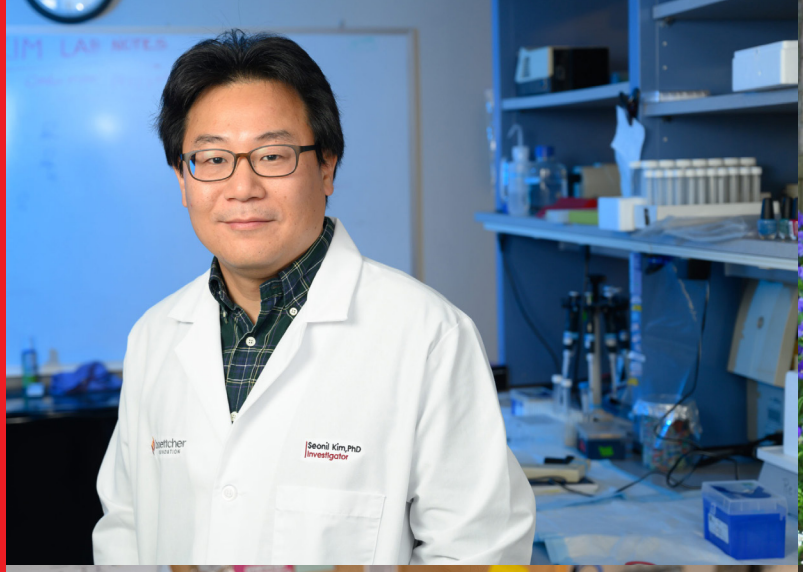
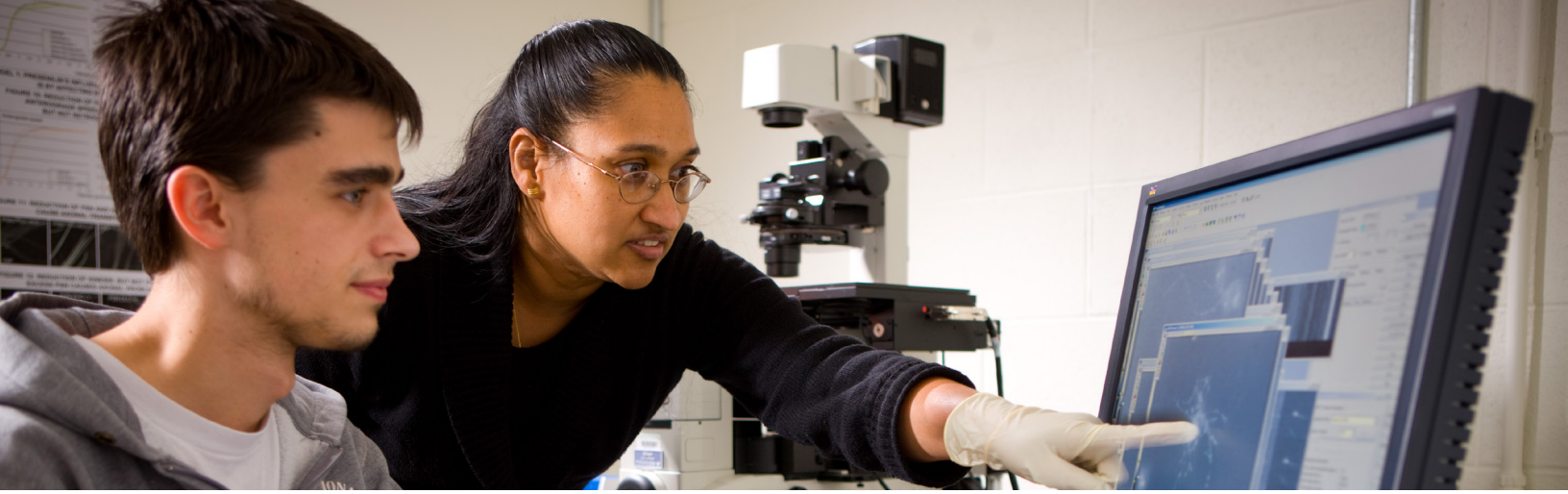




Research for a Better Tomorrow

2023 Alzheimer's Disease Research Projects

BrightFocus® Foundation | Alzheimer's Disease Research



Advancing Research Toward a Cure

Alzheimer's Disease Research, a BrightFocus Foundation program, is on a mission to cure Alzheimer's disease and related dementias and raise awareness about this devastating disease impacting more than 6.7 million Americans age 65 and older.

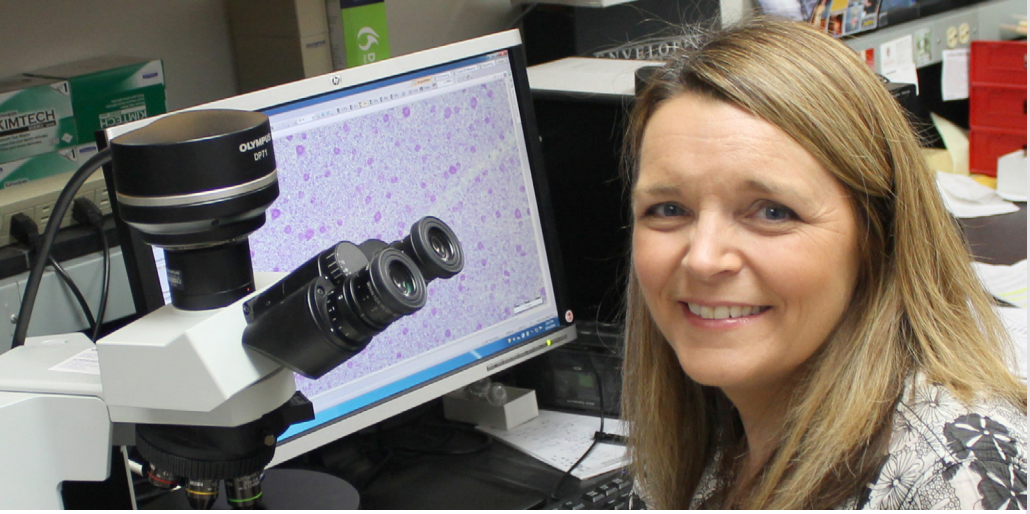
By providing initial funding for highly innovative experimental research and creative ideas, we spark revolutionary approaches and life-saving breakthroughs for this disease, the seventh-leading cause of death in the United States.

We're funding 157 active research projects worldwide.

Since inception:

More than **$175 million** in research grants awarded

2,960 scientists supported



Alzheimer's Disease Research

Meet the Innovators

Our greatest opportunity to find a cure lies in research. Thanks to generous donor support, we have invested more than $175 million in groundbreaking studies aimed at furthering our understanding of Alzheimer's disease.

With our biomedical grants, scientists across the globe have explored and tested thousands of hypotheses regarding the disease's onset and progression, leading to the creation of improved earlier detection strategies and novel treatments.

This research portfolio provides an overview of our current Alzheimer's Disease Research grant projects. Grants are vetted through a rigorous evaluation process by the world's top scientists and clinicians who serve on our scientific review committee.

We are deeply grateful to our donors, whose generosity makes it possible to fund the next generation of researchers pursuing novel, bold, and promising science for tomorrow's cure.

Explore all active grants:

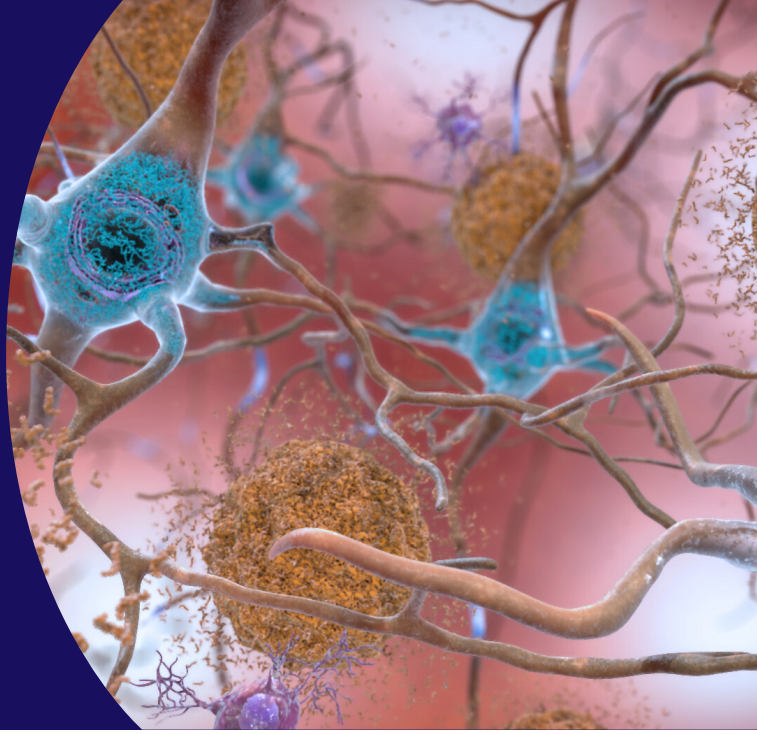
brightfocus.org/ADRgrants

Contents

On the cover: Alzheimer's Disease Research grantees.

Note: This portfolio reflects awarded grants as of July 25, 2023.

Amyloid-Beta



***Above**: In Alzheimer's disease, abnormal levels of the amyloid-beta protein clump together to form plaques (seen in brown) that collect between neurons and disrupt cell function. Image courtesy of National Institute on Aging, NIH.*

There are many versions of amyloid protein in the human body, and most serve a useful role. One type, amyloid-beta, or Aβ, is prone to fragmenting and accumulating in the brain. A healthy brain can break down the protein and eliminate it, but in Alzheimer's disease, Aβ forms hard plaques that are toxic to neurons and sometimes (not always) associated with memory loss and other changes.

Many experts think Aβ may work synergistically with tau—another protein overexpressed in Alzheimer's—to speed neurodegeneration.

With new technologies, researchers can directly measure amyloid plaques—the places where amyloid has accumulated in the brain—and identify affected brain regions, whereas previously, plaques could be seen only at autopsy.

Visualizing How Amyloid-Beta Strands Interact in Alzheimer's Disease

David Boyer, PhD | University of California, Los Angeles
Mentor: David S. Eisenberg, PhD

This work will shed light on how amyloid-beta strands form fibrils. Researchers will tag amyloid-beta molecules with antibodies to use with an advanced cryo-electron microscopy to trace the structural changes from single molecules to fibrils. The results may form the basis for designing drugs that disrupt fibril formation.

This grant is supported by Alzheimer's Los Angeles.

