018607)



**Lea Grinberg, MD, PhD**

(7/1/17 - 6/30/21)

*University of California, San Francisco*

Co-Principal Investigator: Duygu Tosun, PhD

### **A Neuroimaging Biomarker for Asymptomatic Alzheimer's Disease**

This project will develop a biologically-validated clinical MRI template for detecting shrinkage in the locus coeruleus (the part of the brain that responds to stress and panic). This brainstem nucleus is especially vulnerable and earliest-damaged in Alzheimer's disease.

[www.brightfocus.org/grant/A2017560S](http://www.brightfocus.org/grant/A2017560S)



**Chadwick Hales, MD, PhD**

(9/1/20 - 8/30/23)

*Emory University, Atlanta, GA*

### **Identifying Aging and AD-Related Protein Changes In Skin Cells, Blood And Spinal Fluid, That Can Be Used as Markers of Disease or Therapeutic Targets**

Age is the strongest risk factor for Alzheimer's disease (AD) and the wrinkling of our skin. This study will investigate a link between aging and AD-related changes in the skin and the brain. The ultimate goal of the project is to identify new treatment approaches and new markers of aging and AD in the skin, blood, and/or spinal fluid.

[www.brightfocus.org/grant/A20201057S](http://www.brightfocus.org/grant/A20201057S)



**Jason Hassenstab, PhD** (7/1/18 - 6/30/21)  
*Washington University School of Medicine, St. Louis, MO*

**Rapid Assessment of Cognition Using Smartphones to Track Early Changes in Alzheimer’s Disease**

One of the biggest challenges we face in Alzheimer’s disease research and clinical trials is tracking the subtle cognitive changes that appear years before a clinical diagnosis. Standard cognitive tests were not designed for this purpose and thus have poor sensitivity and poor reliability. This study will adapt cognitive measures for rapid and repeatable administration on participant’s personal smartphones with the goal of producing highly reliable assessments.

[www.brightfocus.org/grant/A2018202S](http://www.brightfocus.org/grant/A2018202S)



**Lenora Higginbotham, MD** (9/1/20 – 8/30/22) FELLOWSHIP  
*Emory University, Atlanta, GA*  
Fellowship Mentor: Allan Levey, MD, PhD  
Fellowship Co-Mentor: Nicholas Seyfried, PhD

**Unraveling the Biological Overlap of Alzheimer’s Disease and Dementia with Lewy Bodies**

Dementia with Lewy bodies (DLB) is a disabling disease that is difficult to diagnose because it often looks similar to Alzheimer’s disease (AD). Our research aims to uncover key differences between these two disorders by using cutting edge techniques to analyze protein levels in the brain and its surrounding fluid. Unraveling the biological overlap between these two dementias could help make DLB easier to recognize and effectively treat.

[www.brightfocus.org/grant/A20201577F](http://www.brightfocus.org/grant/A20201577F)



**Xiong Jiang, PhD** (7/1/16 - 6/30/20)  
*Georgetown University, Washington, DC*

**A Novel Non-Invasive MRI-Based Biomarker of Early Stages of Alzheimer’s Disease**

Develop and validate multimodality MRI techniques, a collection of individual techniques which, when they are added together, can help to detect and quantify Alzheimer’s progression, even when it occurs without behavioral symptoms.

[www.brightfocus.org/grant/A2016251S](http://www.brightfocus.org/grant/A2016251S)





**Thomas Karikari, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of Gothenburg, Sweden*

Fellowship Mentor: Kaj Blennow, MD, PhD

Fellowship Co-Mentor: Henrik Zetterberg, MD, PhD

### **A Simple Blood Test to Identify Individuals at Risk of Developing Alzheimer's Disease**

Presently, there is no simple way to diagnose Alzheimer's disease (AD) or to identify individuals likely to develop the disease in the future: current tests require expensive brain imaging or inconvenient puncture of the spine. To address these challenges, we have developed a high-performance blood test that measures a specific disease-related change (called phosphorylation) on a key Alzheimer-associated protein called tau. Initial clinical applications have shown that the new test accurately identifies AD patients and at-risk individuals from healthy patients, and provides important insights into memory decline and brain shrinkage (both key processes associated with the disease) one year ahead of a typical clinical diagnosis. In this study, we propose to investigate, in three uniquely large patient cohorts recruited across three continents and closely monitored for up to a decade, whether our new blood test can predict with high accuracy who is likely to develop AD several years ahead of diagnosis by standard methods, in order to support early treatment, clinical management and recruitment for therapy trials.

[www.brightfocus.org/grant/A2020812F](http://www.brightfocus.org/grant/A2020812F)



**Amir Kashani, MD, PhD**

(2/24/20 – 7/31/21)

*University of Southern California & Roski Eye Institute*

### **Optical Coherence Tomography Angiography Based Assessment of Retinal Capillary Density as a Biomarker of Vascular Cognitive Impairment and Dementia**

Vascular contributions to cognitive impairment and dementia (VCID) arise from stroke and other vascular brain injuries that cause significant changes to memory, thinking, and behavior. VCID often occurs in and contributes to Alzheimer's Disease dementia. The damage in the small blood vessels is very difficult to detect with conventional testing or brain imaging methods like Magnetic Resonance Imaging (MRI). The goal of Dr. Kashani's research is to develop new methods using the eye to detect the onset, progression and severity of VCID.

[www.brightfocus.org/grant/CA2020004](http://www.brightfocus.org/grant/CA2020004)

*This proposal is funded through a partnership between the BrightFocus Foundation and the National Institute of Neurological Disorders and Stroke (NINDS) (as NINDS supplement 3UH3NS100614-04S1). BrightFocus is supporting this study as a part of the NINDS MarkVCID Consortium, of which Dr. Kashani is one of the principal investigators.*



**Hosung Kim, PhD** (7/1/19 - 6/30/22)  
*University of Southern California, Los Angeles, CA*  
Co-Principal Investigator: Arthur Toga, PhD

### **Machine-Learning Applied to Neuroimaging Data Can Predict Brain Biological Age and Acceleration of Aging in Early Alzheimer's Disease**

This proposed research seeks to predict physiological brain age for individuals in healthy condition by leveraging deep learning-based modeling with brain image datasets. This project expands the model to predict how abnormality expands incrementally to different brain areas as mild cognitive impairment and AD develop, as a way to estimate the 'survival' probability explaining the remaining days in healthy status prior to the onset of MCI or AD. Ultimately this could lead to disease-specific risk scoring as a clinical tool to be used in routine patient care.

[www.brightfocus.org/grant/A2019052S](http://www.brightfocus.org/grant/A2019052S)

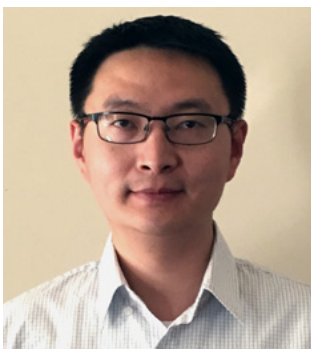


**Sarah Pickles, PhD** (9/1/20 - 8/30/22) FELLOWSHIP  
*Mayo Clinic Jacksonville, FL*  
Mentor: Leonard Petrucelli, PhD

### **Validation of a Biomarker that Could Identify a Subset of Frontotemporal Dementia and Alzheimer's Disease Patients**

Currently the medical field lacks reliable biomarkers to identify a subset of frontotemporal dementia (FTD) and Alzheimer's disease patients with a particular type of pathology in the brain, accumulation of aggregated TAR DNA binding protein (TDP-43). The production of a new molecule, truncated stathmin 2, arising from TDP-43 aggregation, may be a way to indirectly assess TDP-43 pathology. We propose to develop tools to determine if there is an increased amount of truncated stathmin 2 in spinal fluid from AD and FTD patients compared to controls. These findings have the potential to help separate patients who would benefit from particular therapies in upcoming clinical trials.

[www.brightfocus.org/grant/A2020279F](http://www.brightfocus.org/grant/A2020279F)



**Yi Su, PhD** (7/1/17 - 6/30/21)  
*Banner Health, Phoenix, AZ*

### **Neurovascular System Function and its Relationship with Aging and Alzheimer's Disease**

The goal of this project is to test a new way of analyzing the data from positron-emission tomography (PET) brain scan images to examine changes in brain metabolism and the loss of blood-brain barrier integrity as a consequence of aging and AD.

[www.brightfocus.org/grant/A2017272S](http://www.brightfocus.org/grant/A2017272S)



**Peter Tessier, PhD**

(7/1/17 - 8/31/21)

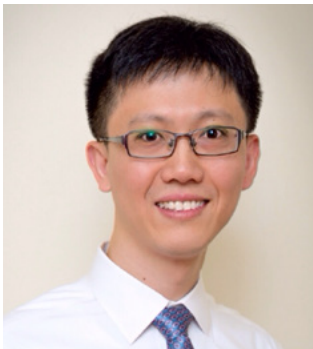
*University of Michigan, Ann Arbor*

Co-Principal Investigators: Brian Ross, PhD & Henry Paulson, MD, PhD

**New Tau Imaging Agents for Early Diagnosis of Alzheimer’s Disease**

These scientists will use an innovative design and evolution method for generating imaging probes specific for tau. These novel probes will be used to image toxic protein particles in mouse models of AD.

[www.brightfocus.org/grant/A2017395S](http://www.brightfocus.org/grant/A2017395S)



**Yong Wang, PhD**

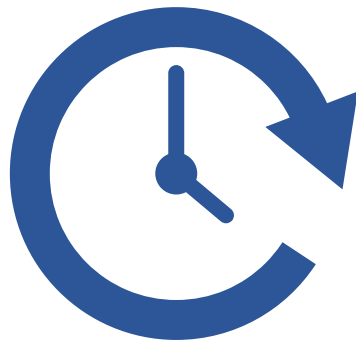
(7/1/17 - 12/31/20)

*Washington University School of Medicine, St. Louis, MO*

**A New Imaging Method to Measure White Matter Damage and Inflammation in Alzheimer’s Disease**

A PET-MRI method has been commonly used to identify tumors or strokes in patients with other diseases. These researchers adapt this method to measure the brain’s injury and immune response in patients who have Alzheimer’s disease, and to get a sense of the problems developing in their brain before memory problems occur.

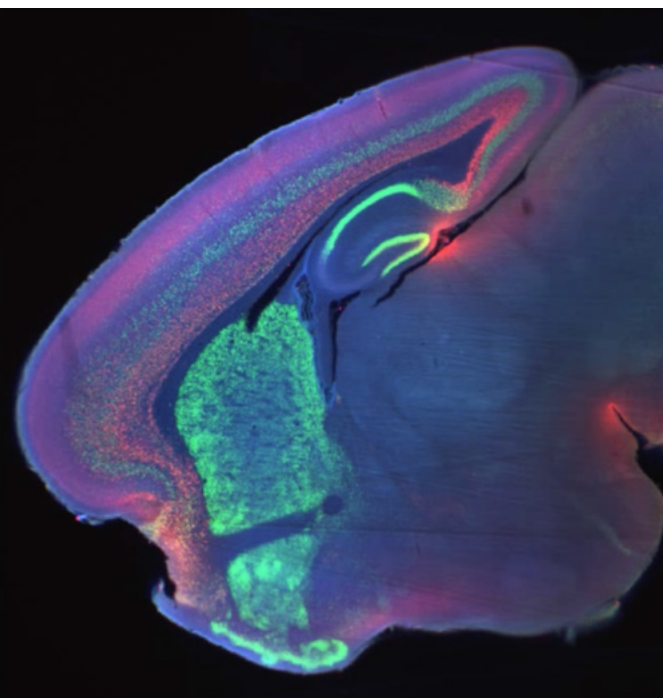
[www.brightfocus.org/grant/A2017330S](http://www.brightfocus.org/grant/A2017330S)



**EVERY  
65  
SECONDS**

**SOMEONE DEVELOPS  
ALZHEIMER’S DISEASE.**

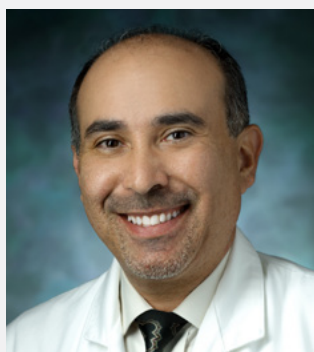
# Brain Blood Circulation in Dementia



As a neurodegenerative disease, Alzheimer's is known for damaging neurons, which are the nerve cells of the brain. And in order for neurons to survive and function properly, they depend on oxygen and glucose carried through the brain's blood vessels, or vascular system. Their needs are great because the brain consumes more energy than any other human organ, up to 20 percent of the body's total supply. The brain relies heavily on an intricately laced system of arteries, veins and capillaries that, in adult brains, stretches an estimated

100 miles in length. For protection, the brain's circulatory system is sealed off from that of the rest of the body by a special blood-brain barrier that helps prevent bacteria, viruses, and other toxic substances from entering. Together, the brain's circulatory system and protective barrier are important to Alzheimer's research because they are key to keeping neurons healthy.

