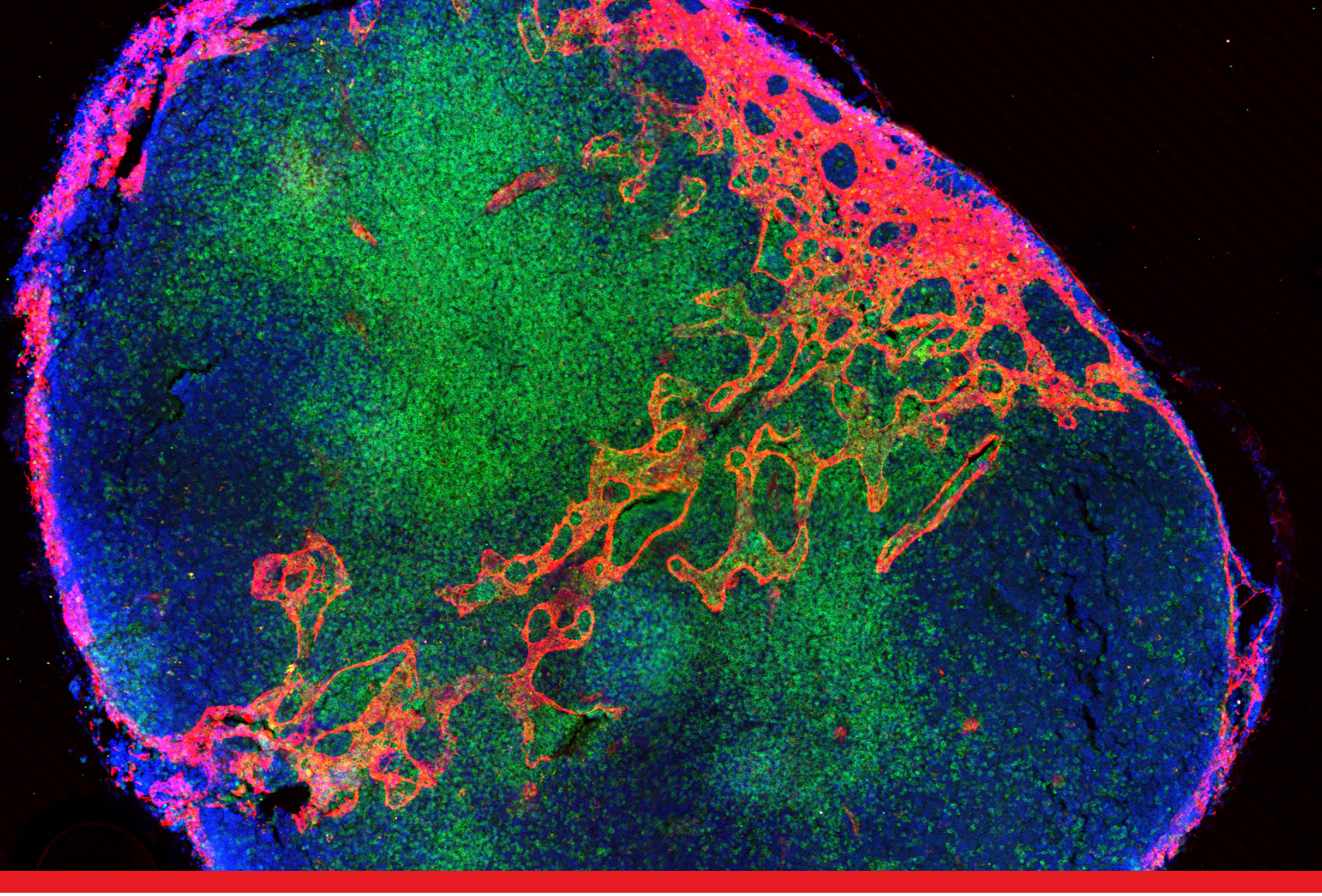


Across the Research Spectrum

Expanding Our Innovative 360° Approach

2022 Alzheimer's Disease Research Projects

BrightFocus® Foundation | Alzheimer's Disease Research

Alzheimer's Disease Research

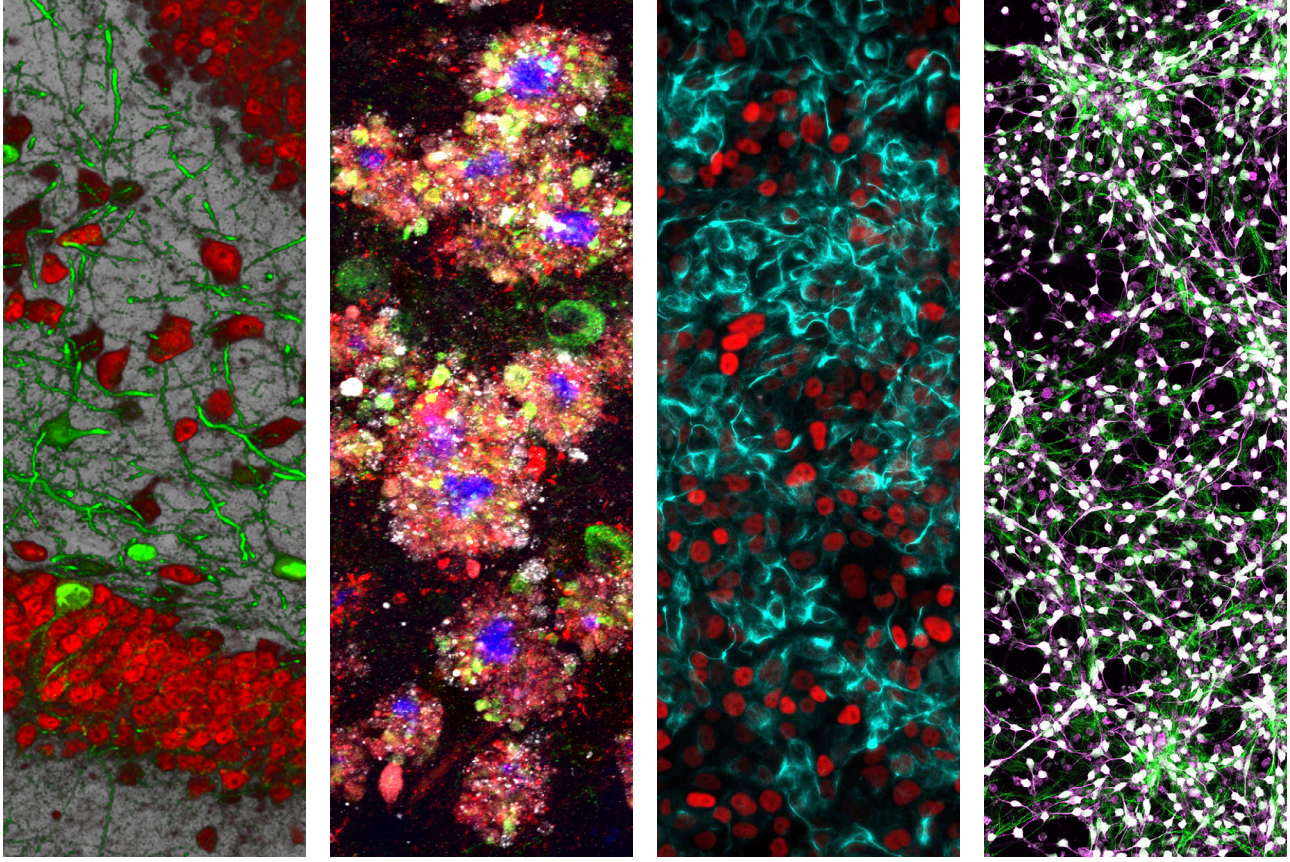
We're Funding 163 Projects Worldwide This Year.

Inside

Scarcely a person alive today has not seen or felt the impact of Alzheimer's disease, which ranks seventh among the leading causes of death in the United States.

By disrupting memories, cognition, personality, and more, Alzheimer's is devastating for the individuals it affects, as well as their family members, friends, and caregivers, and for society as a whole.

Alzheimer's will claim a greater toll as our population ages—unless something more is done.



Left to right: *Page 16, Page 26, Page 56, Page 74.*

With generous donor support, BrightFocus Foundation's Alzheimer's Disease Research (ADR) program has funded nearly $170 million in research to understand and cure Alzheimer's.

With our grants, scientists worldwide have developed and tested thousands of hypotheses about how the disease destroys brain function over time and are investigating hundreds of ideas to diagnose, treat, cure, and prevent Alzheimer's and related dementias.

This research portfolio provides an overview of our 163 ADR grant projects.* Our funding philosophy is to follow the most innovative and promising ideas and proposals that will advance cures for Alzheimer's and related dementias.

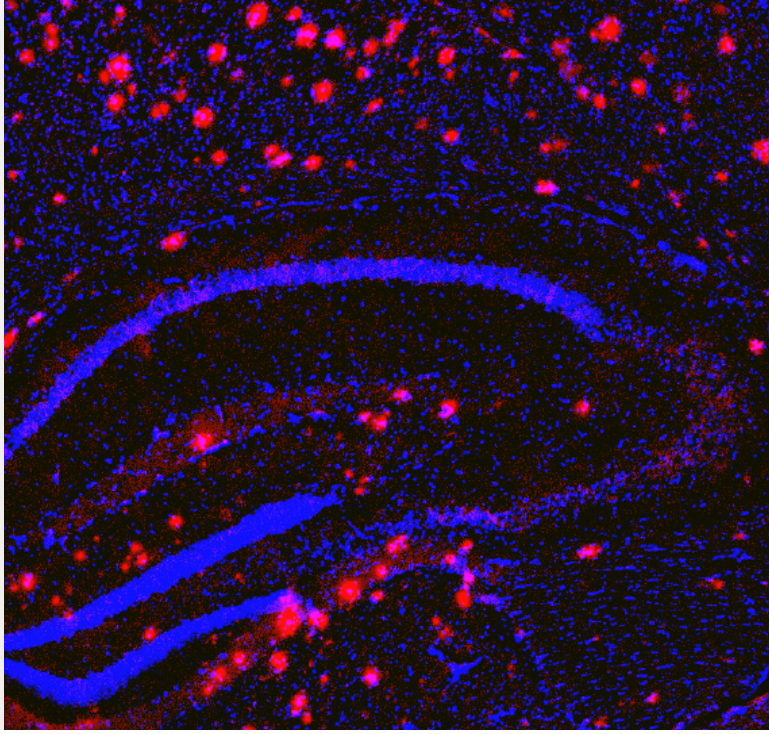
The proposals are evaluated by our Scientific Review Committee of leading Alzheimer's scientists and clinicians, who recommend top-ranked projects reflecting the most cutting-edge research.

We are deeply grateful to our donors, whose generosity makes it possible to grow our ADR program. The research highlighted here offers huge promise and opportunity in fighting this heartbreaking disease.

Cover: *Lymph nodes and surrounding vessels provide the brain with nutrients and may play a role in Alzheimer's disease. Photo courtesy of Sandro Da Mesquita, PhD, Mayo Clinic Jacksonville.*

Note: *Co-principal investigator and fellowship mentor institutions are listed if different from the PI.*
** This portfolio reflects awarded grants as of July 15, 2022.*

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 prone to molecular changes that create fragments that accumulate in the brain.

A healthy brain can break down Aβ and eliminate it, but in Alzheimer's disease, Aβ forms hard, insoluble plaques that are toxic to neurons and are sometimes associated with memory loss and other changes.

In addition, many experts think Aβ may work synergistically with tau—another protein overexpressed in Alzheimer's—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. Photo courtesy of Laura Cox, PhD, Brigham and Women's Hospital & Harvard Medical School.*

Note: *Projects have been arranged in categories according to the Common Alzheimer's Disease Research Ontology classification system, which is used by research-funding agencies around the world and by national and international authorities to track progress toward meeting Alzheimer's research goals.*

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

Lucía Chávez-Gutiérrez, PhD | 9/1/20 – 8/30/23
Vlaams Institute Voor Biotechnologie (BELGIUM)

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 (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 (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

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

Jinghui Luo, PhD | 9/1/20 – 8/31/22
Paul Scherrer Institute (SWITZERLAND)

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 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

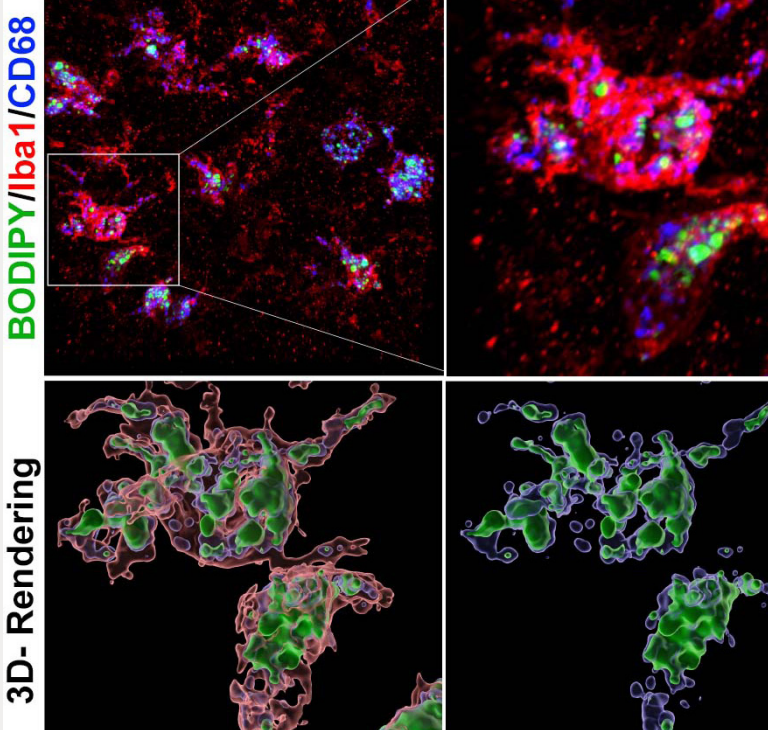
A New Method to Separate Subgroups of Alzheimer's Disease by Measuring sAPPβ in Human Cerebrospinal Fluid

Justyna Dobrowolska Zakaria, PhD | 7/1/19 – 6/30/23
Northwestern University | Co-Principal Investigator: Robert J. Vassar, PhD

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 there is more sAPPβ being made than normal. Also, there is increasing evidence that not every patient's Alzheimer's has the same cause. We want to use sAPPβ, and other proteins such as sAPPα and Aβ, to determine if there are subgroups within Alzheimer's patients that might respond in different ways to drugs that target the disease.

www.brightfocus.org/grant/A2019520S

Biology of Fats & Proteins (*APOE*)



Initially recognized for its role in cardiovascular disease, the apolipoprotein E (*APOE*) gene also plays a role in Alzheimer's disease.

APOE produces a protein that metabolizes fats (lipids) in the body, but has several common variants, or alleles, whose effects vary.

The *APOE4* (ε4) allele is the most prevalent genetic factor associated with late-onset Alzheimer's. Its impact varies based on whether the mutation appears on one or both chromosomes and on a person's race and ethnicity, and scientists are trying to find out 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, whereas *APOE* helps facilitate breakdown of amyloid beta (Aβ) protein located in and around neurons, the ε4 version is less effective at doing so.