Novel Molecules to Tackle Toxic Amyloid-Beta Production in Alzheimer's

Lucía Chávez-Gutiérrez, PhD | Flanders Institute for Biotechnology (Belgium)

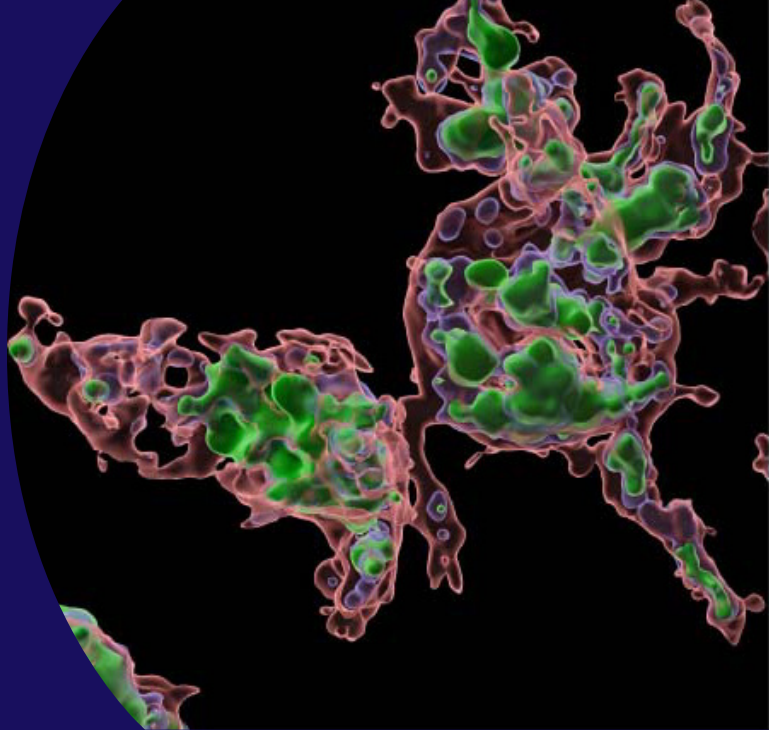
Improperly regulated gamma-secretase can boost production of a toxic form of the Alzheimer's disease protein amyloid-beta. Under proper regulation, the very same enzyme can promote processing of nontoxic amyloid-beta. For this project, researchers aim to examine the molecules responsible for regulating the activity of gamma-secretase. The work is a basis for designing novel molecules that correct gamma-secretase function and promote the formation of nontoxic over toxic amyloid.

Identifying Therapeutic Targets to Prevent Amyloid Accumulation

Arun Upadhyay, PhD | Northwestern University Feinberg School of Medicine
Mentors: Jeffrey N. Savas, PhD & Robert J. Vassar, PhD

This work will focus on proteins that interact with amyloid-beta and show how these interactions change over time and influence the disease course. Proteins involved in early changes in amyloid will be further evaluated for their function in early fibril formation, yielding more information about this key process in Alzheimer's disease and potential treatment targets.

Biology of Fats & Proteins (*APOE*)



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

Initially recognized for its role in cardiovascular disease, the apolipoprotein E (*APOE*) gene (indicated by italics) also is a risk factor in Alzheimer's disease. It produces the APOE protein (indicated by no italics), which metabolizes and transports fats (lipids) in the body.

Among the common variants of *APOE, APOE4* (ε4) 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 by race and ethnicity, which scientists are trying to better understand.

Some clues may lie with the protein's ability to transport fats and interactions within the immune system, where it influences inflammation and a type of cellular damage known as oxidation. It helps facilitate breakdown of Aβ protein in and around neurons, but the ε4 version of the protein is less effective at doing so.

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

Oleg Butovsky, PhD | Brigham and Women's Hospital & Harvard Medical School

APOE is crucial to how microglia, the brain's immune cells, change in association with neurodegeneration. A key question is whether *APOE* variants in neutrophils, another type of immune cell, also control microglia responses and contribute to disease progression. This team has found gender influences on *APOE* variant effects in neutrophils and will extend that work to examine *APOE* variants in microglia-neutrophil interactions, possibly uncovering therapeutic targets in Alzheimer's disease.

Meningeal Lymphatics and *APOE* in Alzheimer's Disease

Sandro Da Mesquita, PhD | Mayo Clinic Jacksonville

This project tests the hypothesis that expression of *APOE4* affects brain function by impairing normal fluid drainage and increasing inflammation in the brain. To address this question, researchers will work with mouse models that do not have the *APOE* gene or that express human *APOE3* or *APOE4* instead and study the cellular and molecular processes involved in regulating the brain's fluid drainage system at different ages.

This grant is supported by the Homer and Annette Thompson Foundation.

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

Jie Gao, PhD | The Ohio State University

APOE4 markedly exacerbates tau buildup and tau-related neurodegeneration in Alzheimer's disease. IDOL is a molecule that regulates production of proteins that interact with APOE, in turn affecting APOE breakdown. Researchers will examine the multiple roles of IDOL and processes underlying its effects in mitigating *APOE4*-mediated tau buildup in Alzheimer's disease, potentially uncovering treatment targets.

Deciphering the Regulation and Expression of APOE in Alzheimer's Disease

Emil Gustavsson, PhD | University College London (UK)
Mentor: Mina Ryten, MD, PhD

Changes to an APOE RNA molecule before the cell "reads" it to build the APOE protein may contribute to Alzheimer's disease risk. For this project, researchers will use a new technology, long-read RNA sequencing, to explore different types of APOE-related RNA produced in Alzheimer's disease. Relying on large, publicly available datasets, the team will generate a landscape of APOE RNA expression patterns in neurons and microglia and correlations with Alzheimer's disease.

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

Alexandra Litvinchuk, PhD | Washington University in St. Louis
Mentor: David Holtzman, MD

Disruption of lipid metabolism in glia is linked to neuroinflammation and neurodegeneration. A significant buildup of lipids in the brain's support cells in aged animals with tau accumulation has recently been observed. In this project, researchers will target a protein responsible for transporting lipids and examine its role in modulating lipid breakdown, using a mouse model of tau buildup. The work will open novel therapeutic avenues for treating tauopathy and Alzheimer's disease.

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

Ana-Caroline Raulin, PhD | Mayo Clinic Jacksonville
Mentor: Guojun Bu, PhD

Variants of the *APOE* gene and the proteins they encode have different effects on Alzheimer's disease status: *APOE4* increases risk, *APOE3* is neutral, and *APOE2* is protective. A rare version of *APOE*, *APOE3*-Christchurch (*APOE3-Ch*), has been shown to be highly protective against Alzheimer's. For this study, researchers will use animal models, stem cells, and "minibrains in a dish" (known as organoids) to understand how *APOE3-Ch* protects against the toxic effects of amyloid-beta accumulation.

High-Density Lipoprotein in Alzheimer's Disease

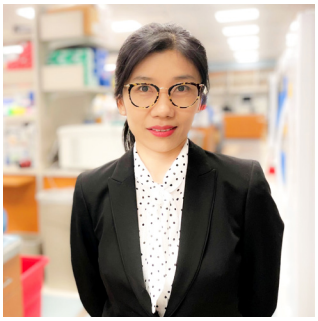
Jerome Robert, PhD | University Hospital of Zürich (Switzerland)

High-density lipoprotein, or HDL, also known as "good" cholesterol, transports lipids in the blood. The effects of factors in the bloodstream on blood vessels and neurons in the brain, including in Alzheimer's disease, are poorly understood. One reason for the lack of information is that good tools for testing these interactions have not been available. Using a human blood vessel grown in a test tube, this research team aims to uncover how HDL promotes brain vessel health.

Modulation of Peripheral APOE for Alzheimer's Disease Therapy

Long-Jun Wu, PhD | Mayo Clinic Rochester

Having the *APOE4* gene increases a person's risk of Alzheimer's disease, whereas *APOE2* is protective against the disease. Using a unique lab model, this study will for the first time test whether converting harmful *APOE4* to protective *APOE2* in the liver can restore brain functions. These findings will provide preclinical evidence for designing future human clinical trials, which may offer individualized treatment strategies based on the *APOE* genotype.



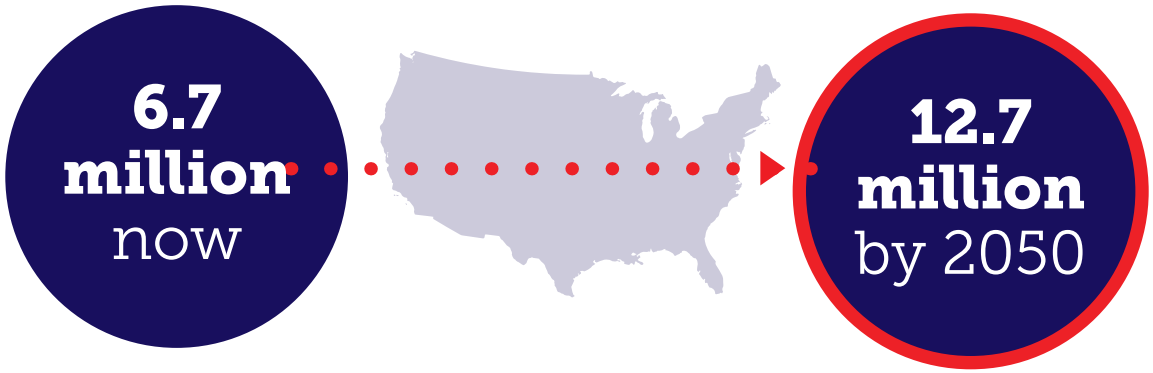
The Influence of Lifestyle Change and the *APOE* Gene in Aging and Alzheimer's Disease

Na Zhao, PhD, MD | Mayo Clinic Jacksonville

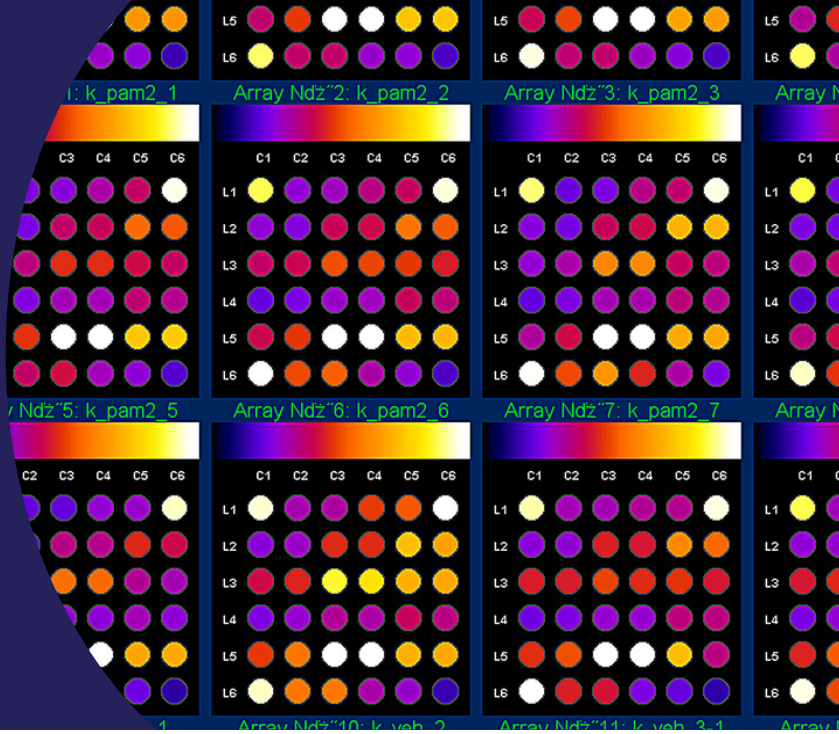
Aging and the *APOE4* gene variant are the greatest risk factors for late-onset Alzheimer's disease. Lifestyle interventions may delay disease onset, and food restriction could be an effective way to extend health span. Whether *APOE4* carriers benefit from preventive lifestyle interventions remains unclear. For this project, researchers will investigate how diet or exercise affects brain health, using animal models of aging or Alzheimer's and with or without the *APOE4* gene.