*Above: View of a developing mouse brain with different types of neurons stained with different colors. (Courtesy of Alexandre Bonnin, PhD, University of Southern California)*



**Peter Abadir, MD**

(7/1/19 - 6/30/22)

Johns Hopkins University, Baltimore, MD

## Brain Changes in Alzheimer's Disease, Role of a Blood Pressure System

Angiotensin receptors are found on brain cells and play an important function in brain vital functions. This study will examine changes in these receptors in brain cells in patients with Alzheimer's dementia. This project will also study the impact of a class of drugs that target these receptors and are commonly used to treat high blood pressure.

[www.brightfocus.org/grant/A2019634S](http://www.brightfocus.org/grant/A2019634S)



**Alexandre Bonnin, PhD** (7/1/19 - 6/30/22)  
*University of Southern California, Los Angeles, CA*  
 Co-Principal Investigator: Axel Montagne, PhD

**Prenatal Inflammation Programs Alzheimer’s Disease Risk Later in Life**

Recent animal model studies suggest a causal link between inflammation during embryonic development and risk of AD-like neuropathology later in life. In light of recent research demonstrating that blood-brain barrier breakdown in the adult brain is a core cause of AD, the hypothesis is that inflammation-mediated disruption of blood-placenta and blood-brain barriers are key factors in the developmental origins of AD.

[www.brightfocus.org/grant/A2019279S](http://www.brightfocus.org/grant/A2019279S)

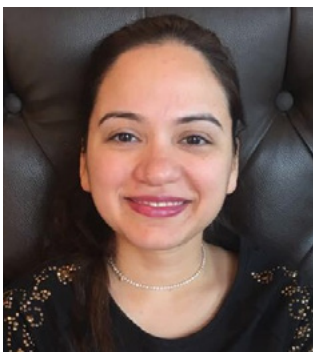


**Scott Counts, PhD** (9/1/20 – 8/30/23)  
*Michigan State University, East Lansing, MI*  
 Co-Principal Investigator: Roxana Carare, MD, PhD, University of Southampton, UK (England)

**The Role of Chemical Messenger Signaling in Removing Alzheimer’s Pathology from the Brain**

The contribution of cerebral amyloid (Abeta) angiopathy (CAA) and cerebrovascular pathology to the progression of Alzheimer’s disease (AD) has received renewed interest in the field. This proposal expounds upon compelling preliminary data to test that degeneration of the locus coeruleus (LC) and cholinergic basal forebrain (CBF) projection systems contribute to cognitive impairment through their damaging effects on intramural peri-arterial drainage (IPAD) of Abeta contributing to AD/CAA. If successful, this proposal will advance the clinical rationale for targeting LC/CBF-mediated IPAD as a disease modifying strategy.

[www.brightfocus.org/grant/A20201187S](http://www.brightfocus.org/grant/A20201187S)



**Saima Hilal, PhD** (7/1/18 - 6/30/21) FELLOWSHIP  
*Erasmus Medical Center, Rotterdam, Netherlands*  
 Fellowship Mentor: Meike W. Vernooij, MD, PhD  
 Fellowship Co-Mentor: M. Arfan Ikram, MD, PhD

**The Impact of ‘Silent’ Small Strokes on Brain Function and Alzheimer’s Development**

These researchers aim to find the cause for Alzheimer’s disease by detecting small strokes using structural and functional brain scans of thousands of people.

[www.brightfocus.org/grant/A2018165F](http://www.brightfocus.org/grant/A2018165F)



**Majken Jensen, PhD**  
*Harvard University, Boston, MA*

(7/1/17 - 6/30/21)

**Using Blood Samples to Assess the Role of Nutritional Factors in Alzheimer’s Risk**

In this project, key healthy dietary patterns will be identified that can form the foundation of dietary recommendations to lower a risk of Alzheimer’s disease.

[www.brightfocus.org/grant/A2017290S](http://www.brightfocus.org/grant/A2017290S)



**Ethan Lippmann, PhD**  
*Vanderbilt University, Nashville, TN*  
Co-Principal Investigator Laura Dugan, MD

(7/1/17 - 12/30/20)

**Identification of Genes/Proteins Involved in Leakage of Blood Vessels in the Brain**

In AD patients, the blood vessels of the brain become leaky, which worsens symptoms like memory loss. This project aims to identify why they become leaky.

[www.brightfocus.org/grant/A2017094S](http://www.brightfocus.org/grant/A2017094S)



**Shannon Macauley-Rambach, PhD**  
*Wake Forest University, Winston-Salem, NC*

(9/1/20 – 8/30/23)

**Targeting Blood Vessel Excitability to Reduce Tau Pathology in Alzheimer’s Disease**

Overactive neurons are thought to be a driver of Alzheimer’s disease pathology. Therefore, identifying new ways to reduce brain excitability is an important strategy for treating Alzheimer’s disease. This proposal will explore how targeting the brain’s vasculature by repurposing an FDA approved drug can dampen overactive neurons and decrease Alzheimer’s pathology.

[www.brightfocus.org/grant/A20201775S](http://www.brightfocus.org/grant/A20201775S)



**Alaina Reagan, PhD**  
*The Jackson Laboratory, Bar Harbor, ME*  
Fellowship Mentor: Gareth Howell, PhD

(9/1/20 – 8/30/22)

FELLOWSHIP

**Investigating How Genetic Risk Contributes to Cerebrovascular Damage in Alzheimer’s and Dementia**

Historically, beta-amyloid plaques and tau tangles have been the focus of Alzheimer’s disease research. However, there is increasing evidence that brain vascular health is a critical component in the progression of the disease. A variant in the MTHFR gene has been linked to both vascular disease and Alzheimer’s in humans, but until now, no animal model represented this risk factor. Here, we have created a novel mouse model to study how MTHFR deficiency affects brain vascular health with age.

[www.brightfocus.org/grant/A2020677F](http://www.brightfocus.org/grant/A2020677F)



**Alex Smith, PhD**

(7/1/18 - 6/30/21)

*University of California, San Francisco, CA*

### **Why Is Brain Glucose Uptake Reduced in Alzheimer's Disease?**

Blood vessels in the brain are surrounded by cells that contain a very large amount of a protein called aquaporin-4. In Alzheimer's disease, the amount of aquaporin-4 around vessels is reduced. This project will test if this is causing the cells to swell around the vessels and block sugar from getting into the brain.

[www.brightfocus.org/grant/A2018351S](http://www.brightfocus.org/grant/A2018351S)



**Lirong Yan, PhD**

(9/1/20 - 8/30/23)

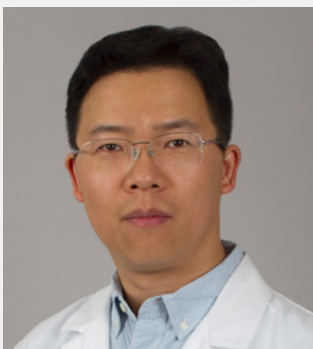
*University of Southern California, Los Angeles*

### **Studying Vascular Dysfunction of Cerebral Perforating Arteries in the Pathogenesis of VCID/AD**

By sharing common vascular risk factors, there is an increasing prevalence of Alzheimer's disease and vascular cognitive impairment/dementia (VCID) with age. Small vessel disease (SVD) induced by the dysfunction of cerebral perforating arteries is one of the frequent vascular pathologies in the aging brain and VCID. The state-of-the-art 7T MRI with increased intrinsic signal to noise ratio (SNR) allows us to image the cerebral perforating arteries directly. In this study, we will optimize two high-resolution MRI techniques at 7T to quantitatively characterize the structure and flow function of cerebral perforating arteries, and study the role of dysfunction of cerebral perforating arteries in the pathogenesis of VCID/AD.

*This grant is made possible in part by support from Alzheimer's Los Angeles.*

[www.brightfocus.org/grant/A20201411S](http://www.brightfocus.org/grant/A20201411S)



**Zhen Zhao, PhD**

(7/1/19 - 6/30/22)

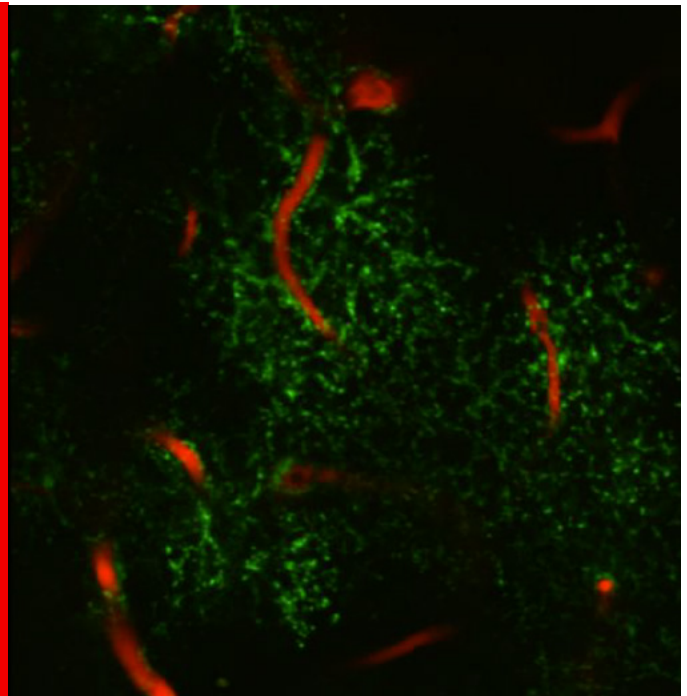
*University of Southern California, Los Angeles*

### **Understanding the Vascular Link Between Traumatic Brain Injury and Alzheimer's Disease**

Traumatic brain injury (TBI) is a leading cause of injury deaths and disabilities in the United States and the most robust environmental risk factor for AD. Vascular impairment is also a hallmark of the pathological events after TBI, including local edema, blood-flow reduction and breakdown of blood-brain barrier, which may significantly increase Alzheimer's risk. This project investigates the link between cerebrovascular impairment induced by TBI and its impact on the susceptibility to AD in animal models.

[www.brightfocus.org/grant/A2019218S](http://www.brightfocus.org/grant/A2019218S)

# Cells & Circuits



The human brain has an estimated 100 billion neurons; thankfully, quite a few to spare. Extending from each of them is a long fiber, known as an “axon,” which can run several feet. Each axon forms a connection, known as a “synapse,” with another neuron, creating a circuit over which brain signals travel. In Alzheimer’s disease (AD), individual neurons die and do not regenerate; yet some brains are resilient and will remodel themselves to meet new communications demands. If a circuit is too damaged to connect by the most direct route, signaling will sometimes take detours,

known as indirect neural pathways. It’s not until the communications network completely breaks down that classic AD symptoms—things like forgetting loved ones, or becoming lost in familiar places—begin to occur. Scientists are studying the brain’s many cells and circuits, looking for ways to preserve communications for as long as possible after the onset of AD.

*Above: From a live animal model, mitochondrial activity (green) in immune cells called astrocytes helps researchers determine whether changes in cell energy processing contribute to Alzheimer’s disease. (Courtesy of Maria Calvo-Rodriguez, PhD, Massachusetts General Hospital)*



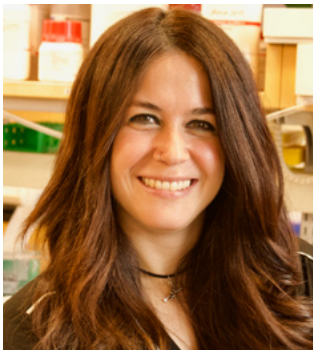
**Marc Aurel Busche, MD, PhD** (7/1/19 - 6/30/22)  
University College London, England, UK

## Mechanisms of Neuronal Dysfunction in Early Alzheimer’s Disease

This project will explore in particular the effects that tau and amyloid proteins seen in the brains of patients with AD have on the activity of interacting nerve cells in the hippocampus, a brain region which is known to be important for learning and memory. Also, it will test an innovative therapeutic strategy and evaluate its ability to repair abnormal activities of nerve cells.

[www.brightfocus.org/grant/A2019112S](http://www.brightfocus.org/grant/A2019112S)





**Maria Calvo-Rodriguez, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
*Massachusetts General Hospital (affiliated with Harvard Medical School), Boston, MA*  
Fellowship Mentor: Brian J. Bacskai, PhD

### **Dysfunction of Mitochondria in Astrocytes in Alzheimer's Disease**

This project will clarify if mitochondria mobility, distribution and calcium dynamics are altered in astrocytes in the pathology of Alzheimer's disease, and eventually determine the contribution of mitochondria and astrocytes to this disease. The final goal is to reverse mitochondrial dysfunction with appropriate drugs, suggesting novel molecular targets for therapeutic development that can be used in people.

