BOLDLY EXPLORING

RESEARCH INSPIRING HOPE

2021 Alzheimer's Disease Research Projects
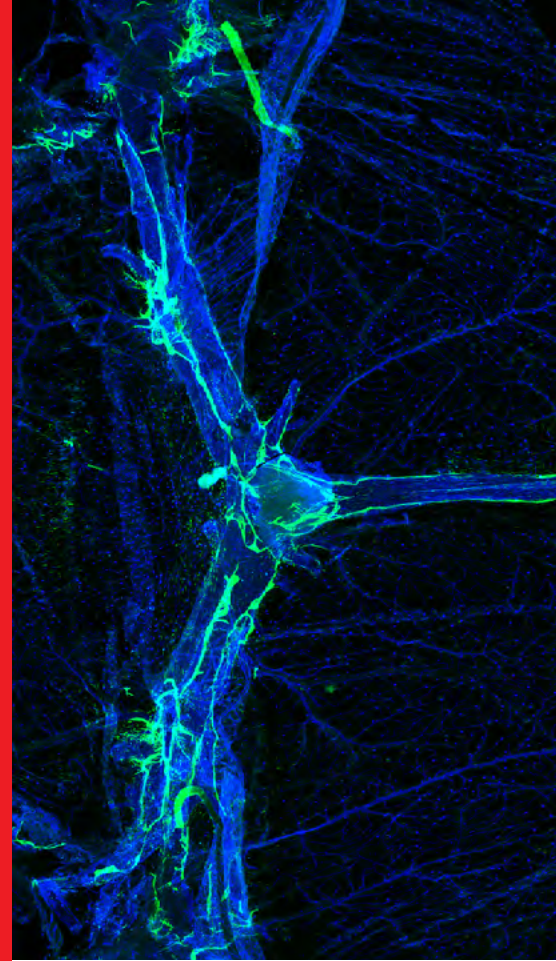
BrightFocus® Foundation | Alzheimer's Disease Research

ALZHEIMER'S DISEASE RESEARCH

WE'RE FUNDING 149 PROJECTS WORLDWIDE THIS YEAR IN RESEARCH.

Inside

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 devastating for individuals; their family members, friends and caregivers; and society as a whole. Alzheimer's (or "AD") will claim a greater toll as our population ages— *unless something more is done.*
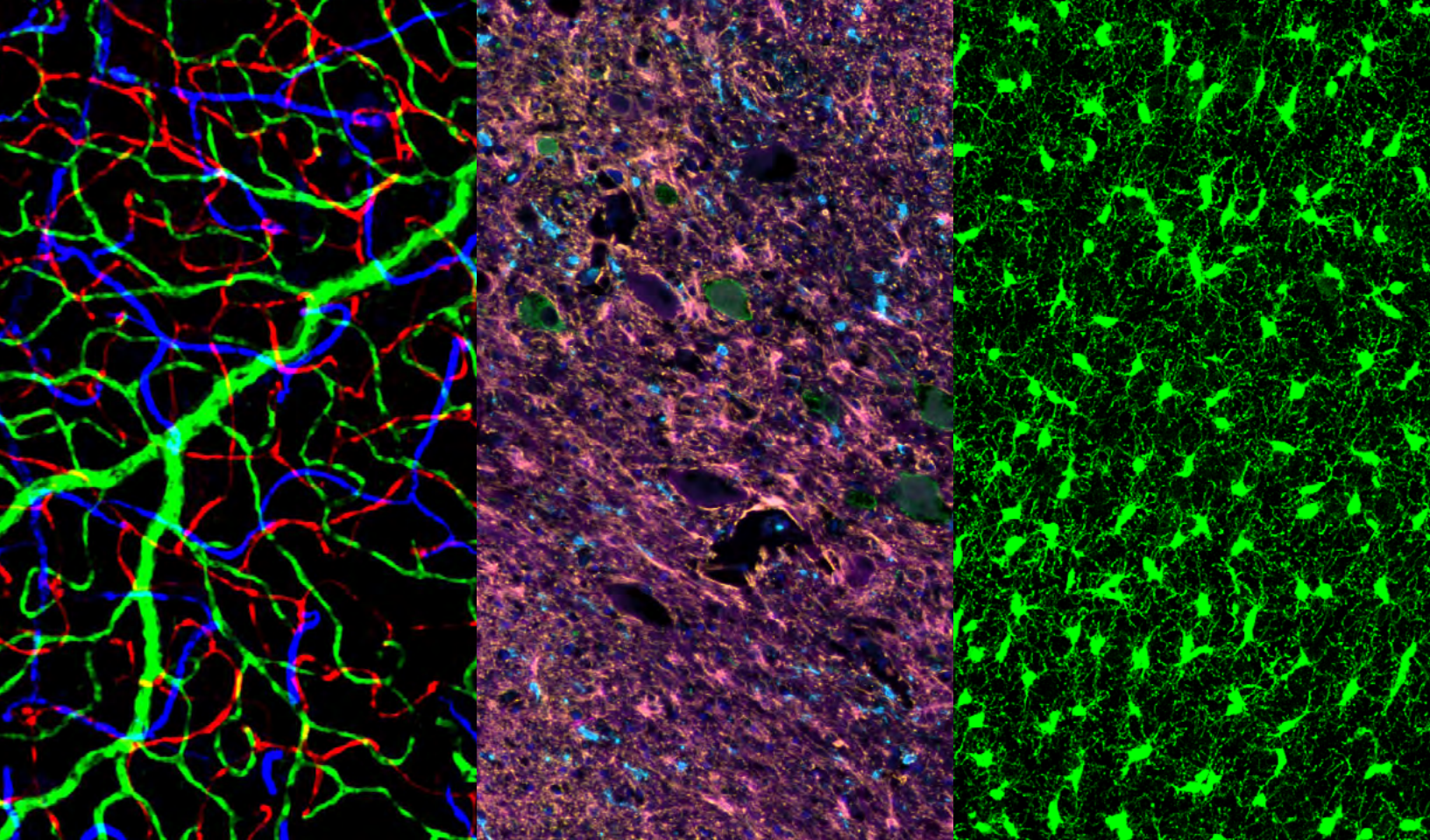
With generous donor support, the Alzheimer's Disease Research (ADR) program, which began in 1985, has funded nearly $155 million in research to understand and cure this disease. With our grants, scientists around the world have developed and tested thousands of hypotheses about how the disease destroys brain function over time. As part of this, they are investigating hundreds of ideas to diagnose, treat, cure, and prevent AD and related dementias.

This yearbook provides an overview of BrightFocus' current ADR grant projects. Our funding philosophy is to follow the most innovative and promising ideas and proposals. Applications from scientists can touch on any aspect that will further understanding and advance cures for AD and related dementias. Each year, the proposals are evaluated by a Scientific Review Committee (SRC) with diverse expertise that includes some of the leading Alzheimer's scientists and clinicians in the world. Our SRC recommends top-ranked projects that reflect the most cutting-edge research in the field. We are deeply grateful to the generosity of our donors to make it possible to grow the breadth and impact of our Alzheimer's Disease Research program. The current portfolio of 149 ADR grants is among our largest ever and offers huge promise and opportunity for building momentum and progress in fighting this most heartbreaking disease.

Note: In this yearbook, active ADR projects have been arranged in categories according to the Common Alzheimer's Disease Research Ontology (CADRO) classification system that 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.

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

*Cover: Mouse retinal neuron layers [used to study AD pathology] (Courtesy of Melanie Samuel, PhD, Baylor College of Medicine, Houston, TX). **Above left to right:** The brain's meninges (blue) and associated lymphatics (green) (Courtesy of Sandro Da Mesquita, PhD, Mayo Clinic Jacksonville, FL); Blood vessels of the retina (Courtesy of Melanie Samuel, PhD, Baylor College of Medicine, Houston, TX); Tau (green), and immune cells (blue and pink) gather in the brain of a person with neurodegeneration from progressive supranuclear palsy. (Courtesy of Kathryn Bowles, PhD, Icahn School of Medicine at Mount Sinai, New York, NY); To study AD, immune cells called microglia are created from stem cells. (Courtesy of Renzo Mancuso, PhD, VIBvzw, Gent, Belgium)*

AMYLOID BETA
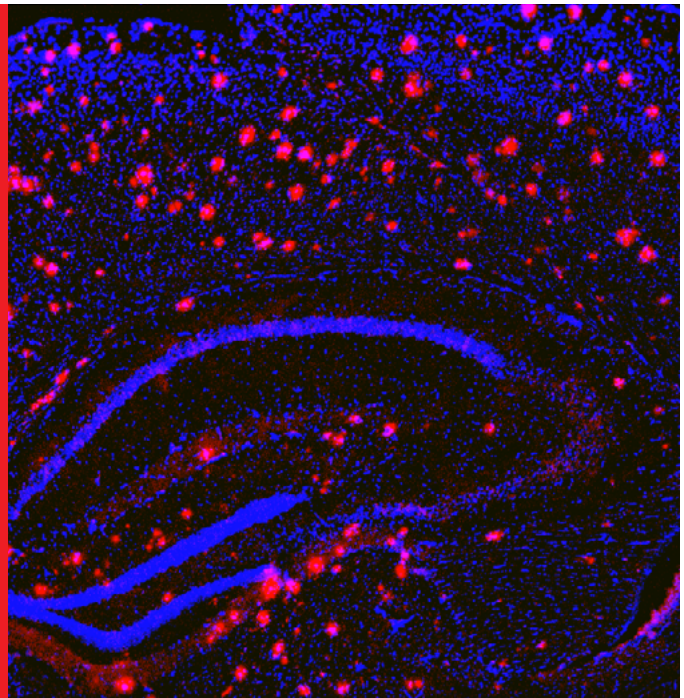
There are many versions of amyloid protein in the human body, and most serve a useful role. Amyloid beta (Aβ) is a type of amyloid that is prone to molecular changes that create fragments that accumulate in the brain. A healthy brain is able to break down Aβ and eliminate it, but in Alzheimer's disease, Aβ forms hard, insoluble plaques that are toxic to neurons and are sometimes (not always) associated with memory loss and other changes. In addition, many experts think Aβ may work synergistically with tau — another protein overexpressed in AD — to speed neurodegeneration. New technologies make it possible to directly measure amyloid plaques to learn which brain regions are affected, whereas they were once only seen at autopsy. Anti-amyloid drugs are being tested in clinical trials, with the hope of preventing formation of Aβ plaques in the future.