A Growing Epidemic

Alzheimer's disease in the United States among people age 65 and older



Biomarkers



Above: *Analysis of protein expression using protein array software.*

Biomarkers are biological indicators that are detectable through minimally invasive procedures to measure changes associated with Alzheimer's disease. Because Alzheimer's-related brain changes can arise 10-20 years before symptoms appear, researchers are focusing on novel biomarkers that support detection in earlier stages of the disease. The best hope of stopping Alzheimer's is to identify it as early as possible.

Alzheimer's biomarkers include elevated blood or cerebrospinal fluid amyloid-beta levels, changes in brain structure and function on advanced neuroimaging, and vascular changes or protein deposits in the retina that mirror those in the brain.

Biomarkers can be used to identify people likely to develop Alzheimer's, track disease progression and treatment efficacy, and identify who needs treatment, when to start it, and what drugs and other strategies will be most successful.

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

Ganesh Babulal, MSCI, OTD, PhD | Washington University School of Medicine in St. Louis

Car crash rates are higher among people with Alzheimer's disease. For several years, these researchers have tested continuous collection of driving behaviors using a device plugged into people's cars. With this Driving Real-World In-Vehicle Evaluation System (DRIVES), they now plan to look at driving patterns associated with early Alzheimer's disease, along with using brain ability tests related to navigation and sensory and physical functions for identifying early Alzheimer's.

Imaging Markers of Blood Clotting in the Alzheimer's Disease Brain

Marta Casquero-Veiga, PhD | Jiménez Díaz Foundation Health Research Institute (Spain)
Mentor: Marta Cortes-Canteli, PhD

Tiny blood clots that can form in the brains of some people with Alzheimer's disease at an early stage may serve as a disease marker and treatment target. For this project, researchers have developed a novel radio-isotope tracer that homes to clotting factors in the brain so that they can be localized and tracked. The results may characterize a tool for diagnosing early Alzheimer's disease and a target for treatments.

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

Carol Yim Lui Cheung, PhD | The Chinese University of Hong Kong (China)

In this study, 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 requires only a routine eye check and represents an inexpensive, noninvasive, efficient, and accessible method to screen for Alzheimer's disease.

Systemic Signals From Skin in Aging and Alzheimer's Disease

Chadwick Hales, MD, PhD | Emory University

Age is the strongest risk factor for Alzheimer's disease and for the wrinkling of skin. For this study, investigators will explore a link between aging and Alzheimer's-related changes in the skin and the brain. Researchers expect to identify new treatment approaches and new markers of aging and Alzheimer's disease in the skin, blood, and/or spinal fluid.

Does Brain Activity in Early Life Predict Future Neurodegeneration?

Keith Hengen, PhD | Washington University in St. Louis

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

Learning From Cognitively Healthy Centenarians to Escape Alzheimer's Disease

Henne Holstege, PhD | VU University Medical Center Amsterdam (The Netherlands)

Researchers will investigate tolerance among centenarians to high levels of Alzheimer's-related proteins in the brain (resilience) and how readily centenarians escape accumulation of these Alzheimer's-related proteins (resistance). The team will use state-of-the-art technology to measure proteins in the blood of 400 cognitively healthy centenarians and their family members to determine whether centenarians have different protective mechanisms for maintaining brain function. This research can help identify lifestyle and genetic factors affecting resilience and resistance to Alzheimer's disease.

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

Amir Kashani, MD, PhD | Wilmer Eye Institute, Johns Hopkins University

Vascular contributions to cognitive impairment and dementia (VCID) arise from stroke and other blood vessel-related brain injuries linked to significant changes in memory, thinking, and behavior. VCID is often associated with Alzheimer's disease dementia. Damage to small blood vessels is difficult to detect with conventional methods, however. The goal of this research is to develop new methods using the eye to detect the onset, progression, and severity of VCID.

This proposal is 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 one of the principal investigators.

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

Katherine Schwetye, MD, PhD | Washington University School of Medicine in St. Louis

Understanding of the dynamics of amyloid-beta protein in the human brain is critical to the development of therapeutics to treat and even cure Alzheimer's disease. This project will use the most advanced imaging technology available to study the rate of plaque pathology development in patients.

The Role of White Matter Injury in Alzheimer's Disease

Zahra Shirzadi, PhD | Massachusetts General Hospital
Mentor: Jasmeer Chhatwal, MD, PhD

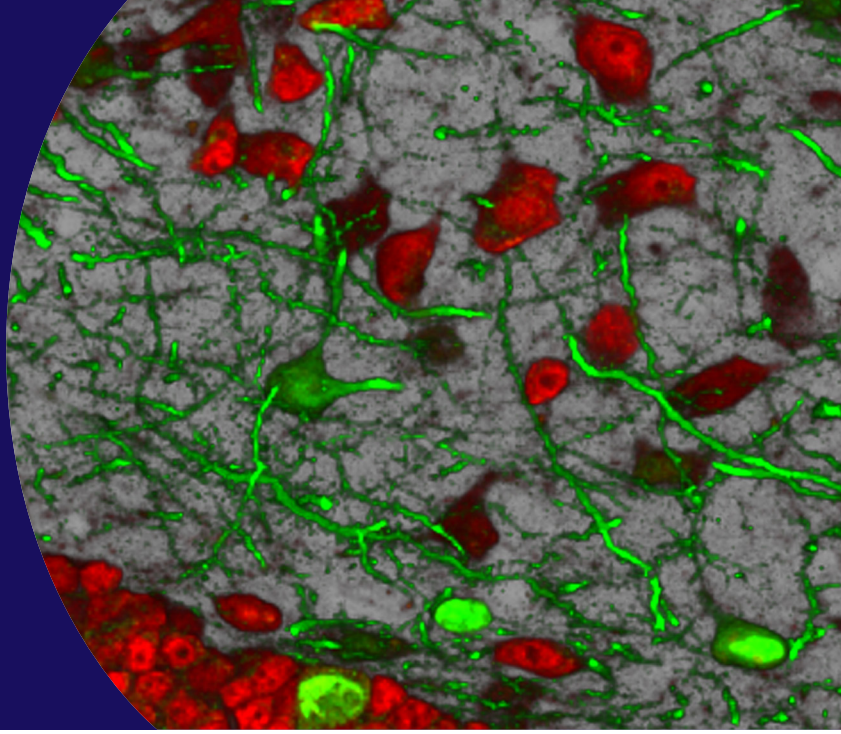
This project will evaluate three factors related to damage to the brain's white matter: amyloid buildup in blood vessels, brain shrinkage, and blood vessel health. The study will rely on a unique resource of MRI images taken over a long period of time in several patient cohorts. Based on the findings, the team plans to develop tools to identify people at high risk for amyloid buildup in the brain's blood vessels or progressive cognitive decline.

Following the Spread of Iron Through the Brain in Alzheimer's Disease

Louise Van der Weerd, PhD | Leiden University Medical Center (The Netherlands)
Co-Principal Investigator: Boyd Kenkhuis, PhD

By tracking iron accumulation across the brain over time, researchers will develop an atlas that visually depicts this process, using brains from hundreds of donors representing different disease stages. Iron accumulation in the brain is a powerful predictor of cognitive decline in Alzheimer's disease, and a pictorial record of the process could form the basis for a standardized staging system for pathological iron accumulation.

Cells & Circuits



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, Autonomous University of Barcelona, Spain.*

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

In Alzheimer's disease, neurons die and do not regenerate, but some brains will remodel to meet new demands from these losses. If a circuit is too damaged to connect by a direct route, signaling can take detours, or indirect neural pathways.

Classic Alzheimer's disease symptoms—forgetting loved ones or becoming lost in familiar places—will emerge only when the communications network breaks down completely.

Scientists are studying the brain's many cells and circuits, looking for ways to preserve communications for as long as possible after Alzheimer's disease onset.

Revealing Early Biomarkers in Alzheimer's Disease

Uri Ashery, PhD | Tel Aviv University (Israel)
Co-Principal Investigator: Shahar Alon, PhD, Bar-Ilan University

Degeneration of contacts between brain neurons is one of the first processes leading to Alzheimer's disease and occurs near amyloid deposits, which are hallmarks of the disease. In this first use of a newly developed platform in Alzheimer's, researchers will detect molecular changes in hundreds of genes in intact brain tissues at early disease stages, along with their associations with specific cell types, proximity to amyloid deposits, and sex differences.

This grant is supported by the Luminescence Foundation.

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

Samuel Barnes, PhD | Imperial College, London (UK)
Co-Principal Investigator: Johanna Jackson, PhD, UK Dementia Research Institute

Loss of connection points, or synapses, between brain cells has been linked to memory loss in Alzheimer's disease. However, not all such connections are lost during the disease, with some reports finding that many of these connections, up to 60%, are retained. 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.

Mapping Brain Connectivity Changes in Alzheimer's Disease

Kevin Beier, PhD | University of California, Irvine

This project will identify brain regions and cell types to target slowing or preventing 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.

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

Limor Cohen, PhD | Harvard University
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.

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

Laura Cox, PhD | Brigham and Women's Hospital & Harvard Medical School

The gut microbiota contains trillions of microbes that promote health and can affect the brain by secreting substances that can influence the immune system or mood. In aging, destabilization of the gut microbiota can contribute to disease. This project investigates how these age-related changes contribute to Alzheimer's disease to find ways to control the microbiome and promote healthy brain aging.