[www.brightfocus.org/grant/A2019488F](http://www.brightfocus.org/grant/A2019488F)



**Inma Cobos, MD, PhD** (7/1/17 - 6/30/20)  
*Stanford University*

### **Alzheimer's in the Human Brain: Focusing on One Neuron at a Time**

What makes some neurons more vulnerable or resistant to disease? This project uses a new technique called "single cell RNA sequencing" to isolate thousands of single neurons from human brain tissue, study all the genes that are expressed in each individual cell, and make cell-to-cell comparisons between normal, early stage and late stage AD.

[www.brightfocus.org/grant/A2017346S](http://www.brightfocus.org/grant/A2017346S)

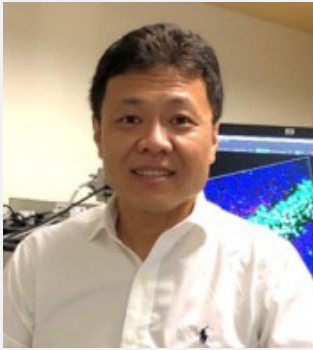


**Camin Dean, PhD** (7/1/19 - 6/30/22)  
*European Neuroscience Institute, Goettingen, Germany*

### **Treating Memory Loss in Alzheimer's Disease by Strengthening Synapses**

The insertion or removal of neurotransmitter receptors at synapses (connections between neurons) can promote learning, or forgetting, respectively. We recently discovered that a specific molecule called synaptotagmin-3 removes neurotransmitter receptors from synapses to promote forgetting. Mice missing synaptotagmin-3 have better memory than normal mice. This project will test whether removing or interfering with the function of this molecule in mice with Alzheimer's disease will improve their memory.

[www.brightfocus.org/grant/A2019586S](http://www.brightfocus.org/grant/A2019586S)



**Heng Du, PhD, MD**  
*The University of Texas at Dallas*

(9/1/20 – 8/30/23)

### **Mitochondrial Calcium Deregulation and Memory Loss in Alzheimer's Disease**

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by gradual cognitive decline currently without effective therapy. Although the detailed molecular mechanisms still remain elusive, defective mitochondrial calcium modulation has been repeatedly linked with synaptic dysfunction and neuronal death in AD milieus. In the proposed study, we will perform an examination of the role of mitochondrial calcium uniporter (MCU) deregulation in the development of mitochondrial and synaptic pathology in AD. Positive findings will foster our understanding of AD and shed light on the development of novel AD therapeutic avenue targeting MCU.

[www.brightfocus.org/grant/A20201159S](http://www.brightfocus.org/grant/A20201159S)



**Sara Gallant, PhD**  
*University of Southern California, Los Angeles*  
Fellowship Mentor: Mara Mather, PhD

(7/1/18 - 6/30/21)

FELLOWSHIP

### **Arousal-Induced Memory Selectivity in Aging and Alzheimer's Disease**

The locus coeruleus is a small brainstem region that becomes active during highly emotional or arousing events and is one of first sites to develop AD-related tau pathology. Using brain imaging, this research will examine functioning of the locus coeruleus under emotional "fight-or-flight" arousal as well as its relation to selective memory processes in aging and AD.

[www.brightfocus.org/grant/A2018449F](http://www.brightfocus.org/grant/A2018449F)



**Sarah Hill, PhD**

(9/1/20 – 8/30/22) FELLOWSHIP

*National Institute of Health/National Institute of Neurological Disorders and Stroke, Bethesda, MD*

Fellowship Co-Mentors: Michael E. Ward, PhD, MD, Jennifer Lippincott-Swartz, PhD, Janelia Research Campus, HHMI

### **Investigating Coordinated Removal of Old and Synthesis of New Materials in Neurons and How These Processes Are Disrupted in Frontotemporal Dementia**

Similar to how grocery stores maintain a full shelf of milk cartons by continually selling milk and obtaining new cartons, cells must balance the removal of old and synthesis of new materials. In neurons, insufficient removal of materials or defects in synthesis lead to loss of neuronal function, accumulation of toxic aggregates, and ultimately neuron death, contributing to the pathogenesis of neurodegenerative diseases such as frontotemporal dementia (FTD). This proposal examines how the distinct processes of removal and synthesis are interrelated. Imaging will be used to determine their physical and temporal relationship; drugs to block removal and determine the effects on synthesis; and neurons created from human cells to best determine the extent to which these processes occur during FTD.

[www.brightfocus.org/grant/A20201086F](http://www.brightfocus.org/grant/A20201086F)



**S. Abid Hussaini, PhD**

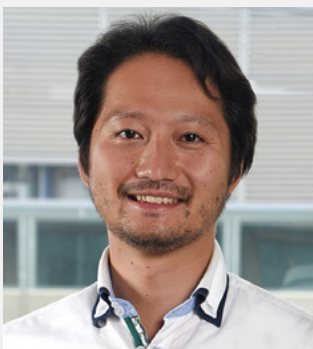
(7/1/19 - 6/30/21)

*Columbia University Irving Medical Center, New York, NY*

### **Does the Brain Region Responsible for Sleep Trigger Alzheimer's Disease?**

The locus coeruleus (LC) of the brain, which is important for sleep and memory, has been shown to have tau deposits (hallmark of Alzheimer's disease) in young adults. Could tau in LC be an early sign of Alzheimer's? By studying the electrical activity of the LC neurons in mice, we will find out if tau is causing LC dysfunction, leading to sleep and memory problems.

[www.brightfocus.org/grant/A2019307S](http://www.brightfocus.org/grant/A2019307S)



**Kei Igarashi, PhD**

(7/1/19 - 6/30/22)

*University of California, Irvine*

### **Rescuing Impaired Memory in Alzheimer's Disease Using Reactivation of Brain Network Activity**

Drs. O'Keefe, Moser and Moser, three Nobel prize researchers, previously found that brain cells called "place cells" and "grid cells" are important to keep our memory. Are these cells broken in Alzheimer's disease (AD)? If so, does fixing of these cells heal memory loss in AD patients? This project will find answers to these questions using animal models of AD.

[www.brightfocus.org/grant/A2019380S](http://www.brightfocus.org/grant/A2019380S)



**Ksenia Kastanenka, PhD**

(9/1/20 – 8/30/23)

*Massachusetts General Hospital & Harvard Medical School, Boston, MA*

### **Non-Neuronal Contribution to Alzheimer's Disease**

Alzheimer's disease (AD) is the major cause of dementia, precipitated by loss of neuronal cells, and is currently without an effective cure. A number of clinical trial failures have been reported due to a lack of clear understanding of AD causes and its progression. This proposal will push the envelope of current AD understanding beyond that of neurons and will address whether non-neuronal cells cause and/or contribute to Alzheimer's progression using state-of-the-art methodology. The insight gained through this line of research will open venues for novel development of therapeutics.

[www.brightfocus.org/grant/A2020833S](http://www.brightfocus.org/grant/A2020833S)



**Thomas Kukar, PhD**

(7/1/19 - 6/30/22)

*Emory University, Atlanta, GA*

### **A New Approach to Understand Why Defects in the Lysosome Pathway Increase the Risk of Developing Alzheimer's Disease**

The health and survival of neurons in the brain is dependent on a recycling pathway carried out by lysosomes, part of the cell that degrade and recycle proteins. Defects in the function of lysosomes are thought to be involved in the development of Alzheimer's disease (AD). We are trying to understand why decreases in a protein called progranulin (PGRN) impair lysosome function and increase the risk of developing AD.

[www.brightfocus.org/grant/A2019355S](http://www.brightfocus.org/grant/A2019355S)



**Tae Ho Lee, PhD**

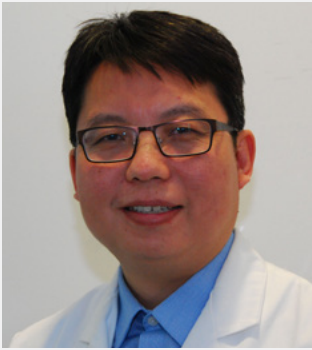
(7/1/17 - 6/30/21)

*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

### **New Mechanism to Regulate Neuron Death in Alzheimer's Disease**

The goal of this project is to study the role of death-associated protein kinase 1 (DAPK1) in AD using mouse models of AD.

[www.brightfocus.org/grant/A2017180S](http://www.brightfocus.org/grant/A2017180S)



**Tao Ma, MD, PhD**

(7/1/17 - 6/30/21)

Wake Forest School of Medicine, Winston-Salem, NC

### **A Potential New Therapeutic Target for Alzheimer's Disease**

This project evaluates the mechanism of Alzheimer's disease that leads to cells making fewer new proteins through the activity of an mRNA translational factor, eEF2, and its associated kinase as the basis for future work to identify novel diagnostic markers and therapeutic targets.

[www.brightfocus.org/grant/A2017457S](http://www.brightfocus.org/grant/A2017457S)



**Arjun Masurkar, MD, PhD**

(7/1/19 - 6/30/21)

New York University, New York, NY

### **Towards New Stimulation Methods to Correct Memory in Alzheimer's Disease**

Memory fails early in Alzheimer's disease because the entorhinal cortex, a brain area first affected by the disease, cannot properly communicate with the hippocampus, the second brain area affected by the disease. However, there is another brain region, the thalamus, that communicates with the hippocampus but is not affected at early stages. This project deciphers the structure and function of the "wiring diagram" between thalamus and hippocampus, and then examines how this functional connectivity changes in AD.

[www.brightfocus.org/grant/A2019602S](http://www.brightfocus.org/grant/A2019602S)

*This grant is made possible in part by the support from the Ping Y. Tai Foundation*



**Randy McIntosh, PhD**

(7/1/17 - 6/30/20)

Baycrest Centre for Geriatric Care, Toronto, Canada

Co-Principal Investigator: Kelly Shen, PhD

### **Building a Personalized Virtual Brain with Alzheimer's Disease to Guide Clinical Decisions**

This research provides software to "reconstruct" the brain, building models of different dementias to characterize the unique features of each disease and cognitive impairment. As this work progresses, it will be used to evaluate the potential of therapeutic interventions.

[www.brightfocus.org/grant/A2017286S](http://www.brightfocus.org/grant/A2017286S)



**Jerome Mertens, PhD**

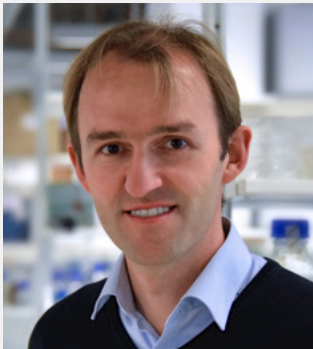
(7/1/19 - 6/30/22)

*University of Innsbruck, Innsbruck, Tyrol, Austria*

### **Reprogramming of Skin Cells from Alzheimer Patients into Brain Neurons to Understand and Fight Cellular Memory Loss on the Molecular Level**

Everybody ages, and unfortunately, this banal fact represents a huge health threat for us, because old age is the major risk factor for many human diseases, with Alzheimer's disease leading the way. Our laboratory has recently found a way to reprogram cultured skin cells from Alzheimer patients directly into brain neurons, which are unique for each patient and also biologically 'remember' how old the patient was. In this project we aim to better understand this connection and try to find ways to give Alzheimer neurons their own memory back.

[www.brightfocus.org/grant/A2019562S](http://www.brightfocus.org/grant/A2019562S)



**Dominik Paquet, PhD**

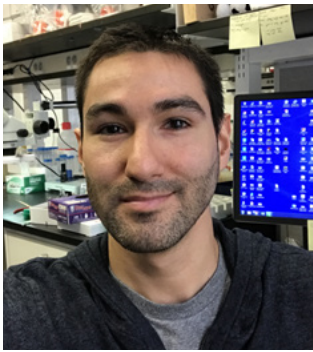
(7/1/19 - 6/30/22)

*Ludwig-Maximilians University, Munich, Germany*

### **A Human Brain-in-a-Dish Model to Investigate Central Factors Required for the Formation of Alzheimer's Disease Pathology**

We currently do not understand well why the brains of Alzheimer patients contain aggregates of proteins and how these aggregates relate to the death of millions of nerve cells over time. To better understand the formation of plaques and tangles, we would like to investigate the building blocks that are required for the formation of Alzheimer's disease (AD). For this purpose, we will turn human stem cells into nerve cells and other cell types found in the human brain, grow them together in a dish to assemble artificial human brain tissue, and introduce alterations in genes and cellular physiology that are typical for patients with inherited forms of AD. We will investigate if these models display Alzheimer pathology in a dish, and then modify the composition of cell types or the function of cells and their genes to learn which factors cause protein aggregation or nerve cell death in AD.