Above: In an Alzheimer's mouse model, amyloid plaque (stained red) builds up in the hippocampus. (Courtesy of Laura Cox, PhD, Brigham and Women's Hospital & Harvard Medical School, Boston, MA).

Rita Batista, PhD   (7/1/19 – 12/31/21)   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

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-β 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

Congcong He, PhD   (7/1/18 - 2/28/22)
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 Aβ metabolism and prevents neuronal inflammation in the Alzheimer's brain.

www.brightfocus.org/grant/A2018100S
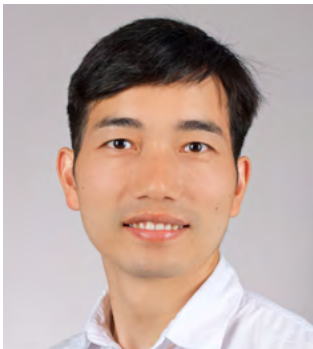
Jinghui Luo, PhD   (9/1/20 – 8/31/22)
Paul Scherrer Institute (PSI), Villigen, Switzerland

A New Method to Determine Alzheimer's and Parkinson's Toxins in the Lipid-Enriched 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

Masato Maesako, PhD (7/1/19 – 6/30/22) 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

Bryndon Oleson, PhD (7/1/19 – 12/31/21) 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

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

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 sAPPβ 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 sAPPβ, and compare this to a healthy patient's brain, to determine if in Alzheimer's disease (AD) there is more sAPPβ 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 sAPPβ, and other proteins such as sAPPα and Aβ, 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

EVERY DAY MORE THAN 1,300 AMERICANS DEVELOP ALZHEIMER'S DISEASE.

BIOLOGY OF FATS & PROTEINS (APOE)
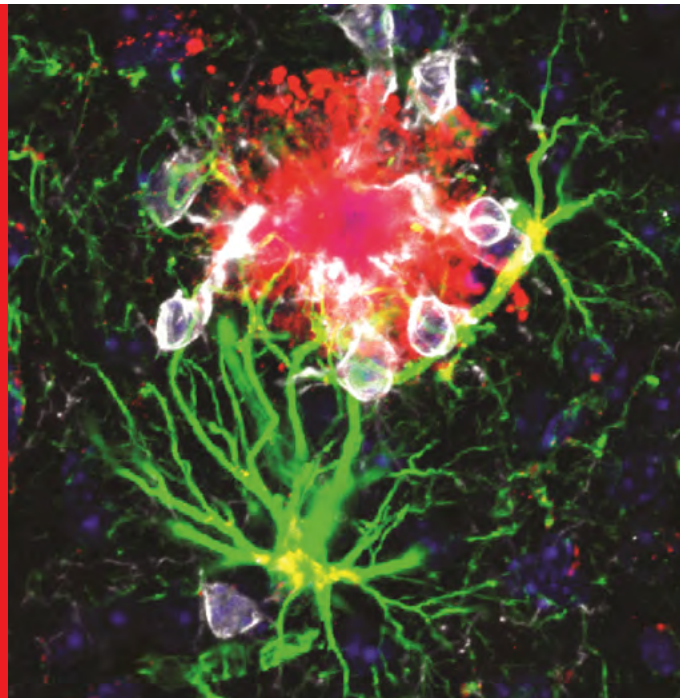
Initially recognized for its role in cardiovascular disease, the *APOE* gene also plays a role in Alzheimer's disease (AD). Its primary function is to regulate a class of proteins involved in the metabolism of fats (lipids) in the body. However, *APOE* has several common variants (or "alleles") whose effects vary. The e4 allele, in particular, is the most prevalent genetic factor associated with late-onset AD, 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: Brain immune cells known as microglia (white) and support cells, astrocytes (green), interact with an amyloid plaque (red). (Courtesy of Oleg Butovsky, PhD, Brigham and Women's Hospital & Harvard Medical School, Boston, MA)

Oleg Butovsky, PhD (07/01/21 – 06/30/24)
Brigham and Women's Hospital & Harvard Medical School, Boston, MA

APOE4 Gender-Dependent Regulation of Neutrophil-Microglia Cross-Talk in Alzheimer's Disease

APOE plays a critical role in inducing microglial phentoypes that are associated with neurodegeneration. A key question is whether *APOE* variants derived from innate immunity peripheral cells (macrophages and neutrophils) also control immune responses driven by microglia and contribute to disease progression. Preliminary data show that human *APOE* variants mediate differential regulation of pro-inflammatory signatures in neutrophils in a sex-dependent manner. Importantly, recent studies identified similar inflammatory signatures in blood neutrophils, which was associated with cognitive decline in AD patients. This proposal aims to investigate the role of *APOE* variants in the regulation of neutrophil-microglia interactions as a therapeutic target for AD.

www.brightfocus.org/A2021022S

Sandro Da Mesquita, PhD (07/01/21 – 06/30/24)
Mayo Clinic Jacksonville, FL

Effects and Mechanisms of *APOE*-Induced Meningeal Lymphatic Remodeling in Alzheimer's disease

This proposal tests the hypothesis that expression of *APOE4* is affecting brain function by impairing the meningeal lymphatic vasculature and, consequently, disturbing brain drainage and increasing neuroinflammation. To address this, male and female mice lacking endogenous *APOE*, or expressing human *APOE3* or *APOE4* instead, will be used to study the cellular and molecular mechanisms involved in the regulation of meningeal lymphatic function at different ages.

www.brightfocus.org/A2021025S

Carl Frieden, PhD (9/1/20 – 8/31/22)
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

Jie Gao, PhD   (07/01/21 – 06/30/24)
The Ohio State University, Columbus, OH

Targeting E3 Ligase IDOL to Mitigate APOE4-Mediated Tau Pathology

Apolipoprotein E4 (APOE4) markedly exacerbates tau pathology and tau-mediated neurodegeneration in Alzheimer's disease (AD). Therefore, targeting APOE4's detrimental effects in tau pathology might serve as a promising strategy for the treatment of AD. IDOL is a novel, major regulator of brain APOE receptor expression, and has a profound impact on APOE metabolism. This study aims to understand the multifactorial role and underlying mechanisms of action of IDOL in mitigating APOE4-mediated tau pathology in AD.

www.brightfocus.org/A2021028S

Lindsey Goodman, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
Baylor College of Medicine, Houston, TX
Fellowship Mentor: Hugo Bellen, DVM, PhD

Defining Connections Between ROS-Induced Glial Lipid Droplets and Tau in Alzheimer's Disease

Two early events that may contribute to AD-onset are the dysregulation of lipids and excess accumulation of reactive oxygen species (ROS). In fly and mouse brains, neurons expressing ROS produce peroxidated lipids that are transferred to glia where they form lipid droplets. Within glia, these lipids are resolved, protecting neurons from ROS-induced damage. Mouse data suggests that tau plays a normal role in the resolution of ROS in the brain prior to the formation of tau tangles. This proposal will investigate how tau functions to mediate ROS in AD by disrupting the formation of lipid droplets and examining tau hyperphosphorylation and aggregation.

www.brightfocus.org/A2021008F

**Emil Gustavsson, PhD**　　　　　(07/01/21 – 06/30/23)　　FELLOWSHIP
University College London, England
Fellowship Mentor: Mina Ryten, MD, PhD

The Landscape and Expression of *APOE* Transcripts in Human Brain and Alzheimer's Disease

Changes to the *APOE* RNA molecule – the template produced by DNA that also translates into proteins, the building blocks in the body – may contribute to the risk of AD. The proposed project will use a new technology called long-read RNA-sequencing to explore the different types of RNA transcripts that are produced in Alzheimer's disease (AD). This will result in a full landscape of *APOE* RNA transcripts to study their expression patterns in neurons and microglia and determine whether function correlates with disease using large, publicly available datasets.

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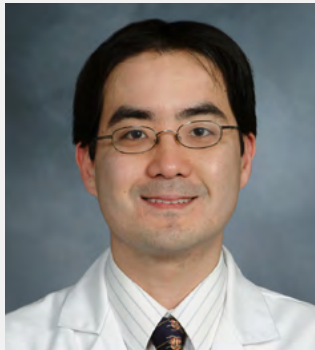
Makoto Ishii, MD, PhD　　　　　(9/1/20 – 8/30/23)
Weill Cornell Medicine, New York, NY

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

**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
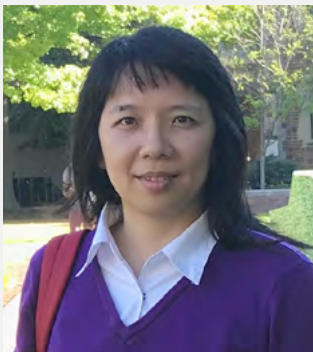
Chia-Chen (Jenny) Liu, PhD   (9/1/20 – 8/30/23)

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

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

Ana-Caroline Raulin, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
Mayo Clinic Jacksonville, FL
Fellowship Mentor: Guojun Bu, PhD

Protective Mechanism of *APOE3*-Christchurch in Alzheimer's Disease

Apolipoprotein E (APOE) is a protein with the principal function of carrying lipids and cholesterol throughout the body. Genetic variants of the *APOE* gene and resulting APOE protein have different effects on Alzheimer's disease status. In particular, *APOE4* increases risk, *APOE3* is neutral, and *APOE2* is protective. Recently, a rare version of *APOE* called *APOE3-*Christchurch *(APOE-Ch)* has been shown to be highly protective against AD. This study will use animal models, human stem cells, and cerebral organoids ('mini-brains in a dish') to understand how *APOE3-Ch* protects the brain from the toxic effects of beta-amyloid accumulation.

www.brightfocus.org/A2021015F

Jerome Robert, PhD (07/01/21 – 06/30/24)
University Hospital of Zürich, Switzerland