Above: *Lipids, or fats (green), accumulate in waste disposal compartments (lysosomes, blue) of the brain's immune cells (microglia, red). Photo courtesy of Alexandra Litvinchuk, PhD, Washington University in St. Louis.*

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

Oleg Butovsky, PhD | 7/1/21 – 6/30/24
Brigham and Women's Hospital & Harvard Medical School

APOE plays a critical role in inducing microglial phenotypes 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 proinflammatory 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 Alzheimer's patients. This proposal aims to investigate the role of *APOE* variants in the regulation of neutrophil-microglia interactions as a therapeutic target for Alzheimer's disease.

www.brightfocus.org/grant/A2021022S

Meningeal Lymphatics and *APOE* in Alzheimer's Disease

Sandro Da Mesquita, PhD | 7/1/21 – 6/30/24
Mayo Clinic Jacksonville

This proposal tests the hypothesis that expression of *APOE4* affects 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/grant/A2021025S

Understanding *APOE*

Carl Frieden, PhD | 9/1/20 – 8/31/22
Washington University School of Medicine in St. Louis

Over 6.5 million people in the U.S. have Alzheimer's disease. Among these individuals, about 50% have a mutant protein called *APOE4*, which is considered the major risk factor for developing late-onset Alzheimer's. The current project investigates the properties of this protein.

www.brightfocus.org/grant/A2020382S

Targeting Brain *APOE* Receptors for the Treatment of Alzheimer's Disease

Jie Gao, PhD | 7/1/21 – 6/30/24
The Ohio State University

Apolipoprotein E4 (*APOE4*) markedly exacerbates tau pathology and tau-mediated neurodegeneration in Alzheimer's disease. Therefore, targeting *APOE4*'s detrimental effects in tau pathology might serve as a promising strategy for the treatment of Alzheimer's. IDOL, a novel major regulator of brain *APOE* receptor expression, 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 Alzheimer's disease.

www.brightfocus.org/grant/A2021028S

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

Emil Gustavsson, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
University College London (UK)
Fellowship Mentor: Mina Ryten, MD, PhD

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 Alzheimer's. 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. 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 data sets.

www.brightfocus.org/grant/A2021009F

The Role of Abca1 in Regulation of Glial Lipid Metabolism in Tauopathy

Alexandra Litvinchuk, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Washington University in St. Louis
Fellowship Mentor: David Holtzman, MD

Disruption of lipid metabolism in glia is linked to neuroinflammation and neurodegeneration. A significant buildup of lipids in glia of aged animals with tau accumulation has recently been observed. This study will assess the role of Abca1 lipid transporter in modulation of glial lipid metabolism in tauopathy mice, thus providing novel therapeutic avenues for treating tauopathy and Alzheimer's disease.

www.brightfocus.org/grant/A2022010F

Exploring the Impacts of *APOE* Genotype Switching from *APOE4* to *APOE2* in the Periphery (Liver and Bloodstream) for Alzheimer's Disease Therapy

Chia-Chen (Jenny) Liu, PhD | 9/1/20 – 8/30/23
Mayo Clinic Jacksonville

Having the *APOE4* gene increases a person's risk of Alzheimer's disease, whereas having *APOE2* is protective for Alzheimer's. 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 test for the first time 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 prevents aging-related memory deficits and reduces Alzheimer's 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

Assessment of Associations Between *APOE4* in the Blood, Behavior, and Alzheimer's Disease–Related Changes Inside the Brain

Henrietta Nielsen, PhD | 7/1/19 – 6/30/23
Stockholm University (SWEDEN)

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 Alzheimer's would facilitate the development of medication to prevent the disease.

www.brightfocus.org/grant/A2019446S

How a Rare *APOE* Variant Protects Against Alzheimer's Disease

Ana-Caroline Raulin, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Mayo Clinic Jacksonville | Fellowship Mentor: Guojun Bu, PhD

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 Alzheimer's disease. This study will use animal models, induced human stem cells, and cerebral organoids ("minibrains in a dish") to understand how *APOE3-Ch* protects the brain from the toxic effects of beta-amyloid accumulation.

www.brightfocus.org/grant/A2021015F

High-Density Lipoprotein in Alzheimer's Disease

Jerome Robert, PhD | 7/1/21 – 6/30/24
University Hospital of Zürich (SWITZERLAND)

The role of the brain's blood vessels in Alzheimer's disease is well recognized, as they help to clear the buildup of cerebral waste and cardiovascular diseases' risk factors such as diabetes, hypertension, and dyslipidemia, which are associated with increased risk of Alzheimer's. However, how blood-circulating factors exactly affect brain vessel and neuron health remains poorly understood, mainly due to the lack of an 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/grant/A2021037S

The Influence of Lifestyle Change and *APOE* Gene in Aging and Alzheimer's Disease

Na Zhao, PhD, MD | 7/1/21 – 6/30/24
Mayo Clinic Jacksonville

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

www.brightfocus.org/grant/A2021046S

Biomarkers

Biomarkers are biological indicators that can be detected through minimally invasive procedures to measure changes associated with Alzheimer's disease.

The field is focused on novel biomarkers that can be used to detect brain changes in earlier disease stages because gradual changes in the brain occur some 10-20 years before the onset of Alzheimer's symptoms.

The need for earlier treatment makes the search for biomarkers critical as the best hope of stopping Alzheimer's is during this preclinical phase.

Examples of biomarkers include measuring elevated amyloid beta (Aβ) levels in the blood and/or cerebrospinal fluid, using advanced neuroimaging to detect changes in brain structure and function, and monitoring the eye to identify vascular changes or protein deposits in the retina that mirror those in the brain.

Biomarkers can help identify who is most likely to develop Alzheimer's in the future and what type they are likely to develop.

They can also provide reliable measures of disease progression and efficacy of treatments, which will help guide treatment decisions in the future, identifying who needs treatment, when to start it, and what drugs and other strategies will be most successful.

Above: *A researcher from the lab of Ganesh Babulal, MSCI, OTD, PhD, holding a device used to collect data on driving behaviors in older adults which can serve as biomarkers of Alzheimer's disease. Photo courtesy of Washington University in St. Louis.*

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

Ganesh Babulal, MSCI, OTD, PhD | 9/1/20 – 8/30/23
Washington University School of Medicine in St. Louis

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's disease. 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, using 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 Alzheimer's 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 Alzheimer's more accurately.

www.brightfocus.org/grant/A20201142S

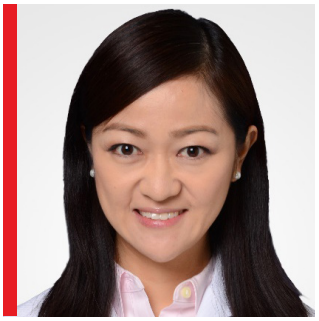
Investigating Neuropeptides as Biomarkers and Novel Therapeutics for Alzheimer's Disease

Becky Carlyle, PhD | 7/1/19 – 5/31/23
University of Oxford (UK)

Alzheimer's disease 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 Alzheimer's. Recent studies have found that neuropeptides are widely dysregulated in Alzheimer's and might play roles in the disease process. In this proposal, we investigate whether neuropeptides may be used to more accurately assess Alzheimer's patients and whether supplementation with these peptides might eventually prove a new potential therapy for Alzheimer's disease.

www.brightfocus.org/grant/A2019128S

This grant is made possible by the support from the Luminescence Foundation.



Recognizing "Retinal Fingerprint" for Alzheimer's Disease Using Artificial Intelligence

Carol Yim Lui Cheung, PhD | 7/1/18 – 6/30/23
The Chinese University of Hong Kong (CHINA)

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, noninvasive, efficient, and accessible method to screen for Alzheimer's disease.

www.brightfocus.org/grant/A2018093S

Identifying Aging and Alzheimer's Disease–Related Protein Changes in Skin Cells, Blood, and Spinal Fluid That Can Be Used as Markers of Disease or Therapeutic Targets

Chadwick Hales, MD, PhD | 9/1/20 – 8/30/23
Emory University

Age is the strongest risk factor for Alzheimer's disease and the wrinkling of our skin. This study will investigate a link between aging and Alzheimer's-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 Alzheimer's disease in the skin, blood, and/or spinal fluid.

www.brightfocus.org/grant/A20201057S

Does Brain Activity in Early Life Predict Future Neurodegeneration?

Keith Hengen, PhD | 7/1/22 – 6/30/25
Washington University in St. Louis

Symptoms of Alzheimer's disease only emerge after toxic proteins have taken a significant toll on the circuitry of the brain. Effective intervention is believed to be stymied by the inability to detect the disease until it is too late to make a difference. This study utilizes a novel method to predict Alzheimer's before symptoms appear by measuring brain activity in both humans and mouse models.

www.brightfocus.org/grant/A2022038S

Recipient of the Distinguished Investigator Award for Alzheimer's Disease Research.

Unraveling the Biological Overlap of Alzheimer's Disease and Dementia With Lewy Bodies

Lenora Higginbotham, MD | 9/1/20 – 8/31/22 | FELLOWSHIP
Emory University
Fellowship Mentors: Allan Levey, MD, PhD & Nicholas Seyfried, PhD

Dementia with Lewy bodies (DLB) is a disabling disease that is difficult to diagnose because it often looks similar to Alzheimer's disease. 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.

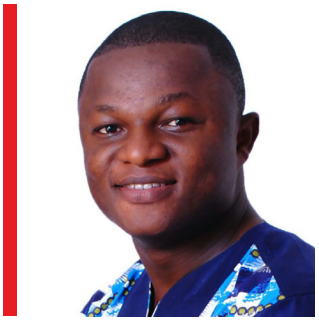
www.brightfocus.org/grant/A20201577F

Learning from Cognitively Healthy Centenarians to Escape Alzheimer's Disease

Henne Holstege, PhD | 7/1/21 – 6/30/24
VU University Medical Center Amsterdam (THE NETHERLANDS)

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

www.brightfocus.org/grant/A2021031S



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

Thomas Karikari, PhD | 9/1/20 – 8/30/22 | FELLOWSHIP
University of Gothenburg (SWEDEN) | Fellowship Mentors: Kaj Blennow, MD, PhD & Henrik Zetterberg, MD, PhD

There is no simple way to diagnose Alzheimer's disease or to identify individuals likely to develop the disease. Current tests require expensive brain imaging or inconvenient puncture of the spine. We have developed a high-performance blood test that measures a specific disease-related change (phosphorylation) on a key Alzheimer-associated protein called tau. In this study, we propose to investigate whether our new blood test can predict with high accuracy who is likely to develop Alzheimer's several years ahead of diagnosis by standard methods to support early treatment, clinical management, and recruitment for therapy trials.

www.brightfocus.org/grant/A2020812F

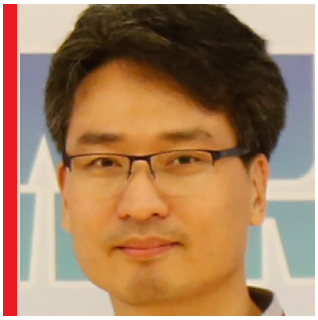
Optical Coherence Tomography Angiography Based Assessment of Retinal Capillary Density as a Biomarker of Vascular Cognitive Impairment and Dementia

Amir Kashani, MD, PhD | 2/24/20 – 8/31/23
Wilmer Eye Institute, Johns Hopkins University

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 contributes to Alzheimer's disease dementia. Small blood vessel damage is very difficult to detect with conventional testing or brain imaging methods like MRI. The goal of this research is to develop new methods using the eye to detect the onset, progression, and severity of VCID.

www.brightfocus.org/grant/CA2020004

Funded through a partnership between 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 a principal investigator.



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

Hosung Kim, PhD | 7/1/19 – 6/30/23
University of Southern California | Co-Principal Investigator: Arthur Toga, PhD

This research seeks to predict physiological brain age for healthy individuals 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 Alzheimer's develop to estimate the "survival" probability explaining the remaining days in healthy status prior to the onset of mild cognitive impairment or Alzheimer's disease. This could lead to disease-specific risk scoring as a clinical tool to be used in routine patient care.

www.brightfocus.org/grant/A2019052S

Validation of a Biomarker That Could Identify a Subset of Frontotemporal Dementia and Alzheimer's Disease Patients

Sarah Pickles, PhD | 9/1/20 – 8/30/22 | FELLOWSHIP
Mayo Clinic Jacksonville | Fellowship Mentor: Leonard Petrucelli, PhD

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 Alzheimer's and FTD patients compared to controls. These findings could help separate patients who would benefit from particular therapies in upcoming clinical trials.

www.brightfocus.org/grant/A2020279F

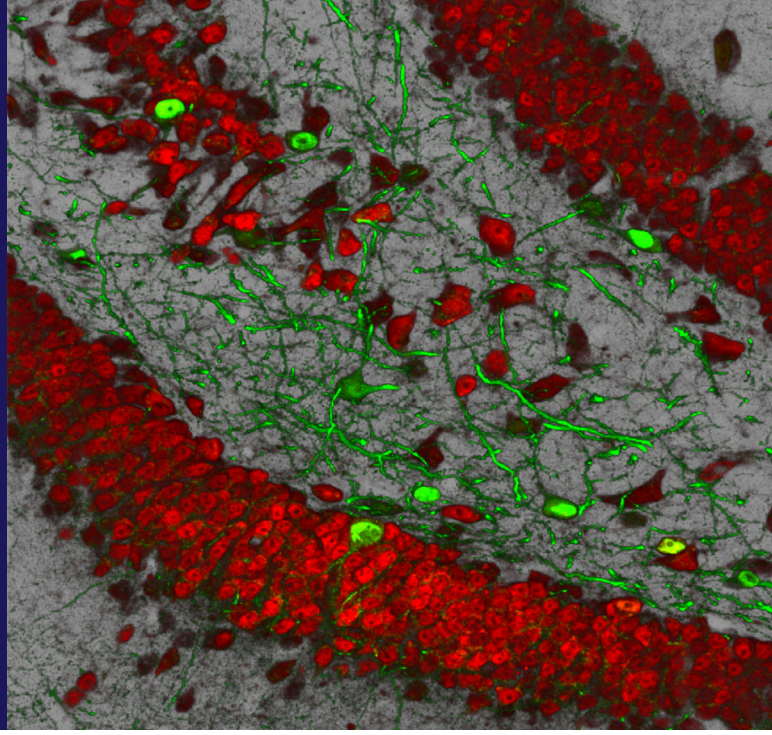
A New Way to Image Amyloid Plaque Growth in Human Alzheimer's Disease

Katherine Schwetye, MD, PhD | 7/1/17 – 6/30/23
Washington University School of Medicine in St. Louis

Critical to the development of therapeutics that may treat and even cure Alzheimer's disease 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

Cells & Circuits



The human brain has an estimated 100 billion neurons. Extending from each is a long fiber, or axon, that can run several feet. Each axon forms a connection, or synapse, with another neuron, creating a circuit over which brain signals travel.

In Alzheimer's disease, 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, or indirect neural pathways.

It's not until the communications network completely breaks down that classic Alzheimer's disease symptoms—forgetting loved ones or becoming lost in familiar places—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 Alzheimer's disease.

Above: *Confocal microscope image showing localization of neurons (red) and some activated neurons (green) in the hippocampus of an adult mouse brain. Photo courtesy of Carlos Saura, PhD, Universitat Autonoma de Barcelona.*

Revealing Early Biomarkers in Alzheimer's Disease

Uri Ashery, PhD | 7/1/22 – 6/30/25
Tel Aviv University (ISRAEL)
Co-Principal Investigator: Shahar Alon, PhD, Bar-Ilan University

Degeneration of synaptic contacts between neurons in the brain is one of the first processes that lead to Alzheimer's disease. This occurs near amyloid deposits, which are the main hallmarks of Alzheimer's. This project will use a newly developed platform for the first time in Alzheimer's to detect molecular changes of hundreds of genes in intact brain tissues at early disease stages and relate them to specific cell types, proximity to amyloid deposits, and sex differences.

www.brightfocus.org/grant/A2022029S

This grant is made possible by the support from the Luminescence Foundation.

Nucleus Incertus: Mapping Its Anatomy in Alzheimer's Disease Pathology

Camila de Avila Dal Bo, PhD, MSc | 7/1/21 – 6/30/23 | FELLOWSHIP
Arizona State University and Banner Sun Health Research Institute
Fellowship Mentor: Diego Mastroeni, PhD

Certain areas in the brainstem, such as the locus coeruleus, are highly vulnerable to neurodegenerative conditions, including Alzheimer's disease. A recent landmark paper 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/grant/A2021006F

Why Are Specific Connections Between Brain Cells Lost in Alzheimer's?

Samuel Barnes, PhD | 7/1/22 – 6/30/25
Imperial College of Science, Technology and Medicine London (UK) Co-Principal Investigator: Johanna Jackson, PhD, UK Dementia Research Institute

Loss of synaptic connection points between brain cells has been linked to memory loss in Alzheimer's disease. However, not all synapses are lost during the disease, with some reports finding ~60% synaptic survival. This project aims to understand the molecules and response properties that make some synapses vulnerable and others resilient. New medical approaches will be developed to boost synapse survival in Alzheimer's.

www.brightfocus.org/grant/A2022030S

Mapping Brain Connectivity Changes in Alzheimer's Disease

Kevin Beier, PhD | 7/1/22 – 6/30/25
University of California, Irvine

This project will identify brain regions and cell types to target to slow or prevent the development of Alzheimer's disease before symptom onset. Previously identified brain circuits will be perturbed to determine functional consequences of cell-specific inhibition within these circuits.

www.brightfocus.org/grant/A2022031S

Mechanisms of Neuronal Dysfunction in Early Alzheimer's Disease

Marc Aurel Busche, MD, PhD | 7/1/19 – 12/30/22
University College London (UK)

This project will explore the effects that tau and amyloid proteins seen in the brains of patients with Alzheimer's disease have on the activity of interacting nerve cells in the hippocampus, a brain region that 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

Molecular Mechanisms of Axonal Pathology in Alzheimer's Disease

Yifei Cai, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Yale University | Fellowship Mentor: Jaime Grutzendler, MD

Amyloid deposits in Alzheimer's disease are surrounded by axons with abnormally enlarged bulbous structures. These structures severely affect axonal conduction of signals, which 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/grant/A2021003F

Advanced Imaging of the Spatial Organization of Brain Cells in Alzheimer's Disease

Limor Cohen, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Harvard University | Fellowship Mentor: Xiaowei Zhuang, PhD

This project aims to develop a new method to map many different cell types with unique expression patterns in healthy and Alzheimer's disease brains. This information will then be used to understand which cell types in which cellular environments are vulnerable to tau accumulation in Alzheimer's disease.

www.brightfocus.org/grant/A2022052F

Dissecting the Influence of the Gut Microbiota on the Brain in Alzheimer's Disease

Laura Cox, PhD | 7/1/21 – 6/30/24
Brigham and Women's Hospital & Harvard Medical School

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.