[www.brightfocus.org/grant/A2019604S](http://www.brightfocus.org/grant/A2019604S)



**Gustavo Rodriguez, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*Columbia University Irving Medical Center, New York, NY*

Fellowship Mentor: S. Abid Hussaini, PhD

### **Improving the Quality of Spatial Information Processing by Combating Dysfunctional Neuronal Activity in Alzheimer's Disease Mouse Models**

In mouse models of AD pathology, amyloid beta leads to overactive neuron signaling and poor spatial information processing, which may be aggravated by tau build-up. Using sophisticated recording techniques, this project will measure the content and quality of spatial information transmitted by large numbers of neurons affected by amyloid beta and tau pathology. Dysfunctional neuronal populations will be selectively targeted to correct their aberrant firing patterns, with the overall goal of improving the quality of spatial information carried by large numbers of neurons.

[www.brightfocus.org/grant/A2019382F](http://www.brightfocus.org/grant/A2019382F)



**Isabel Salas, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*The Salk Institute for Biological Studies, La Jolla, CA*

Fellowship Mentor: Nicola Allen, PhD

### **Using Astrocyte Factors to Prevent Synaptic Alterations in Alzheimer's Disease**

The brain is the center of command of our bodies, controlling our motion, our behavior and our feelings. Its main components, the neurons, process information by making specialized connections (synapses) between them, assisted by other important types of cells: the astrocytes. Alzheimer's disease (AD) is associated with alterations in these connections. In this project I aim to restore the correct function of astrocytes, to rescue synaptic defects, in mouse models affected by AD and make a step further towards the cure of this devastating disorder.

[www.brightfocus.org/grant/A20201645F](http://www.brightfocus.org/grant/A20201645F)



**Min-Kyoo Shin, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

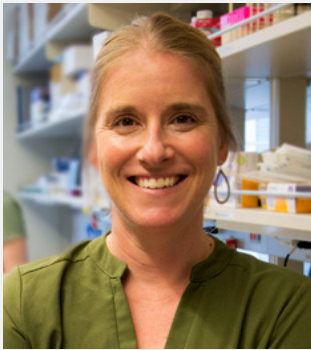
Case Western Reserve University, Cleveland, OH

Fellowship Mentor: Andrew A. Pieper, MD, PhD

### **Determination of Whether a Novel Biological System in the Brain Regulates Nerve Cell Death and Behavioral Abnormalities in Alzheimer's Disease**

We have discovered a new biological system governing neurodegeneration in traumatic brain injury: enzymatic activity of 15-prostaglandin dehydrogenase (15-PGDH) in the brain that controls levels of prostaglandin E2, which protects neurons. We also have preliminary evidence that levels of 15-PGDH are pathologically increased in animal models of Alzheimer's disease (AD), as well as in the human AD brain. This project will rigorously determine whether this increase in 15-PGDH plays a role in nerve cell death and behavioral learning problems in a mouse model of AD.

[www.brightfocus.org/grant/A2019551F](http://www.brightfocus.org/grant/A2019551F)



**Jessica Young, PhD**

(7/1/18 - 6/30/21)

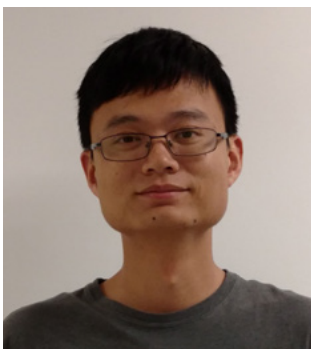
University of Washington School of Medicine, Seattle, WA

### **A New Method to Assess Cellular Dysfunction in Alzheimer's Using Human Neurons**

The overall goal is to use "induced pluripotent stem cell technology," derived from adult human cells, to better understand pathogenic events that may occur early on in neurons that could represent novel therapeutic targets for Alzheimer's disease (AD). The focus is on the endosomal network (how proteins are moved within a cell), which may become dysfunctional in AD before amyloid and tau deposits are reported.

[www.brightfocus.org/grant/A2018656S](http://www.brightfocus.org/grant/A2018656S)

*This grant is made possible in part by support from the Jerome Jacobson Foundation.*



**Yingjun Zhao, PhD**

(7/1/18 - 6/30/21)

FELLOWSHIP

Xiamen University, China

Fellowship Mentor: Huaxi Xu, PhD, Sanford-Burnham Prebys Medical Discovery Institute, La Jolla, CA

### **A Novel Approach for Memory Improvement in Alzheimer's Disease**

The goal of this project is to understand how proteins that are overproduced in AD, such as apoptosin, can alter the brain to disrupt communication between neurons to cause problems with memory.

[www.brightfocus.org/grant/A2018214F](http://www.brightfocus.org/grant/A2018214F)

*This grant is made possible in part by the support from the J.T. Tai Foundation.*



# Finding New Drugs and Treatments for Alzheimer's Disease



Years of innovative and dedicated research have paid off with the discovery of numerous factors contributing to Alzheimer's disease (AD) pathology. These discoveries have produced a bounty of "druggable targets," and with a disease as complex as this one, it's very helpful to find multiple points where it may be possible to slow or halt its progress. Unfortunately, only a handful of potential disease-modifying treatments has ever made it to the point of being tested in clinical trials. While many have not met their primary endpoints and been discontinued, many treatments are still being developed today. Support is needed for the

type of high-risk, high-reward early research where discoveries in basic science may lead to the development of molecules and compounds aimed at reducing toxic protein buildup in AD, improving clearance of toxic particles, and delivering treatments to brain areas. The contributions gained from these exploratory projects at early stages are essential to get the next generation of drugs and therapies to patients.

*Above: Dr. Gunawardena looks on as a student prepares a sample. (Courtesy of Shermali Gunawardena, PhD, State University of New York, Buffalo)*



**Christelle Anaclet, PhD** (9/1/20 – 8/30/23)  
*University of Massachusetts Medical School, Worcester, MA*  
Co-Principal Investigator: Heinrich Gompf, PhD

### **Understanding the Beneficial Role of Sleep in Cognitive Deficits**

Cognitive deficits and sleep disruption are the two major symptoms of Alzheimer's disease (AD). Given that sleep is necessary for cognition, we will test sleep enhancement as an interventional strategy for reducing the burden of the cognitive deficit in AD, using our new and unique mouse model of sleep enhancement. We will investigate, for the first time, the mechanism by which sleep benefits memory, providing new targets for developing pharmacological and interventional strategies to treat sleep and cognitive symptoms in AD.

[www.brightfocus.org/grant/A2020321S](http://www.brightfocus.org/grant/A2020321S)

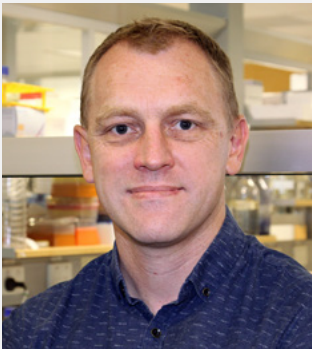


**Michele Cavallari, MD, PhD** (9/1/20 – 8/30/23)  
*Harvard Medical School & Brigham and Women's Hospital, Boston, MA*

### **Washing Alzheimer's Disease Off the Brain**

Alzheimer's disease (AD) is the most common cause of dementia in the aging population, yet there is no cure to stop the progression of the disease. We propose to study a protective mechanism that drains potentially harmful toxins associated with the development of AD, such as beta-amyloid and tau proteins, outside the brain, and that has been recently characterized in animal models. We will use data from two large international studies of AD to investigate this mechanism in subjects at high risk for developing dementia associated with the disease. In investigating this mechanism for the first time in humans, our study could set the ground for future development and testing of therapeutic approaches to prevent the development of Alzheimer's dementia.

[www.brightfocus.org/grant/A2020653S](http://www.brightfocus.org/grant/A2020653S)



**Brett Collins, PhD** (7/1/18 - 6/30/21)  
*The University of Queensland, Brisbane, Australia*

### **Stabilizing the Retromer Protein Complex with Molecular Chaperones for Alzheimer's and Parkinson's Diseases**

Cellular processes regulating protein turnover could be manipulated to prevent the build-up of the toxic beta amyloid peptides that cause neurological failure. This work will develop novel small molecules and peptides with the goal to enhance this protein turnover in neurons, and provide a starting point for designing new Alzheimer's drugs.

[www.brightfocus.org/grant/A2018627S](http://www.brightfocus.org/grant/A2018627S)



**Simone Crivelli, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of Kentucky, Lexington, KY*

Fellowship Mentor: Erhard Bieberich, PhD

Fellowship Co-Mentor: Pilar Martinez-Martinez, PhD, Maastricht University (The Netherlands)

### **Protecting Brain Cells From Death Using Lipid Metabolic Drugs as a New Treatment for Alzheimer's Disease**

There is still no cure for Alzheimer's disease (AD), therefore, a major challenge for researchers in the field is to develop new therapies that prevent or delay onset of this disease. During the AD process brain cells, including neurons, are under attack by high levels of the lipid ceramide. The consequence of this elevation is that neurons are not able to produce enough energy and are more easily programmed to die. Hence, in this research proposal, we propose to reduce ceramide levels in the brain to protect neurons from dying as a new therapy for AD.

[www.brightfocus.org/grant/A20201464F](http://www.brightfocus.org/grant/A20201464F)



**Brati Das, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of Connecticut Health Center, Farmington, CT*

Fellowship Mentor: Riqiang Yan, PhD

### **Improving Cognitive Function in AD Therapy Using a Combinatorial Approach of Reducing Disease Progression and Increasing Memory**

Amyloid beta ( $A\beta$ ) is the main component of amyloid plaques found in the brains of Alzheimer patients. Production of  $A\beta$  is nearly stopped by inhibiting BACE1 enzyme. Therefore, BACE1 inhibitors are used to reduce  $A\beta$  production and amyloid deposition. But their use can lead to many side effects that impact learning and storage of memory. Therefore, it is critical to develop new therapeutic strategies. We propose to use BACE1 inhibitor drugs in combination with mGluR activator drugs. This combination therapy will stop the disease progression and help in memory retention at the same time. We will test our strategy in mice in the current study. Positive results from this study could lead to treatments providing a better quality of life for Alzheimer's patients.

[www.brightfocus.org/grant/A20201729F](http://www.brightfocus.org/grant/A20201729F)



**Mar Hernandez Guillamon, PhD** (7/1/17 - 6/30/21)  
*Vall d'Hebron Research Institute, Barcelona, Spain*

### **Modulating Brain Cholesterol to Treat Alzheimer's Disease**

The aim of this proposal is to determine the effect of a new treatment based on the administration of a natural modified protein, the ApoA-I-Milano variant, able to mobilize lipids in a transgenic mouse model of Alzheimer's disease.

[www.brightfocus.org/grant/A2017243S](http://www.brightfocus.org/grant/A2017243S)



**Shermali Gunawardena, PhD** (7/1/18 - 6/30/21)  
*State University of New York Buffalo, Buffalo, NY*

### **A Novel Therapeutic Device to Clear Axonal Blocks to Prevent Alzheimer's Disease**

The research team is using a highly innovative approach to develop synthetic biomolecules that will deliver therapeutics to specific sites within the brain to modify defects that activate Alzheimer's disease pathways.

[www.brightfocus.org/grant/A2018509S](http://www.brightfocus.org/grant/A2018509S)



**Patrick Kehoe, PhD** (7/1/16 - 6/30/21)  
*University of Bristol, England, United Kingdom*  
Co-Principal Investigators Scott Miners, PhD & Mark Good, PhD

### **Helping the Brain to Fight Back Against Alzheimer's—Using Old Drugs for New Purposes**

These researchers are investigating whether a drug already developed, but unlicensed for use in people for blood pressure, and previously not considered in Alzheimer's disease (AD), can protect against both cognitive decline and tissue damage in an established mouse model of AD.

[www.brightfocus.org/grant/A2016582S](http://www.brightfocus.org/grant/A2016582S)



**Eunhee Kim, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*Massachusetts General Hospital & Harvard Medical School*

Fellowship Mentor: Rudolph E. Tanzi, PhD

### **The Impact of the Exercise Hormone Irisin on Astrocytes in Alzheimer's Disease**

Exercise reduces the risk of developing Alzheimer's disease (AD) by up to 50 percent and protects against AD by modulating the inflammation which is heavily dependent on brain immune cells: astrocytes. Irisin is a novel exercise-induced hormone that has been identified to play a role in beneficial aspects of exercise. This work aims to understand the functional role of the exercise-hormone irisin in AD pathogenesis, and the underlying molecular mechanism of the neuroprotective effects of irisin in AD by regulating astrocytes. The data obtained in this proposal will advance our knowledge of irisin and astrocytes in AD, and ultimately be directed toward novel therapeutic designs that mimic the beneficial effects of exercise.