The Role of HDL Containing APOE in Alzheimer's Disease

The role of the brain's blood vessels in Alzheimer's disease is well recognized, as they help to clear the build up of cerebral waste and cardiovascular diseases' risk factors such as diabetes, hypertension and dyslipidemia which, are associated with increased risk of Alzheimer's disease. However, how blood-circulating factors exactly affect brain vessel and neuron health remains poorly understood mainly due to the lack of adequate experimental system with which to study how the human brain and blood interact. Using a human blood vessel grown in the test tube, we aim here to uncover how blood lipid transporter namely high-density lipoprotein (HDL, the good cholesterol) promotes brain vessel health.

www.brightfocus.org/A2021037S

Na Zhao, PhD, MD (07/01/21 – 06/30/24)
Mayo Clinic Jacksonville, Jacksonville, FL

APOE Genotype-Dependent Effects of Life-Style Intervention in Healthy Aging and Alzheimer's Disease

Aging and the apolipoprotein E4 (*APOE4*) gene are the greatest risk factors for late-onset Alzheimer's disease (AD). While many therapies have failed in clinical trials, research shows that life-style interventions can delay disease onset. Food restriction has been recognized as one of the most effective ways to extend healthspan, however, it is unclear whether genetically susceptible individuals such as *APOE4* carriers can still benefit from preventive life-style interventions. As such, this proposal plans to investigate how diet control or exercise affects brain health using animal models with aging or AD, and with or without the *APOE4* gene.

www.brightfocus.org/A2021046S

BIOMARKERS
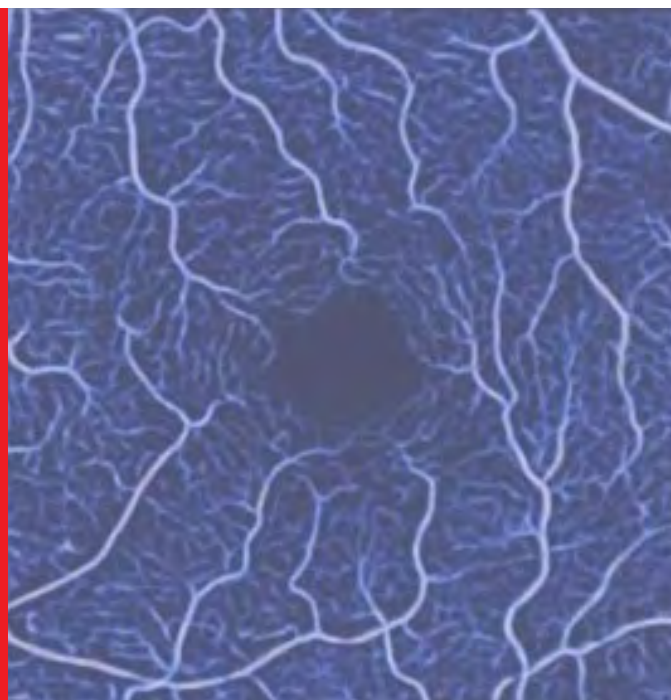
Biomarkers are early markers of biological changes associated with Alzheimer's disease (AD), which may begin causing gradual changes in the brain some 10-20 years before the onset of symptoms. The best hope of stopping AD is during this phase, and the need for earlier treatment makes the search for biomarkers critically important. Numerous types of biomarkers are already in use or being developed, including tests to measure elevated amyloid beta (Aβ) levels in blood and/ or cerebrospinal fluid; use of advanced imaging to detect tiny changes in brain structure; techniques identifying Aβ protein deposits in the retina of the eye that mirror those in the brain; and early behavioral changes that may signal disease onset. 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 new 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: Blood vessels of the eye may reveal signs of early dementia. (Courtesy of Amir Kashani, MD, PhD, Johns Hopkins University, Wilmer Eye Institute)

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.

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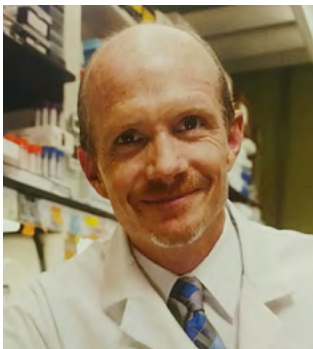
Randall Bateman, MD (7/1/17 - 9/30/21)
Washington University School of Medicine, St. Louis, MO
Co-Principal Investigators: Norelle C. Wildburger, PhD & Robert Schmidt, MD, PhD

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

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

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 (Aβ) 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

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

Jill M. Goldstein, PhD (3/30/18 - 3/30/22)

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

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

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

Henne Holstege, PhD   (07/01/21 – 06/30/24)
VU University Medical Center Amsterdam, Netherlands

Blood-Based Markers for Alzheimer's Pathology in Cognitively Healthy Centenarians: Revealing Mechanisms of Resistance and Resilience

This proposal will investigate to what extent centenarians can tolerate high levels of Alzheimer related proteins in their brains (resilience) and to what extent centenarians escape the accumulation of these Alzheimer related proteins (resistance). State of the art technology will be used to measure proteins in the blood of 400 cogntively healthy centenarians and their family members to determine whether centenarians use different protective mechansims to maintain brain function. This research can help identify lifestyle and genetic factors that influence resilience and resistance.

www.brightfocus.org/A2021031S

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

Amir Kashani, MD, PhD　　　　　　(2/24/20 – 7/31/21)
Johns Hopkins University, Wilmer 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

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

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

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

BRAIN BLOOD CIRCULATION IN DEMENTIA
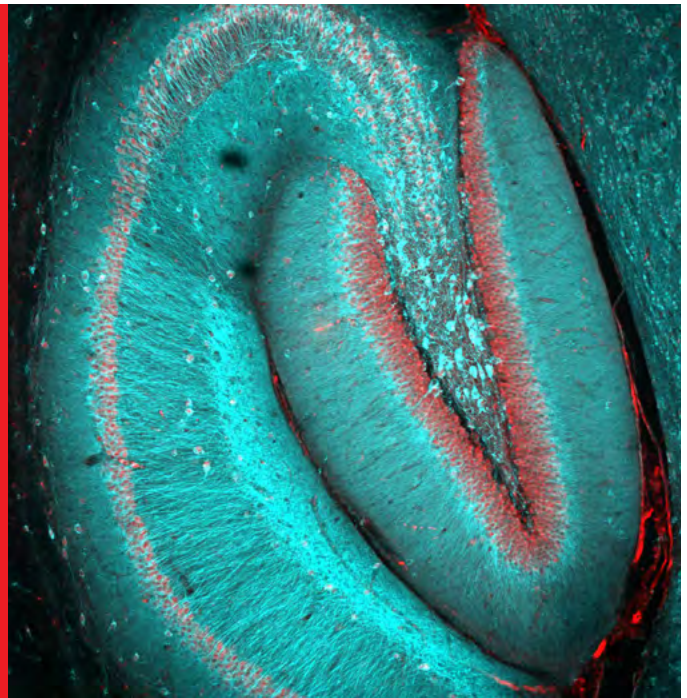
As a neurodegenerative disease, Alzheimer's is known for damaging neurons, which are the nerve cells of the brain. To survive and function properly, neurons depend on oxygen and glucose carried through the brain's blood vessels, or vascular system. Their needs are great because the brain consumes more 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: Alzheimer's may be affected by "cross talk" between blood vessels and neurons in the hippocampus, shown here. (Courtesy of Melanie Samuel, PhD, Baylor College of Medicine, Houston, TX)

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

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

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

Whitney Freeze, PhD   (01/01/22 – 12/31/23)   FELLOWSHIP

Leiden University Medical Center, Leiden, Netherlands
Fellowship Co- Mentor: Louise van der Weerd, PhD
Fellowship Co-Mentor: Susanne van Veluw, PhD
Harvard University, Boston, MA

Detecting Leaky Vessels in Cerebral Amyloid Angiopathy - A Novel Approach

This project combines state of the art magnetic resonance imaging techniques with detailed post-mortem examinations to explore associations between BBB leakage, subtle hemorrhagic brain pathology, and cognitive functioning in patients with cerebral amyloid angiopathy. The success of this project will ultimately provide the field with a new tool to predict risk of hemorrhages in dementia at an early stage, which will be pivotal in the selection of individuals for amyloid-modifying therapies, and for the development of new drugs to prevent the formation of bleeds.

www.brightfocus.org/A2021007F
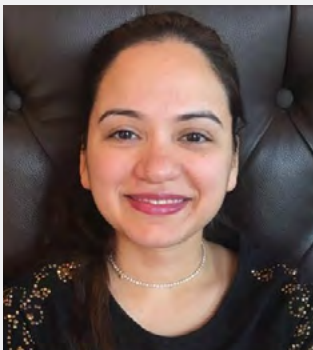
Saima Hilal, PhD   (7/1/18 - 6/30/22)   FELLOWSHIP

National University of Singapore
Fellowship Mentor: Meike W. Vernooij, MD, PhD
Erasmus University Medical Center, Rotterdam, Netherlands
Fellowship Co-Mentor: M. Arfan Ikram, MD, PhD
Erasmus University Medical Center, Rotterdam, Netherlands

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

Majken Jensen, PhD   (7/1/17 - 11/30/21)

Harvard University, Boston, MA

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

Ethan Lippmann, PhD   (7/1/17 - 12/31/21)
Vanderbilt University, Nashville, TN
Co-Principal Investigator Laura Dugan, MD

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

Shannon Macauley-Rambach, PhD   (9/1/20 – 8/30/23)
Wake Forest University, Winston-Salem, NC

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

Alaina Reagan, PhD   (9/1/20 – 8/30/22)   FELLOWSHIP
The Jackson Laboratory, Bar Harbor, ME
Fellowship Mentor: Gareth Howell, PhD

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

Melanie Samuel, PhD   (07/01/21 – 06/30/24)