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

Hongjun Fu, PhD | The Ohio State University

Spreading of abnormal tau proteins occurs in both Alzheimer's disease and progressive supranuclear palsy (PSP), causing neurodegeneration. Because animal models do not fully replicate the complexity of these diseases, researchers will use cerebral organoids (miniature brains) grown from human-induced pluripotent stem cells containing wild-type or mutated tau. By treating the organoids with different tau seeds, the team will identify which cell types are vulnerable in Alzheimer's and PSP and why.

Identifying Brain-Wide Network Disruptions That Underlie Alzheimer's Disease

Ariel Gilad, PhD | Hebrew University of Jerusalem (Israel)

The main aim of this work is to identify brain-wide changes in neural networks that contribute to Alzheimer's disease. Researchers will record brain network activity in mouse models during the completion of cognitive tasks. The team plans to follow these patterns throughout each subject's lifespan to learn how individual traits affect these brain networks in Alzheimer's disease. The work could someday lead to individualized treatments for Alzheimer's disease.

Imaging the Rescue of Memory in Alzheimer's Disease Mouse Models

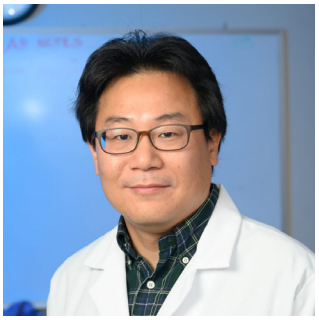
Matthew Isaacson, PhD | Cornell University
Mentor: Nozomi Nishimura, PhD

Working with a mouse model of Alzheimer's disease, project researchers will track blood flow in the brain before and after treatment with an antibody that restores blood flow. At the same time, they will assess whether the increased blood flow rescues neural activity in the Alzheimer's model, with a focus on the hippocampus, which is key to forming and accessing long-term memories.

Nonneuronal Contribution to Alzheimer's Disease

Ksenia Kastanenka, PhD | Massachusetts General Hospital & Harvard Medical School

Clinical trial failures in Alzheimer's disease result in part from the lack of a clear understanding of Alzheimer's causes and its progression. Using state-of-the-art methodology, researchers will push the envelope of current Alzheimer's understanding beyond neurons to address whether nonneuronal cells cause or contribute to Alzheimer's progression. The insight gained through this line of research will open venues for novel development of therapeutics.



Selective Cholinergic Activation Improves Hippocampal Activity

Seonil Kim, PhD | Colorado State University

Changes in brain rhythms (synchronized activity between nerve cells) in the hippocampus have been linked to memory impairments associated with Alzheimer's disease. These alterations in brain rhythms can be detected before people with Alzheimer's disease experience signs of memory loss. For this project, researchers will investigate whether aberrant brain activity and memory loss can be prevented or perhaps reversed in the early stages of Alzheimer's disease.

Understanding Brain Networks Causing Memory Impairments in Alzheimer's Disease

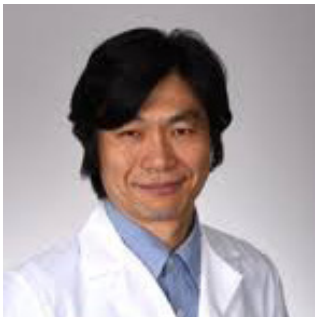
Tatsuki Nakagawa, PhD | University of California, Irvine
Mentor: Kei Igarashi, PhD

The processes underlying Alzheimer's disease are becoming better characterized, but the type of neuronal brain activity that is lost in Alzheimer's disease remains unclear. An understanding of this feature could lead to therapies to prevent memory loss in Alzheimer's. In this project, researchers will identify the underlying causes of brain cell dysfunction and test artificial reactivation of brain cell activity to restore associative memory in a mouse model of Alzheimer's.

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

Isabel Salas, PhD | The Salk Institute for Biological Studies
Mentor: Nicola Allen, PhD

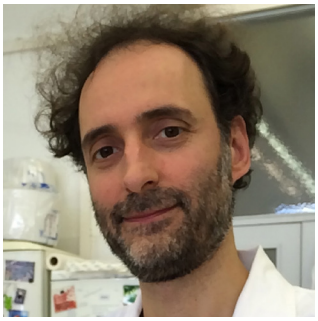
Neurons process information by making specialized connections with each other, called synapses, with assistance from other important types of cells, called astrocytes. Alzheimer's disease is associated with alterations in these connections. The aim of this project is to restore the correct function of astrocytes to rescue synaptic defects, using mouse models of Alzheimer's. The findings will be a further step toward a cure for this devastating disease.



The Relationship Between Sleep and Alzheimer's Disease Progression

Takashi Sato, PhD | Medical University of South Carolina
Mentor: Nicola Allen, PhD

Sleep disturbance is both an early symptom and an exacerbating factor of Alzheimer's disease. This project addresses the interaction between sleep and Alzheimer's progression using advanced microscopy and optical stimulation. Key components of the neural circuits underlying sleep first will be identified. Then, specific parts of these circuits will be manipulated during sleep to enhance sleep-related brain activity and determine how these manipulations affect cognition and Alzheimer's progression.



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

Carlos Saura, PhD | 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 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 this disruption 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.

Genomics: DNA Blueprint for Alzheimer's

Genes carry the instructions that cells use to make proteins, which build, operate, and repair tissue. Even slight changes to these instructions can result in an abnormally functioning protein, possibly affecting an individual's risk of a disease like Alzheimer's.

Only early-onset Alzheimer's disease, however, is consistently linked to mutations in known genes, representing about 10% of cases. The remaining 90% are associated with genetic risk variants scattered throughout the genome.

Researchers use powerful technologies to find genetic variations, patterns, and interactions in people with and without Alzheimer's. Other factors, such as environment and lifestyle, also can affect risk.

Genomics studies focus on triggers of Alzheimer's disease, how genes interact with the environment to influence risk, who is most at risk and might benefit from new treatments, and how treatments can be individually tailored.

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

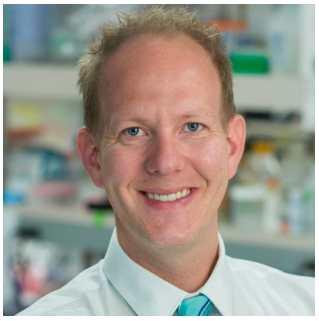
Kathryn Bowles, PhD | University of Edinburgh (UK)

Progressive supranuclear palsy and frontotemporal dementia are associated with 4R tau accumulation and with mutations in *MAPT*, the gene for tau. Researchers will develop brain organoids bearing these mutations and analyze them to identify early changes associated with 4R tau and disease development. Genetic sequencing on human brain tissues with the same *MAPT* mutations will be used to validate the findings and characterize how 4R tau accumulation affects the brain.

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

Camila de Avila Dal Bo, PhD | Arizona State University and Banner Sun Health Research Institute
Mentor: Diego Mastroeni, PhD

The nucleus incertus (NI), a brainstem region, was recently established as having a key role in memory, engaging in neural communication with the hippocampus, another brain region crucial for learning and memory. The specific functions and features of NI neurons in humans are currently unknown. The main goal of this project is to investigate the NI in humans and elucidate its role in dementia and Alzheimer's disease pathology.



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

Mark Ebbert, PhD | University of Kentucky

Many genes are known to be involved in Alzheimer's disease, but exactly how they are involved is unclear. The aim of this project is to identify DNA and RNA changes that drive Alzheimer's disease development and progression. The findings are expected to point the way to markers that might identify early Alzheimer's and lead to the development of meaningful therapies.

Systems Genetics Analysis of Alzheimer's Disease-Related Sleep Disruption

Niran Hadad, PhD | The Jackson Laboratory
Mentor: Catherine Kaczorowski, PhD

Traditional mouse models of Alzheimer's disease have yielded substantial insights regarding sleep loss in Alzheimer's disease. However, these models lack the genetic diversity needed to identify gene variants related to individual risk for Alzheimer's-related sleep loss and cognitive decline. Using a well-characterized, genetically diverse mouse model of Alzheimer's that better represents the complexity of human genetic diversity, researchers will identify variants related to individual risk for developing Alzheimer's-related sleep loss.

Validating the Receptor PILRA as an Alzheimer's Therapeutic Target

David Verne Hansen, PhD | Brigham Young University

Among emerging Alzheimer's therapeutics are drugs intended to promote the protective functions of microglia, the brain's immune cells. Most of these therapeutics target direct activation of TREM2, a key protein in microglial activation and maintenance of brain tissue. Researchers will explore whether blocking other microglial proteins could enable enhanced TREM2 function in microglial activation, offering a potentially safer approach than chronic activation of all microglia and possibly other cell types.

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

Ulrich Hengst, PhD | Columbia University

To sort out cell substances for breakdown or recycling, cell structures called endosomes form complexes with many other proteins, including transferrins. A transferrin complex linked to amyloid is proposed to regulate the retromer, another protein complex involved in sorting. Researchers will investigate whether this transferrin complex deregulates production of retromer components, interfering with this sorting, and whether removing one of these transferrins affects Alzheimer's pathology in a mouse model.

The Role of Small RNAs in Alzheimer's Disease

Laura Ibanez, PhD | Washington University in St. Louis

Researchers will characterize different populations of small RNAs (sRNAs) in the brain, plasma, and cerebrospinal fluid of individuals with Alzheimer's disease. The biological role of these RNAs will be investigated by identifying which sRNAs in these samples are different between cases and controls. The sRNAs will be used to generate tools for disease prediction, and researchers will use cellular models to investigate the biological consequences of dysregulating the identified sRNAs.

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

Justin Miller, PhD | University of Kentucky
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, the age of disease onset, and the 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.