[www.brightfocus.org/grant/A2020870F](http://www.brightfocus.org/grant/A2020870F)



**WonHee Kim, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*Tufts University, Boston, MA*

Fellowship Mentor: Giuseppina Tesco, MD, PhD

### **Understanding Alzheimer's Disease to Avoid Side Effects of Drugs**

Pharmaceutical companies have developed a drug, called BACE inhibitor, that has the potential to prevent and cure Alzheimer's disease (AD). However, it is still uncertain whether this drug is safe for AD patients. Prior research suggests that this medicine could cause worsen side effects in people born with Down syndrome or carrying a specific genetic mutation causing AD. The goal of this project is to better understand AD caused by genetic risk factors, and ultimately find a safe drug treatment for AD patients.

[www.brightfocus.org/grant/A2019021F](http://www.brightfocus.org/grant/A2019021F)



**Anna Orr, PhD**

(7/1/19 - 6/30/22)

*Weill Cornell Medicine, New York, NY*

Co-Principal Investigator: Adam Orr, PhD

### **Alleviating Alzheimer's Disease with Novel Therapeutic Agents that Can Precisely Block the Production of Reactive Oxygen**

Aging and neurodegenerative disease are associated with the accumulation of free radicals (also called oxidative stress) in the brain and other organs. Oxidative stress can damage cells and organs, promote disease, and impair brain function. We recently discovered small molecules that can block specific causes of oxidative stress without affecting normal cell functions. This research project will test whether these small molecules have therapeutic benefits in experimental models of dementia.

[www.brightfocus.org/grant/A2019363S](http://www.brightfocus.org/grant/A2019363S)



**Manveen Sethi, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*Boston University, Boston, MA*

Fellowship Mentor: Joseph Zaia, PhD

### **Deciphering the Alzheimer's Disease Glyco-code**

Alzheimer's disease (AD) is a leading cause of dementia, involving cognitive decline, loss of independence and behavioral issues. Identifying the bio-molecular deregulation associated with AD is crucial to decode the underpinning disease mechanisms, to discover new biomarkers, and to improve treatment strategies. This project will utilize an analytical workflow, allowing the exploration of the structure and biology of proteins and glycans in AD from patient tissue specimens. Outcomes of this project will benefit AD patients by generating the fundamental, previously unattainable, glycobio-logical knowledge required to improve the diagnosis and treatment of AD.

[www.brightfocus.org/grant/A2020687F](http://www.brightfocus.org/grant/A2020687F)



**Saul Villeda, PhD**

(9/1/20 – 8/30/23)

*University of California, San Francisco*

### **Role of Platelet-derived Factors in Ameliorating Alzheimer's Disease Pathology**

Aging alters the adult brain in ways that lead to impaired learning and memory, and an increased risk for Alzheimer's disease (AD). A growing body of work indicate that factors in young blood have the potential to reverse age-related impairments in the brain in animal models of aging and AD. The proposed study will determine the therapeutic potential of young platelets, and platelet-derived circulating factors, to reverse neurodegenerative phenotypes in a mouse model of AD, and elucidate their downstream mechanisms of action. The results will have significant translational potential, identifying a blood-based therapeutic intervention to restore functions underlying AD-related cognitive impairments and broadly counter dementia-related neurodegenerative diseases.

[www.brightfocus.org/grant/A20201492S](http://www.brightfocus.org/grant/A20201492S)



**Benjamin Wolozin, MD, PhD**

(9/1/20- 08/20/23)

*Boston University, Boston, MA*

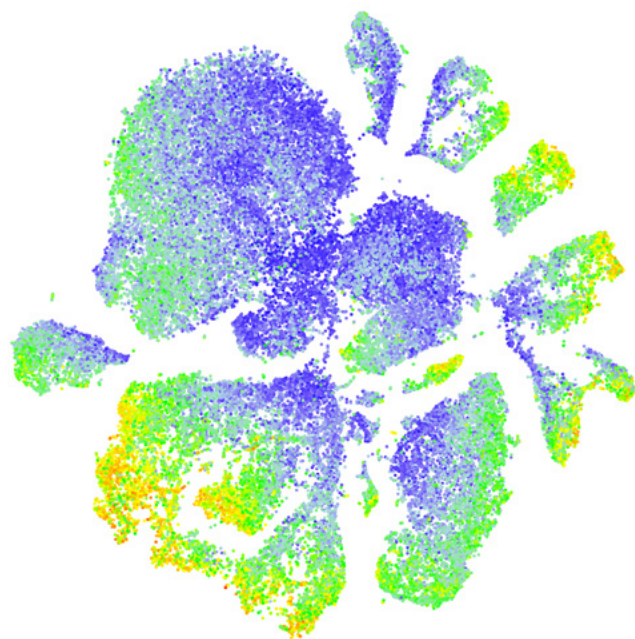
Co-Principal Investigator: Ahmad Khalil, PhD

### **Development of Synthetic Gene Feedback Circuits to Prevent Tau Aggregation**

This proposal uses a radically novel approach termed "synthetic biology", which uses concepts from electrical engineering to design new types of genetic therapy for AD. New synthetic gene circuits will be created that can detect and then remove harmful tau pathology as it appears in the brains of patients with AD. These new therapies will selectively target only those nerve cells that actually have pathology, increasing the effectiveness while reducing the potential for unwanted side effects.

[www.brightfocus.org/grant/CA2020002](http://www.brightfocus.org/grant/CA2020002)

# Genomics: DNA Blueprint for Alzheimer's



Genes are the “master blueprint” that instructs our cells to make unique proteins which in turn build, operate, and repair human tissue. Humans have an estimated 24,000 genes along our 23 matched pairs of chromosomes (46 in all), and “genomics” refers to the field that studies all of them at once. Even slight changes in a gene on one or both chromosomes can produce a protein that functions abnormally, possibly causing or increasing/decreasing the risk of a disease such as Alzheimer's. However, only one type of Alzheimer's disease (AD)—early-onset forms, representing less than 10 percent—can be traced consistently to changes, or mutations, in identified genes. The remaining 90 percent—late-onset AD—is associated with small genetic irregularities occurring throughout the genome. Using powerful and fast new technologies, researchers working in genomics look for

variations, patterns, and interactions among all genes in hundreds of thousands of people. So far, several dozen “regions of interest” have been identified, only it gets complicated because gene signaling can be turned “on” or “off” by additional factors, such as environment and lifestyle. Thanks to genomics, all this is being sorted out, and ultimately will help provide answers to basic questions, such as: What causes AD to start? How do genes interact with environment to raise or lower Alzheimer's risk? Who is most at risk and apt to benefit from new treatments? What's most likely to work in any given individual (“personalized medicine”)?

*Above: In this analysis of brain cells from patients with dementia, each dot represents a unique cell. The closer together they are, the closer their corresponding genetic information. (Courtesy of Elise Marsan, PhD, University of California, San Francisco)*



**Holly Cukier, PhD**

(7/1/18 - 6/30/21)

*University of Miami, Miami, FL*

Co-Principal Investigator: Derek Dykxhoorn, PhD

### **Elucidating the Roles of ABCA7 in Neurons and Glia Created from Alzheimer's Patients' Adult Stem Cells**

This project seeks to investigate the role of a gene shown to be a risk factor for AD, ABCA7, and the consequence of a mutation that was first identified in African Americans. Using two cell types from induced pluripotent stem cells generated from African Americans, the researchers will investigate how this deletion may affect the normal way neurons and microglia develop, and how that may lead to AD.

[www.brightfocus.org/grant/A2018197S](http://www.brightfocus.org/grant/A2018197S)



**Mark Ebbert, PhD**

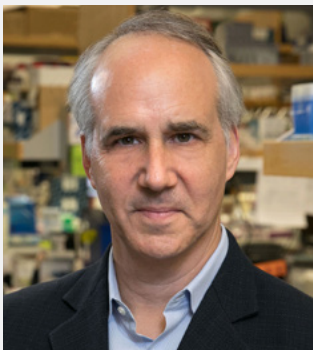
(9/1/20 - 8/30/23)

*University of Kentucky, Lexington, KY*

### **Identifying Therapeutic Targets and Biomarkers to Facilitate a Meaningful Therapy and a Pre-Symptomatic Alzheimer's Diagnostic**

Many genes are known to be involved in Alzheimer's disease, but exactly how they are involved is unclear. This project hopes to identify DNA and RNA changes that drive Alzheimer's disease development and progression.

[www.brightfocus.org/grant/A2020161S](http://www.brightfocus.org/grant/A2020161S)



**Daniel Geschwind, MD, PhD**

(7/1/18 - 6/30/21)

*University of California, Los Angeles*

Co-Principal Investigator: Jessica Rexach, MD, PhD

### **Identifying Disease Mechanisms in Neurodegeneration Using Genomics and Bioinformatics**

Using cutting edge technology, these researchers will profile the different cells of the dementia brain at unprecedented resolution to understand the complexity of the brain's different cell types, which presents a unique challenge to scientific inquiry.

[www.brightfocus.org/grant/A2018700S](http://www.brightfocus.org/grant/A2018700S)





**Elise Marsan, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of California, San Francisco*

Fellowship Mentor: Eric J. Huang, MD, PhD

Fellowship Co-Mentor: Arnold Kriegstein, MD, PhD

### **Finding Aberrant Glial and Neuronal Dysfunctions that Promote Neurodegeneration in Alzheimer's Disease and Related Dementia**

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are two highly related neurodegenerative diseases that share several key clinical, genetic and neuropathological features. The goal of my project is to harness the cutting-edge single cell transcriptomic technology to uncover common transcriptomic signatures that contribute to disease progression in AD and FTLD. Results from this study will provide important insights to disease mechanisms and an enriched resource for the scientific community. Ultimately, these results will help us to discover new treatments for these devastating diseases.

[www.brightfocus.org/grant/A2020443F](http://www.brightfocus.org/grant/A2020443F)



**Justin Miller, PhD**

(9/1/20 – 8/30/23)

FELLOWSHIP

*Brigham Young University, Provo, UT*

Fellowship Mentor: John S. K. Kauwe, PhD

### **Identifying Groups of Alzheimer's Disease Patients with Slower Disease Progression**

This project uses machine learning to group individuals with similar health trajectories based on genetics, clinical tests, and neuroimages. These subtypes will be used to assess differences in the rate of cognitive decline, the age of disease onset, and the age of death for each proposed subtype using a longitudinal dataset spanning 20 years. Identifying AD subtypes will allow future studies to improve diagnoses for patients, identify subtype-specific drug targets, calculate disease trajectories for each subtype, focus clinical trials on specific subtypes, and eventually develop subtype-specific treatment plans.

[www.brightfocus.org/grant/A2020118F](http://www.brightfocus.org/grant/A2020118F)



**Michael Miller, MD, PhD** (9/1/20 – 8/30/22) FELLOWSHIP  
*Brigham and Women's Hospital & Harvard Medical School, Boston, MA*  
Fellowship Mentor: Christopher Walsh, MD, PhD, Boston Children's Hospital  
& Harvard Medical School, Boston, MA

### **Gene Changes in Individual Cells Assessed Across the Progression of Alzheimer's Disease**

Alzheimer's disease (AD) and other neurodegenerative diseases involve a loss of brain function and brain cells over time and eventually cause death, affecting one third of people over the age of 85. Recent research has found that brain cells build up new mutations in the DNA (known as somatic mutations) as we get older, which appears to harm the brain cells. This proposal will test the hypothesis that somatic mutations contribute in important ways to the pathologic progression of AD, and are related to other kinds of disease damage in brain cells, including oxidative stress.

[www.brightfocus.org/grant/A20201292F](http://www.brightfocus.org/grant/A20201292F)



**Bede Portz, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
*University of Pennsylvania, Philadelphia, PA*  
Fellowship Mentor: James Shorter, PhD

### **New Protein Modifiers and Therapeutic Targets to Combat Toxic RNA Foci in Frontotemporal Dementia**

Frontotemporal dementia is caused by expanded repeats in the C9orf72 gene, which encode toxic repeat RNAs that aggregate, forming RNA foci. This project will elucidate the machinery overwhelmed by C9orf72 repeat expansion by testing the hypothesis that DDX3X is an RNA disaggregase capable of dissolving these foci, and by screening for new protein modifiers of C9orf72 RNA foci in live cells.