Baylor College of Medicine, Houston, TX

Co-Principal Investigator: Joshua Wythe, PhD

Pericyte Neuron Crosstalk and the Progression of Alzheimer's Disease

Alzheimer's disease (AD) affects millions of individuals, and co-morbities such as vascular disease can significantly accelerate cognitive decline. Alterations to neuron and blood vessel communication may drive these outcomes. This study aims to understand how AD disrupts energy homeostasis and neurovascular coupling through specialized vascular structures called pericyte nanotubes.

www.brightfocus.org/A2021039S

Alex Smith, PhD   (7/1/18 - 6/30/22)

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

Xiaowei Wang, PhD (07/01/21 – 06/30/23) FELLOWSHIP

The University of California, San Francisco
Fellowship Co-Mentor: Douglas Gould, PhD
Fellowship Co-Mentor: Tyson Kim, MD, PhD
Fellowship Co-Mentor: Scott Earley, PhD
University of Nevada, Reno

Determining Mechanisms of Age-Related Cerebrovascular Dysfunction in a Genetic Model of Cerebral Small Vessel Disease

Type IV collagen (encoded by COL4A1 and COL4A2 genes) is a fundamental component of the vascular basement membrane – a sheet-like structure around blood vessels that provides physical support and acts as a platform for signaling. Patients with mutations in COL4A1 or COLA2 have very high prevalence of cerebral small vessel diseases and genetic association studies also implicate these two genes in general cerebrovascular health. Col4a1 mutant mice faithfully replicate human pathologies and show age-dependent loss of cerebrovascular tone, which could further cause cognitive impairment. Using this mouse model, this proposal aims to identify the early vascular changes and underlying molecular mechanisms that ultimately lead to the age-dependent loss of cerebrovascular tone.

www.brightfocus.org/A2021018F

Cheryl L Wellington, PhD (07/01/21 – 06/30/24)

University of British Columbia, Vancouver, Canada

The Role of Peripheral APOE in the High Density Lipoprotein Fraction in Vascular Contributions to Alzheimer's Disease

APOE is made both within the brain and outside the brain, but the "brain" and "blood" pools of APOE are separated by the blood brain barrier. Most patients with Alzheimer's disease (AD) have problems with the blood vessels in their brain, including cerebral amyloid angiopathy (CAA), which is the deposition of amyloid-beta (Aß) in the brain's blood vessels. Circulating high-density lipoprotein (HDL) particles, or "good cholesterol", can help Aß from getting stuck in the vessel wall as it moves from "brain" to "blood". Importantly, ~6% of HDL also contains APOE, and these APOE-HDL particles seem to be the best at helping Aß from getting stuck in the vessel. This project uses a new method to measure APOE-HDL in ~2000 blood samples from people with dementia vs. people resistant to dementia and use additional test tube approaches to study how APOE-HDL acts on the small blood vessels of the brain.

www.brightfocus.org/A2021045S

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.

www.brightfocus.org/grant/A20201411S

This grant is made possible in part by support from Alzheimer's Los Angeles.
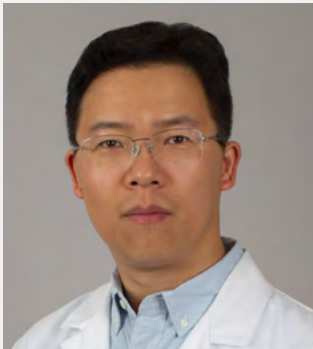
**Zhen Zhao, PhD**   (7/1/19 - 6/30/22)
University of Southern California, Los Angeles

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

CELLS & CIRCUITS
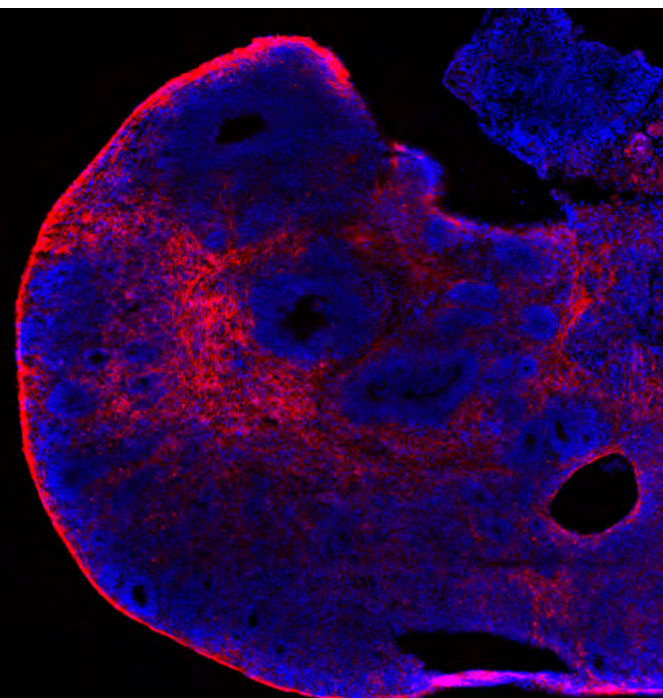
The human brain has an estimated 100 billion neurons; thankfully, quite a few to spare. Extending from each of them is a long fiber, known as an "axon," which can run several feet. Each axon forms a connection, known as a "synapse," with another neuron, creating a circuit over which brain signals travel. 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: Tau protein (red) spreads in a frontotemporal dementia brain organoid. (Courtesy of Hongjun Fu, PhD, The Ohio State University, Columbus, OH)

Moustafa Algamal, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
Massachusetts General Hospital, Boston, MA
Fellowship Mentor: Ksenia Kastanenka, PhD

Restoring Sleep and Memory Deficits in Alzheimer's Disease by Targeting Somatostatin Interneurons

Slow-wave sleep is closely associated with memory performance in healthy individuals and is also disrupted in Alzheimer's disease. This project aims to find and activate the group of neurons responsible for slow-wave sleep regulation and improve their function in Alzheimer's disease mouse models through two different approaches. The first approach will utilize a novel genetic technology to activate these neurons with light, followed by assessing memory and pathology of Alzheimer's disease in animals. The second approach will rely on pharmacological approaches to support the function of these neurons.

www.brightfocus.org/A2021001F

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

Yifei Cai, Ph.D   (07/01/21 – 06/30/23)   FELLOWSHIP
Yale University, New Haven, CT
Fellowship Mentor: Jaime Grutzendler, MD

Molecular Mechanisms of Axonal Pathology in Alzheimer's Disease

Amyloid deposits in Alzheimer's disease are surrounded by axons with abnormally enlarged bulbous structures. These structures severely affect axonal conduction of signals and that this may be correlated with memory loss in humans. The goal of this project is to investigate the molecular and cellular mechanisms involved in the formation of these bulbs and determine if reversing this pathology is possible, and if so whether this can restore normal axonal function.

www.brightfocus.org/A2021003F

Laura Cox, PhD (07/01/21 – 06/30/24)
Brigham and Women's Hospital & Harvard Medical School, Boston, MA

The Microbiota Cell-Type Specific Regulation of AD Pathogenesis

The gut microbiota contains trillions of microbes that promote health by producing vitamins, defending against bad bacteria, or training the immune system. The gut microbiota also affects the brain by secreting substances that can affect the immune system or mood. In aging, the gut microbiota becomes destabilized and can contribute to disease. This project investigates how age-related microbiota changes contribute to Alzheimer's disease to find ways to control the microbiome and promote healthy brain aging.

www.brightfocus.org/A2021024S

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
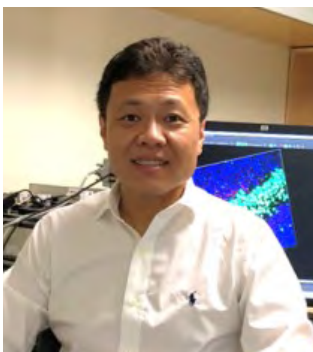
Heng Du, PhD, MD (9/1/20 – 8/30/23)
The University of Texas at Dallas

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
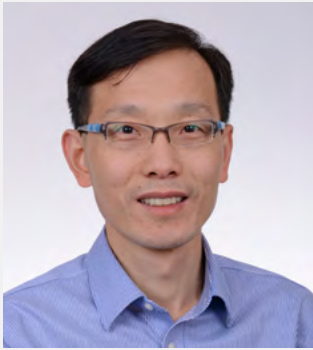
Hongjun Fu, PhD (07/01/21 – 06/30/24)
The Ohio State University, Columbus, OH

Cerebral Organoids to Investigate Cellular and Neuronal Network Vulnerability in Alzheimer's Disease and Progressive Supranuclear Palsy

Abnormal tau proteins spread between cells in the brain in both Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) causing neurodegeneration and dysfunction. Tau build up has also been found to spread in animal models, however, these models don't fully replicate the molecular, structural, and genetic complexity of these diseases. We propose to use cerebral organoids or miniature brains grown from human induced pluripotent stem cells containing wild-type or a tau mutation and treat them with different tau seeds to investigate which cell types are vulnerable in AD and PSP and why.

www.brightfocus.org/A2021027S

Sara Gallant, PhD (7/1/18 - 6/30/21) FELLOWSHIP
University of Southern California, Los Angeles
Fellowship Mentor: Mara Mather, PhD

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
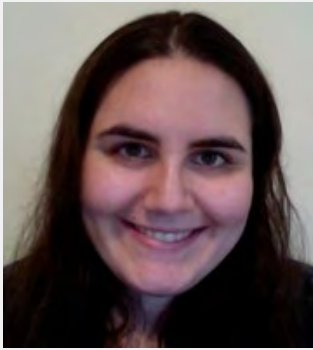
Sarah Hill, PhD   (9/1/20 – 8/30/22)   FELLOWSHIP

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

S. Abid Hussaini, PhD   (7/1/19 - 11/30/21)

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

Kei Igarashi, PhD   (7/1/19 - 6/30/23)

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

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

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

Tae Ho Lee, PhD (7/1/17 - 6/30/22)
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

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
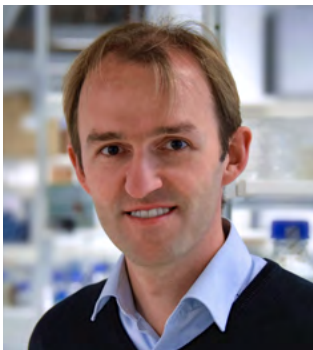
Dominik Paquet, PhD　　　　　(7/1/19 - 6/30/22)
Ludwig-Maximilians University, Munich, Germany