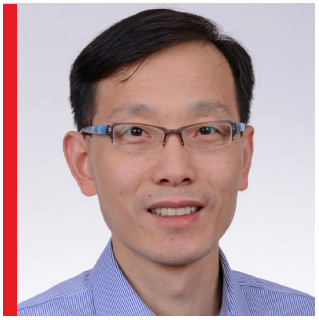
www.brightfocus.org/grant/A2021024S

Treating Memory Loss in Alzheimer's Disease by Strengthening Synapses

Camin Dean, PhD | 7/1/19 – 3/31/23
The German Center for Neurodegenerative Diseases (GERMANY)

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

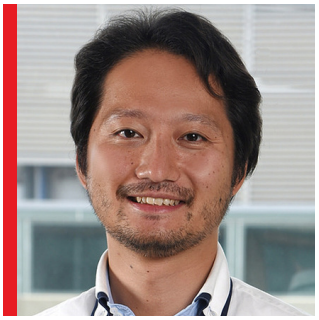


Human "Minibrains" to Study Alzheimer's and Progressive Supranuclear Palsy

Hongjun Fu, PhD | 7/1/21 – 6/30/24
The Ohio State University

Abnormal tau proteins spread between cells in the brain in both Alzheimer's disease and progressive supranuclear palsy (PSP), causing neurodegeneration and dysfunction. Tau buildup 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 Alzheimer's and PSP and why.

www.brightfocus.org/grant/A2021027S



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

Kei Igarashi, PhD | 7/1/19 – 6/30/22
University of California, Irvine

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

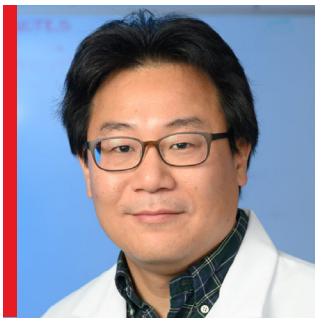
www.brightfocus.org/grant/A2019380S

Non-Neuronal Contribution to Alzheimer's Disease

Ksenia Kastanenka, PhD | 9/1/20 – 8/31/23
Massachusetts General Hospital & Harvard Medical School

This proposal will push the envelope of current Alzheimer's 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



Selective Cholinergic Activation Improves Hippocampal Activity

Seonil Kim, PhD | 7/1/23 – 6/30/25
Colorado State University

Changes in brain rhythms in the hippocampus have been linked to memory impairments associated with Alzheimer's disease. Importantly, these alterations in brain rhythms can be detected before Alzheimer's disease patients display signs of memory loss. This project investigates whether aberrant brain activity and memory loss can be prevented or perhaps reversed in the early stages of Alzheimer's disease.

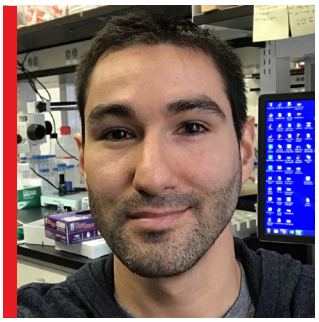
www.brightfocus.org/grant/A2022039S

Understanding Brain Networks Causing Memory Impairments in Alzheimer's Disease

Tatsuki Nakagawa PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of California, Irvine | Fellowship Mentor: Kei Igarashi, PhD

Although the molecular and cellular mechanisms of Alzheimer's disease are becoming elucidated, it is still unclear what type of neuronal brain activity is lost in Alzheimer's. In this project, the underlying causes of brain cell dysfunction will be identified, and artificial reactivation of brain cell activity will be tested to restore associative memory in Alzheimer's mice.

www.brightfocus.org/grant/A2022018F



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

Gustavo Rodriguez, PhD | 7/1/19 – 12/31/22 | FELLOWSHIP
Columbia University Irving Medical Center
Fellowship Mentor: S. Abid Hussaini, PhD

In mouse models of Alzheimer's pathology, amyloid beta leads to overactive neuron signaling and poor spatial information processing, which may be aggravated by tau buildup. 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.

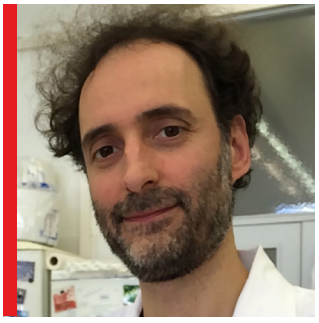
www.brightfocus.org/grant/A2019382F

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

Isabel Salas, PhD | 9/1/20 – 8/31/23 | FELLOWSHIP
The Salk Institute for Biological Studies
Fellowship Mentor: Nicola Allen, PhD

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 is associated with alterations in these connections. In this project I aim to restore the correct function of astrocytes, rescue synaptic defects in mouse models affected by Alzheimer's disease and take another step toward the cure of this devastating disorder.

www.brightfocus.org/grant/A20201645F



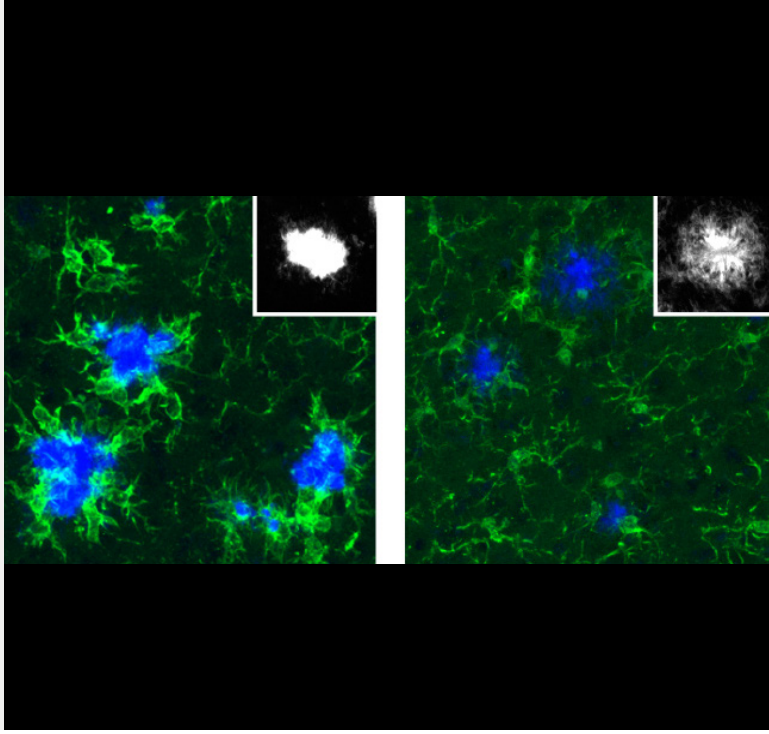
Targeting Memory Circuits as a Therapeutic Strategy in Alzheimer's Disease

Carlos Saura, PhD | 7/1/22 – 6/30/25
Autonomous University of Barcelona (SPAIN)
Co-Principal Investigator: Arnaldo Parra-Damas, PhD

Disruption of memory neural circuits contributes to pathology, neurodegeneration, and memory loss early in Alzheimer's disease, but the mechanisms involved remain unknown. This project will employ novel state-of-the art mouse models and techniques to unravel the mechanisms underlying memory circuit disruption and how it contributes to memory loss early in Alzheimer's. Finally, novel pharmacogenetic and gene therapy approaches will be developed to activate neural circuits and memory in Alzheimer's disease.

www.brightfocus.org/grant/A2022047S

Genomics: DNA Blueprint for Alzheimer's



Genes are the "master blueprint" instructing our cells to make unique proteins that in turn build, operate, and repair tissue.

Even slight changes in a gene on one or both chromosomes can produce a protein that functions abnormally, possibly affecting an individual's risk of a disease like Alzheimer's.

However, only one type of Alzheimer's disease—early onset, representing less than 10% of cases—can be traced consistently to changes, or mutations, in identified genes. The remaining 90%—late onset—is associated with small genetic irregularities occurring throughout the genome.

Genomic researchers are using powerful technologies to look for variations, patterns, and interactions among all genes in people with and without Alzheimer's.

Although several dozen regions of interest have been associated with Alzheimer's, it's complicated because gene signaling can be switched on or off by other factors (e.g., environment and lifestyle).

Genomics will help reveal what triggers Alzheimer's disease, how genes interact with the environment to raise or lower risk, who is most at risk and apt to benefit from new treatments, and how we can tailor treatment to individuals.

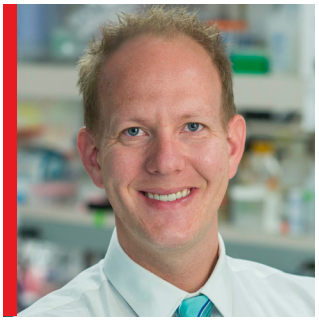
Above: *Activated microglia can help prevent neuronal injury and wall off amyloid plaques from healthy tissue at early stages of the disease. TREM2 is a protein necessary for this protective effect; without it (right panel), this protective process is disrupted. Photo courtesy of David Verne Hansen, PhD, Brigham Young University.*

Single Cell Profiling of Brain Tissue and Stem Cell Models of Tauopathy

Kathryn Bowles, PhD | 7/1/21 – 6/30/24
University of Edinburgh (UK)

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.

www.brightfocus.org/grant/A2021021S



Identifying Therapeutic Targets and Biomarkers to Facilitate a Meaningful Therapy and a Presymptomatic Alzheimer's Diagnostic

Mark Ebbert, PhD | 9/1/20 – 8/31/23
University of Kentucky

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

The Role of Small RNAs in Alzheimer's Disease

Laura Ibanez, PhD | 7/1/21 – 6/30/24
Washington University in St. Louis

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

www.brightfocus.org/grant/A2021033S

Illuminating the Functions of Genes Mutated in Alzheimer's Disease

Harini Iyer, PhD | 1/1/22 – 12/31/23 | FELLOWSHIP
Stanford University | Fellowship Mentor: William Talbot, PhD

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 microglia 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/grant/A2021011F

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

Elise Marsan, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
University of California, San Francisco | Fellowship Mentors: Eric J. Huang, MD, PhD & Arnold Kriegstein, MD, PhD

Alzheimer's disease 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 cutting-edge single-cell transcriptomic technology to uncover common transcriptomic signatures that contribute to disease progression in Alzheimer's and FTLD. Results from this study will provide important insights into 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

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

Justin Miller, PhD | 9/1/20 – 8/30/23 | FELLOWSHIP
University of Kentucky | Fellowship Mentor: John S.K. Kauwe, PhD

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, age of disease onset, and age of death for each proposed subtype using a longitudinal dataset spanning 20 years. Identifying Alzheimer's 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

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

Michael Miller, MD, PhD | 9/1/20 – 8/31/23 | FELLOWSHIP
Brigham and Women's Hospital & Harvard Medical School
Fellowship Mentor: Christopher Walsh, MD, PhD, Boston Children's Hospital

Alzheimer's disease 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 appear to harm the brain cells. This proposal will test the hypothesis that somatic mutations contribute in important ways to the pathologic progression of Alzheimer's and are related to other kinds of disease damage in brain cells, including oxidative stress.

www.brightfocus.org/grant/A20201292F

Assessment of Tandem Repeat Variation in Alzheimer's Disease

Alejandro Martin Trujillo, PhD | 7/1/22 – 6/30/25
Icahn School of Medicine at Mount Sinai

Tandem repeats (TRs) are stretches of DNA composed of two or more contiguous copies of a sequence arranged in head-to-tail pattern (e.g., CAG-CAG-CAG) that, in some cases, gain additional copies and become expanded. Due to technical limitations, TRs are usually untraceable using standard procedures, being largely ignored in standard genetics studies. However, new bioinformatics tools are now able to screen the whole genome for repeat expansions and TR variants. Using these tools, the genomes of thousands of Alzheimer's disease cases and controls will be screened for TR variants that are associated with Alzheimer's risk.

www.brightfocus.org/grant/A2022043S

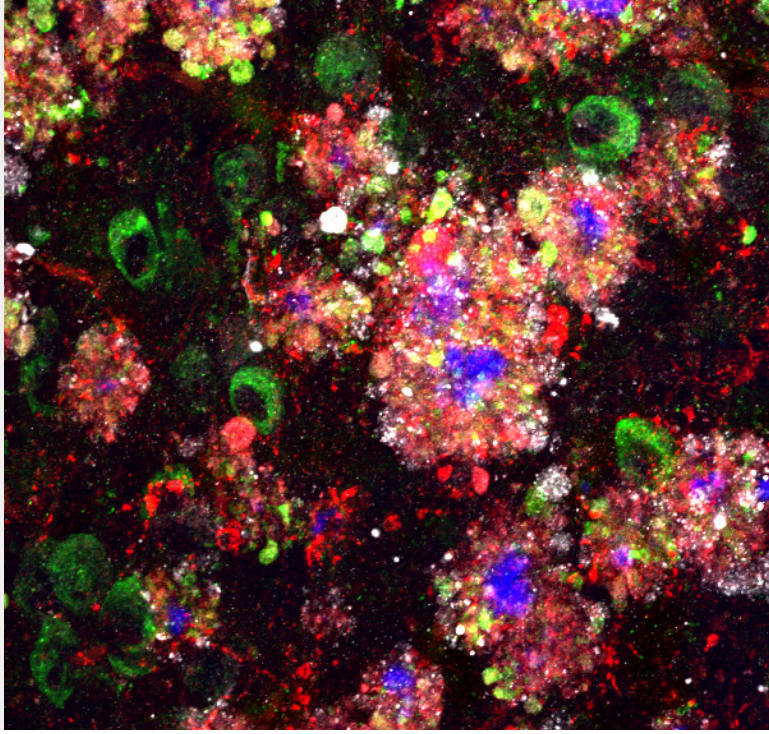
A New Method That Uses the 3D Structure of the Human Genome to Identify the Genetic Basis of Alzheimer's Disease

Ivana Quiroga, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
University of North Carolina at Chapel Hill
Fellowship Mentor: Douglas Phanstiel, PhD

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. We will use modern genomic and gene-editing techniques in a novel immune brain cell model generated from induced human 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

Immunity & Inflammation



One theory about Alzheimer's disease is that it may be triggered in part by a breakdown in the brain's immune system. Normally the brain can "take out the garbage"—clear damaged cells and unwanted particles and dispose of them into the bloodstream.

However, a chronic rise in unwanted debris, including toxic amyloid beta (Aβ) and tau proteins, can short-circuit that process, causing chronic inflammation and cell damage.

Microglia are the brain's primary immune cells responding to the buildup of abnormal proteins and clearing components of dead or damaged cells. Under normal conditions, they maintain equilibrium, clear unwanted particles, and respond to injuries and infections.

In Alzheimer's, they take on a disease-associated signature and exacerbate disease mechanisms by releasing proinflammatory molecules that increase cyclic inflammatory processes, contributing to protein misfolding and energy dysfunction.

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

Above: *Fluorescent staining of dying neuronal connections (green) around amyloid beta deposits (blue) show immune (red) and waste clearance (gray) involvement. Photo courtesy of Miguel Moutinho, PhD, Indiana University.*

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

Sadaf Amin, PhD | 9/1/20 – 8/31/23 | FELLOWSHIP
Weill Cornell Medicine | Fellowship Mentor: Li Gan, PhD

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 (e.g., 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

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

Darrick T. Balu, PhD | 7/1/19 – 8/31/22
McLean Hospital, Harvard Medical School

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

Understanding TREM2 Signaling as an Alzheimer's Disease Target

Thomas John Brett, PhD | 7/1/22 – 6/30/25
Washington University in St. Louis | Mentor: Michael Gross, PhD

Current studies indicate that TREM2, a receptor molecule found in the brain, plays an important role in neuronal health. It has emerged as a critical potential drug target to develop treatments for Alzheimer's disease. Our project will determine how TREM2 engages amyloid beta and identify how other potential drug molecules modulate this interaction. Understanding and modulating this interaction will enable the development of therapeutics for Alzheimer's disease that target TREM2.

www.brightfocus.org/grant/A2022032S

The Roles of TREM2 Interaction with C1q in Alzheimer's Disease

Xiaofen Chen, PhD | 7/1/21 – 6/30/24
Xiamen University (CHINA)

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 and other neurodegenerative diseases. This project will study the mechanism by which TREM2 modulates Alzheimer's-related pathways in microglia and neurons to influence cognition and pathology in mouse models.

www.brightfocus.org/grant/A2021023S

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

Juan Codocedo, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
Indiana University | Fellowship Mentor: Gary Landreth, PhD

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

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

Maud Gratuze, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
Washington University School of Medicine in St. Louis
Fellowship Mentor: David Holtzman, MD

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

www.brightfocus.org/grant/A2020257F

Validating the Receptor PILRA as an Alzheimer's Therapeutic Target

David Verne Hansen, PhD | 7/1/22 – 6/30/25
Brigham Young University

The emerging landscape of Alzheimer's therapeutics includes drugs intended to promote the protective functions of microglia, the brain's immune cells. Most of these therapeutics seek to directly activate TREM2, a key receptor for microglial activation and healthy CNS tissue maintenance. This proposal explores the therapeutic potential of blocking microglial checkpoint proteins as an indirect way of enabling more robust TREM2 function at sites of microglial activation, which may be safer than chronic activation of all microglia and possibly other cell types.

www.brightfocus.org/grant/A2022037S

Understanding the Microglia Cell Surface in Alzheimer's Disease

Brandon Holmes, MD, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of California, San Francisco
Fellowship Mentors: James Wells, PhD & Martin Kampmann, PhD

The microglia surfaceome serves as a critical cellular hub that enables neuroprotective, neurotoxic, and neuroinflammatory signaling in the diseased brain. The ability to precisely target and manipulate diverse microglia states holds tremendous experimental, diagnostic, and therapeutic potential. The proposed project will use innovative technologies to comprehensively define the surfaceome changes of Alzheimer's disease microglia and will provide the first human cell-surface protein map in this cell type and disease context.

www.brightfocus.org/grant/A2022008F

Recipient of the Dr. Edward H. Koo Postdoctoral Fellowship Award for Alzheimer's Disease Research.