[www.brightfocus.org/grant/A2019612F](http://www.brightfocus.org/grant/A2019612F)



**Ivana Quiroga, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of North Carolina at Chapel Hill, NC*

Fellowship Mentor: Douglas Phanstiel, PhD

### **A New Method That Uses the 3D Structure of the Human Genome to Identify the Genetic Basis of Alzheimer's Disease**

Treatment options for Alzheimer's disease have been elusive, in large part because the genetic causes of this disease are still largely unknown. The aim of this project is to integrate existing data with a novel experimental approach to identify genes that are linked to the development of Alzheimer's disease. For that we will use modern genomic and gene editing techniques in a novel immune brain cell model generated from stem cells. Our work will break down existing barriers by using innovative techniques to speed the identification and characterization of unknown genes responsible for this disease. This will establish basic knowledge that the scientific community requires to develop new diagnostic and therapeutic approaches to detect and treat Alzheimer's.

[www.brightfocus.org/grant/A2020203F](http://www.brightfocus.org/grant/A2020203F)



**Farid Rajabli, PhD**

(7/1/18 - 6/30/20)

FELLOWSHIP

*University of Miami, Miami, FL*

Fellowship Co-Mentors: Margaret A. Pericak-Vance, PhD, Gary W. Beecham Jr., PhD

### **Evaluating the Role of Ethnicity, Race, and Genetic Ancestry in Alzheimer's Disease**

The goal of this project is to evaluate the role of race/ethnicity and examine ancestry-specific genetic variants in a multi-ethnic dataset. The researchers aim to identify novel areas of the genome that correlate risk of AD with genetic ancestry.

[www.brightfocus.org/grant/A2018556F](http://www.brightfocus.org/grant/A2018556F)



**Jeffery Vance, MD, PhD**

(7/1/18 - 6/30/21)

*University of Miami, FL*

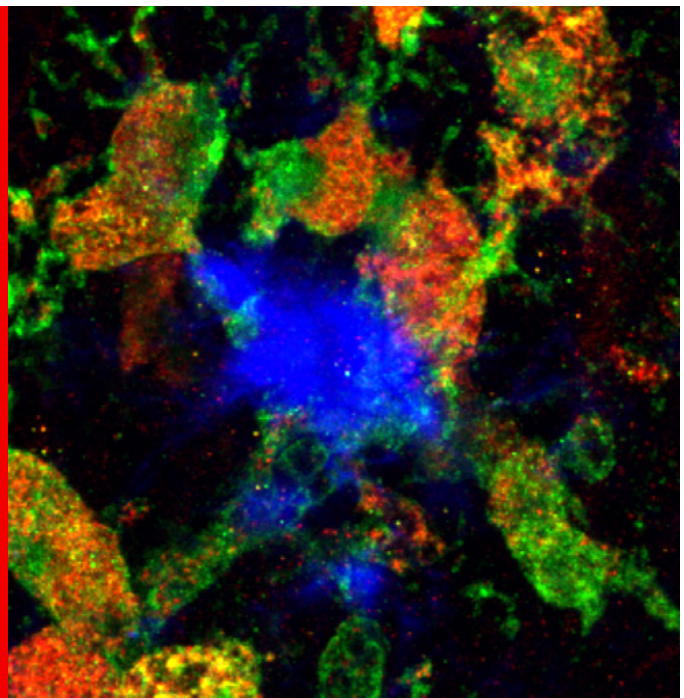
Co-Principal Investigators: Margaret A. Pericak-Vance, PhD, Gary W. Beecham, PhD & Anthony Griswold, PhD

### **Using Population Sequence Differences to Identify a DNA Change that Reduces the Risk of ApoE for Developing Alzheimer's Disease**

Carriers of ApoE4 with African ancestry have a lower risk for AD than carriers of European ancestry. These researchers have isolated the genetic region that protects African ApoE4 carriers and will use this study to identify DNA changes among the populations that can be tested in biological models.

[www.brightfocus.org/grant/A2018425S](http://www.brightfocus.org/grant/A2018425S)

# Immunity & Inflammation



One theory about Alzheimer’s disease (AD) is that it may be triggered, in part, by a breakdown in the brain’s immune system. Normally our brain has ways of clearing damaged cells and unwanted particles in its midst and disposing them into the bloodstream—which can be thought of as “taking out the garbage.” However, a chronic rise in unwanted debris, including toxic amyloid beta (A $\beta$ ) and tau proteins, can short-circuit that process and lead to chronic inflammation and cell damage.

Grantees are looking at what causes the immune response to become unbalanced and whether there are ways to help the brain’s cells and immune system do a better job of fighting Alzheimer’s.

*Above: This close-up of brain cells from an animal model shows lipid droplets (red) accumulating in immune cells called microglia (green) that are surrounding amyloid plaques (blue). (Courtesy of Christel Claes, PhD, University of California, Irvine)*



**Sadaf Amin, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

Weil Cornell Medicine, New York, NY

Fellowship Mentor: Li Gan, PhD

## Studying the Role of a Novel Innate Immunity Pathway in Inducing Brain Inflammation and Damage in Alzheimer’s Disease

There is a high level of neuroinflammation in the brains of Alzheimer’s patients. These inflammatory factors are secreted by stressed cells and lead to deterioration of other cell types (eg, neurons) present in the brain. This proposal intends to study the molecular pathways that govern this inflammatory response inside the brain and target them to limit the neuronal damage that leads to cognitive deficits and memory loss in Alzheimer’s disease.

[www.brightfocus.org/grant/A20201312F](http://www.brightfocus.org/grant/A20201312F)



**Darrick T. Balu, PhD** (7/1/19 - 6/30/22)  
*McLean Hospital (Harvard Medical School), Belmont, MA*

### **Understanding How Inflammation Kills Brain Cells During Alzheimer's Disease Progression**

As Alzheimer's disease progresses, inflammation changes the characteristics of particular cells in the brain called astrocytes. Inflammatory astrocytes release chemical compounds that are toxic to neurons. This project aims to understand how one of the molecules released by reactive astrocytes kills neurons, in hopes of finding new drugs to treat patients with Alzheimer's disease.

[www.brightfocus.org/grant/A2019034S](http://www.brightfocus.org/grant/A2019034S)

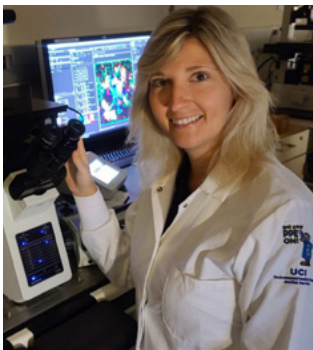


**Wei Cao, PhD** (7/1/18 - 6/30/21)  
*Baylor College of Medicine, Houston, TX*

### **New Immune Molecule in Inflamed Alzheimer's Brain**

This project will study a new family of cytokines, recently detected in Alzheimer's brains, that participate in the inflammatory process.

[www.brightfocus.org/grant/A2018377S](http://www.brightfocus.org/grant/A2018377S)



**Christel Claes, PhD** (9/1/20 - 8/30/22) FELLOWSHIP  
*University of California, Irvine*  
Fellowship Mentor: Mathew Blurton-Jones, PhD

### **Examining How the TREM2 R47H Mutation Affects Microglial Lipid Content and the Interactions Between Human Microglia and AD pathology Within the Brain**

Our recent studies show that when we transplant healthy human stem cell-derived microglia carrying a normal version of the gene, TREM2, into the brain of Alzheimer mice that develop amyloid plaques (a main characteristic of this disease), human microglia near the plaques show similarities to peripheral 'foam cells', which are immune cells filled with lipids and linked with another disease called atherosclerosis. As TREM2 is a lipid-sensor expressed by microglia, we now want to study the lipid content and the reaction of human microglia that carry the TREM2 R47H mutation to amyloid plaques in this specialized mouse model, to greatly improve our understanding of how this mutation can increase Alzheimer's risk, which will in turn allow scientists to find treatments that increase the functionality of microglia to protect our brain from the damage caused by these amyloid plaques.

[www.brightfocus.org/grant/A20201625F](http://www.brightfocus.org/grant/A20201625F)



**Juan Codoceo, PhD** (1/1/21 – 12/30/23) FELLOWSHIP  
*Indiana University, Indianapolis, IN*  
Fellowship Mentor: Gary Landreth, PhD

### **Is Hexokinase 2 a Molecular Link Between TREM2 Signaling and Microglial Activity in Alzheimer Disease?**

Alzheimer's disease is a neurodegenerative disorder that induces the activation of the brain immune cells, the microglia. Mutations in a gene expressed only in microglia, TREM2, increase the risk of late-onset Alzheimer's. However, the molecular mechanisms involved in TREM2 function are not fully understood. In this study, we want to evaluate if TREM2 can induce metabolic changes in the microglia through the regulation of hexokinase 2 an important enzyme of the metabolism of glucose.

[www.brightfocus.org/grant/A20201166F](http://www.brightfocus.org/grant/A20201166F)



**Hemraj Dodiya, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
*University of Chicago, Chicago, IL*  
Fellowship Mentor: Sangram S. Sisodia, PhD

### **Microbiome Influences Microglia Phenotypes and Beta-Amyloid Amyloidosis in a Sex-Specific Manner**

These experiments will assess the role of gender-specific gut microbes in regulating inflammation and beta-amyloid deposition using mouse models of Alzheimer's disease (AD). This will advance understanding of link between different gut microbes and AD susceptibility in men and women.

[www.brightfocus.org/grant/A2019032F](http://www.brightfocus.org/grant/A2019032F)



**Alireza Faridar, MD** (7/1/19 – 6/30/21) FELLOWSHIP  
*Houston Methodist Research Institute, Houston, TX*  
Fellowship Mentor: Stanley H. Appel, MD

### **Does Immune System Play a Role as a Potential Therapeutic Target in Alzheimer's Disease?**

Regulatory T cells (Tregs) are the major immunomodulatory cell in the blood that might lose functionality in Alzheimer's disease (AD). For the first time in AD research, dysfunctional Tregs will be expanded in dishes to restore their suppressive function and the impact of these expanded/normalized Tregs on Alzheimer's pathology will be evaluated.

[www.brightfocus.org/grant/A2019083F](http://www.brightfocus.org/grant/A2019083F)



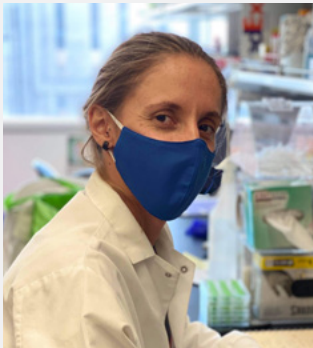
**Charles Glabe, PhD**  
*University of California, Irvine*

(7/1/18 - 6/30/21)

### **Mechanism of Neuronal Death in Alzheimer's Disease**

Cell death pathways that are involved in the progression of the inflammatory response, one of the hallmarks of Alzheimer's disease (AD), are of highest interest. Detailed knowledge about this specific type of inflammatory cell death pathway in AD brains might allow us to identify potential therapeutic strategies to prevent neurodegeneration.

[www.brightfocus.org/grant/A2018718S](http://www.brightfocus.org/grant/A2018718S)



**Maud Gratuze, PhD**  
*Washington University in St. Louis, MO*  
Fellowship Mentor: David Holtzman, MD

(9/1/20 - 8/30/22) FELLOWSHIP

### **Evaluating the Role of Immune Cells in the Brain and a Related Protein, TREM2, on Alzheimer's Disease Pathology**

Aggregation of the tau protein in the brain is a hallmark of Alzheimer's disease (AD), and the propagation of aggregated tau protein is strongly associated with neurodegeneration and dementia. In addition, brain immune cells, known as microglia, play a crucial role in AD and the propagation of tau pathology in the brain. Indeed, mutations in TREM2, a protein found on microglia, are one of the strongest genetic risk factors for AD. Therefore, we will investigate if decreasing microglia or TREM2 levels in the brain can modulate tau propagation.

[www.brightfocus.org/grant/A2020257F](http://www.brightfocus.org/grant/A2020257F)



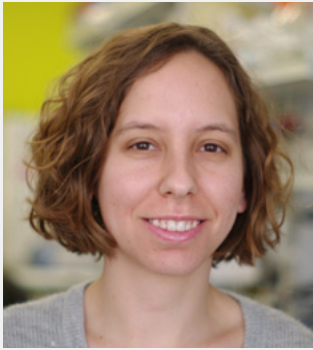
**Benjamin Hogan, PhD**  
*The University of Queensland, Brisbane, Australia*  
Co-Principal Investigator: Neil Bower, PhD

(7/1/18 - 6/30/21)

### **Characterization of Waste Clearance Pathways in the Vertebrate Brain**

This project aims to develop a new understanding of how a specific cell type in the brain, called mural lymphatic endothelial cells, clears waste from aging brains.