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
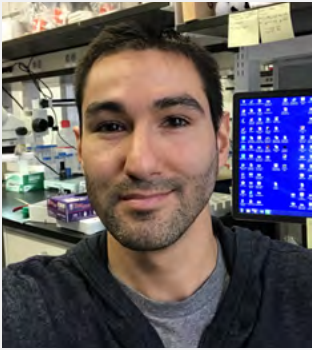
Gustavo Rodriguez, PhD   (7/1/19 – 6/30/22)   FELLOWSHIP

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

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
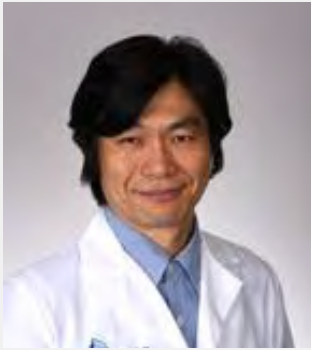
Takashi Sato, PhD (07/01/21 – 06/30/24)
Medical University of South Carolina, Charleston, SC

Neural Circuit Mechanisms Underlying Sleep Disruption in Alzheimer's Disease Model Mice

Sleep disturbance is both an early symptom of AD in the prodromal phase, and one of the factors that exacerbates AD. This project will study the interaction between sleep and AD progression using advanced microscopy and optical stimulation. Key components of the neural circuts that contribute to sleep will be identified and specific components of the neural circuit will be manipulated during sleep to enhance sleep-related activity in the brain and examine how these manipulations affect AD progression and cognition.

www.brightfocus.org/A2021041S

Min-Kyoo Shin, PhD (7/1/19 – 6/30/22) 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
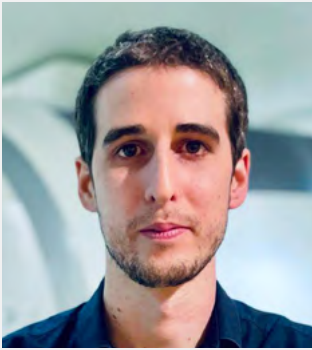
Maxime Van Egroo, PhD (07/01/21 – 06/30/23) FELLOWSHIP
Maastricht University, Netherlands
Fellowship Mentor: Heidi Jacobs, PhD

The Brainstem Locus Coeruleus: Potential Bridge Between Sleep-Wake Disruption and Alzheimer's Disease Pathogenesis

The proposed project postulates that a tiny region located deep in the brain, the brainstem locus coeruleus (Latin for 'blue spot', LC), is particularly important for the link between sleep-wake disturbances and the earliest manifestations of AD. Indeed, the LC is a crucial structure in the consolidation of the sleep-wake cycle and has been demonstrated to be among the first regions affected by AD. This research aims to use advanced brain imaging methods to extensively characterize the LC in healthy adults across the lifespan, in order to determine how modifications in the structure and function of the LC relate to changes in the sleep-wake cycle, in the accumulation of hallmark AD pathologies, and ultimately to cognitive decline.

www.brightfocus.org/A2021016F
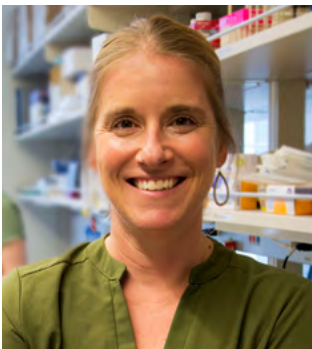
Jessica Young, PhD (7/1/18 - 6/30/22)
University of Washington School of Medicine, Seattle, WA

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

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

FINDING NEW DRUGS & TREATMENTS

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 some did not meet their primary endpoints and were discontinued, other treatments are still being developed today. Ahead, 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

Michele Cavallari, MD, PhD   (9/1/20 – 8/30/23)

Brigham and Women's Hospital & Harvard Medical School, 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

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

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 (Aβ) is the main component of amyloid plaques found in the brains of Alzheimer patients. Production of Aβ is nearly stopped by inhibiting BACE1 enzyme. Therefore, BACE1 inhibitors are used to reduce Aβ 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

Shermali Gunawardena, PhD   (7/1/18 - 6/30/22)
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

Patrick Kehoe, PhD   (7/1/16 - 6/30/22)
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

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

WonHee Kim, PhD (7/1/19 – 6/30/22) 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

Marianne Leger, PhD (01/04/2021 – 01/03/2023)
Caen-Normandy University, Caen, France

LOU Rat as a Model of Cognitive Resilience in Alzheimer's Disease

This project will aim to model cognitive resilience in rodents by combining a rat model of successful aging with a model of early Alzheimer's disease (AD). The hypothesis tests whether these rats are resilient to AD pathology, resulting in intact cognition compared to AD rats. The involvement of the serotonergic system will be evaluated to determine potential therapeutic targets that may promote resilience to AD.

www.brightfocus.org/grant/CA2021013

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

Timothy Sargeant, PhD (07/01/21 – 06/30/24)
South Australian Health and Medical Research Institute, Adelaide, Australia
Co-Principal Investigator: Julien Bensalem, PhD
Co-Principal Investigator: Leonie Heilbronn, PhD,
University of Adelaide, Australia

Reduced Protein Intake Counteracts Alzheimer's Disease: Examination of Nutrition Signaling and the Lysosomal System

The brain's clearance system, called autophagy, works less efficiently with age, resulting in the accumulation and spread of toxic disease associated proteins. Autophagy can destroy amyloid plaques associated with Alzheimer's disease and it can be activated using drugs or, by restricting certain nutrients in the diet. In mice, reducing the amount of protein in food decreases the amount of plaque material that accumulates in the brain. These findings will be applied to humans to determine whether reducing the amount of protein consumed in the average diet increases autophagy; for comparative purposes, the same dietary changes will be applied to mice with AD.

www.brightfocus.org/A2021040S

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 biomolecular 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, glycobiological knowledge required to improve the diagnosis and treatment of AD.

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

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

GENOMICS: DNA BLUEPRINT FOR ALZHEIMER'S
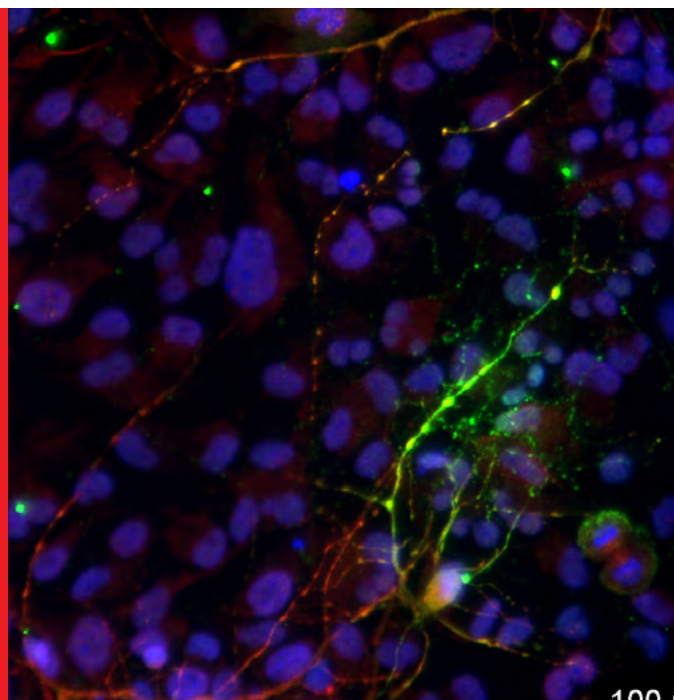
Genes are the "master blueprint" that instructs our cells to make unique proteins which in turn build, operate, and repair human tissue. Humans have an estimated 24,000 genes along our 23 matched pairs of chromosomes (46 in all), and "genomics" refers to the field that studies all of them at once. Even 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 a model system, neurons (shown in red) are derived from stem cells carrying a genetic mutation that increases tau accumulation (shown in green). (Courtesy of Kathryn Bowles, PhD, Icahn School of Medicine at Mount Sinai, New York, NY).

Kathryn Bowles, Ph.D   (07/01/21 – 06/30/24)
Icahn School of Medicine at Mount Sinai, New York, NY

Single Cell Profiling of MAPT Splicing Mutation iPSC-Derived Organoids and Brain Tissue

Progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) are age-related dementias associated with the accumulation of 4R Tau. PSP and FTD can be caused by specific mutations on the gene encoding for Tau, MAPT. A panel of iPSC lines that carry specific PSP/FTD mutations and have increased 4R Tau expression, will be used to generate 3D brain organoids. Gene expression analyses and phenotypic assays will be conducted to identify early changes associated with 4R Tau and the development of disease. Next, bulk and single-nuclei sequencing will be carried out on brain tissues from individuals with the same MAPT mutations to validate these changes and thoroughly characterize the impact of 4R Tau accumulation in adult human brain.

www.brightfocus.org/A2021021S

Camila de Avila Dal Bo, PhD, M.Sc.   (07/01/21 – 06/30/23)   FELLOWSHIP
Mayo Clinic Arizona, Scottsdale, AZ
Fellowship Mentor: John David Fryer, PhD

Nucleus Incertus of the Brain: Mapping its Genomic Expression and Changes in Alzheimer's Disease

Certain areas in the brainstem, such as the locus coeruleus, are highly vulnerable to neurodegenerative conditions, including Alzheimer's disease. A recent landmark paper published in Science established a key role for the brainstem region known as the nucleus incertus (NI) in memory, by confirming in mice strong neural communication between the NI and the hippocampus, a brain region crucial for learning and memory. In humans, the specific functions of NI neurons and their chemical messengers, precise distribution, and connectivity, are currently unknown. The main goal of this project is to investigate the NI in humans and elucidate the role of the NI in dementia and Alzheimer's disease pathology.

www.brightfocus.org/A2021006F

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

Niran Hadad, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
The Jackson Laboratory, Bar Harbor, ME
Fellowship Mentor: Catherine Kaczorowski, PhD