How Immune Cells Impair Neuronal Health and Function in Alzheimer's Disease

Soyon Hong, PhD | 7/1/21 – 6/30/24
University College London (UK)

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

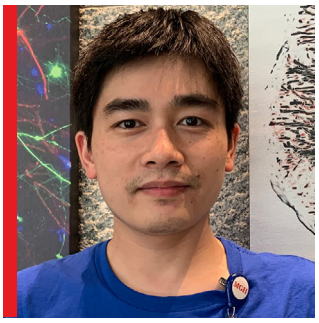
www.brightfocus.org/grant/A2021032S

Mapping the Crosslink of Senescence and Inflammation in Neurodegeneration

Violeta Duran Laforet, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
UMass Chan Medical School
Fellowship Mentors: Dorothy Schafer, PhD & Michael Heneka, MD, PhD, German Center for Neurodegenerative Diseases (GERMANY)

Aging is the major risk factor for Alzheimer's disease. Senescence, a hallmark of aging, is a process by which a cell no longer can proliferate. Since microglia, the primary immune cell of the central nervous system, become senescent in Alzheimer's, this project will investigate if they initiate the inflammatory process in the aging brain and study if senescent cells are present in specific locations within the brain. This project will use an innovative approach called MERFISH to look at hundreds of genes directly in tissue. Ultimately, this study could result in identifying new therapeutic targets.

www.brightfocus.org/grant/A2022006F



The Role of TREM2 T96K Mutation in Alzheimer's Disease

Hoang Le, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Massachusetts General Hospital
Fellowship Mentors: Ana Griciuc, PhD & Rudolph E. Tanzi, PhD

This proposed study aims to understand the impact of the Alzheimer's-associated mutation TREM2 T96K on Alzheimer's pathogenesis using a novel mouse model of Alzheimer's disease as well as in vitro microglial models. The insights obtained should be useful for Alzheimer's drug discovery and development targeting TREM2.

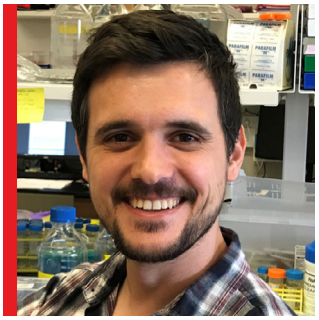
www.brightfocus.org/grant/A2022009F

Genetics and Lipids: At the Crossroads of Inflammation and Alzheimer's Disease

Renzo Mancuso, PhD | 7/1/21 – 6/30/23
Vlaams Institute Voor Biotechnologie (BELGIUM)

Genetic studies reveal a link between neuroinflammation and susceptibility for Alzheimer's disease, suggesting that inflammation might be a driver of the disease as opposed to a consequence. This project aims to determine the link between Alzheimer's genetic risk, microglia, and lipid metabolism by combining novel models where induced human stem cell–derived microglia are injected in Alzheimer's 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 Alzheimer's brain in a crucial human system.

www.brightfocus.org/grant/A2021034S



Is the Niacin Receptor HCAR2 Protective in Alzheimer's Disease?

Miguel Moutinho, PharmD, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Indiana University | Fellowship Mentor: Gary Landreth, PhD

Increased dietary niacin intake has been associated with reduced risk of Alzheimer's disease. Niacin is able to cross the blood-brain barrier and activate the niacin receptor HCAR2. This receptor induces beneficial effects in other disease models by modulation of brain-resident immune cells (microglia). This project examines whether HCAR2 regulates a protective response of microglia in Alzheimer's, which can be pharmacologically stimulated with a clinical formulation of niacin.

www.brightfocus.org/grant/A2022017F

Metabolic Reprogramming of Microglia in Alzheimer's Disease

Jonas J. Neher, PhD | 7/1/21 – 6/30/24
German Center for Neurodegenerative Diseases (GERMANY)

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 Alzheimer's. 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 Alzheimer's pathology, with a particular focus on molecular and functional changes in microglia, pathological hallmarks of Alzheimer's and, most importantly, cognitive function.

www.brightfocus.org/grant/A2021035S

Studying the Role of Microglial LXR in Control of Alzheimer's Risk Genes

Anna Podlesny-Drabiniok, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Icahn School of Medicine at Mount Sinai
Fellowship Mentor: Alison Goate, PhD

Analysis of genetic factors contributing to Alzheimer's disease 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 Alzheimer's 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 Alzheimer's risk gene, BHLHE40/41, are master regulators of microglial phagocytosis using human cells carrying Alzheimer's mutations.

www.brightfocus.org/grant/A2021014F

Exploring Microglial Activation in Normal Physiology and Disease

Gabriela Farias Quipildor, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Icahn School of Medicine at Mount Sinai
Fellowship Mentor: Stephen Salton, MD, PhD

During normal aging and Alzheimer's disease, microglia, the primary immune cell in the brain, have shown to have a different phenotype, morphology, and function upon activation. However, there are still many unknowns in relation to the different activation states of microglia. This study proposes to dissect the involvement of key regulators of microglial activation in normal physiology and disease and provide new insights on the role of microglia in Alzheimer's pathogenesis with the potential to unearth new therapeutic targets.

www.brightfocus.org/grant/A2022007F

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

Erin Reed-Geaghan, PhD | 7/1/21 – 6/30/24
Northeast Ohio Medical University

In addition to the pathological hallmarks of amyloid plaques and neurofibrillary tangles, Alzheimer's disease is characterized by a robust inflammatory response in the brain. Women are disproportionately affected in Alzheimer's and have more inflammation, but the reasons 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/grant/A2021036S

A New Intervention to Control Inflammation in Alzheimer's Disease

Yuxiang Sun, MD, PhD | 7/1/19 – 6/30/23
Texas A&M University

Low-grade chronic inflammation is a hallmark of aging, and inflammation in the brain causes and worsens Alzheimer's disease. 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 Alzheimer's.

www.brightfocus.org/grant/A2019630S

Reprogramming Microglia Through Astrocyte Manipulation in Alzheimer's Brain

Julia TCW, PhD | 7/1/22 – 6/30/25
Boston University

The strongest genetic risk factor for late-onset Alzheimer's disease is *APOE4*. With the goal of explaining how *APOE4* influences risk of Alzheimer's, this project will suppress an *APOE4* risk signal and understand the mechanism of cellular reprogramming to prevent Alzheimer's in our brain-in-a-dish model. This approach can potentially identify new drug targets of *APOE4* and open doors to novel therapeutic modalities.

www.brightfocus.org/grant/A2022049S

Metabolism Driving Cell Death and Inflammation in Alzheimer's Disease

Larissa Traxler, PhD | 2/1/23 – 1/31/25 | FELLOWSHIP
University of Innsbruck (AUSTRIA) | Fellowship Mentor: Jerome Mertens, PhD

Previous work has demonstrated that Alzheimer's-specific induced neurons behave similarly to cancer cells, as they de-differentiate toward a precursor state. However, instead of initiating proliferation, neurons get vulnerable to stress-induced programmed cell death. This project will deeply characterize pyruvate kinase M (PKM) in this process in postmitotic neurons and assess PKM as a therapeutic target for reversing the Alzheimer's phenotype.

www.brightfocus.org/grant/A2022024F

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

Nicholas Varvel, PhD | 7/1/19 – 6/30/23
Emory University

A subset of people with Alzheimer's disease 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. These studies will determine if seizure-induced monocyte entry into the brain enhances the progression of Alzheimer's.

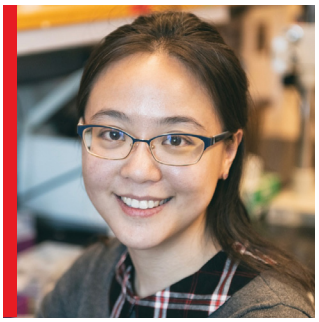
www.brightfocus.org/grant/A2019077S

Understanding the Role of the Immune System in Frontotemporal Dementia

Rebecca Wallings, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
University of Florida | Fellowship Mentor: Malu Tansey, PhD

Evidence suggests that microglia are not the only culprit in frontotemporal dementia (FTD), but rather, immune cells normally found in circulating blood (monocytes) infiltrate 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. This research aims to unveil the role of peripheral immune cells and dysfunctional lysosomes in the development of FTD.

www.brightfocus.org/grant/A2021017F

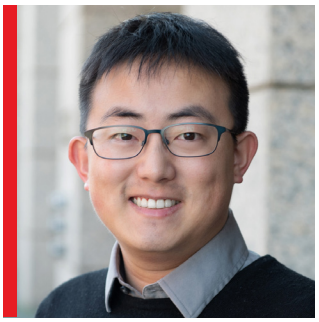


Curbing Inflammation at the Brain's Barrier in Alzheimer's Disease

Huixin Xu, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Boston Children's Hospital
Fellowship Mentors: Mark Andermann, PhD & Maria Lehtinen, PhD

The ultimate goal is to enable treatments for Alzheimer's disease that curb brain inflammation at the barriers separating the brain from the rest of the body, focusing on a tissue called the choroid plexus. Newly developed imaging tools will be used to explore blood-borne immune cells entering the choroid plexus in Alzheimer's disease models and test for barrier breakdown and blood vessel leakage.

www.brightfocus.org/grant/A2022026F



Neurovascular and Immune Mechanisms in Alzheimer's Pathogenesis

Zhaoqi Yan, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
The J. David Gladstone Institutes
Fellowship Mentor: Katerina Akassoglou, PhD

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 multipronged experimental design to examine the cerebrovascular mechanisms regulating neuronal dysfunction in Alzheimer's.

www.brightfocus.org/grant/A2021019F

Characterizing the Role of Microglial GPR56 in Alzheimer's Disease

Beika Zhu, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
University of California, San Francisco
Fellowship Mentor: Xianhua Piao, MD, PhD

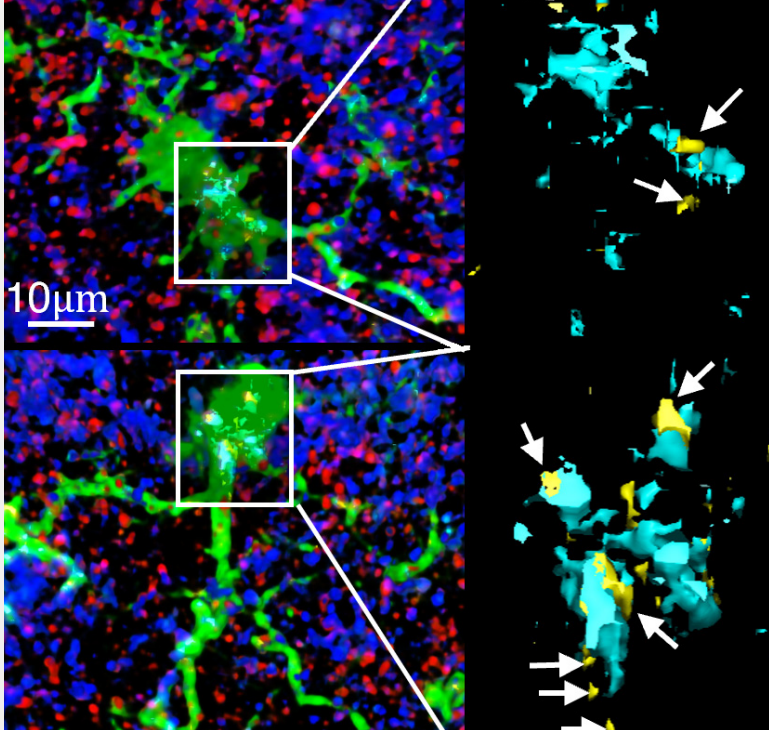
This proposal will test the hypothesis that microglial GPR56, a cell surface protein that receives signals from neighboring cells, plays a role in maintaining brain function and stops Alzheimer's disease progression. GPR56 function will be determined by generating a new mouse model where GPR56 activity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

www.brightfocus.org/grant/A2021020F

Every 65 seconds

someone in the U.S. develops Alzheimer's disease.

Metabolism & Bioenergetics



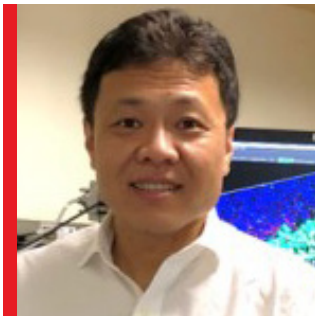
The brain consumes 20% of the body's total energy supply, more than any other organ.

With no reserve energy supplies to draw on, it depends on reliable metabolic function to convert glucose and/or alternative fuel sources, such as glycogen, ketone bodies, and amino acids, into usable power.

Unfortunately, glucose metabolism declines with age. This process is intensified in Alzheimer's and is one of the earliest and most consistent signs of the disease.

Metabolic dysregulation not only impacts brain processing speeds and cognition, but dysfunctional mitochondria (aka the energy power plants of cells) contribute to a neurotoxic environment by releasing reactive oxygen species and other molecules that evoke inflammatory responses in microglia.

Above: *Oxidative stress causes mitochondrial damage that interferes with microglial activation in Alzheimer's disease. Photo courtesy of Lan Guo, PhD, University of Kansas Center for Research.*

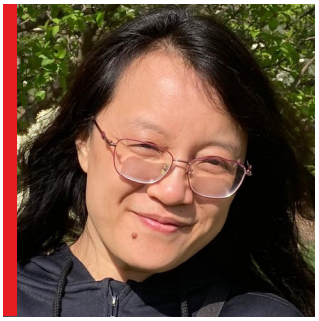


Mitochondrial Calcium Deregulation and Memory Loss in Alzheimer's Disease

Heng Du, MD, PhD | 1/1/21 – 12/31/23
University of Texas at Dallas

Alzheimer's disease is a chronic neurodegenerative disorder characterized by gradual cognitive decline currently without effective therapy. Although the detailed molecular mechanisms remain elusive, defective mitochondrial calcium modulation has been repeatedly linked with synaptic dysfunction and neuronal death in Alzheimer's 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 Alzheimer's. Positive findings will foster our understanding of Alzheimer's and shed light on the development of novel Alzheimer's therapeutic avenues targeting MCU.

www.brightfocus.org/grant/A20201159S

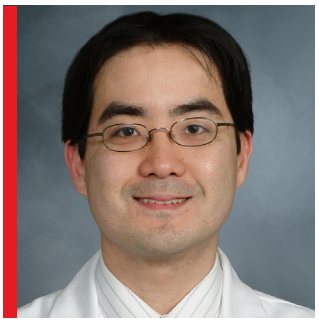


Mitochondrial DNA Damage and Microglial Activation in Alzheimer's Disease

Lan Guo, PhD | 7/1/22 – 6/30/25
University of Kansas Center for Research

This project aims to investigate a cause-effect relationship between oxidative damage and subsequent leakage of mitochondrial DNA (mtDNA) with the inflammatory microglial response that contributes to Alzheimer's disease pathology. Positive results will reveal a novel mitochondrial pathway of neuroinflammation in Alzheimer's and hold promise to develop innovative therapies.

www.brightfocus.org/grant/A2022036S



The Role of Signaling Factors That Modulate Immune and Metabolic Function in Alzheimer's Disease

Makoto Ishii, MD, PhD | 9/1/20 – 8/30/23
Weill Cornell Medicine

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, 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 the 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 memory loss and determine how they are involved in the overall disease process.

www.brightfocus.org/grant/A2020363S

Leptin Protein and its Involvement in Alzheimer Disease in Down Syndrome

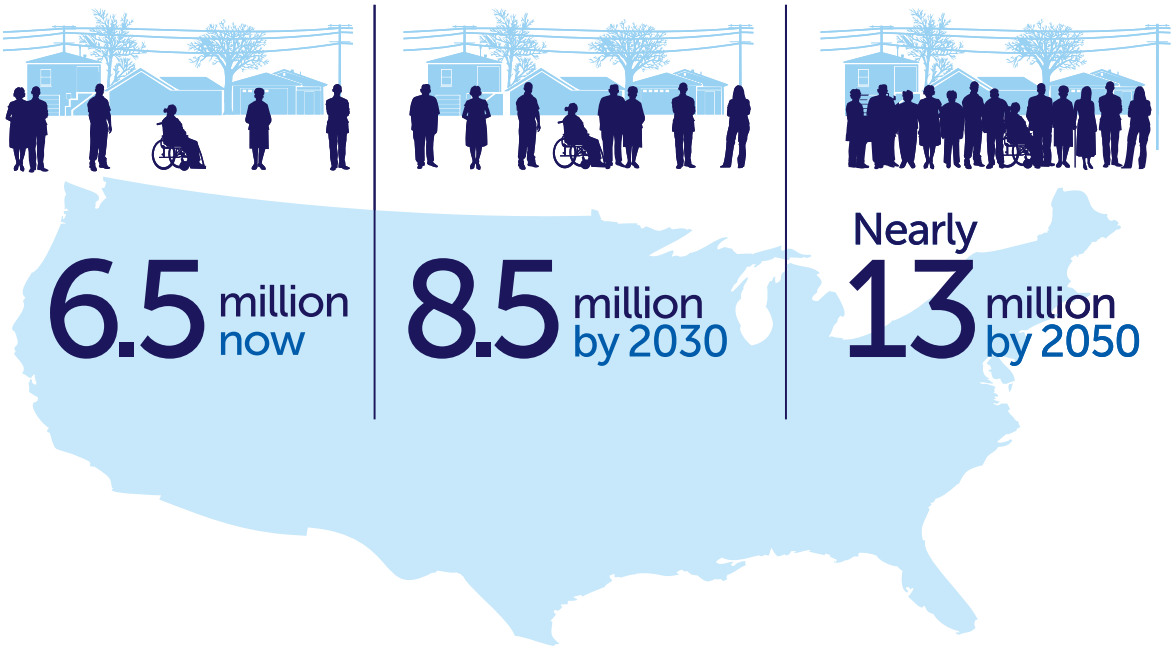
Lorena Sordo Sordo, MSc, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
University of California, Irvine | Fellowship Mentor: Elizabeth Head, PhD

People with Down syndrome (DS) have a high risk of developing Alzheimer's disease. Midlife obesity and late-life weight loss increase the risk of Alzheimer's. Since people with DS tend to be overweight, they may have an even greater risk of developing Alzheimer's. This project will determine whether leptin—a hormone that regulates appetite and food intake that is released in response to the amount of fat tissue in the body—is associated with abnormal deposition of toxic proteins in people with DS, with and without Alzheimer's.