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

Michael Miller, MD, PhD | Brigham and Women's Hospital & Harvard Medical School
Mentor: Christopher Walsh, MD, PhD, Boston Children's Hospital

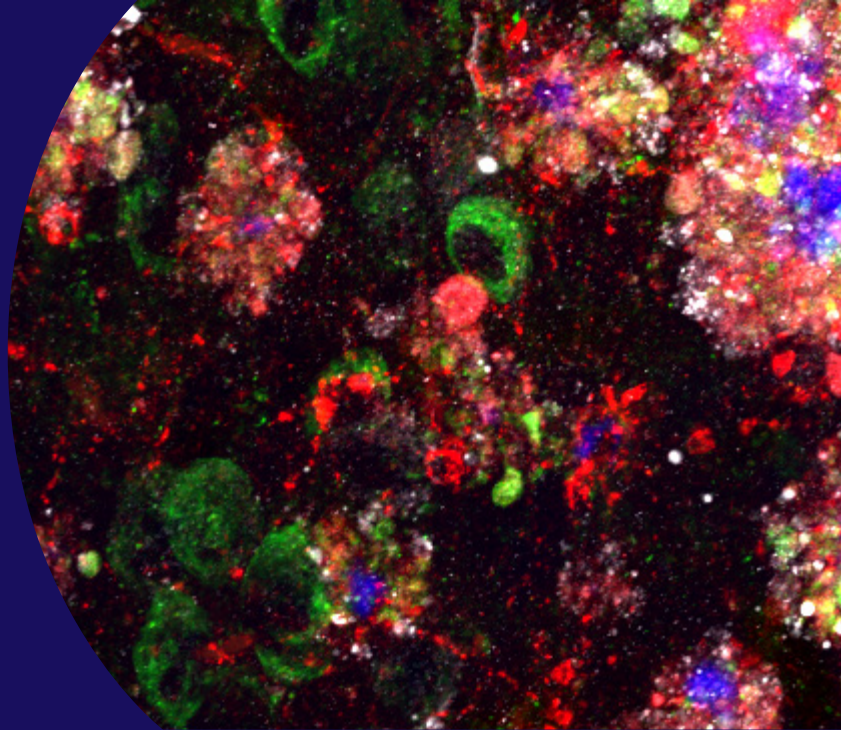
Recent research indicates that with age, brain cells build up new mutations in the DNA (known as somatic mutations), which appear to harm brain cells. This work will test the hypothesis that somatic mutations contribute in important ways to the pathologic progression of Alzheimer's and are related to other kinds of disease damage in brain cells, including oxidative stress.

Assessment of Tandem Repeat Variation in Alzheimer's Disease

Alejandro Martin Trujillo, PhD | Icahn School of Medicine at Mount Sinai

Tandem repeats (TRs) are stretches of DNA composed of two or more adjacent copies of a sequence arranged in head-to-tail pattern (e.g., CAG-CAG-CAG) that, in some cases, gain additional copies, expanding the number of repeats. 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.

Immunity & Inflammation



***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.*

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

However, a chronic buildup of debris, including toxic amyloid-beta and tau proteins, can short-circuit the cleanup process, causing chronic inflammation and cell damage.

Microglia are the brain's primary immune cells. Under normal conditions, they maintain equilibrium, clear unwanted particles, and respond to injuries and infections. In Alzheimer's, they acquire a disease-associated profile and release proinflammatory molecules that exacerbate disease mechanisms, including protein misfolding and energy dysfunction.

Researchers are looking at the causes of this imbalance and how to support cells, including microglia, in fighting Alzheimer's.

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

Sadaf Amin, PhD | Weill Cornell Medicine
Mentor: Li Gan, PhD

The brains of people with Alzheimer's disease have high levels of inflammation. Inflammatory factors are secreted by stressed cells and lead to deterioration of other cell types (e.g., neurons) in the brain. The project aim is to study the molecular pathways that govern this inflammatory response as potential targets for limiting the neuronal damage that leads to cognitive deficits and memory loss in Alzheimer's disease.

Understanding TREM2 Signaling as an Alzheimer's Disease Target

Thomas John Brett, PhD | Washington University School of Medicine in St. Louis
Mentor: Michael Gross, PhD

TREM2, a protein that interacts with other molecules in the brain, plays an important role in neuronal health and is a critical potential drug target in Alzheimer's disease. Our project will determine how TREM2 engages with amyloid-beta and identify molecules that modulate this interaction. An understanding of these processes and modulators will enable the development of therapeutics for Alzheimer's disease that target TREM2.

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

Xiaofen Chen, PhD | Xiamen University (China)

TREM2 is a protein specifically expressed in microglia, the immune cells of the brain. Variations in TREM2 have been linked to increased risk for Alzheimer's and other neurodegenerative diseases. For this project, researchers will study the mechanism by which TREM2 modulates Alzheimer's-related pathways in microglia and neurons to influence cognition and pathology in mouse models of the disease.

Mapping the Crosslink of Senescence and Inflammation in Neurodegeneration

Violeta Duran Laforet, PhD | UMass Chan Medical School
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 cells can no longer give rise to new cells. Microglia, the brain's primary immune cells, become senescent in Alzheimer's disease. Using an innovative approach called MERFISH, researchers will examine hundreds of genes in tissue samples to investigate whether microglia initiate inflammation in the aging brain and where the senescent cells are located. The findings may yield new therapeutic targets.

Understanding the Microglia Cell Surface in Alzheimer's Disease

Brandon Holmes, MD, PhD | University of California, San Francisco
Mentors: James Wells, PhD & Martin Kampmann, PhD

Proteins on the microglia cell surface, known as the surfaceome, are a critical hub for neuroprotective, neurotoxic, and neuroinflammatory signaling in the diseased brain. Being able to precisely target and manipulate diverse microglia states holds tremendous experimental, diagnostic, and therapeutic potential. Researchers will use innovative technologies to comprehensively define surfaceome changes in Alzheimer's disease microglia, yielding the first human cell-surface protein map in this cell type and disease context.

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

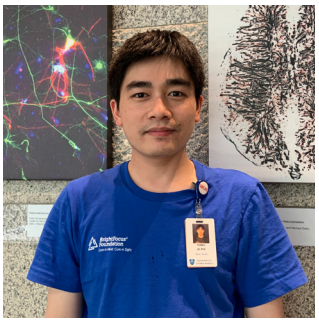
Soyon Hong, PhD | University College London (UK)

"Activated" microglia surrounding amyloid plaques in Alzheimer's brains are called disease-associated microglia, or DAMs. Pilot studies implicate DAM-like cells early on in Alzheimer's models when synapses are vulnerable to loss. Using mouse models and human samples, researchers will test whether DAMs facilitate synapse loss in Alzheimer's via upregulation of a protein called SPP1, or osteopontin, and determine whether this effect depends on other immune proteins known as the complement system.

Illuminating the Functions of Genes Mutated in Alzheimer's Disease

Harini Iyer, PhD | Stanford University
Mentor: William Talbot, PhD

Microglia chew up dead cells and fight infections in the brain. Material they ingest passes through the lysosome for breakdown and recycling. Mutations in genes associated with microglia and lysosome function have been identified in people with Alzheimer's disease. Researchers will investigate the relevance of these genes for normal microglial and lysosomal activity and how mutations may lead microglia to switch from being beneficial to being harmful to brain cells.



The Role of TREM2 T96K Mutation in Alzheimer's Disease

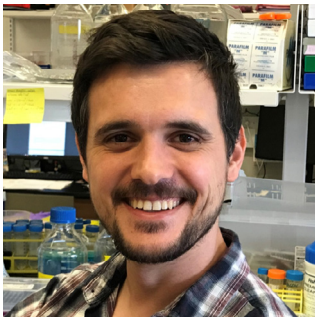
Hoang Le, PhD | Massachusetts General Hospital
Mentors: Ana Griciuc, PhD & Rudolph E. Tanzi, PhD

The aim of this work is 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 models of microglia, the immune cells of the brain. The insights obtained should be useful for Alzheimer's drug discovery and development targeting TREM2.

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

Renzo Mancuso, PhD | Vlaams Institute Voor Biotechnologie (Belgium)

Neuroinflammation is linked to Alzheimer's disease susceptibility in genetic studies, suggesting inflammation as a driver rather than consequence of the disease. Researchers will dissect the contribution of microglia and lipid metabolism in the Alzheimer's brain by examining links between Alzheimer's genetic risk, microglia, and lipid metabolism. The team will use stem cell-derived microglia injected into Alzheimer's mouse models and single cell RNA sequencing for in-depth analysis of microglial function.



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

Miguel Moutinho, PharmD, PhD | Indiana University
Mentor: Gary Landreth, PhD

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

Metabolic Reprogramming of Microglia in Alzheimer's Disease

Jonas J. Neher, PhD | German Center for Neurodegenerative Diseases (Germany)

Microglia are immune cells with a "barrier function" of shielding the brain from amyloid plaque damage. Mutations that disrupt this barrier lead to heightened Alzheimer's disease risk, but genetic elimination of a newly identified molecular pathway significantly strengthens the barrier. Researchers will characterize the long-term effects of manipulating this pathway in two independent mouse models of Alzheimer's, focusing on molecular and functional changes in microglia, Alzheimer's pathology, and cognitive function.

Exploring Microglial Activation in Normal Physiology and Disease

Gabriela Farias Quipildor, PhD | Icahn School of Medicine at Mount Sinai
Mentor: Stephen Salton, MD, PhD

During normal aging and Alzheimer's disease, microglia, the brain's primary immune cells, take on new features when they are activated. The mechanisms involved in the different activation states of microglia are largely unknown, however. Researchers will dissect the involvement of key regulators of microglial activation in normal and disease states to yield new insights into the role of microglia in Alzheimer's pathogenesis, potentially identifying new therapeutic targets.

Targeting Brain Immune Cells as a Novel Therapeutic in Alzheimer's Disease

Carla Rothlin, PhD | Yale University
Co-Principal Investigator: Sourav Ghosh, PhD

A microglial protein that seems to confer protection against Alzheimer's disease is the focus of this project. Researchers will evaluate each separate function of this protein, AXL, to identify which one is associated with the protective effects. AXL is promising in part because drugs that target it have been being developed for many years, and a natural molecule that activates it has already been identified.

Pinning Down How Alzheimer's Risk Gene *BIN1* Controls Brain Immune Responses

Ari Sudwarts, PhD | University of South Florida
Mentor: Gopal Thinakaran, PhD

The focus of this project is a protein, B1N1, that microglia package for delivery to target cells. Researchers will track proteins that interact with B1N1 in activated microglia and their effects on target cells. The work is expected to result in a useful molecular tool for studying the link between risk genes and specific cell types in Alzheimer's and other diseases.

A New Intervention to Control Inflammation in Alzheimer's Disease

Yuxiang Sun, MD, PhD | 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.

Reprogramming Microglia Through Astrocyte Manipulation in the Alzheimer's Brain

Julia TCW, PhD | 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.

Metabolism Driving Cell Death and Inflammation in Alzheimer's Disease

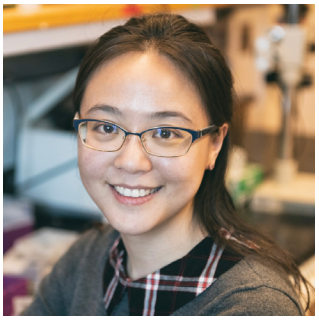
Larissa Traxler, PhD | University of Innsbruck (Austria)
Mentor: Jerome Mertens, PhD

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 become 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.