Systems Genetics Analysis of Alzheimer's Disease Related Sleep Disruption

Traditional mouse models of Alzheimer's disease have provided substantial insights into possible mechanisms causing sleep loss in Alzheimer's disease. However, these model lacks the genetic diversity required to identify genes conferring individual risk to develop AD-related sleep loss and subsequent cognitive decline. The work proposed here seeks to identify genes that underlie an individuals' risk for developing Alzheimer's-related loss of sleep using a well-characterized, genetically diverse mouse model of AD that better models the complexity of human genetic diversity.

www.brightfocus.org/A2021010F

Ulrich Hengst, PhD   (07/01/21 – 06/30/24)
Columbia University, New York, NY

Transcriptional Dysregulation of the Endocytic Machinery in AD

Endosomes form complexes with multiple other proteins, including transferrins (TF), to perform intracellular sorting of substances that will ultimately be degraded or recycled. A new TF complex that is associated with amyloid has been identified and is proposed to transcriptionally regulate components of the retromer, a multiprotein complex that mediates the sorting and transport of proteins out of early endosomes. This project will determine the sufficiency of the TF complex to deregulate the expression of retromer components and to cause endosomal trafficking defects, and investigate whether AD pathology is altered in mice lacking one of the TFs.

www.brightfocus.org/A2021030S

Laura Ibanez, PhD   (07/01/21 – 06/30/24)
The Washington University, St. Louis, MO

Pathophysiology of sRNAs in Alzheimer's Disease

This proposal will characterize the different populations of small RNAs in brain, plasma, and cerebrospinal fluid of individuals with Alzheimer disease. Their biological role will be investigated by: i) identifying which small RNAs are different between cases and controls in each specimen (brain, plasma and cerebrospinal fluid); ii) use small RNAs to generate tools that allow disease prediction, and iii) use cellular models to investigate the biological consequences of dysregulating the identified small RNAs.

www.brightfocus.org/A2021033S

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

Justin Miller, PhD (9/1/20 – 8/30/23) FELLOWSHIP
University of Kentucky
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

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

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

Jeffery Vance, MD, PhD   (7/1/18 - 6/30/22)
*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

ALZHEIMER'S DISEASE IN THE UNITED STATES

More than **6** million now

8 million by 2030

Nearly **13** million by 2050
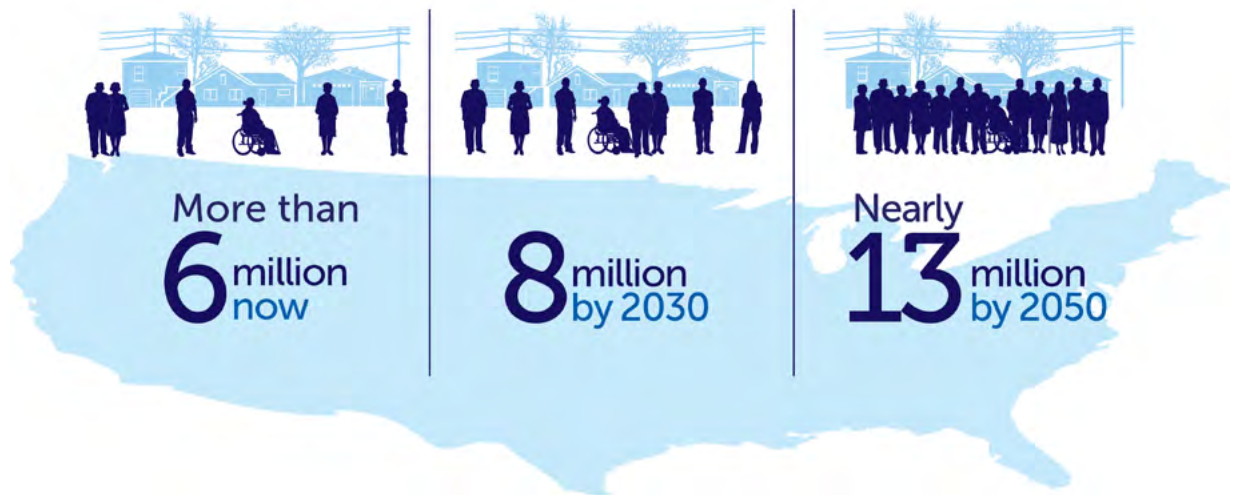
IMMUNITY & INFLAMMATION
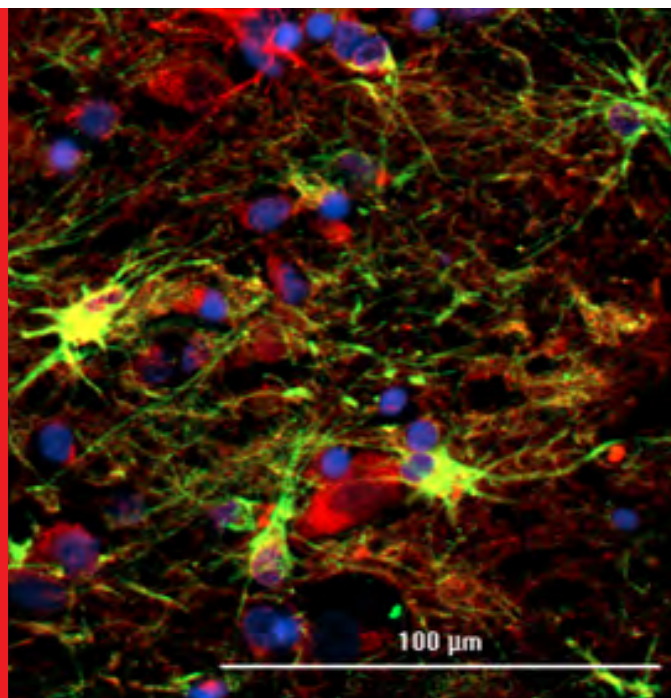
One theory about Alzheimer's disease (AD) is that it may be triggered, in part, by a breakdown in the brain's immune system. Normally our brain has ways of clearing damaged cells and unwanted particles in its midst and disposing them into the bloodstream—which can be thought of as "taking out the garbage." However, a chronic rise in unwanted debris, including toxic amyloid beta (Aβ) 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: Inflammatory cells (green) interact with support cells called astrocytes (red) in the hippocampus of a person with Alzheimer's disease. (Courtesy of Benedetta Assetta, PhD, Brown University, Providence, RI).

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

Benedetta Assetta, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
Brown University, Providence, RI
Fellowship Mentor: Yu-Wen Alvin Huang, MD, PhD

Astroglial Inflammatory Signaling in Alzheimer's Disease

Neuroinflammation sits at the center of Alzheimer's disease pathogenesis. This study will investigate the regulatory role of CHI3L1, an inflammatory molecule that correlates with Alzheimer's disease development. The biological mechanisms of CHI3L1 in Alzheimer's disease pathology will be studied using patient derived stem cells and animal models. Unraveling this process will greatly advance our knowledge on the contribution of neuroinflammation to Alzheimer's disease pathogenesis and provide potential targets for the development of therapeutics.

www.brightfocus.org/A2021002F

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

Xiaofen Chen, PhD   (07/01/21 – 06/30/24)
Xiamen University, Xiamen, China

Physical Interaction of TREM2 and C1q in Alzheimer's Disease

Triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor specifically expressed in microglia. Coding variations in TREM2 have been reported to increase the risk for Alzheimer's disease (AD) and other neurodegenerative diseases. This project will study the mechanism by which TREM2 modulates AD-related pathways in microglia and neurons to influence cognition and pathology in mouse models.

www.brightfocus.org/A2021023S

Juan Codocedo, 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

Hemraj Dodiya, PhD (7/1/19 – 6/30/22) 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

**Alireza Faridar, MD** (7/1/19 – 8/31/21) 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
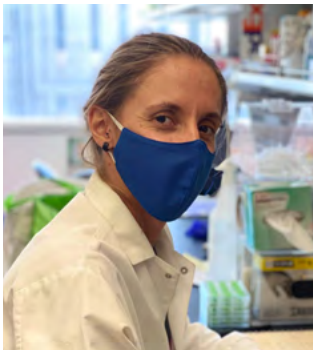
Maud Gratuze, PhD (9/1/20 – 8/30/22) FELLOWSHIP
Washington University in St. Louis, MO
Fellowship Mentor: David Holtzman, MD

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

Soyon Hong, PhD (07/01/21 – 06/30/24)
University College London, England

Immune Mechanisms of Synapse Loss in Alzheimer's Disease

Recent single-cell profiling studies have shown that certain 'activated' microglia surround amyloid plaques in AD brains and express a unique set of genes, hence coined 'disease-associated macrophages' (DAMs). What DAMs do and whether DAMs are beneficial or detrimental are not known. Pilot data suggest that DAM-like cells are expressed early in AD models when synapses are vulnerable to loss. This proposal will test the hypothesis that DAMs facilitate synapse loss in AD via upregulation of SPP1 (Osteopontin) and, dertermine whether this is complement dependent, using in vivo mouse and in vitro models as well as human AD brains.

www.brightfocus.org/A2021032S

Harini Iyer, PhD (01/01/22 – 12/31/23) FELLOWSHIP
Stanford University, Redwood City, CA
Fellowship Mentor: William Talbot, PhD

Lysosomal Signaling in Microglia and Alzheimer's Disease

Microglia chew up dead cells and fight infections in the brain to make sure that other brain cells, such as neurons, function normally. When microglia eat bacteria or dead material, this material passes through the lysosome, where it gets recycled or broken up into smaller pieces. DNA mutations in people with Alzheimer's disease occur in genes that are important for migroglia and lysosome function. This project will investigate how these genes are important for the normal activity of microglia and lysosomes and how, over time, they can cause microglia to switch from being good for the brain to harming brain cells.

www.brightfocus.org/A2021011F

Renzo Mancuso, PhD (07/01/21 – 06/30/24)
Vlaams Institute Voor Biotechnologie (VIB), Flanders, Belgium