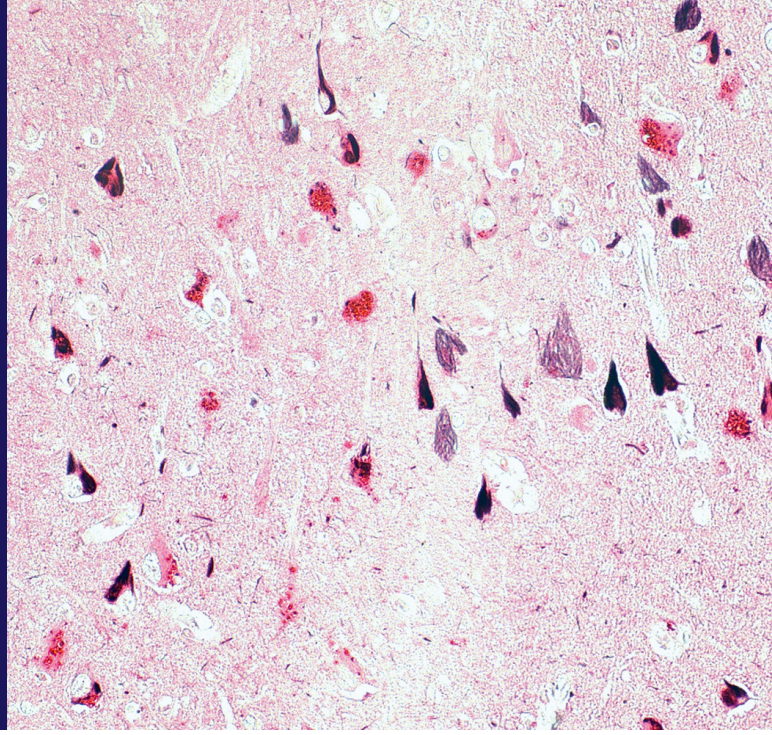
www.brightfocus.org/grant/A2022021F

A Growing Epidemic

ALZHEIMER'S DISEASE IN THE UNITED STATES



Other Misfolded Proteins



Most dementia diagnosed in people over 80 years old is of mixed etiology, meaning it results from more than one disease or cause.

Misfolded proteins and other disease mechanisms interact to exacerbate disease pathology and worsen clinical symptoms, including cognitive impairment.

Many misfolded proteins are hallmarks of other diseases (e.g., frontotemporal dementia, ALS, and Parkinson's), and the presence of a second misfolded protein in Alzheimer's, in addition to amyloid, increases the extent of cognitive impairment.

Vascular dementia, where blood circulation to the brain is compromised, is another frequent contributor to mixed dementia. Clinically distinguishing between dementias is important for therapies that target specific proteins.

Above: *An Alzheimer's disease brain showing neurodegeneration (gray) and misfolded TDP-43 (red). Photo courtesy of Sandra O. Tomé, PhD, Catholic University of Leuven, Belgium.*

Stathmin-2 as a New Biomarker and Disease Modifier in Alzheimer's Disease

Ana Rita Agra de Almeida Quadros, PhD | 7/1/22 – 6/30/24
FELLOWSHIP | Massachusetts General Hospital
Fellowship Mentor: Clotilde Lagier-Tourenne, MD, PhD

TDP-43 is one of the proteins that abnormally accumulates in up to 50% of Alzheimer's disease patients. Stathmin-2, a protein crucial for neuronal function, is lost in neurons with abnormal TDP-43. This project will determine whether Stathmin-2 is altered in people with Alzheimer's disease and represents a new potential therapeutic target for patients with TDP-43 pathology.

www.brightfocus.org/grant/A2022002F

Drivers of Vulnerability to Alzheimer's Disease Neuropathological Changes

Nicole Liachko, PhD | 7/1/22 – 6/30/25
Seattle Institute for Biomedical and Clinical Research

Over half of Alzheimer's disease patients exhibit neuronal aggregates of the protein TDP-43 as a co-pathology in addition to amyloid plaques and neurofibrillary tangles. The presence of TDP-43 pathology correlates with worse brain atrophy, more severe cognitive impairment, and more rapid cognitive decline. Therefore, understanding its contribution to neurodegenerative disease processes is a critical need in the field. This work will characterize mechanisms underlying neuron vulnerabilities to TDP-43 in Alzheimer's disease and identify new therapeutic targets and strategies.

www.brightfocus.org/grant/A2022041S

Investigating TDP-43 Biology in Alzheimer's Disease and LATE: Impact on the Clinical Diagnosis

Sandra O. Tomé, MSc, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Catholic University of Leuven (BELGIUM)
Fellowship Mentor: Dietmar Thal, MD

A link between Alzheimer's disease and other tauopathies, including LATE, is the presence of pathological aggregates with TDP-43 protein. In LATE, it is the major cause of the disease while in Alzheimer's, it accumulates alongside amyloid ß and tau proteins, worsening cognition. A relevant question is whether the TDP-43 pathology observed in Alzheimer's and LATE is molecularly similar and how it impacts the clinical diagnosis of these patients.

www.brightfocus.org/grant/A2022019F

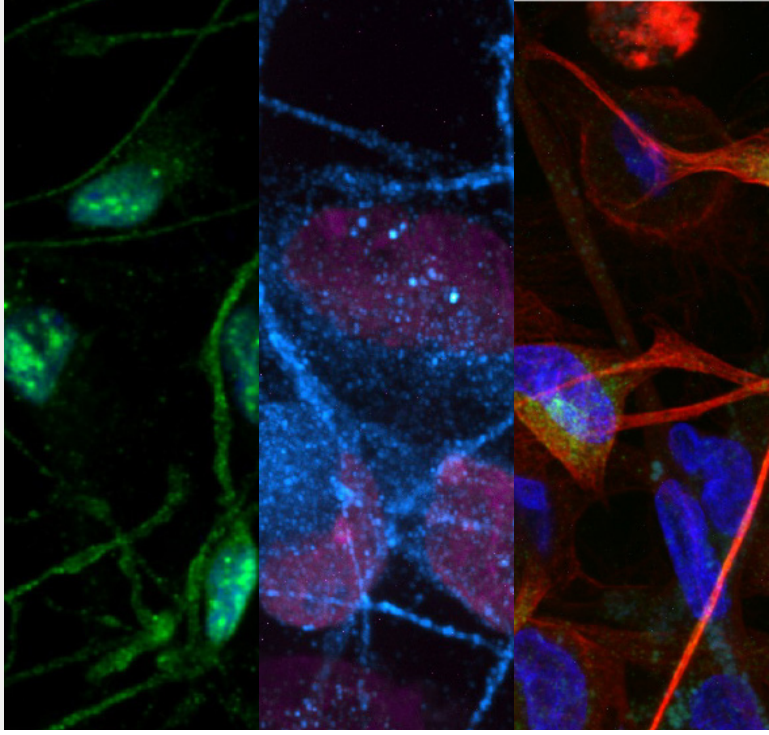
Fingerprinting In Vivo and In Vitro Prion Strains

Hyunjun Yang, PhD | 9/1/20 – 11/30/22 | FELLOWSHIP
University of California, San Francisco
Fellowship Mentors: William DeGrado, PhD & Carlo Condello, PhD

Alzheimer's disease is associated with the misfolding of tau and Aβ proteins. Alzheimer's shares important molecular characteristics with classical prion protein (PrP) 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

Research Tools & Resources



When embarking on a research project, having the right preliminary information and tools can make or break its success, especially in understudied areas, and taking the first steps requires time and funding.

ADR grants support the development of resources used to conduct, translate, and disseminate high-quality dementia research, including shared data and tissue repositories, along with collaborative projects aimed at accelerating new knowledge, disease models, and interventions.

Precompetitive Analytical Validation of SV2A PET as a Biomarker of Synaptic Density (SV2A PET Project)

Sjoerd Finnema, PhD | 12/1/21 – 11/30/23 | BOLD IDEAS INITIATIVE
Foundation for the National Institutes of Health

Brain cells (neurons) communicate through connections called synapses. Synaptic loss is one of the earliest biomarkers for Alzheimer's disease and highly correlates with cognitive performance. This project seeks to develop a novel marker (or ligand) that can be used in PET imaging to detect synaptic loss as an early biomarker for Alzheimer's.

www.brightfocus.org/grant/CA2021012

Above: *Neurons grown in a dish derived from skin cells obtained from individuals with Alzheimer's disease. Photo courtesy of Silvia Pelucchi, PhD, Mertens Lab, University of Innsbruck, Austria.*

International Brain Bank for Down Syndrome–Related Alzheimer's Disease

Ann-Charlotte Granholm-Bentley, PhD, DDS | 7/1/18 – 10/31/23
University of Colorado Anschutz Medical Campus | BOLD IDEAS INITIATIVE | Co-Principal Investigators: Elizabeth Head, PhD, University of California, Irvine & Elliott Mufson, PhD, Barrow Neurological Institute

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

Advancing the Promising Cerebroprotectant AST-004 to Human Traumatic Brain Injury Clinical Trials

William Korinek, PhD | 7/2/21 – 7/1/23 | BOLD IDEAS INITIATIVE
Astrocyte Pharmaceuticals | Co-Principal Investigators: Theodore Liston, PhD & James Lechleiter, PhD, University of Texas Health Science Center

Astrocyte has developed AST-004, a promising therapeutic for traumatic brain injury (TBI). AST-004 has significant efficacy across a broad range of preclinical TBI models, demonstrating reductions in cell death, brain swelling, and markers of neuronal and astrocyte injury. In a TBI mouse model, our treatment approach reduced long-term neurological deficits in motor coordination and anxiety. AST-004 has shown preliminary efficacy in Alzheimer's disease with increased brain cell viability in two Alzheimer's mouse models. This project will result in an Investigational New Drug application with the FDA.

www.brightfocus.org/grant/CA2021014

Jointly funded with the Medical Technology Enterprise Consortium.

Mitochondrial Prodrug to Treat Repeated Mild Traumatic Brain Injury

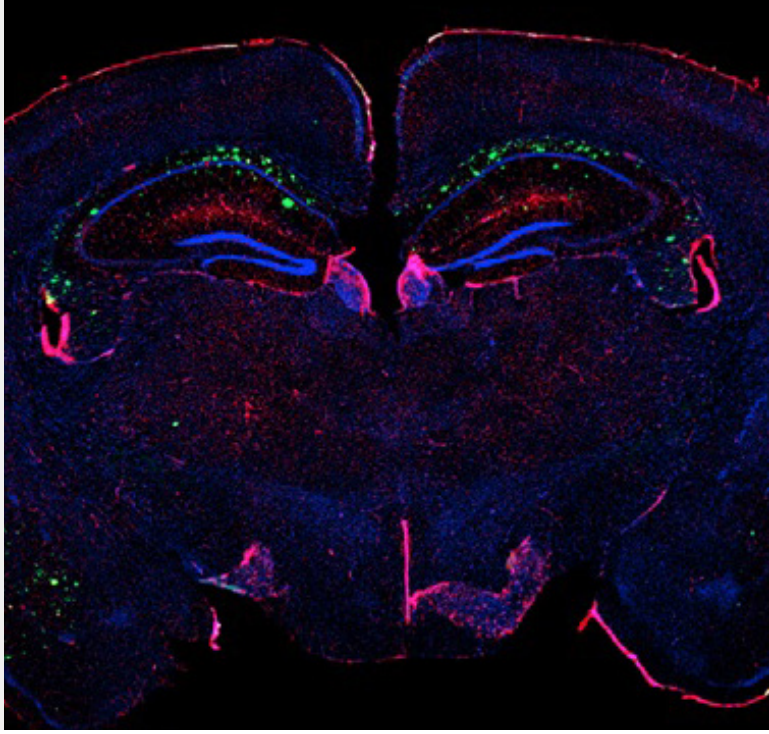
Patrick Sullivan, PhD | 9/8/21 – 9/7/23 | BOLD IDEAS INITIATIVE
University of Kentucky Research Foundation
Co-Principal Investigators: William Brad Hubbard, PhD; John Geisler, PhD & Robert Alonso, Mitochon Pharmaceuticals

This study aims to test the safety and efficacy of a mitochondrial stabilizing drug, MP201. Traumatic brain injuries, especially when repetitive, can lead to oxidative stress and mitochondrial dysfunction that can contribute to dementia. MP201 has been shown to be therapeutically effective in multiple animal models and clinical indications and will be used for a full Investigational New Drug-enabling toxicology package with the FDA.

www.brightfocus.org/grant/CA2021015

Jointly funded with the Medical Technology Enterprise Consortium.

Sex-Based Differences



Women are disproportionately affected by Alzheimer's and account for two-thirds of Alzheimer's-related diagnoses.

At one time their greater disease burden was attributed to women's longer life expectancies compared to men, given that age is the greatest risk factor for the disease.

But in recent years, additional sex-based differences in genetics and immunity have been identified. Hormones and underlying risks—higher rates of depression in women than men—are actively being explored at all levels of Alzheimer's research, from cell studies to epidemiology to treatment trials.

Above: *Red brain blood vessels are shown in relation to green amyloid plaques. Photo courtesy of Charly Abi Ghanem, PhD, Albany Medical College.*

Influence of Testosterone on Dementia in Male Mice

Charly Abi Ghanem, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Albany Medical College | Fellowship Mentors: Kristen Zuloaga, PhD & Sally Temple, PhD, Neural Stem Cell Institute, Regenerative Research Foundation

Low testosterone levels in men are a risk factor for dementia and are associated with cognitive decline. This study will investigate the effects of testosterone removal and treatment on cognitive decline and pathology in a new mouse model of multietiology dementia.

www.brightfocus.org/grant/A2022001F

Identifying Women-Specific and Men-Specific Risk Factors for Alzheimer's Disease

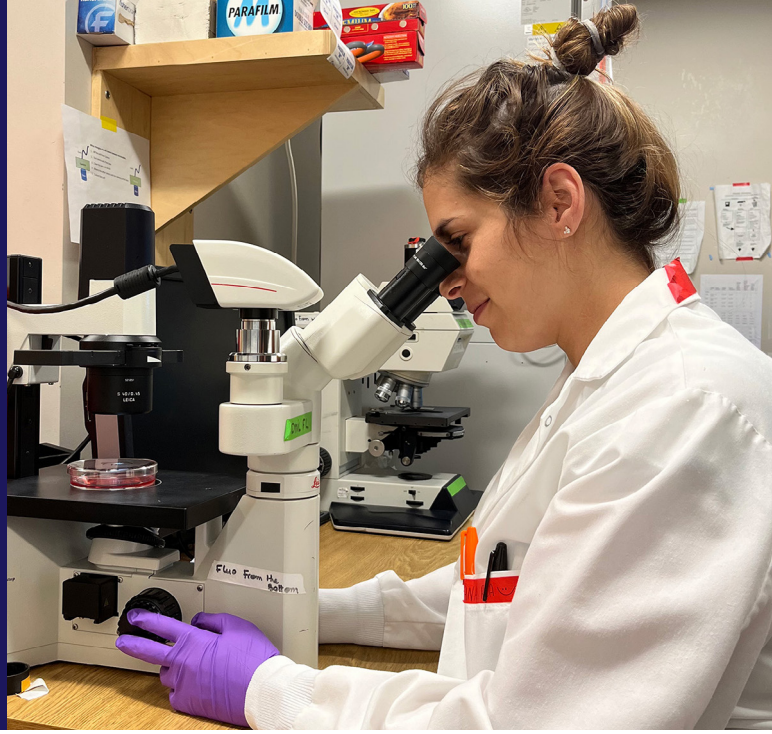
Gael Chetelat, PhD | 7/1/22 – 6/30/24
University of Caen Normandy (FRANCE)

This project will identify sex-specific risk profiles associated with Alzheimer's disease in order to contribute to the development of sex-specific diagnostic procedures for early detection of dementia and of sex-personalized interventions.

www.brightfocus.org/grant/CA2022001

In partnership with Fondation Vaincre Alzheimer.

Sleep & Circadian Rhythm



Chronic sleep disruption plays a role in Alzheimer's disease.