Understanding the Role of the Immune System in Frontotemporal Dementia

Rebecca Wallings, PhD | University of Florida
Mentor: Malu Tansey, PhD

The brain's microglia may not be the only immune cells involved in frontotemporal dementia (FTD). Blood immune cells called monocytes infiltrate the brain and could be implicated in neurodegeneration. Lysosomes, cell organelles responsible for protein recycling and cell signaling, are key to immune cell function and may be dysregulated in FTD monocytes. Using mouse models and patient samples, researchers will examine the role of monocytes and dysfunctional lysosomes in FTD.



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

Huixin Xu, PhD | Boston Children's Hospital
Mentors: Mark Andermann, PhD & Maria Lehtinen, PhD

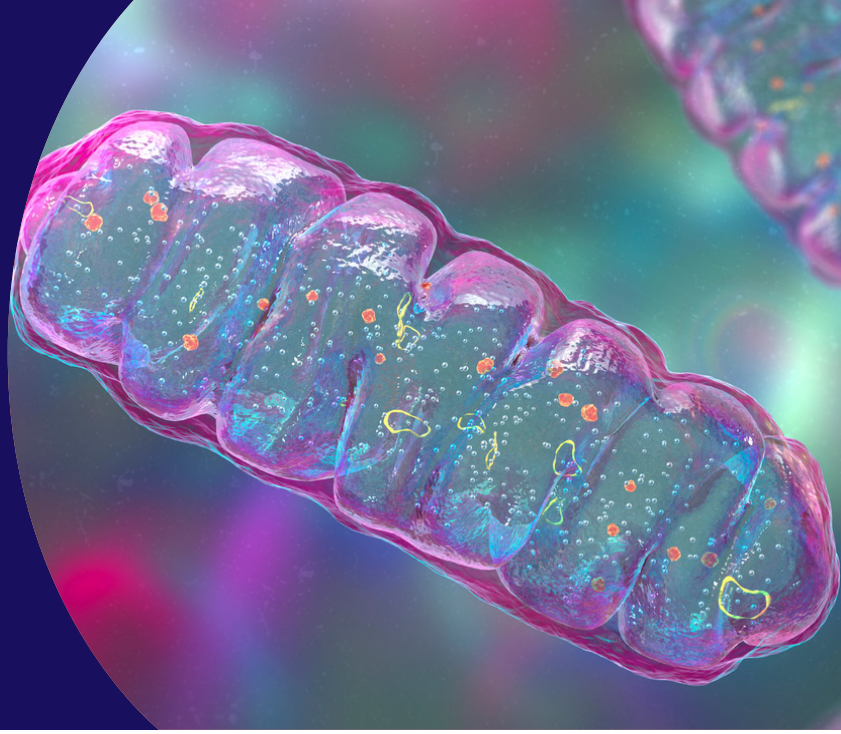
The project goal is to enable treatments for Alzheimer's disease that curb brain inflammation at the barriers separating the brain from the rest of the body. The focus is on a network of blood vessels and other cells called the choroid plexus. Researchers will use newly developed imaging tools to explore blood-borne immune cells entering the choroid plexus in Alzheimer's disease models and to test for barrier breakdown and blood vessel leakage.

How the Brain's Support Cells Interact With Fats and Contribute to Alzheimer's Disease

Till Zimmer, PhD | Weill Cornell Medicine
Mentors: Anna G. Orr, PhD & Adam L. Orr, PhD

For this work, researchers will take a first look at how different factors affect astrocyte lipid processing in dementia. In Alzheimer's disease, astrocytes may fail to offer the appropriate lipid support, leaving neurons to become dysfunctional or even degenerate. The research team also will assess how the newly identified astrocyte-processed lipids affect nerve cell function, adding links to the chain connecting how the brain uses lipids and related processes in the development of Alzheimer's disease.

Metabolism & Bioenergetics

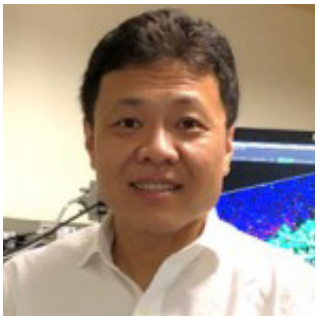


Above: *A 3D illustration of mitochondria, a membrane-enclosed cellular organelle that produces energy in the body.*

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 aging, and this decline is one of the earliest and most consistent events in Alzheimer's disease.

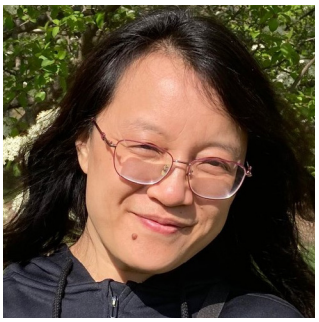
Metabolic dysregulation impacts brain processing speeds and cognition, and dysfunctional mitochondria (known as the "power plants" of cells) contribute to a neurotoxic environment by releasing reactive oxygen species and other molecules that evoke inflammatory responses in microglia.



Mitochondrial Calcium Deregulation and Memory Loss in Alzheimer's Disease

Heng Du, MD, PhD | University of Kansas Center for Research

Defective mitochondrial calcium modulation has been repeatedly linked with synaptic dysfunction and neuronal death in Alzheimer's disease research. In this study, researchers will examine the role of mitochondrial calcium uniporter (MCU) deregulation in the development of mitochondrial and synaptic pathology in Alzheimer's. Positive findings will enhance our understanding of Alzheimer's and shed light on the development of novel Alzheimer's therapeutic avenues targeting MCU.



Mitochondrial DNA Damage and Microglial Activation in Alzheimer's Disease

Lan Guo, PhD | University of Kansas Center for Research

The project aim is to investigate a cause-effect relationship between oxidative damage and subsequent leakage of mitochondrial DNA 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 potential for the development of innovative therapies.

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

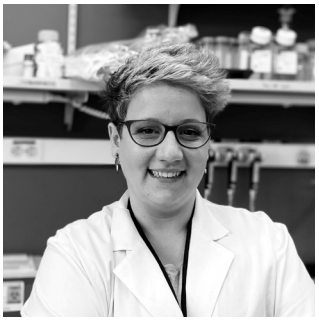
Makoto Ishii, MD, PhD | Weill Cornell Medicine

During the earliest stages of Alzheimer's disease, when memory is relatively intact, significant changes in immune and metabolic function contribute to the disease, although what causes these changes is unclear. Researchers will 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.

Characterizing the Range of Tau Forms Linked to Different Brain Diseases

Henry Pan, PhD | University of California, San Francisco
Mentors: Carlo Condello, PhD & William DeGrado, PhD

Researchers on this project aim to develop a tool to rapidly screen for different types of tau protein in cells and animal models, which can be used to confirm or isolate the specific tau being studied. This work is expected to generate a tool to rule in or rule out the validity of current rodent models of tau protein variants and ensure that studies focus on models using variants that are most like those in humans.



Testing Candidate Therapies Targeting Dysfunction of Support Cells in Alzheimer's Disease

Maria Virtudes Sanchez-Mico, PhD | Massachusetts General Hospital
Mentor: Brian Bacskai, PhD

In this work, researchers will evaluate whether dysfunction in astrocytes tracks with buildup of disease-related amyloid-beta in the brain. They will follow these processes in real time using powerful, sophisticated tools and then assess how two candidate treatments fare in restoring proper astrocyte function. The results are expected to highlight potential early targets for treatments in Alzheimer's disease.

Leptin Protein and Its Involvement in Alzheimer Disease in Down Syndrome

Lorena Sordo, MSc, PhD | University of California, Irvine
Mentor: Elizabeth Head, PhD

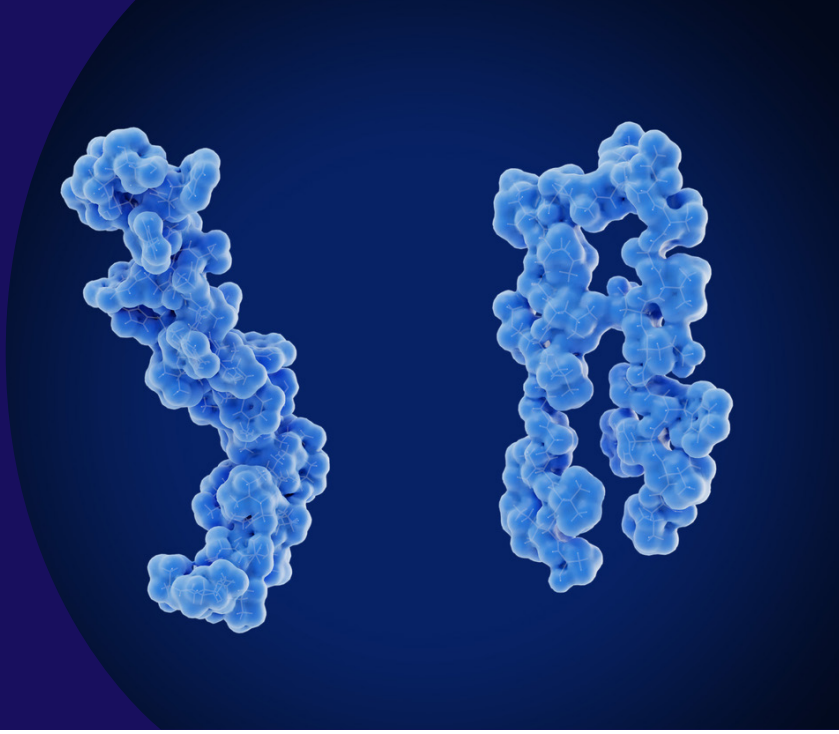
People with Down syndrome (DS) have a high risk of developing Alzheimer's disease. Midlife obesity and late-life weight loss also increase the risk. People with DS tend to be overweight, possibly entailing additional risk of developing Alzheimer's. Researchers will assess whether the appetite-regulating hormone leptin is associated with abnormal deposition of toxic proteins in people with DS and with and without Alzheimer's.

Testing a Mitochondria-Targeting Compound in Alzheimer's Disease

Qi Wang, PhD | Swiss Federal Institute of Technology (Switzerland)
Mentor: Johan Auwerx, MD, PhD

Damage to mitochondria well before symptoms of Alzheimer's disease emerge is the focus of this project. Researchers will assess whether a compound called 9-TB can support healthy stress responses in mitochondria. The aim is to set the stage for Phase I clinical studies of similar drug candidates that generate this healthy mitochondrial stress response.

Other Misfolded Proteins



Above: *An illustration of the amyloid beta protein (left) and its misfolded form (right), which accumulate in the brain as amyloid plaques.*

Most dementia diagnosed in people over 80 years old is of mixed etiology, meaning that 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, such as frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease, and the presence of a second misfolded protein in Alzheimer's, in addition to amyloid, increases the extent of cognitive impairment. Vascular dementia, in which 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.