From Genetics to the Cellular Phase of Alzheimer's Disease: Untangling the Role of Lipid Pathways in Microglia Responses to Amyloid Pathology

Genetic studies reveal a link between neuroinflammation and susceptibility for Alzheimer's disease (AD), suggesting that inflammation might be a driver of the disease opposed to just a consequence. This project aims to determine the link between AD genetic risk, microglia, and lipid metabolism by combining novel models where human stem cell derived microglia are injected in AD mice, and single cell RNA sequencing is used for in depth analysis of microglial function. By doing this, we will be able to dissect the contribution of microglia and lipid metabolism in the AD brain in a crucial human system.

www.brightfocus.org/A2021034S

Jonas J Neher, PhD (07/01/21 – 06/30/24)
German Center for Neurodegenerative Diseases, Bonn, Germany

The Role of HIF-1a in the Microglial Response to Alzheimer's Disease Pathology

One role of microglia is to shield the brain from the damaging effects of amyloid plaques – this is called the microglial 'barrier function'. Importantly, genetic mutations that disrupt this microglial barrier lead to a strongly increased risk for developing AD. Preliminary work identified a previously unknown molecular target whose genetic elimination significantly increases the microglial barrier around amyloid plaques. This project will characterize the long-term effects of manipulating this molecular pathway in two independent animal models of AD pathology, with a particular focus on molecular and functional changes in microglia, pathological hallmarks of AD and most importantly, cognitive function.

www.brightfocus.org/A2021035S

Anna Podlesny-Drabiniok, PhD (07/01/21 – 06/30/23) FELLOWSHIP
Icahn School of Medicine at Mount Sinai, New York, NY
Fellowship Mentor: Alison Goate, PhD

Investigating the Role of Liver X Receptors in Control of Alzheimer's Disease Risk Genes and Lipid Clearance in hiPSC-derived Microglia

Analysis of genetic factors contributing to Alzheimer's disease (AD) point to the critical role of brain immune cells (microglia) and functions that they exert such as efficient removal of dying cells in the process called phagocytosis. In AD brains, immune cells are unable to properly remove amyloid plaques, and they sustain inflammation contributing to disease progression. This project will test whether liver X receptors and the AD risk gene, BHLHE40/41, are master regulators of microglial phagocytosis using human cells carrying AD mutations.

www.brightfocus.org/A2021014F

Erin Reed-Geaghan, PhD (07/01/21 – 06/30/24)
Northeast Ohio Medical University, Rootstown, OH

Developmental Determinants of Sexually Divergent Neuroinflammatory Processes in Alzheimer's Disease

In addition to the pathological hallmarks of amyloid plaques and neurofibrillary tangles, Alzheimer's disease (AD) is characterized by a robust inflammatory response in the brain. Women are disproportionally affected in AD, and have more inflammation, but the reasons for these sex differences are unclear. The studies in this proposal are designed to identify the developmental processes that establish and perpetuate the sex differences in this inflammatory response.

www.brightfocus.org/A2021036S

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

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

Rebecca Wallings, PhD (07/01/21 – 06/30/23)   FELLOWSHIP
University of Florida, Gainesville, FL
Fellowship Mentor: Malu Tansey, PhD

The Role of the Peripheral Immune System in FTD-GRN; Increasing Understanding for Future Therapeutic Target Development

Previous evidence suggests that microglia are not the only culprit in Frontotemporal dementia (FTD), but rather, immune cells normally found in circulating blood (monocytes) infiltrate into the brain and may play a role in neurodegeneration. Lysosomes, organelles in cells responsible for protein recycling and cell signaling, are crucial for proper immune cell function, and may be dysregulated in FTD monocytes. Using a combination of mouse models and FTD-patient samples, this research aims to unveil the role of these peripheral immune cells and dysfunctional lysosomes in the development of FTD.

www.brightfocus.org/A2021017F
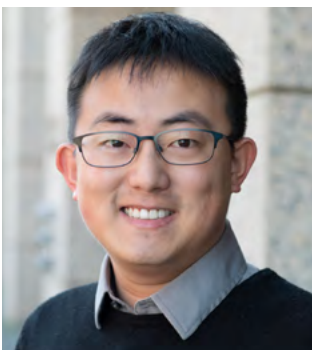
Zhaoqi Yan, PhD (07/01/21 – 06/30/23)   FELLOWSHIP
The J. David Gladstone Institutes, San Francisco, CA
Fellowship Mentor: Katerina Akassoglou, PhD

Fibrinogen-Mediated Innate Immune Activation and Neuronal Dysfunction in Alzheimer's Disease

Fibrinogen, a blood coagulation protein, deposits in the brains of people with Alzheimer's disease and causes microglia activation, oxidative stress, neuronal loss, and cognitive impairment. This proposal will use a multi-pronged experimental design to examine the cerebrovascular mechanisms regulating neuronal dysfunction in AD. State-of-the-art imaging will be used to study the interaction of fibrinogen and neurons in living mice with subcellular resolution. The transcriptional machinery underlying fibrinogen-mediated oxidative stress will be determined and used to generate a global transcriptional atlas in the brain of AD mice at single-cell level.

www.brightfocus.org/A2021019F

Beika Zhu, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
The University of California, San Francisco
Fellowship Mentor: Xiannhua Piao, MD, PhD

Characterizing the Role of Microglial GPR56 in Alzheimer's Disease

This proposal will test the hypothesis that microglial GPR56, a cell surface protein that receives signals from neighboring cells, plays a role in maintaining brain function and stops Alzheimer's disease progression. CPR56 function will be determined by generating a new mouse model where CPR56 activity is inhibted, or knocked down. Investigating changes in inflammatory responses, memory, and motor function, will elucidate the mechanisms by which GPR56 mediates Alzheimer's disease onset and progression.

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EVERY
65
SECONDS

SOMEONE DEVELOPS ALZHEIMER'S DISEASE.

RESEARCH TOOLS & RESOURCES
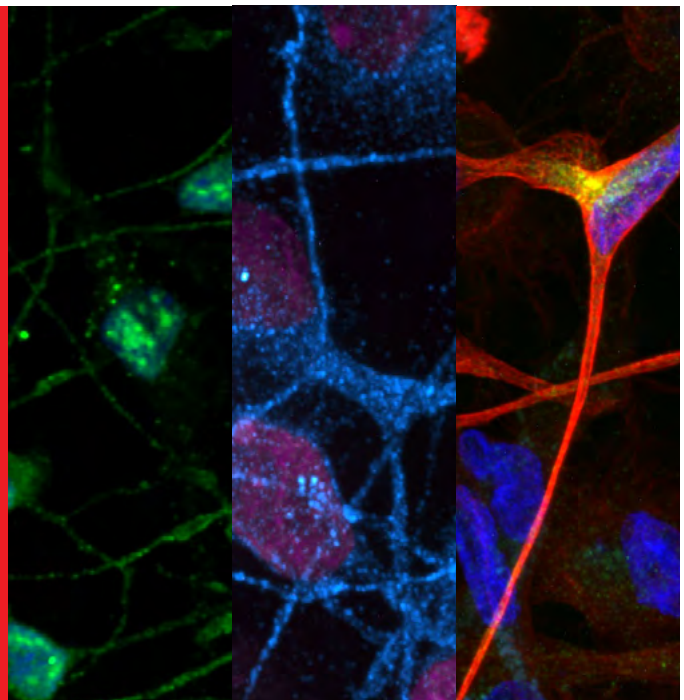
When designing a research project, having the right preliminary information and tools to rely on can make or break its success, especially in understudied areas. Yet these first steps take time and expense to complete. BrightFocus Alzheimer's Disease Research funding supports the development of resources 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: Neurons grown in a dish derived from skin cells obtained from individuals with Alzheimer's disease. (Courtesy of Silvia Pelucchi, PhD, Mertens Lab, University of Innsbruck, Austria)

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

THE IMPACT OF TAU
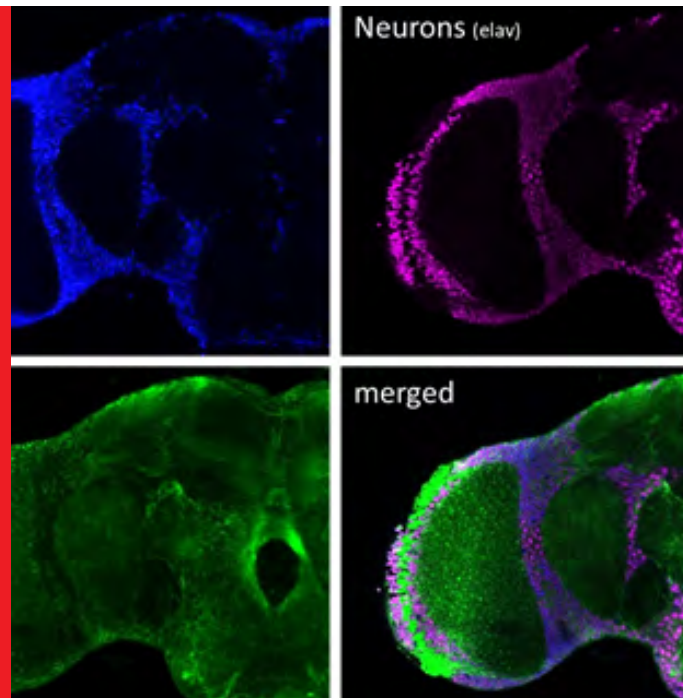
As a protein associated with Alzheimer's disease (AD), tau is abundant inside neurons, where its fibrous shape lends stability to tubes that transport nutrition and waste to different cellular locations. However, in AD, tau goes through molecular changes that cause it to misshape and collect in messy tangles. Unlike amyloid beta (Aβ) 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 Aβ 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: Fruit flies (Drosophilia) express tau in neurons and can be used to study tau protein accumulation and spread. (Courtesy of Lindsey Goodman, PhD, Baylor College of Medicine, Houston, TX)

Jose Abisambra, 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

Ottavio Arancio, MD, PhD   (7/1/18 - 6/30/22)
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

Michelle Farrell, PhD   (7/1/19 – 1/31/22)   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