The brain depends on nightly deep sleep to flush itself of waste material and toxins, including misfolded proteins, and to break down and dispose of amyloid beta plaques present in early Alzheimer's.

Sleep patterns are governed by circadian rhythms, the body's 24-hour master clock that synchronizes essential functions, including the sleep-wake cycle.

This biological clock is influenced by environmental cues, including light, and possibly by factors tied to neurodegeneration. Changes in sleep patterns are common in Alzheimer's, even before cognitive disturbances.

A major research question is whether sleep disruption is a symptom of Alzheimer's-related neurodegeneration and can serve as an early warning, or whether it's a contributing factor that can be treated.

Above: *Dr. Quadros looking at neuronal cells under the microscope. Photo courtesy of Ana Rita Agra de Almeida Quadros, PhD, Massachusetts General Hospital.*

Targeting Sleep Deficits to Restore Memory Function in Alzheimer's Disease

Moustafa Algamal, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Massachusetts General Hospital
Fellowship Mentor: Ksenia Kastanenka, PhD

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/grant/A2021001F

The Role of Sleep in Alzheimer's Disease Disparities

Omonigho Bubu, MD, PhD | 7/1/22 – 6/30/25
New York University School of Medicine

This proposal will examine whether Blacks with obstructive sleep apnea (OSA) exhibit higher tau and greater neurodegeneration for a given level of amyloid burden compared to whites. The proposal will also examine the role of socioeconomic status, cumulative stress exposure, and vascular risk as mediators of any observed race-specific effects in microlevel sleep physiology and inflammation on tau and neurodegeneration. The long-term goal is to increase sleep quality and control vascular risk using noninvasive ambulatory methods as novel therapeutic targets for Alzheimer's prevention in Blacks.

www.brightfocus.org/grant/A2022033S

Systems Genetics Analysis of Alzheimer's Disease Related Sleep Disruption

Niran Hadad, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
The Jackson Laboratory | Fellowship Mentor: Catherine Kaczorowski, PhD

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

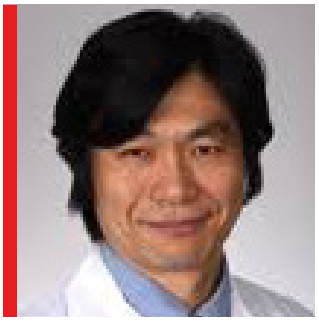
www.brightfocus.org/grant/A2021010F

Relationship Between Sleep Loss and Protein Buildup in Alzheimer's Disease

Christopher Daniel Morrone, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Centre for Addiction and Mental Health (CANADA)
Fellowship Mentor: Wai Haung (Ho) Yu, PhD

This project tests the hypothesis that sleep loss and protein recycling failure are interactive events in Alzheimer's disease that precede memory loss and predict disease progression. The effects of sleep on memory, neuronal function, and markers of protein recycling and pathology will be investigated to see if improving protein recycling can rescue cognition. Artificial intelligence models will be used to assess the contribution of these biological events to predict memory loss and disease risk, facilitating the discovery of novel biomarkers and treatments for Alzheimer's disease.

www.brightfocus.org/grant/A2022016F

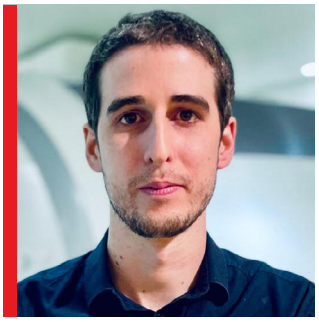


The Relationship Between Sleep and Alzheimer's Disease Progression

Takashi Sato, PhD | 7/1/21 – 6/30/24
Medical University of South Carolina

Sleep disturbance is both an early symptom of Alzheimer's disease in the prodromal phase and one of the factors that exacerbates the disease. This project will study the interaction between sleep and Alzheimer's progression using advanced microscopy and optical stimulation. Key components of the neural circuits 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 to examine how these manipulations affect Alzheimer's progression and cognition.

www.brightfocus.org/grant/A2021041S

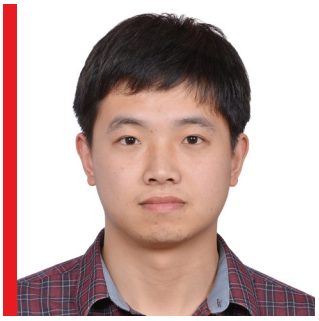


The Brainstem Locus Coeruleus: Potential Bridge Between Sleep-Wake Disruption and Alzheimer's Disease Pathogenesis

Maxime Van Egroo, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Maastricht University (THE NETHERLANDS)
Fellowship Mentor: Heidi Jacobs, PhD

The proposed project postulates that a tiny region located deep in the brain, the brainstem locus coeruleus (LC) is important for the link between sleep-wake disturbances and the earliest manifestations of Alzheimer's. 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 Alzheimer's. 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, to accumulation of hallmark Alzheimer's pathologies, and ultimately to cognitive decline.

www.brightfocus.org/grant/A2021016F



Sleep Restoration, Microglia, and Alzheimer's Disease

Qiuchen Zhao, MD, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Massachusetts General Hospital
Fellowship Mentor: Stephen Gomperts, MD, PhD

Alzheimer's disease is associated with profound sleep disturbances that contribute to disease progression, particularly at early stages of the disease. Effective strategies to restore sleep will be developed using state-of-the-art laboratory technologies to determine sleep's effects on memory function and pathological progression of Alzheimer's. Microglial responses to sleep rescue will be assessed using a multipronged design to study morphological, functional, and genetic changes in microglia.

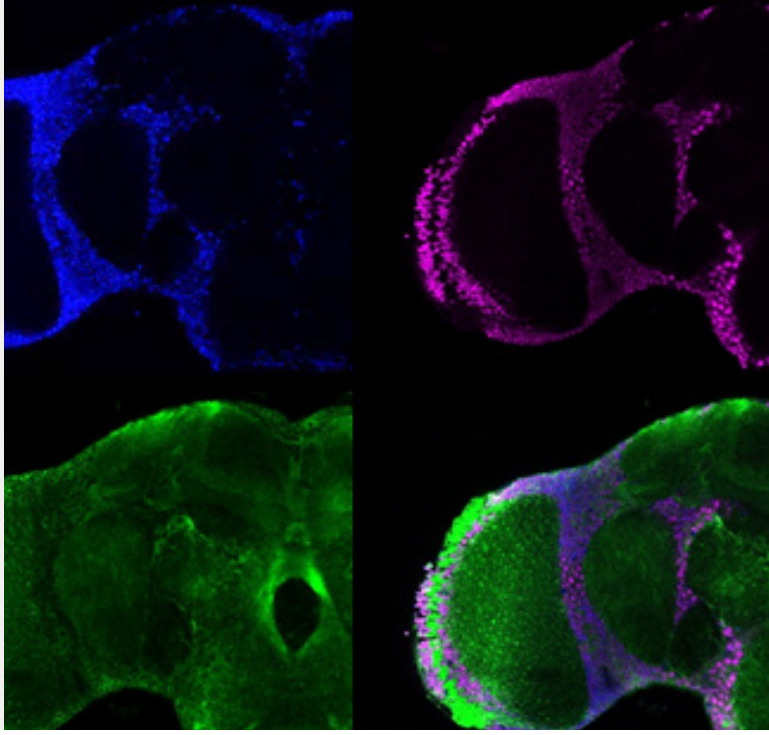
www.brightfocus.org/grant/A2022028F

Worldwide,

at least 50 million people are believed to be living with Alzheimer's disease or other dementias.

If breakthroughs are not discovered, that number could exceed 152 million by 2050.

The Impact of Tau



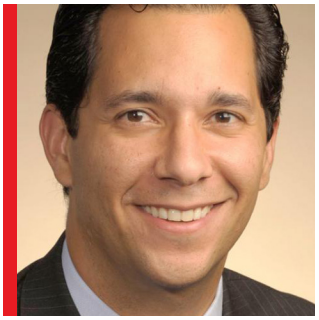
Tau is another protein associated with Alzheimer's disease. Found abundantly inside neurons, its fibrous shape lends stability to tubes that transport nutrition and waste in and out of the brain.

However, in Alzheimer's, tau goes through molecular changes that cause it to misshape and collect in messy tangles.

Unlike amyloid plaques, which can form years and even decades before Alzheimer's symptoms occur, tau tangles typically are a sign that Alzheimer's is rapidly getting worse.

Current theories hold that misfolded amyloid beta and tau proteins interact in ways that lead to disease progression, and scientists are investigating how tau is involved in spreading Alzheimer's throughout the brain.

Above: *Fruit flies* (Drosophilia) *express tau in neurons and can be used to study tau protein accumulation and spread. Photo courtesy of Lindsey Goodman, PhD, Baylor College of Medicine.*

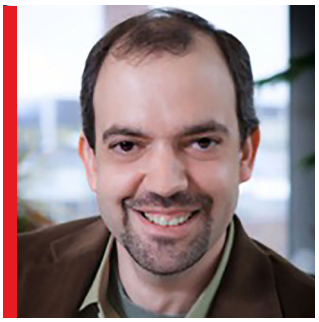


Twisting Away Toxic Proteins in Alzheimer's Disease

Jose Abisambra, PhD | 9/1/20 – 8/31/23
University of Florida

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 that can disaggregate tau aggregates into smaller nontoxic entities. The goal of this proposal is to elucidate the mechanisms of this disaggregation toward 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



How Are Phosphates Removed from Tau?

Jason Gestwicki, PhD | 7/1/21 – 6/30/24
University of California, San Francisco
Co-Principal Investigator: Daniel Southworth, PhD

Tau that 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/grant/A2021029S

Defining Connections between Oxidative Stress and the Disease Protein, Tau

Lindsey Goodman, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Baylor College of Medicine | Fellowship Mentor: Hugo Bellen, DVM, PhD

Two early events that may contribute to Alzheimer's 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 Alzheimer's by disrupting the formation of lipid droplets and examining tau hyperphosphorylation and aggregation.

www.brightfocus.org/grant/A2021008F

Detecting the Shape-Changing Protein Tau in Alzheimer's Disease

Lukasz Joachimiak, PhD | 7/1/19 – 9/30/22
University of Texas Southwestern Medical Center

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

Do Protein Levels and Brain Structure Impact Cognition in Alzheimer's Disease?

Nicole McKay, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Washington University School of Medicine in St. Louis
Fellowship Mentor: Tammie Benzinger, MD, PhD

In the years leading up to Alzheimer's disease diagnosis, the brain begins to deteriorate. Scientists believe that abnormal forms of the tau protein may be partially responsible for these changes. This excessive and abnormal tau can spread along white matter pathways, causing a breakdown in the way our brain functions. This project aims to understand how levels of tau impact the integrity of brain pathways and lead to a decline in cognition.

www.brightfocus.org/grant/A2022013F

Tau Phosphorylation in Preclinical and Symptomatic Alzheimer's Disease

Karin Meeker, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Washington University School of Medicine in St. Louis
Fellowship Mentor: Beau Ances, MSc, MD, PhD

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 Alzheimer's. 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 Alzheimer's.

www.brightfocus.org/grant/A2021012F

Do Post-Translational Modifications Cause Tau to Shapeshift?

Sue-Ann Mok, PhD | 7/1/22 – 6/30/25
University of Alberta (CANADA) | Co-Principal Investigator: Carlo Condello, PhD, University of California, San Francisco

In Alzheimer's disease, molecules of tau protein form very specific shapes as they stack together to create large structures called aggregates that contribute to development and progression of disease. If the factors that cause tau to take on the specific shapes can be identified, it may be possible to prevent this pathological process. This project uses advanced biochemical technologies to study hundreds of potential factors, called post-translational modifications, and identify the key factors leading to the tau shapes observed in Alzheimer's.

www.brightfocus.org/grant/A2022044S

Tau Variants in Blood to Diagnose and Stage Alzheimer's Disease

Laia Montoliu-Gaya, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of Gothenburg (SWEDEN)
Fellowship Mentor: Kaj Blennow, MD, PhD

A reliable blood test would have great potential for diagnosis of Alzheimer's disease. In recent years, many assays have been developed to measure different pathological variants of a protein called tau in blood. When trying to determine which variant is the best biomarker, studies can only compare the assays, but not the levels of the variants because they are measured differently. We have developed a novel method that can compare all these variants at the same time in the same sample. This method will be used to determine the best blood biomarker for the different stages of Alzheimer's.

www.brightfocus.org/grant/A2022015F

Characterizing Heterogeneity of Tau Pathology in Alzheimer's Disease

Alexa Pichet Binette, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
Lund University (SWEDEN) | Fellowship Mentor: Oskar Hansson, MD, PhD

This study will use the latest positron emission tomography marker to image tau deposition in a large, longitudinal, well-characterized cohort ranging from preclinical 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 mechanisms that underlie the accumulation of pathology and cognitive decline.

www.brightfocus.org/grant/A2021013F

Identification of Proteins That Reduce Pathological Aggregates in the Brain

Wilfried O. Rossoll, PhD | 7/1/21 – 6/30/24
Mayo Clinic Jacksonville

The goal of this project is to identify which proteins associate with tau protein aggregates that may contribute to tau pathology in Alzheimer's. 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 Alzheimer's.

www.brightfocus.org/grant/A2021038S

Tau Treatment Targets for Alzheimer's Disease

Kristie Stefanoska, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
The Flinders University of South Australia (AUSTRALIA)
Fellowship Mentor: Arne Ittner, PhD

The progression of Alzheimer's disease correlates with the abnormal accumulation of tau. Tau undergoes modification, which subsequently causes it to collect with other tau proteins and form larger, abnormal structures in the brain. Disease-promoting sites on tau are essential in driving modifications in this protein, and this proposal will investigate how removing the disease-promoting sites on tau could reduce abnormal modification of tau and thus be used as a novel therapeutic approach to mitigate processes underlying Alzheimer's disease.

www.brightfocus.org/grant/A2022022F

Determining How Circadian Rhythm Regulates Sleep Fragmentations in Tauopathy

Masashi Tabuchi, PhD | 7/1/21 – 6/30/24
Case Western Reserve University School of Medicine

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/grant/A2021043S

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

Shuo Wang, PhD | 9/1/20 – 8/30/22 | FELLOWSHIP
Baylor College of Medicine | Fellowship Mentor: Hui Zheng, PhD

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

Why Does the Transport of Molecules into the Nucleus Fail in Alzheimer's?

Susanne Wegmann, PhD | 7/1/21 – 6/30/24
German Center for Neurodegenerative Diseases (GERMANY)

The aberrant interactions of tau with nucleopore proteins, or 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 Alzheimer's 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/grant/A2021044S

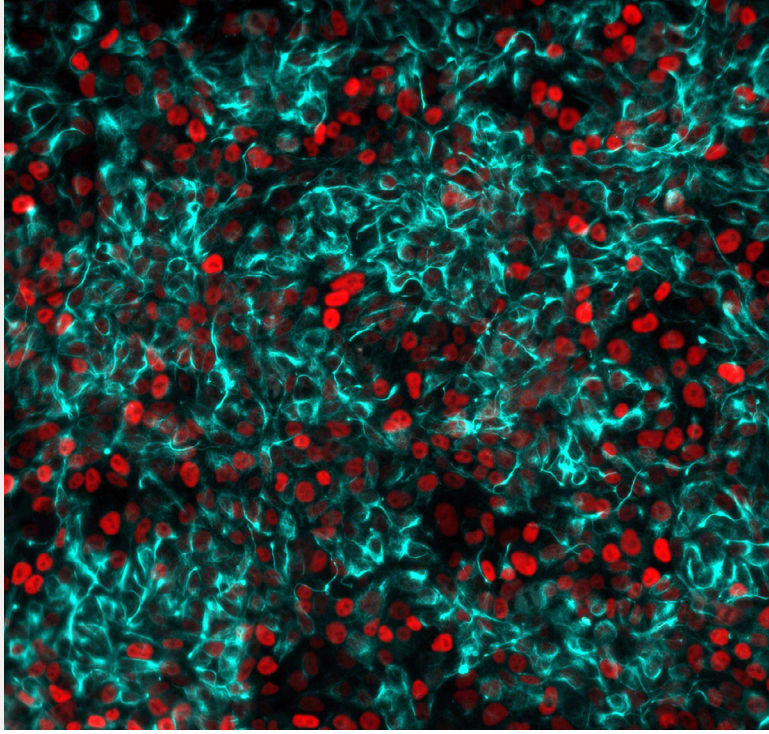
A Novel Way to Expand Human-Derived Pathogenic Tau Seeds in a Cell-Free System

Hong Xu, PhD | 9/1/20 – 8/30/22 | FELLOWSHIP
University of Pennsylvania | Fellowship Mentor: Virginia Man-Yee Lee, PhD

Tau aggregates (tauopathy seeds) enriched from the postmortem brains of Alzheimer's disease 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 Alzheimer's 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



Translational research refers to the effort to take basic science knowledge from the lab or research setting into the real world as potential treatments or cures—to translatet science into useful ways of diagnosing, treating, and managing Alzheimer's disease.

This can take many different forms, from using smartphone-based testing to monitor cognitive status to finding ways to improve sleep and exercise, both of which are lifestyle activities associated with brain health and potential protective benefits.

The essential process of testing new drugs and interventions relies on volunteers who participate in clinical trials and other studies.

These activities help speed drugs, treatments, and critical knowledge to the marketplace and put them in the hands of people living with Alzheimer's today and those at risk in the future.