[www.brightfocus.org/grant/A2018807S](http://www.brightfocus.org/grant/A2018807S)



**Celeste Karch, PhD** (7/1/18 - 6/30/21)  
*Washington University School of Medicine, St. Louis, MO*

**Defining the Role of CXCR4 in Alzheimer’s Disease**

Common variants in a chemokine receptor found in microglia, CXCR4, contribute to tauopathies. The objective of this study is to begin to determine how CXCR4 drives Alzheimer’s disease (AD) and whether an existing drug improves tauopathy outcomes in a mouse model of AD.

[www.brightfocus.org/grant/A2018349S](http://www.brightfocus.org/grant/A2018349S)



**Timothy Miller, MD, PhD** (7/1/18 - 6/30/21)  
*Washington University School of Medicine, St. Louis, MO*

**Decreasing a Novel Genetic Risk Factor for Alzheimer’s and its Effect on Pathology and Cognition in Mouse Models**

A gene involved in inflammatory responses (TREM2) increases risk for developing Alzheimer’s disease (AD) and mediates the accumulation of amyloid beta in the brains of experimental mouse models. These researchers will use TREM2-lowering antisense oligonucleotides to explore new avenues for future treatments for AD.

[www.brightfocus.org/grant/A2018169S](http://www.brightfocus.org/grant/A2018169S)



**Yuxiang Sun, MD, PhD** (7/1/19 - 6/30/22)  
*Texas A&M University, College Station, TX*

**A New Intervention to Control Inflammation in Alzheimer’s Disease**

Low-grade chronic inflammation is a hallmark of aging, and inflammation in the brain causes and worsens Alzheimer’s disease (AD). We have evidence that suppression of a gene called GHS-R in immune cells produces an anti-inflammatory effect in the brain and improves spatial memory. The goal of this proposal is to determine the role of GHS-R in immune cells in AD.

[www.brightfocus.org/grant/A2019630S](http://www.brightfocus.org/grant/A2019630S)



**Nicholas Varvel, PhD** (7/1/19 - 6/30/22)  
*Emory University, Atlanta, GA*

**Brain-Invading Monocytes at the Intersection of Alzheimer’s Disease and Seizures**

A certain subset of people with Alzheimer’s disease (AD) suffer from seizures, in addition to memory loss. We have recently identified an immune cell type, called a monocyte, that enters the brain after seizures. The studies are designed to determine if seizure-induced monocyte entry into the brain enhances the progression of AD.

[www.brightfocus.org/grant/A2019077S](http://www.brightfocus.org/grant/A2019077S)



# Research Tools and Resources



When designing a research project, having the right preliminary information and tools to rely on can make or break its success, especially in understudied areas. Yet these first steps take time and expense to complete. BrightFocus Alzheimer's Disease Research funding supports the development of resources used to conduct, translate, and disseminate high quality dementia

research, including shared data and tissue repositories, and collaborative projects aimed at accelerating new knowledge, disease models, and interventions.

*Above: Dr. Granholm-Bentley next to a model of a human brain. (Courtesy of Ann-Charlotte Granholm-Bentley, PhD, DDS)*



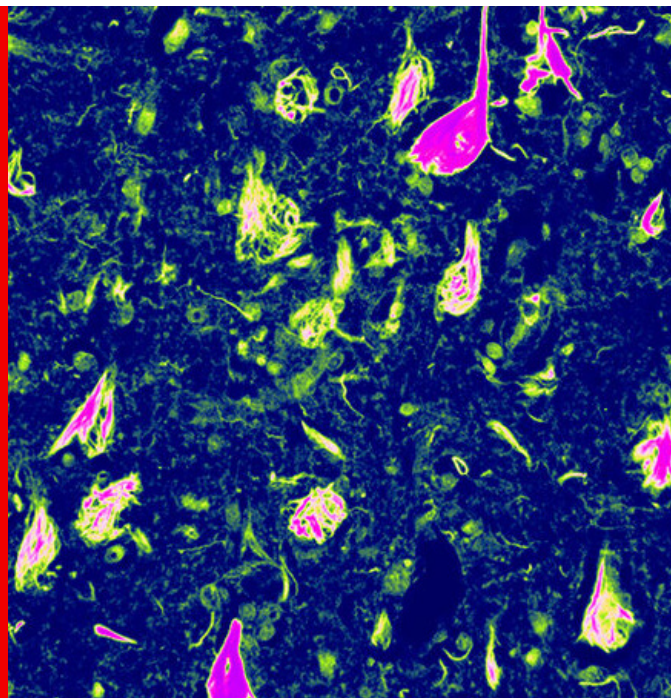
**Ann-Charlotte Granholm-Bentley, PhD, DDS** (7/1/18 - 10/31/22)  
*University of Denver, CO*

## **International Brain Bank for Down Syndrome-Related Alzheimer's Disease**

The focus of this special project is to develop a strong collaborative network between six different research groups, with the long-term goal to determine the neurobiological mechanisms underlying the onset of Alzheimer's disease-type dementia in Down syndrome.

[www.brightfocus.org/grant/CA2018010](http://www.brightfocus.org/grant/CA2018010)

# Tangling with Tau



As a protein associated with Alzheimer's disease (AD), tau is abundant inside neurons, where its fibrous shape lends stability to tubes that transport nutrition and waste in and out. However, in AD, tau goes through molecular changes that cause it to misshape and collect in messy tangles. Unlike A $\beta$  plaques, which can form years and even decades before AD symptoms occur, tau tangles typically are a sign that AD is rapidly getting worse.

Current theories hold that A $\beta$  and tau interact in ways to make that happen, and scientists are investigating how tau may be involved in spreading AD throughout the brain.

*Above: Abnormal tau tangles (pink) reflect a build-up of tau protein in the Alzheimer's brain. (Courtesy of Edward Lee, MD, PhD, Assistant Professor of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania)*



**Ottavio Arancio, MD, PhD** (7/1/18 - 6/30/21)

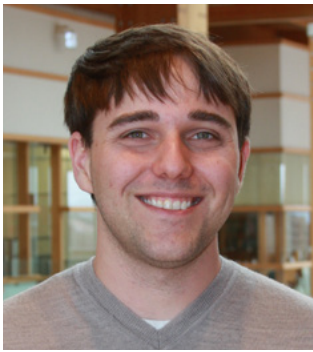
Columbia University, New York, NY

Co-Principal Investigator: Russell Nicholls, PhD

## Identifying How Tau Impairs Nerve Cell Communication in Alzheimer's Disease

Toxic forms of tau play a central role in AD and other neurodegenerative conditions, in part by interfering with how neurons connect to each other at synapses (the tiny gap where electrical signals are transmitted). The goal of this project is to better understand how tau interferes with synaptic function so that we can develop effective strategies to block the impairments it causes.

[www.brightfocus.org/grant/A2018816S](http://www.brightfocus.org/grant/A2018816S)



**Nick Cochran, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

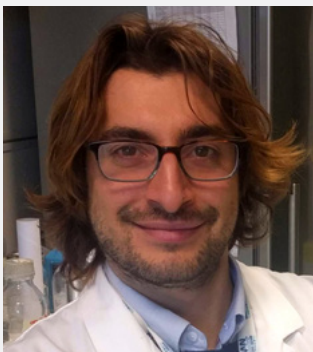
*HudsonAlpha Institute for Biotechnology, Huntsville, AL*

Fellowship Mentor: Richard M. Myers, PhD

### **How an Important Gene for Alzheimer's, Called MAPT, is Turned On**

This project will find out how the MAPT gene, which encodes tau, is turned on in neurons. Tau causes problems in Alzheimer's disease (AD), and scientists think that reducing tau might be helpful as a treatment. Figuring out how MAPT is turned on in neurons might help determine how to turn it off and reduce tau in AD.

[www.brightfocus.org/grant/A2019129F](http://www.brightfocus.org/grant/A2019129F)



**Luca Colnaghi, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*Instituto di Ricerche Farmacologiche Mario Negri, Milan, Italy*

Fellowship Mentor: Luana Fioriti, PhD

### **Molecular Mechanisms in Alzheimer's Disease**

Protein aggregation and deposition in the brain is a striking feature of several neurodegenerative disorders, including Alzheimer's disease (AD). The aim of this proposal is to understand the role of understudied post-translational modifications, such as ubiquitin and ubiquitin-like modifications, towards tau aggregation and deposition using mouse models of AD.

[www.brightfocus.org/grant/A2019296F](http://www.brightfocus.org/grant/A2019296F)



**Cara Croft, PhD**

(7/1/18 - 12/30/20)

FELLOWSHIP

*University of Florida, Gainesville*

Fellowship Mentor: Todd E. Golde, MD, PhD

### **Using Brain Slices to Understand and Target Tau in Alzheimer's Disease**

This project uses mouse models and an engineered, non-infectious virus delivery system to make the animal brains develop similar buildup of tau that is seen in Alzheimer's patients. These are compared to mouse tissue without tau to see why or if these cells die. Then, novel treatments to prevent or reverse the buildup of tau will be tested.

[www.brightfocus.org/grant/A2018149F](http://www.brightfocus.org/grant/A2018149F)



**Karen Duff, PhD** (7/1/17 – 6/30/20)  
Columbia University, New York, NY  
Co-Principal Investigator: Natura Myeku, PhD

### **Slowing Alzheimer's Disease by Enhancing Cellular Garbage Disposal**

This project tests the effectiveness in animal models of a drug that stimulates the brain's own "garbage disposal units" (the proteasome) to remove the toxic proteins that form clumps in the brain and cause the memory loss.

[www.brightfocus.org/grant/A2017393S](http://www.brightfocus.org/grant/A2017393S)

*This grant is made possible in part by support from Lois and Duane Luallin in memory of Denver E. Perkins and Edwin H. Luallin.*

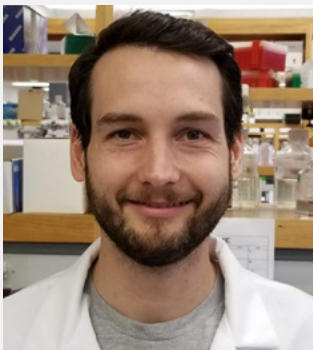


**Michelle Farrell, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
Massachusetts General Hospital & Harvard Medical School, Boston, MA  
Fellowship Mentor: Reisa A. Sperling, MD

### **Improving Detection of the Earliest Signs of Alzheimer's Disease to Help Prevent Memory Loss**

The project aims to use brain imaging (PET scans) in healthy older adults to visualize the earliest signs of amyloid plaques, and determine how the buildup of these amyloid plaques contributes to the appearance of tau tangles inside brain cells and subtle changes in memory and thinking. This research will provide urgently needed information about the early stages of development of Alzheimer's disease (AD), and help the next generation of prevention trials target individuals who are at an optimal point in the development of AD for successful intervention.

[www.brightfocus.org/grant/A2019029F](http://www.brightfocus.org/grant/A2019029F)



**Garrett Gibbons, PhD** (7/1/19 – 6/30/21) FELLOWSHIP  
University of Pennsylvania, Philadelphia, PA  
Fellowship Mentor: John Q. Trojanowski, MD, PhD

### **Blood Test to Identify and Distinguish Alzheimer's from Other Neurodegenerative Diseases**

There are currently no blood tests to determine if a person has Alzheimer's disease (AD). It can be difficult to determine whether a person with dementia has AD, a different neurodegenerative disease, or both simultaneously. The research team has created a new antibody, named GT-38, that detects a form of tau protein present in AD but not the other neurodegenerative diseases. GT-38 will be used to develop a test for blood or cerebral spinal fluid to distinguish AD from other neurodegenerative diseases.

[www.brightfocus.org/grant/A2019263F](http://www.brightfocus.org/grant/A2019263F)



**Chadwick Hales, MD, PhD** (7/1/17 - 6/30/20)  
*Emory University, Atlanta, GA*

### **How Proteins Contribute to the Formation and Spread of Pathology in the Alzheimer's Disease Brain**

This project studies how three specific proteins that support RNA processing in healthy brains will seed tangle-like aggregates in AD using cell cultures and animal models of the disease.

[www.brightfocus.org/grant/A2017281S](http://www.brightfocus.org/grant/A2017281S)



**Zhuohao He, PhD** (7/1/18 - 6/30/21)  
*University of Pennsylvania, Philadelphia*  
Co-Principal Investigator: Virginia Man-Yee Lee, PhD

### **Studying a Type of Tau Protein that Aggregates in Alzheimer's Disease Brains**

This project investigates a distinct form of pathological tau in Alzheimer's disease (AD) and will further create antibodies capable of recognizing such AD-specific pathological protein.

[www.brightfocus.org/grant/A2018802S](http://www.brightfocus.org/grant/A2018802S)



**Lukasz Joachimiak, PhD** (7/1/19 - 6/30/22)  
*University of Texas Southwestern Medical Center, Dallas, TX*

### **Detecting the Shape Changing Protein Tau in Alzheimer's Disease**

The tau protein normally adopts a "good" shape and with age converts into a "bad" shape. This project aims to understand how tau changes into the "bad" shape to help understand how to detect this in patients and develop therapies to prevent it.