Spreading of Harmful Proteins by Support Cells in Alzheimer's Disease

Olga Chechneva, PhD | Shriners Children's Northern California

Researchers will assess the effectiveness of a commercial dietary supplement on slowing accumulation of tau tangles. The research team will synthesize small molecules that bear effective features of the supplement and test how well they prevent tau accumulation in tissue samples from Alzheimer's disease brains. The most effective small molecules will undergo further testing to analyze how their structure influences their activity against tau misfolding.

Disrupted Nuclear Protein Trafficking in Frontotemporal Dementia

Alyssa Coyne, PhD | Johns Hopkins University School of Medicine

A shared protein factor between frontotemporal dementia and amyotrophic lateral sclerosis is the focus of this project. A variant of this protein is tied to dysfunctional nuclear surveillance in neurons that leads to buildup of another protein, TDP-43, implicated in these two diseases and in Alzheimer's disease. For this work, researchers will follow the steps from failed surveillance to cell injury, highlighting potential therapeutic targets for preventing this injury.

Drivers of Vulnerability to Alzheimer's Disease Neuropathological Changes

Nicole Liachko, PhD | Seattle Institute for Biomedical and Clinical Research

The presence of TDP-43 aggregates in neurons correlates with worse brain atrophy, more severe cognitive impairment, and more rapid cognitive decline in Alzheimer's disease. Understanding the contribution of TDP-43 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.

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

Ana Rita Agra de Almeida Quadros, PhD | Massachusetts General Hospital
Mentor: Clotilde Lagier-Tourenne, MD, PhD

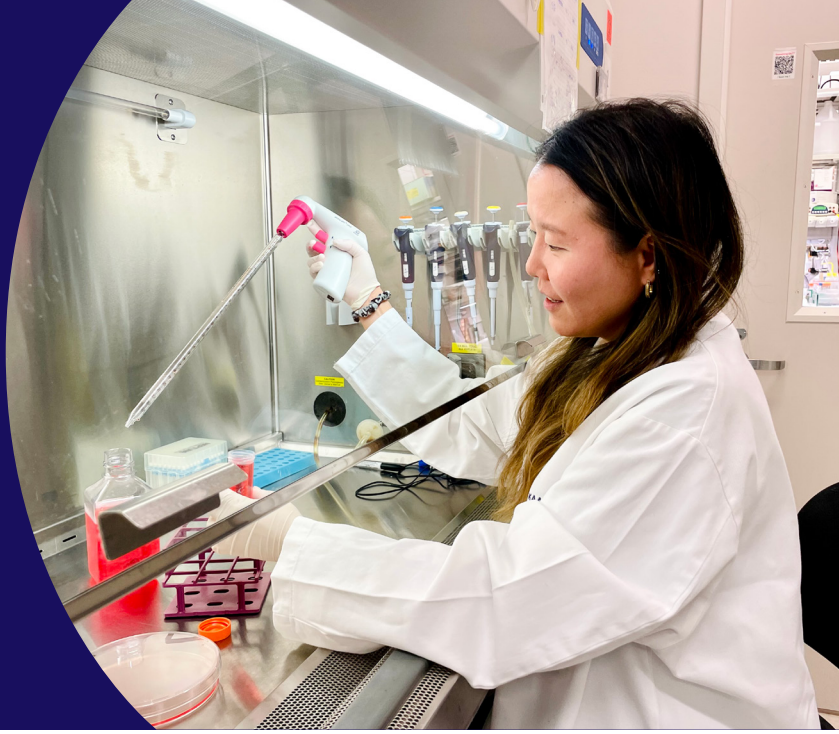
TDP-43 is one of the proteins that abnormally accumulates in up to 50% of patients with Alzheimer's disease. Stathmin-2, a protein crucial for neuronal function, is lost in neurons with abnormal TDP-43. This project will determine whether Stathmin-2 is altered in people with Alzheimer's disease and represents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

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

Sandra O. Tomé, MSc, PhD | Catholic University of Leuven (Belgium)
Mentor: Dietmar Thal, MD

LATE, or limbic-predominant age-related TDP-43 encephalopathy, is a type of dementia. Pathological aggregates with TDP-43 protein are a commonality of Alzheimer's disease and other tauopathies, such as LATE. In LATE, this aggregation is the major cause of the disease, whereas in Alzheimer's, amyloid-beta and tau proteins also accumulate, worsening cognition. Researchers will assess molecular similarities in TDP-43 pathology between Alzheimer's and LATE and how it impacts the clinical diagnosis.

Research Tools & Resources



Above: *Dr. Chung doing a cell culture experiment in the lab. Photo courtesy of Daheun Chung, PhD, Baylor College of Medicine.*

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.

Our 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

Sjoerd Finnema, PhD | Foundation for the National Institutes of Health

Brain cells (neurons) communicate through connections called synapses. Synaptic loss is one of the earliest biomarkers of Alzheimer's disease and highly correlates with cognitive performance. In this project, researchers plan 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.

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

Ann-Charlotte Granholm-Bentley, PhD, DDS | University of Colorado Anschutz Medical Campus
Co-Principal Investigators: Elizabeth Head, PhD, University of California, Irvine; Elliott Mufson, PhD, Barrow Neurological Institute

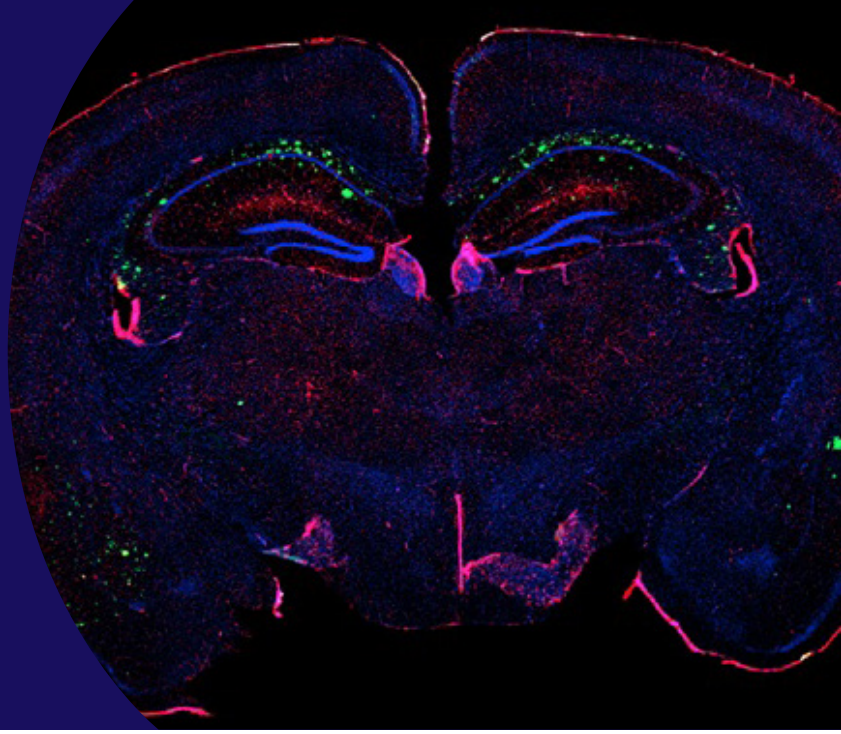
The focus of this special project is to develop a strong collaborative network among six research groups, with the long-term goal of determining the neurobiological mechanisms underlying the onset of Alzheimer's disease-type dementia in Down syndrome.

Expanding and Enhancing LASI-DAD for Better Understanding of Alzheimer's and Dementia

Jinkook Lee, PhD | University of Southern California

The Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study of 4,096 older adults is the only nationally representative study on late-life cognition and dementia in India. Researchers will expand the project by analyzing chemical tags on DNA that affect how genes are used, known as epigenetics. They also will further validate participants' dementia status. The findings will yield valuable dementia-related epigenetic information from a large study population.

Sex-Based Differences



Above: *Brain blood vessels (red) shown in relation to amyloid plaques (green). Photo courtesy of Charly Abi Ghanem, PhD, Albany Medical College.*

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 their longer life expectancies compared with 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—such as 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.

Influence of Testosterone on Dementia in Male Mice

Charly Abi Ghanem, PhD | Albany Medical College
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 reflecting multiple causes of dementia.

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

Gael Chetelat, PhD | University of Caen Normandy (France)

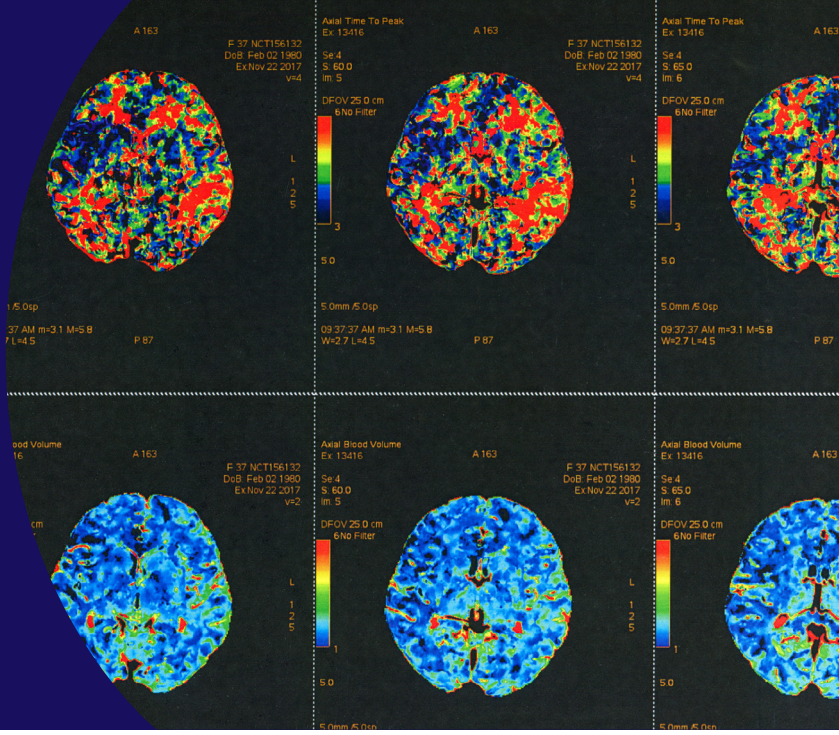
This project will identify sex-specific risk profiles associated with Alzheimer's disease. The aim is to contribute to the development of sex-specific diagnostic procedures for early detection of dementia and of sex-specific interventions.

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

Erin Reed-Geaghan, PhD | 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 for these sex differences are unclear. The studies in this proposal are designed to identify the developmental processes that establish and perpetuate sex differences in this inflammatory response.