Jason Gestwicki, PhD   (07/01/21 – 06/30/24)
The University of California, San Francisco
Co-Principal Investigtor: Daniel Southworth, PhD

De-Phosphorylation of Tau by Chaperone Complexes

Tau is abnormally modified by phosphorylation and phosphorylation at specific sites may precede disease. While the enzymes that add phosphorylation groups are well known, there has been significantly less attention paid to the enzymes, termed phosphatases, that remove these modifications. Exciting preliminary results showed that specific 'helper' proteins, or chaperones, can bind to tau and recruit a specific phosphatase, PP5. This study will use cutting edge techniques to look at protein structures and interactions of chaperones with PP5 to determine whether these interactions are important for removing phosphorylations from tau.

www.brightfocus.org/A2021029S
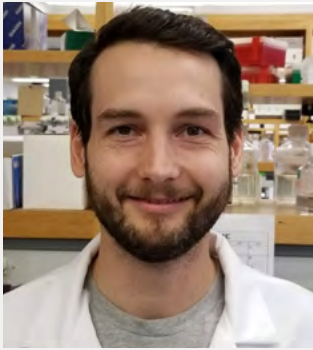
Garrett Gibbons, PhD (7/1/19 – 12/31/21) FELLOWSHIP
University of Pennsylvania, Philadelphia, PA
Fellowship Mentor: John Q. Trojanowski, MD, PhD

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

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

Karin Meeker, PhD (07/01/21 – 06/30/23) FELLOWSHIP
Washington University School of Medicine, St. Louis, MO
Fellowship Mentor: Beau Ances, MD, PhD, MSc

Tau Phosphorylation in Preclinical and Symptomatic Autosomal Dominant Alzheimer Disease

Changes in blood tau levels, cognitive tests, and brain network connectivity can be used as biomarkers to map disease progression and indicate conversion from preclinical to clinical AD. It is unknown, however, how various phosphorylation sites on tau are associated with brain network organization and whether they contribute to the propagation of tau through brain networks. This study will use neuroimaging, cerebrospinal fluid, and cognitive markers to characterize and stage the temporal and spatial progression of tauopathy occurring during the transition period in autosomal dominant AD.

www.brightfocus.org/A2021012F

Alexa Pichet Binette, PhD   (07/01/21 – 06/30/23)   FELLOWSHIP
Lund University, Malmoe, Sweden
Fellowship Mentor: Oskar Hansson, MD, PhD

Characterization of Tau Pathology Heterogeneity Across the Alzheimer's Disease Spectrum

This study will use the latest positron emission tomography marker to image tau deposition in a large, longitudinal, well-characterized cohort ranging from pre-clinical older adults to people with dementia. Participants will be grouped according to their different tau subtypes and additionally characterized using biofluidic, genetic, and cognitive measurements to understand the mechansims that underlie the accumulation of pathology and cognitive decline.

www.brightfocus.org/A2021013F

Wilfried O. Rossoll, PhD   (07/01/21 – 06/30/24)
Mayo Clinic Jacksonville, FL

Identifying Novel Modifiers of Tau Aggregation and Pathology Using Proximity Proteomics

The goal of this project is to identify proteins that associate with tau protein aggregates that may contribute to tau pathology in AD. A novel method to precisely map the composition of insoluble protein aggregates in the context of living brain tissue via proximity labeling and proteomic analysis will be used to overcome the limitations of classical affinity-purification methods. This approach has been further optimized to study the transition of tau from its physiological to its pathological form in cultured neurons and brain tissue models of AD.

www.brightfocus.org/A2021038S

Masashi Tabuchi, PhD   (07/01/21 – 06/30/24)
Case Western Reserve University, Cleveland, OH

Clock-Driven Sleep Fragmentations in Tauopathy

The overall objective of this proposal is to elucidate the role that inactivation states of voltage-gated sodium channels play in the regulation of circadian rhythms and sleep in Alzheimer's disease and related tauopathies. This proposal will test through comparative, both in vivo (Drosophila) and in vitro (iPS cells), assessments our central hypothesis that manipulations of inactivation states of voltage-gated sodium channels in Alzheimer's disease lead to molecular and cellular alterations resulting in dysfunctional circadian rhythms, sleep alterations, and disease progression.

www.brightfocus.org/A2021043S

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

Susanne Wegmann, PhD (07/01/21 – 06/30/24)
German Center for Neurodegenerative Diseases, Bonn, Germany

Understanding Tau-Induced Nuclear Transport Deficits in Alzheimer's Disease

The aberrant interactions of Tau with nucleopore proteins, nucleoporins (Nups), induce a pronounced impairment in nucleocytoplasmic transport processes, whereby two mechanisms seem to play a role: direct binding of soluble tau to Nups in pore complexes, and co-aggregation of Nups with Tau in cytosolic neurofibrillary tangles, the hallmark Tau pathological change in Alzheimer's brains. To understand how Tau interacts with and impairs nuclear pores, the Tau:Nup interactome will be determined in human neurons and these findings will be correlated with the status of human AD brains. Cells equipped with a nuclear transport reporter will be used to screen for small molecules and genetic modifiers of Tau-induced nuclear transport deficits.

www.brightfocus.org/A2021044S

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

TRANSLATIONAL RESEARCH & CLINICAL INTERVENTIONS

PiB PET: Amyloid Burden

FTP PET: Tau Burden
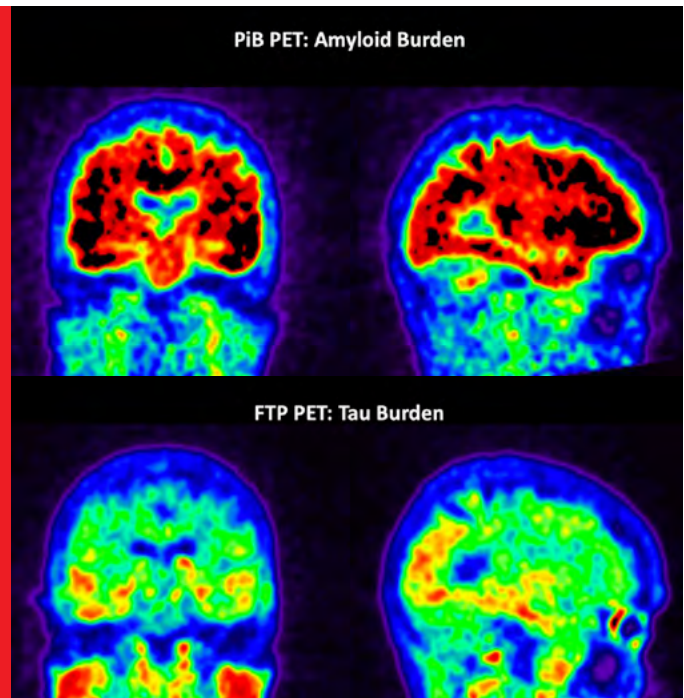
"Translational" research refers to the effort to take basic science knowledge from the laboratory or research setting into the "real world" in the form of potential treatments or cures. In this context, it refers to the act of literally "translating" science into useful ways of diagnosing, treating, managing, or even preventing Alzheimer's disease (AD). These innovations can take many different forms, such as using smartphone-based testing to monitor cognitive status in AD, or 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 other studies that 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: PET images show the accumulation of amyloid and tau proteins in a person with Alzheimer's disease. (Courtesy of Xi Chen, PhD, The University of California, Berkeley)

Xi Chen, PhD (10/01/21 – 09/30/23) FELLOWSHIP
The University of California, Berkeley
Fellowship Mentor: William Jagust, MD

The Relationship Between Amyloid/Tau Pathology and Different Memory Processes Underlying Memory Aging

The proposed project, focusing on early stage Alzheimer's disease (AD), will examine the brain and behavioral deficits in older adults with normal cognitive performance but already harboring AD pathology. This study will use functional MRI to investigate how different brain regions activate when participants view pictures of an object, a scene, and an object in a scene. Participants will complete a surprise memory test on the pictures 20 minutes later. These results will isolate brain activities that are critical for successful memory. PET imaging will then be used to visualize the deposition of Aß and tau in the brain to determine the specific effect these proteins have on different domains of memory performance (object, scene, and integrated object-scene memory) and what brain regions are most affected.

www.brightfocus.org/A2021004F

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

Nicolai Franzmeier, PhD   (07/01/21 – 06/30/24)
Ludwig Maximilian University of Munich, Germany

The Role of Brain Connectivity as a Mechanistic Link Between Amyloid and Tau Pathology Spread in Alzheimer's Disease

Amyloid pathology is assumed to trigger the spread of tau pathology across interconnected brain regions. Other studies have shown that neuronal activity enhances tau spreading across connected neurons. This study addresses whether tau spreading across connected brain regions is specifically enhanced by amyloid-induced hyperconnectivity in AD patients. Using cutting-edge neuroimaging protocols in AD patients, this study will determine whether early amyloid deposition is associated with neuronal hyperactivity, thereby triggering tau spread.

www.brightfocus.org/A2021026S

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

Joshua Grill, PhD   (7/1/18 - 6/30/22)
University of California, Irvine

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

Giacomo Koch, MD, PhD   (7/1/19 - 6/30/22)
IRCCS Santa Lucia Foundation, Rome, Italy
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

Sanjeev Kumar, MD   (7/1/18 - 6/30/23)
Centre for Addiction and Mental Health, Toronto, Ontario, Canada
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 Zomorrodi, 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

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

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. Thie 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

Aristeidis Sotiras, PhD   (07/01/21 – 06/30/24)
Washington University in St. Louis, MO

Detecting and Characterizing Preclinical AD Using AI and Structural MRI

The proposed project will develop Artificial Intelligence (AI) tools based on Deep Learning (DL) that use widely available imaging, cognitive and clinical data to identify individuals that show early signs of Alzheimer's pathology and predict their future cognitive performance. Such tools are crucial for improving clinical care by enabling early diagnosis and intervention. Additionally, they can reduce clinical trial costs by enabling targeted recruitment of homogeneous groups of individuals at increased risk of cognitive decline and progression to Alzheimer's Disease dementia.

www.brightfocus.org/A2021042S

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