Above: *Early neuronal differentiation of progenitor cells, in cyan, from human-induced pluripotent stem cells, in red. Photo courtesy of Dominik Paquet, PhD, Ludwig Maximilian University of Munich, Germany.*

Understanding the Beneficial Role of Sleep in Cognitive Deficits

Christelle Anaclet, PhD | 9/1/20 – 8/31/23
University of California, Davis
Co-Principal Investigator: Heinrich Gompf, PhD

Cognitive deficits and sleep disruption are the two major symptoms of Alzheimer's disease. 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 Alzheimer's, 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 Alzheimer's.

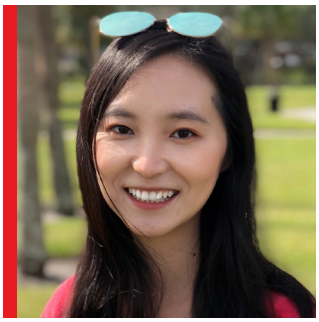
www.brightfocus.org/grant/A2020321S

Washing Alzheimer's Disease Off the Brain

Michele Cavallari, MD, PhD | 9/1/20 – 8/31/23
Brigham and Women's Hospital & Harvard Medical School

Alzheimer's disease 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 Alzheimer's (e.g., beta amyloid and tau proteins) outside the brain that has been recently characterized in animal models. We will use data from two large international studies of Alzheimer's 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



Understanding Early Effects of Amyloid and Tau in Different Memory Domains

Xi Chen, PhD | 10/1/21 – 9/30/23 | FELLOWSHIP
University of California, Berkeley | Fellowship Mentor: William Jagust, MD

The proposed project, focusing on early-stage Alzheimer's disease, will examine the brain and behavioral deficits in older adults with normal cognitive performance who are already harboring Alzheimer's 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 and what brain regions are most affected.

www.brightfocus.org/grant/A2021004F

Gene Correction as a Therapy for Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Caused by the C9orf72 Mutation

Claire Clelland, MD, PhD | 10/1/20 – 8/31/23 | FELLOWSHIP
University of California, San Francisco
Fellowship Mentors: Bruce Conklin, MD, University of California, San Francisco, and Gladstone Institutes & Li Gan, PhD, Weill Cornell Medicine

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 be applicable to many other repeat expansion and single gene disorders.

www.brightfocus.org/grant/A20201490F

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

Simone Crivelli, PhD | 9/1/20 – 1/31/23 | FELLOWSHIP
University of Kentucky | Fellowship Mentors: Erhard Bieberich, PhD & Pilar Martinez-Martinez, PhD, Maastricht University (THE NETHERLANDS)

There is still no cure for Alzheimer's disease; therefore, a major challenge for researchers in the field is to develop new therapies that prevent or delay onset of this disease. During the Alzheimer's 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 Alzheimer's.

www.brightfocus.org/grant/A20201464F

Improving Cognitive Function in Alzheimer's Therapy Using a Combinatorial Approach of Reducing Disease Progression and Increasing Memory

Brati Das, PhD | 9/1/20 – 11/30/22 | FELLOWSHIP
University of Connecticut Health Center
Fellowship Mentor: Riqiang Yan, PhD

Amyloid beta (Aβ) is the main component of amyloid plaques found in the brains of Alzheimer's 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. 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. Positive results could lead to treatments providing a better quality of life for Alzheimer's patients.

www.brightfocus.org/grant/A20201729F

A Novel Test for Alzheimer's Disease Based on DNA Circulating in Blood

Yuval Dor, PhD | 7/1/22 – 6/30/25
Hebrew University of Jerusalem (ISRAEL)

This project aims to establish a novel type of blood test—a liquid biopsy—to identify and monitor cell death in the brain and in other key tissues in patients developing Alzheimer's disease. The approach is based on a new technology that allows us to determine the tissue sources of DNA molecules released from dying cells to the blood, using cell type–specific DNA methylation patterns. The assay will be applied to blood samples obtained from healthy individuals, people with mild cognitive impairment that go on to develop Alzheimer's disease, and patients with established disease.

www.brightfocus.org/grant/A2022035S

This award is made possible through the support of The Sephardic Foundation on Aging.

Does Aß Drive Tau Spreading in Alzheimer's Disease?

Nicolai Franzmeier, PhD | 7/1/21 – 6/30/24
Ludwig Maximilian University of Munich (GERMANY)

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 Alzheimer's patients. Using cutting-edge neuroimaging protocols in Alzheimer's patients, this study will determine whether early amyloid deposition is associated with neuronal hyperactivity, thereby triggering tau spread.

www.brightfocus.org/grant/A2021026S

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

Peter Fried, PhD | 9/1/20 – 8/30/23
Beth Israel Deaconess Medical Center & Harvard Medical School

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, 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 Alzheimer's. 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 Alzheimer's 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

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

Jill M. Goldstein, PhD | 3/30/18 – 9/30/22
Massachusetts General Hospital & Harvard Medical School

This project will support the launch 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

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

Eunhee Kim, PhD | 9/1/20 – 12/31/22 | FELLOWSHIP
Massachusetts General Hospital & Harvard Medical School
Fellowship Mentor: Rudolph E. Tanzi, PhD

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

www.brightfocus.org/grant/A2020870F

Identifying Disease Mechanisms in Neurodegeneration Using Electrophysiology

Sanjeev Kumar, MD | 7/1/18 – 6/30/23
Centre for Addiction and Mental Health (CANADA)
Co-Principal Investigators: Tarek Rajji, MD, FRCPC, Daniel Blumberger, MD, FRCPC, Zafiris J. Daskalakis, MD, PhD, FRCPC, Benoit H. Mulsant, MD, FRCPC, Bruce G. Pollock, MD, PhD & Reza Zomorrodi, PhD; Corinne E. Fischer, MD, FRCPC, St. Michael's Hospital

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 noninvasive brain stimulation technique called transcranial direct current stimulation to treat it.

www.brightfocus.org/grant/A2018667S

More Sensitive Measures Towards the Early Detection of Alzheimer's Disease

Stephanie Leal, PhD | 7/1/22 – 6/30/25
William Marsh Rice University

The cause of Alzheimer's disease is unknown. We have begun to understand which brain regions are impacted decades before clinical symptom onset. However, current research has not utilized tasks sensitive enough to detect the earliest changes in memory that could predict Alzheimer's. This proposal will use sensitive memory tasks that target the earliest brain regions impacted in Alzheimer's. Paired with state-of-the-art brain imaging techniques, early cognitive and brain changes in Alzheimer's will be identified before clinical symptoms manifest, which could aid in earlier interventions to prevent or slow Alzheimer's.

www.brightfocus.org/grant/A2022040S

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

Marianne Leger, PhD | 1/04/21 – 1/03/23
University of Caen Normandy (FRANCE)

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. The hypothesis tests whether these rats are resilient to Alzheimer's pathology, resulting in intact cognition compared to Alzheimer's rats. The involvement of the serotonergic system will be evaluated to determine potential therapeutic targets that may promote resilience to Alzheimer's.

www.brightfocus.org/grant/CA2021013

In partnership with Fondation Vaincre Alzheimer.

Circadian Regulation, Autonomic Function, and Alzheimer's Disease

Peng Li, PhD | 9/1/20 – 8/30/23
Brigham and Women's Hospital & Harvard Medical School

Using a novel noninvasive 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 and cognitive decline in elderly people at early, preclinical stages. This project may potentially provide new intervention targets in future clinical studies of Alzheimer's and can lay the groundwork for the design of novel, unobtrusive, cost-efficient tools for long-term monitoring of cognitive impairment or risk for Alzheimer's.

www.brightfocus.org/grant/A2020886S

Home-Based Noninvasive Brain Stimulation for Mild Alzheimer's Disease

Brad Manor, PhD | 7/1/22 – 6/30/25
Hebrew Rehabilitation Center
Co-Principal Investigator: Alvaro Pascual-Leone, MD, PhD

Memory loss and executive dysfunction are two hallmarks of Alzheimer's disease that map onto different, spatially distinct brain networks. This study will combine and simultaneously deliver two different types of transcranial current stimulation (tCS) to provide multisymptom relief to older adults with mild Alzheimer's. By stimulating more than one brain network at the same time and studying the relationship between the electrical fields created by tCS and individual therapeutic benefit, this trial will help develop tCS interventions with maximal impact on daily life function for this population.

www.brightfocus.org/grant/A2022042S

Identifying a Disease-Modifying Treatment for Alzheimer's

Courtney Marshall, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of Pennsylvania School of Medicine
Fellowship Mentor: Virginia Y.M. Lee, PhD

This project will test the efficacy of a clinically approved CK2 inhibitor in Alzheimer's disease models.

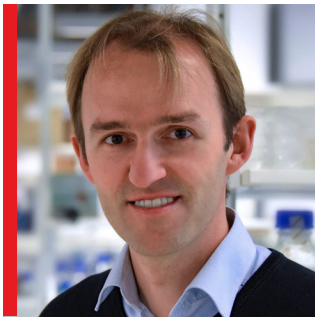
www.brightfocus.org/grant/A2022012F

Measuring Brain Aging in Early-Onset Alzheimer's Disease

Peter Millar, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Washington University School of Medicine in St. Louis
Fellowship Mentor: Eric McDade, DO

Recent machine learning tools can measure how "old" a person's brain appears compared to other healthy brains. In symptomatic Alzheimer's disease, brains appear older than expected (e.g., a 75-year-old Alzheimer's brain might resemble a healthy 84-year-old's brain). This study will assess people with a rare genetic mutation for early-onset Alzheimer's disease to test if their brains begin to appear older as they approach their expected dementia onset. These analyses will evaluate whether clinicians can use this brain-age approach to identify people with very early Alzheimer's pathology and predict Alzheimer's risk.

www.brightfocus.org/grant/A2022014F

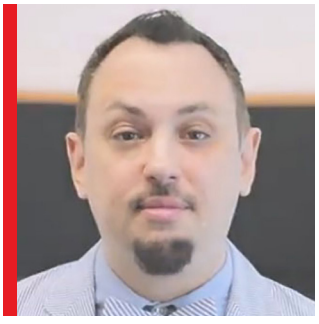


A Human Stem Cell–Based Model of Tau-Related Dementias

Dominik Paquet, PhD | 7/1/22 – 6/30/25
Ludwig Maximilian University of Munich (GERMANY)

Investigating the mechanisms leading to nerve cell decline in dementias requires experimental disease models. This project will develop a human model of tau-related dementias, such as Alzheimer's and FTD. The tau protein plays a central role in dementia formation and nerve cell death. But its regulation in human nerve cells differs from mice, which are currently used as models. Using brain cells derived from induced human stem cells and genome editing with CRISPR, we aim to generate brain tissue with genetic alterations in the tau gene leading to dementia in patients, to investigate human disease mechanisms.

www.brightfocus.org/grant/A2022045S



Tailoring Transcranial Direct Current Stimulation Therapy for People with Alzheimer's Disease

Carlos Roncero, PhD | 7/1/22 – 6/30/25
Baycrest Centre for Geriatric Care (CANADA)

Transcranial direct current stimulation (tDCS) is a new potential therapy for improving the quality of life for people living with Alzheimer's disease. Further work is needed for understanding how tDCS could be optimized and which individuals are the best candidates for receiving this form of therapy. The proposed project will test a new intensity level of tDCS that may produce stronger results in people with Alzheimer's disease and collect participant information to identify who best responds to tDCS. These results will help us optimize and tailor tDCS for people with Alzheimer's disease.

www.brightfocus.org/grant/A2022046S

Dissemination of MIND at Home Dementia Care Model to Drive Health Care Transformation and Greater Value

Quincy Samus, PhD | 7/1/20 – 6/30/23 | BOLD IDEAS INITIATIVE
Johns Hopkins Bayview Medical Center

MIND at Home is a home-based dementia care coordination model that systematically assesses and addresses a broad range of dementia-related care needs that place elders at risk for health disparities, hospitalizations, unwanted long term care placement, poor quality of life, and family caregivers at risk for burnout and health impacts. This grant supports a partnership to strategically advance the dissemination and translation of the MIND at Home model to achieve greater care coordination and value for a vulnerable cognitively impaired population.

www.brightfocus.org/grant/CA2021001

Reducing Dietary Protein for the Prevention of Alzheimer's Disease

Timothy Sargeant, PhD | 7/1/21 – 6/30/24
South Australian Health and Medical Research Institute (AUSTRALIA)
Co-Principal Investigators: Julien Bensalem, PhD; Leonie Heilbronn, PhD, University of Adelaide

The brain's clearance system, called autophagy, works less efficiently with age, resulting in the accumulation and spread of toxic disease associated proteins. Autophagy, which can destroy amyloid plaques associated with Alzheimer's disease, 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 increases autophagy.

www.brightfocus.org/grant/A2021040S

Deciphering the Alzheimer's Disease Glyco-Code

Manveen Sethi, PhD | 9/1/20 – 12/31/22 | FELLOWSHIP
Boston University | Fellowship Mentor: Joseph Zaia, PhD

Identifying the biomolecular deregulation associated with Alzheimer's is crucial to decode the underpinning disease mechanisms, discover new biomarkers, and improve treatment strategies. This project will utilize an analytical workflow, allowing the exploration of the structure and biology of proteins and glycans in Alzheimer's from patient tissue specimens. Outcomes of this project will generate the fundamental, previously unattainable, glycobiological knowledge required to improve the diagnosis and treatment of Alzheimer's.

www.brightfocus.org/grant/A2020687F

Imaging Probes for Precision Medicine in Alzheimer's Disease

Sahil Sharma, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Memorial Sloan Kettering Cancer Center
Fellowship Mentor: Gabriela Chiosis, PhD

Matching patients to the right medicine is a goal of the future in medicine. This proposal aims to build tools that can be used to image and select those Alzheimer's disease patients who are most likely to benefit from a new experimental medicine with disease-modifying potential. This medicine developed by my laboratory, works by rebalancing cellular networks and brain circuits. In mouse models, it reverted cognitive dysfunction and is currently in clinical evaluation in Alzheimer's and related disorders. Tools developed here have immediate translational potential.

www.brightfocus.org/grant/A2022020F

Brain Rhythms to the Rescue: Stimulation to Protect the Brain From Stress

Annabelle Singer, PhD | 7/1/22 – 6/30/25
Georgia Institute of Technology

Chronic stress leads to a twofold or more increased risk for Alzheimer's disease. This project uses novel noninvasive brain stimulation to prevent stress-induced pathology including memory impairment, anxiety, loss of connections between neurons, and overactive immune responses. Because this stimulation is noninvasive, it will readily translate to humans to potentially reduce the risk of developing Alzheimer's disease.

www.brightfocus.org/grant/A2022048S

Using Predictive Algorithms to Improve Recruitment in Alzheimer's Clinical Trials

Aristeidis Sotiras, PhD | 7/1/21 – 6/30/24
Washington University in St. Louis

The project will develop artificial intelligence tools based on deep learning that use widely available imaging, as well as cognitive and clinical data, to identify individuals who 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/grant/A2021042S

Efficient Brain Delivery of Neuroprotective Antibodies for Treating Alzheimer's Disease

Peter Tessier, PhD | 7/1/22 – 6/30/24
University of Michigan
Co-Principal Investigator: Colin Greineder, MD, PhD

Monoclonal antibodies are revolutionizing the treatment of human diseases. However, these large molecules poorly penetrate the blood-brain barrier, which greatly limits their use for treating Alzheimer's disease. We have developed a novel approach for delivering antibodies to the brain by attaching a small protein to mediate antibody entry into the brain. This work seeks to evaluate the therapeutic efficacy of delivering an antibody to the brain that stimulates neuroprotective signaling and prevents neuronal death in animal models of Alzheimer's disease.

www.brightfocus.org/grant/A2022050S

Role of Platelet-Derived Factors in Ameliorating Alzheimer's Disease Pathology

Saul Villeda, PhD | 9/1/20 – 8/31/23
University of California, San Francisco

A growing body of work indicates that factors in young blood have the potential to reverse age-related impairments in the brain. This study will determine the therapeutic potential of young platelets, and platelet-derived circulating factors, to reverse neurodegenerative phenotypes in a mouse model of Alzheimer's and elucidate their downstream mechanisms of action. The results will have significant translational potential, identifying a blood-based therapeutic intervention to restore functions underlying Alzheimer's-related cognitive impairments and broadly counter dementia-related neurodegenerative diseases.

www.brightfocus.org/grant/A20201492S

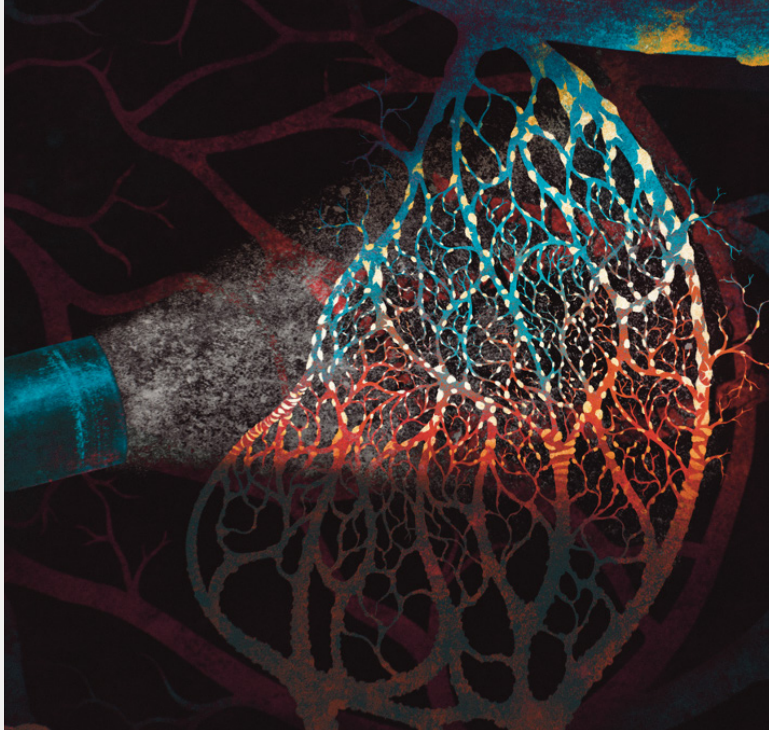
Development of Synthetic Gene Feedback Circuits to Prevent Tau Aggregation

Benjamin Wolozin, MD, PhD | 2/1/20 – 1/31/23
BOLD IDEAS INITIATIVE | Boston University
Co-Principal Investigator: Ahmad Khalil, PhD

This proposal uses a radically novel approach, synthetic biology, which uses concepts from electrical engineering to design new types of genetic therapy for Alzheimer's disease. New synthetic gene circuits will be created that can detect and remove harmful tau pathology as it appears in the brains of patients with Alzheimer's. 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

Vascular Contributions to Dementia



Vascular dementia is the most common co-occurrence with Alzheimer's disease. As a neurodegenerative disease, Alzheimer's is known for damaging neurons, 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 organ, up to 20% of the body's total supply.