[www.brightfocus.org/grant/A2019060S](http://www.brightfocus.org/grant/A2019060S)

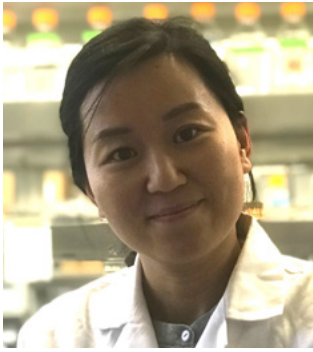


**John Koren, PhD** (9/1/20 - 8/30/23)  
*University of Florida, Gainesville, FL*

### **Twisting Away Toxic Proteins in Alzheimer's Disease**

Tau aggregation is a major pathogenic factor in Alzheimer's disease. Our studies have identified a family of proteins that alter tau aggregation, including one member of this family which can disaggregate tau aggregates into smaller non-toxic entities. The goal of this proposal is to elucidate the mechanisms of this disaggregation towards the ultimate goal of designing therapeutic strategies that mimic this activity. These studies will identify the properties and number of members of this protein family that present this activity while simultaneously examining the properties of tau that facilitate toxic aggregation and accumulation.

[www.brightfocus.org/grant/A20201621S](http://www.brightfocus.org/grant/A20201621S)



**Wenyan Sun, PhD**

(7/1/19 – 6/30/21)

FELLOWSHIP

*University of Texas Health Science Center at San Antonio, San Antonio, TX*  
Fellowship Mentor: Bess Frost, PhD

### **Determine Whether PIWIL and piRNAs are Dysregulated in Tau Transgenic Mice and Human Neurodegenerative Tauopathies**

Recently, research with fruit flies identified a new mechanism to address tau toxicity and jumping genes through PIWI protein and PIWI-interacting RNAs (piRNAs). To investigate if this mechanism is conserved in vertebrate tauopathy, this project will whether this same mechanism is intact in mouse models of AD so that model can be used to whether piRNAs identified in AD are directly bound to PIWI-like proteins and are relevant to brain cell death in AD.

[www.brightfocus.org/grant/A2019223F](http://www.brightfocus.org/grant/A2019223F)



**Shuo Wang, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*Baylor College of Medicine, Houston, TX*  
Fellowship Mentor: Hui Zheng, PhD

### **Understanding the Role of Lysosome in Brain Function and Alzheimer's Disease**

Accumulation of tau aggregates influences brain health and cognition in Alzheimer's patients. These aggregates are degraded by an intracellular organelle called the lysosome. TFEB plays a critical role in regulating lysosomal function and its clearance ability. Our proposal investigates how TFEB works with the goal to identify ways to harness the lysosomal function to promote brain health and combat age-associated neurodegenerative diseases.

[www.brightfocus.org/grant/A2020845F](http://www.brightfocus.org/grant/A2020845F)



**Hong Xu, PhD**

(9/1/20 – 8/30/22)

FELLOWSHIP

*University of Pennsylvania, Philadelphia, PA*  
Fellowship Mentor: Virginia Man-Yee Lee, PhD

### **A Novel Way to Expand Human-Derived Pathogenic Tau Seeds in a Cell Free System**

Tau aggregates (tauopathy seeds) enriched from the postmortem brains Alzheimer's disease (AD) patients exhibit specific biological activity of inducing normal tau into misfolded pathological tau. But the quantity and quality of the tauopathy seeds are very much limited. In the study, we will explore the seeding mechanism of the human tau seeds using in vitro reactions for a better understanding of the pathogenesis of AD and other tauopathies. Moreover, we want to amplify tauopathy seeds in vitro by making use of the self-propagating features of them and promote future studies of tau pathology transmission.

[www.brightfocus.org/grant/A20201731F](http://www.brightfocus.org/grant/A20201731F)

# Translational Research & Clinical Interventions



“Translational” research refers to the effort to take basic science knowledge from the laboratory or research setting into the “real world” in the form of potential treatments or cures. In this context, it refers to the act of literally “translating” science into useful ways of diagnosing, treating, and managing Alzheimer’s disease (AD). These innovations can take many different forms, such as using smartphone-based testing to monitor cognitive status in AD, to finding ways for individuals with AD to get better sleep and exercise, since scientists have associated these lifestyle activities with brain health and possible protective benefits. Another very important undertaking is that of

testing new drugs and interventions in humans once they are deemed safe, and this is done through clinical trials and another studies which rely on volunteers who are willing to participate. These activities will help speed drugs, treatments, and critical knowledge from “bench to bedside” and put them in the hands of people living with AD today or facing the risk of it in the future.

*Above: Dr. Koch (left) administers a non-invasive form of brain stimulation known as repetitive transcranial magnetic stimulation (rTMS) to a patient with mild Alzheimer’s disease (seated) in hopes of improving memory skills. (Courtesy of Giacomo Koch, MD, PhD, IRCCS Santa Lucia Foundation in Rome, Italy)*



**Claire Clelland, MD, PhD**

(10/1/20 – 9/30/22) FELLOWSHIP

*University of California, San Francisco*

Fellowship Mentor: Bruce Conklin, MD, University of California, San Francisco and Gladstone Institutes

Fellowship Co-Mentor: Li Gan, PhD, Weil Cornell Medicine, New York, NY

### **Gene Correction as a Therapy for Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) caused by the C9orf72 Mutation**

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are two fatal and incurable neurodegenerative diseases linked by a shared genetic cause – a heterozygous hexanucleotide (GGGGCC) repeat expansion in a single allele of the C9orf72 gene. The goal of this work is to develop novel CRISPR based therapeutic gene editing technologies and test whether gene editing can reverse the cellular pathology caused by this repeat expansion in patient derived cells. The results of these studies will advance our use of CRISPR technologies for therapeutic editing in FTD/ALS, inform our understanding of the regulation of C9orf72 gene, and will be applicable to many other repeat expansion and single gene disorders.

[www.brightfocus.org/grant/A20201490F](http://www.brightfocus.org/grant/A20201490F)



**Peter Fried, PhD**

(9/1/20 – 8/30/23)

*Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, MA*

### **Testing New Markers of Brain Function that May Be Sensitive to Early Signs of Alzheimer's Disease in Older Adults Who Still Have Normal Cognition**

The goal of this study is to develop tests that can detect changes in the activity of the brain at the earliest stage of Alzheimer's disease (AD), before patients start showing symptoms, which is known as "preclinical Alzheimer's disease." We will recruit healthy older adults with normal cognition and use a new blood test that can detect the proteins—called amyloid—that are linked to AD. We will collect a range of measures of the activity of the brain and relate the measures to the amount of amyloid. Knowing more about what changes are occurring in the brain in preclinical AD and how to measure them will help researchers develop new therapies to change the course of the disease to delay or prevent dementia.

[www.brightfocus.org/grant/A20201288S](http://www.brightfocus.org/grant/A20201288S)





**Joshua Grill, PhD**  
*University of California, Irvine*

(7/1/18 - 6/30/21)

### **Improving Recruitment to Prodromal Alzheimer's Disease Clinical Trials**

Most Alzheimer's clinical trials now enroll patients with mild cognitive impairment, which in many cases may be an early form of Alzheimer's disease. This project will identify the challenges to enrolling these patients in clinical trials and develop methods to improve recruitment to these critical studies.

[www.brightfocus.org/grant/A2018405S](http://www.brightfocus.org/grant/A2018405S)



**Giacomo Koch, MD, PhD**  
*IRCCS Santa Lucia Foundation, Rome, Italy*

(7/1/19 - 6/30/22)

Co-Principal Investigator Martorana Alessandro, MD, PhD, Rome University Tor Vergata (Rome, Italy)

### **Magnetic Stimulation to Treat Alzheimer's Disease**

The primary aim of this project is to investigate a non-invasive brain stimulation, repetitive transcranial magnetic stimulation (rTMS), on memory skills in patients with mild Alzheimer's disease (AD). rTMS is considered a safe, well tolerated and relatively cheap treatment. The appealing idea of our intervention is to improve memory by directly modulating the activity of precuneus, a key area of the brain linked to memory impairment. This project will provide a valid treatment to slow the worsening of symptoms and improve quality of life for those with AD and their caregivers.

[www.brightfocus.org/grant/A2019523S](http://www.brightfocus.org/grant/A2019523S)



**Sanjeev Kumar, MD**  
*Centre for Addiction and Mental Health, Toronto, Ontario, Canada*

(7/1/18 - 6/30/21)

Co-Principal Investigators: Tarek Rajji, MD; Daniel Blumberger, MD; Zafiris J. Daskalakis, MD; Corinne E. Fischer, MD; Nathan Herrmann, MD; Benoit H. Mulsant, MD; Bruce G. Pollock, MD; & Reza Zomorodi, PhD

### **Identifying Disease Mechanisms in Neurodegeneration Using Electrophysiology**

Agitation and aggression affect the majority of patients with Alzheimer's disease. Medications used to treat these symptoms are associated with many side effects. This project will use magnetic brain stimulation and electroencephalography to understand the mechanisms of agitation and use a non-invasive brain stimulation technique called transcranial direct current stimulation (tDCS) to treat it.

[www.brightfocus.org/grant/A2018667S](http://www.brightfocus.org/grant/A2018667S)



**Peng Li, PhD**

(9/1/20 – 8/30/23)

*Brigham and Women’s Hospital & Harvard Medical School, Boston, MA*

**Circadian Regulation, Autonomic Function, and Alzheimer’s Disease**

Cure for Alzheimer’s disease is still lacking. It is important to identify the risk factors for the disease and its multiple impacts on body functions in order to prevent or slow down the progression of the disease and treat related symptoms. Using novel non-invasive assessment of circadian regulation and autonomic function by wearable technology, this project is designed to determine whether changes in these two important physiological functions can predict the development and progression of Alzheimer’s disease (AD) and cognitive decline in the elderly people at early, preclinical stages. This project may potentially provide new intervention targets in future clinical studies of AD, and can lay the groundwork for the design of novel unobtrusive, cost-efficient tools for long-term monitoring of cognitive impairment or risk for AD.

[www.brightfocus.org/grant/A2020886S](http://www.brightfocus.org/grant/A2020886S)



**Robert Newton, Jr., PhD**

(7/1/17 - 6/30/21)

*Pennington Biomedical Research Center, Baton Rouge, LA*

**Program for African American Cognition and Exercise (PAACE)**

The goal of this project is to increase the knowledge of the effects of a physical activity program on dementia prevention in African-American adults.

[www.brightfocus.org/grant/A2017547S](http://www.brightfocus.org/grant/A2017547S)



**Stephanie Rainey-Smith, PhD**

(7/1/18 - 12/30/20)

FELLOWSHIP

*Edith Cowan University, Perth, Western Australia, Australia*

Fellowship Mentor: Ralph N. Martins, PhD

**Can Good Sleep Prevent Alzheimer’s Disease?**

This study will explore the relationship between sleep, memory, thinking, and markers of brain health by investigating whether improved sleep causes better memory and thinking, slows protein build up in the brain, and slows the shrinking of the brain.

[www.brightfocus.org/grant/A2018402F](http://www.brightfocus.org/grant/A2018402F)



**Quincy Samus, PhD**

(7/1/20 – 6/30/22)

*Johns Hopkins Bayview Medical Center, Baltimore, MD*

## **Dissemination Of MIND At Home Dementia Care Model To Drive Health Care Transformation And Greater Value**

Evidence-based dementia care model that assesses and addresses a broad range care needs that place elders living at home with dementia and their family members at risk for a host of undesirable outcomes including hospitalizations, unwanted long term care placement, poor quality of life, health disparities, caregiver burnout. This grant partners with University of Maryland Baltimore County, Jade Gong & Associates LLC, and Johns Hopkins Home Care Group, with the support of Maryland Primary Care Program, Maryland Medicaid, and Johns Hopkins Alliance for Patients to advance the dissemination of the MIND at Home model into real world practice. Grant activities will include a cost benefit analysis to understand the program's value to payers and providers; engagement of primary care providers and health plans participating in the Maryland Primary Care Program (MDPCP) to understand provider needs and potential interest in the MIND at Home Program; and finally refinement of the MIND at Home program delivery process and financing model based on these newly captured data. Results from this work will inform the dissemination of the MIND at Home program into MDPCP and learnings will likely generalize to broader, national health care cost reduction initiatives in the future.

**[www.brightfocus.org/grant/CA2021001](http://www.brightfocus.org/grant/CA2021001)**



## Programs

Alzheimer's Disease Research  
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