The brain relies heavily on an intricately laced system of arteries, veins, and capillaries that, in adults, stretches out an estimated 60,000 miles.

For protection, the brain's circulatory system is sealed off from the rest of the body's 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 and are key to keeping neurons healthy.

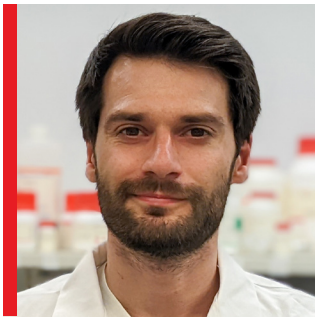
Above: *A drawing by Valentina Galata illuminates the three segments of the brain's blood-brain barrier vasculature: venous blue veins, capillary multicolored thread-like veins, and arterial red veins. Photo courtesy of Andrew Yang, PhD, University of California, San Francisco.*

Brain Changes in Alzheimer's Disease: The Role of a Blood Pressure System

Peter Abadir, MD | 7/1/19 – 6/30/23
Johns Hopkins University

Angiotensin receptors are found on brain cells and play an important role 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



Cerebral Blood Flow Dysfunction in Alzheimer's Disease

Antoine Anfray, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Weill Cornell Medicine | Fellowship Mentor: Costantino Iadecola, PhD

Accumulating evidence suggests that early alterations in brain blood flow contribute to Alzheimer's disease. Individuals with *APOE4*, a leading genetic risk factor for Alzheimer's, have reduced blood flow to the brain; however, the underlying mechanisms are unknown. Therefore, the aim of this project is to study the brain blood flow dysfunction caused by *APOE4* with the goal of identifying new pathways that could be used to develop new drugs for the prevention and treatment of dementia.

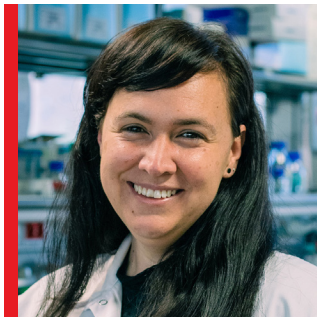
www.brightfocus.org/grant/A2022003F

Prenatal Inflammation Programs Alzheimer's Disease Risk Later in Life

Alexandre Bonnin, PhD | 7/1/19 – 6/30/23
University of Southern California
Co-Principal Investigator: Axel Montagne, PhD

Recent animal model studies suggest a causal link between inflammation during embryonic development and risk of Alzheimer's-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 Alzheimer's, the hypothesis is that inflammation-mediated disruption of blood-placenta and blood-brain barriers are key factors in the developmental origins of Alzheimer's.

www.brightfocus.org/grant/A2019279S



The Impact of Midlife Cardiovascular Health on Brain's Well-Being

Marta Cortes-Canteli, PhD | 7/1/22 – 6/30/25
Spanish National Centre for Cardiovascular Research (SPAIN)
Co-Principal Investigators: Juan Domingo Gispert, PhD; Valentin Fuster, MD, PhD

Cardiovascular risk factors increase the likelihood of developing memory problems in the elderly, and cardiovascular disorders and Alzheimer's disease appear together in symptomatic stages. As both diseases share risk factors and have long subclinical phases, we propose to analyze what is happening during the 10–20 years before the symptoms of both pathologies appear. These studies will decipher whether unhealthy lifestyle choices in your 50s have negative consequences for your brain and contribute to memory problems a decade later.

www.brightfocus.org/grant/A2022034S

This award is made possible through the support of The Sephardic Foundation on Aging.

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

Scott Counts, PhD | 9/1/20 – 8/30/23
Michigan State University | Co-Principal Investigators: Timothy Collier, PhD & Roxana Carare, MD, PhD, University of Southampton (UK)

The contribution of cerebral amyloid angiopathy (CAA) and cerebrovascular pathology to the progression of Alzheimer's disease 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 periarterial drainage (IPAD) of Abeta contributing to Alzheimer's/CAA. If successful, this proposal will advance the clinical rationale for targeting LC/CBF-mediated IPAD as a disease-modifying strategy.

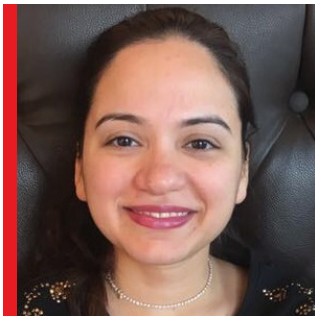
www.brightfocus.org/grant/A20201187S

Neurovascular Changes During Midlife Hypertension and Alzheimer's Disease

Christian Crouzet, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of California, Irvine
Fellowship Mentors: Bernard Choi, PhD & David Cribbs, PhD

Midlife hypertension is an increasingly important risk factor for Alzheimer's disease and related dementias. This project will investigate how hypertension affects the progression of Alzheimer's disease from a blood flow, cognitive, and pathological perspective through midlife. It will test if antihypertensive medication can slow the progression of Alzheimer's disease and improve cognitive function.

www.brightfocus.org/grant/A2022005F



The Impact of "Silent" Small Strokes on Brain Function and Alzheimer's Development

Saima Hilal, PhD | 7/1/18 – 12/31/22 | FELLOWSHIP
National University of Singapore (SINGAPORE)
Fellowship Mentors: Meike W. Vernooij, MD, PhD & M. Arfan Ikram, MD, PhD, Erasmus University Medical Center (THE NETHERLANDS)

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

Detecting Leaky Vessels in Cerebral Amyloid Angiopathy

Whitney Freeze, PhD | 1/1/22 – 12/31/23 | FELLOWSHIP
Leiden University Medical Center (THE NETHERLANDS)
Fellowship Mentors: Louise van der Weerd, PhD; Susanne van Veluw, PhD, Massachusetts General Hospital

This project combines state-of-the-art MRI techniques with detailed postmortem examinations to explore associations between brain-blood barrier 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 the development of new drugs to prevent the formation of bleeds.

www.brightfocus.org/grant/A2021007F

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

Shannon Macauley-Rambach, PhD | 9/1/20 – 8/31/23
Wake Forest University

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

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

Alaina Reagan, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
The Jackson Laboratory | Fellowship Mentor: Gareth Howell, PhD

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

Declines in Neuron-Vasculature Crosstalk as a Cause of Alzheimer's Disease

Melanie Samuel, PhD | 7/1/21 – 6/30/24
Baylor College of Medicine
Co-Principal Investigator: Joshua Wythe, PhD

Alzheimer's disease affects millions of individuals, and comorbities 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 Alzheimer's disrupts energy homeostasis and neurovascular coupling through specialized vascular structures called pericyte nanotubes.

www.brightfocus.org/grant/A2021039S

Is *APOE* the Missing Link for the Safe Removal of Vascular Amyloid?

Susanne van Veluw, PhD | 7/1/22 – 6/30/25
Massachusetts General Hospital

Cerebral amyloid angiopathy (CAA) is a disease in which amyloid builds up in the blood vessels of the brain, which can cause bleeding and dementia. There are currently no treatments for CAA, and removing amyloid with immunotherapy is not recommended due to a high bleeding risk. This risk is further increased in CAA patients with an *APOE4* genotype. A recent study suggested that removing *APOE*, which is co-deposited with amyloid, could be a safe alternative. However, it remains unclear whether removing *APOE* improves CAA and protects blood vessels. This project will test this in a mouse model.

www.brightfocus.org/grant/A2022051S

How Does Aging Damage the Blood Vessels in Cerebral Small Vessel Disease

Xiaowei Wang, PhD | 7/1/21 – 6/30/23 | FELLOWSHIP
University of California, San Francisco
Fellowship Mentors: Douglas Gould, PhD & Tyson Kim, MD, PhD; Scott Earley, PhD, University of Nevada

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/grant/A2021018F

How "Good Cholesterol" May Help in Alzheimer's Disease

Cheryl L. Wellington, PhD | 7/1/21 – 6/30/24
University of British Columbia (CANADA)

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 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 ~2,000 blood samples from people with dementia versus people resistant to dementia and uses additional test tube approaches to study how *APOE-HDL* acts on the small blood vessels of the brain.

www.brightfocus.org/grant/A2021045S

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

Lirong Yan, PhD | 9/1/20 – 8/31/23
Northwestern University

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/Alzheimer's.

www.brightfocus.org/grant/A20201411S

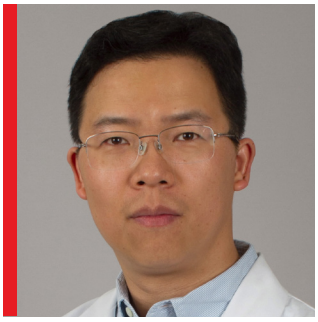
This grant is made possible in part by support from Alzheimer's Los Angeles.

How Genes in the Vascular Half of the Brain Confer Alzheimer's Risk

Andrew Yang, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
University of California, San Francisco | Fellowship Mentor: Saul Villeda, PhD

Late-onset Alzheimer's disease is associated with dozens of risk variants operating in diverse cell types. Elucidating the functions of these risk variants is critical to inform treatments but is challenging, in part because the vascular half of human brain cell types has eluded powerful single-cell assays. This project utilizes a new vascular-capturing VINE-seq technique to comprehensively identify the cells and genes expressing dysregulated Alzheimer's variants. Bioorthogonal labeling approaches will determine how Alzheimer's variants dysregulate brain vascular transport functions to promote Alzheimer's risk.

www.brightfocus.org/grant/A2022027F



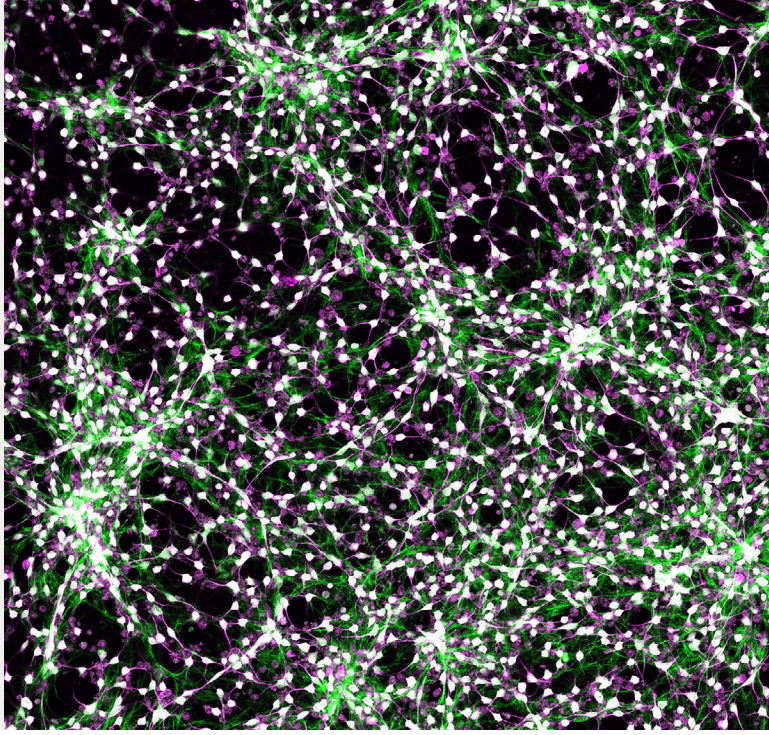
Understanding the Vascular Link Between Traumatic Brain Injury and Alzheimer's Disease

Zhen Zhao, PhD | 7/1/19 – 6/30/23
University of Southern California

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 Alzheimer's disease. Vascular impairment is also a hallmark of the pathological events after TBI, including local edema, blood-flow reduction, and breakdown of the 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 Alzheimer's in animal models.

www.brightfocus.org/grant/A2019218S

Waste-Clearance Mechanisms



In addition to the immune-mediated clearance mechanisms carried out by microglia, individual cells undergo a process of self-eating, or autophagy.

By cleaning out old, used, or misprocessed proteins, a cell can self-rejuvenate to optimize health and function.

Endosomes and lysosomes are cellular compartments responsible for breaking down and recycling or removing waste.

Endolysosomal pathway abnormalities are an early feature of Alzheimer's disease and are closely related to genetic risk factors.

As an organ, the brain has its own lymphatic system associated with the brain's blood vessels, or meninges.

Meningeal lymphatics drain the fluid from within and around the brain and carry immune cells to and from the brain.

Impaired clearance of toxic proteins through meningeal lymphatics is not only a likely contributor to Alzheimer's pathology but also a novel target for therapeutic interventions.

Above: *Neurons derived from human skin cells can mimic disease processes in a dish. Photo courtesy of Ching-Chieh Chou, PhD, Stanford University.*

Studying Lysosomal Vulnerability in Aging and Alzheimer's

Ching-Chieh Chou, PhD | 7/1/22 – 6/30/24 | FELLOWSHIP
Stanford University | Fellowship Mentor: Judith Frydman, PhD

Deficient waste clearance mechanisms are critical to the development of Alzheimer's disease, but deficits in human neurons are not fully understood. This project reprograms human skin cells into brain cells to determine how and why clearance mechanisms are disrupted in Alzheimer's.

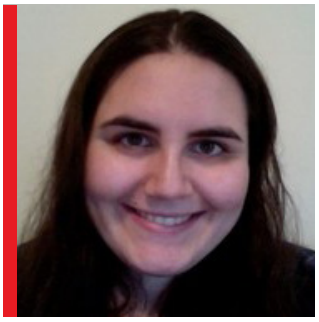
www.brightfocus.org/grant/A2022004F

Elucidating How Amyloid-Beta Changes Protein Expression in Alzheimer's Disease Brain

Ulrich Hengst, PhD | 7/1/21 – 6/30/24
Columbia University

Endosomes form complexes with other proteins, including transferrins (TF), to perform intracellular sorting of substances that will ultimately be degraded or recycled. A new TF complex associated with amyloid 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 cause endosomal trafficking defects, and investigate whether Alzheimer's pathology is altered in mice lacking one of the TFs.

www.brightfocus.org/grant/A2021030S

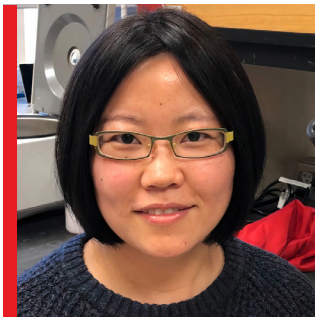


Investigating Coordinated Removal of Old and Synthesis of New Materials in Neurons and How These Processes Are Disrupted in Frontotemporal Dementia

Sarah Hill, PhD | 9/1/20 – 8/31/22 | FELLOWSHIP
National Institute of Neurological Disorders and Stroke | Fellowship Mentors: Michael E. Ward, PhD, MD & Jennifer Lippincott-Swartz, PhD, Janelia Research Campus, Howard Hughes Medical Institute

In neurons, insufficient removal of materials or defects in synthesis lead to loss of function, accumulation of toxic aggregates, and ultimately neuron death, contributing to the pathogenesis of neurodegenerative diseases such as frontotemporal dementia. This proposal examines how the distinct processes of removal and synthesis are interrelated.

www.brightfocus.org/grant/A20201086F



Identification of Protein Biomarkers for Aging and Alzheimer's

Xiaojing Sui, PhD | 10/1/22 – 9/30/24 | FELLOWSHIP
Northwestern University | Fellowship Mentor: Richard Morimoto, PhD

This study will identify the proteins that go awry in aging and Alzheimer's disease using an advanced technology that can screen thousands of proteins at a time. The goal of the project is to identify new protein biomarkers of aging and Alzheimer's disease and provide new treatment targets.

www.brightfocus.org/grant/A2022023F

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