Sleep & Circadian Rhythm



Above: *MRI scans of the brain.*

Chronic sleep disruption plays a role in Alzheimer's disease. The brain depends on nightly deep sleep to flush waste material and toxins, including misfolded proteins, and break down and dispose of amyloid-beta plaques present in early Alzheimer's.

Sleep patterns are governed by circadian rhythm, 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.

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

Moustafa Algamal, PhD | Massachusetts General Hospital
Mentor: Ksenia Kastanenka, PhD

Slow-wave sleep is disrupted in Alzheimer's disease. Researchers plan to identify and activate the neurons responsible for slow-wave sleep regulation and improve their function in Alzheimer's disease models. The first approach will use a novel genetic technology in these models to activate the neurons with light, followed by assessments of memory and Alzheimer's pathology. The second approach relies on pharmacological methods to support the function of these neurons.

The Role of Sleep in Alzheimer's Disease Disparities

Omonigho Bubu, MD, PhD | New York University School of Medicine

Researchers will examine whether Black people with obstructive sleep apnea experience higher tau accumulation and greater neurodegeneration for a given level of amyloid burden compared with white people. They also will assess socioeconomic status, cumulative stress exposure, and vascular risk as mediators of any race-specific effects. The long-term goal is to improve sleep quality and control vascular risk using noninvasive ambulatory methods as novel therapeutic targets for Alzheimer's prevention in Black people.

Disrupted Sleep Cycles and Alzheimer's Disease Risk

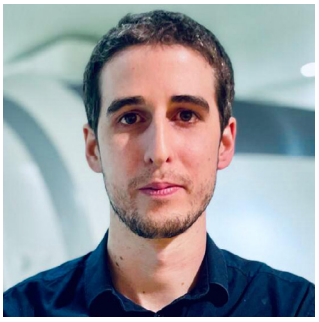
Jingyuan Chen, PhD | Massachusetts General Hospital

Researchers will use cutting-edge imaging to track metabolic changes in the synapses during sleep-wake cycles in people with and without known risk for Alzheimer's disease. In addition, the team will follow how the use of glucose tracks with brain waves associated with Alzheimer's. The work will reveal more of the picture of how Alzheimer's disease and disrupted sleep are linked.

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

Christopher Daniel Morrone, PhD | Centre for Addiction and Mental Health (Canada)
Mentor: Wai Haung (Ho) Yu, PhD

In this project, researchers will investigate the effects of sleep on memory, neuronal function, and markers of protein recycling and pathology to see if improving protein recycling can rescue cognition. They will use artificial intelligence models 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.



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

Maxime Van Egroo, PhD | Maastricht University (The Netherlands)
Mentor: Heidi Jacobs, PhD

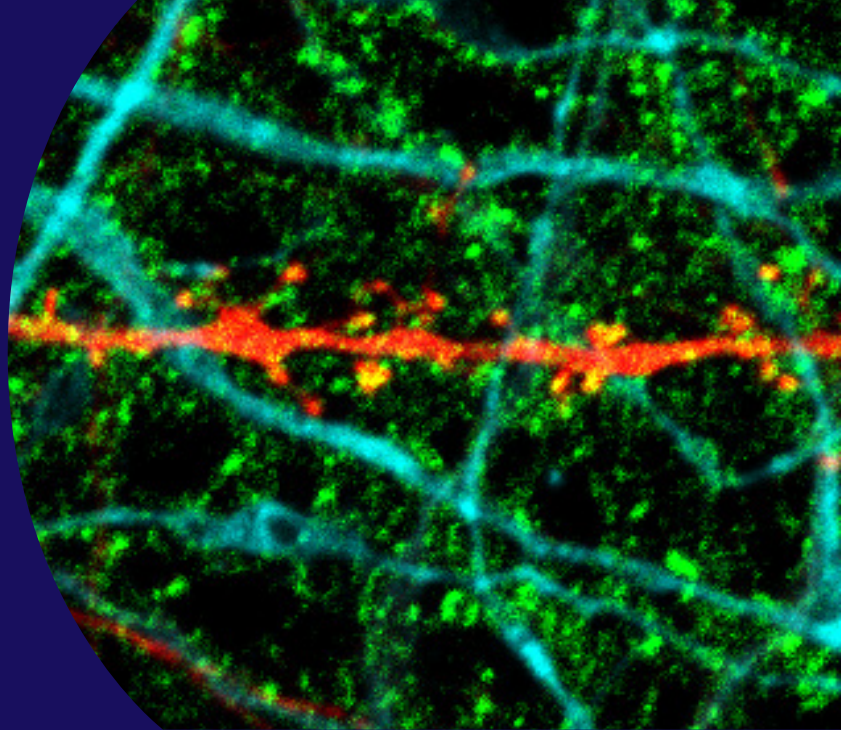
The brainstem region known as the locus coeruleus, or LC, is crucial to sleep-wake cycle consolidation and is among the first regions affected by Alzheimer's. The project aim is to use advanced brain-imaging methods to extensively characterize the LC in healthy adults across the lifespan. Researchers will determine how modifications in LC structure and function relate to sleep-wake cycle alterations, accumulation of hallmark Alzheimer's pathologies, and ultimately cognitive decline.

Sleep Restoration, Microglia, and Alzheimer's Disease

Qiuchen Zhao, MD, PhD | Massachusetts General Hospital
Mentor: Stephen Gomperts, MD, PhD

Alzheimer's disease is associated with profound sleep disturbances that contribute to disease progression, particularly at the 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.

Tau

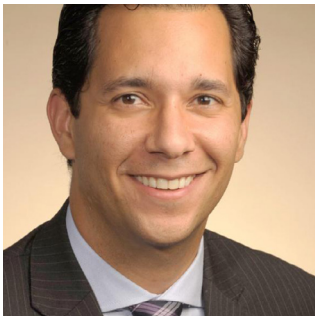


Above: *Immunofluorescence image of tau (orange) in brain cells. Photo courtesy of Kristie Stefanoska, PhD, Flinders University of South Australia.*

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 become misshapen 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.



Twisting Away Toxic Proteins in Alzheimer's Disease

Jose Abisambra, PhD | University of Florida

This research group has identified a family of proteins that alter tau aggregation, including one that can disaggregate tau aggregates into smaller nontoxic entities. The project aim is to elucidate the mechanisms of this disaggregation to facilitate design of therapeutic strategies that mimic this activity. Researchers will identify members of this protein family that exhibit this activity and examine the properties of tau that facilitate toxic aggregation and accumulation.

Does the Little-Studied Big Tau Protect Against Alzheimer's Disease?

Daheun Chung, PhD | Baylor College of Medicine
Mentor: Huda Y. Zoghbi, MD

This project brings the focus to the Alzheimer's-related protein big tau, a relatively uncommon form of tau, to determine if it protects against Alzheimer's. The research team will use mouse models to examine proteins that interact with big tau, which could highlight treatment targets for Alzheimer's disease.

How Are Phosphates Removed From Tau?

Jason Gestwicki, PhD | University of California, San Francisco
Co-Principal Investigator: Daniel Southworth, PhD

Enzymes that add phosphate groups to tau and affect its disease-related status are well-known, but less attention has gone to enzymes, termed phosphatases, that remove these phosphates. Specific "helper" proteins, or chaperones, can bind to tau and recruit a specific phosphatase, PP5. Researchers 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 phosphates from tau.

Defining Connections Between Oxidative Stress and the Disease Protein Tau

Lindsey Goodman, PhD | Baylor College of Medicine
Mentor: Hugo Bellen, DVM, PhD

Lipid dysregulation and accumulation of reactive oxygen species (ROS) are implicated in early Alzheimer's disease. In animal studies, glia resolve droplets of dysregulated lipids transferred by neurons, protecting neurons from ROS-induced damage. Tau may play a normal role in the resolution of ROS in the brain before tau tangles form. Researchers will investigate how tau mediates ROS in Alzheimer's by disrupting lipid droplet formation and examine tau hyperphosphorylation and aggregation.

A Newly Discovered Version of Toxic Tau as a Therapeutic Target in Alzheimer's Disease

Daniel C. Lee, PhD | University of Kentucky Research Foundation

The potential for citrullinated tau to be especially toxic is the focus of this project. Researchers will assess two therapeutic approaches targeting citrullinated tau, either preventing the citrullination or vaccinating against the citrullinated form. The team will test both potential therapies in animal models of Alzheimer's disease, comparing their effects on disease progression and cognitive decline and opening up a new area of research in Alzheimer's disease.

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

Nicole McKay, PhD | Washington University School of Medicine in St. Louis
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, abnormal tau can spread along white matter pathways, causing a breakdown in brain functions. The aim of this project is to understand how tau levels impact the integrity of brain pathways and lead to a decline in cognition.

Do Post-Translational Modifications Cause Tau to Shapeshift?

Sue-Ann Mok, PhD | University of Alberta (Canada)
Co-Principal Investigator: Carlo Condello, PhD, University of California, San Francisco

Tau protein forms specific shapes as the molecules stack together into aggregates that contribute to the development and progression of Alzheimer's disease. If the factors that drive tau to take on the specific shapes can be identified, this pathological process might be prevented. Researchers will use advanced biochemical technologies to study hundreds of potential factors, called post-translational modifications, and identify key factors leading to the tau shapes observed in Alzheimer's.

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

Laia Montoliu-Gaya, PhD | University of Gothenburg (Sweden)
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.

Exploring the Origins of Tau Pathology in the Human Brainstem Locus Coeruleus

Meaghan Morris, PhD, MD | Johns Hopkins University School of Medicine

This project focuses on the locus coeruleus, where the Alzheimer's disease-related protein tau first begins building up in the brain. The study will involve brain samples from people with and without dementia across a range of ages to track how tau first accumulates and spreads. Researchers hope that the origin story of how tau takes over the brain will offer a window into the origins of Alzheimer's disease itself.

Characterizing Heterogeneity of Tau Pathology in Alzheimer's Disease

Alexa Pichet Binette, PhD | Lund University (Sweden)
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.

The Role of the Basal Forebrain in Early Detection of Alzheimer's Disease

Joost Michiel Riphagen, MD, PhD | Massachusetts General Hospital
Mentor: Keith A. Johnson, MD

Using cutting-edge imaging techniques, researchers will follow the progression of tau buildup in a region at the bottom of the brain called the basal nucleus of Meynert. This region has many connections to other brain regions and plays an important role in memory. Detection of tau accumulation in this structure could allow for the earliest recognition of Alzheimer's disease-related processes and support earlier detection and treatment.

Identification of Proteins That Reduce Pathological Aggregates in the Brain

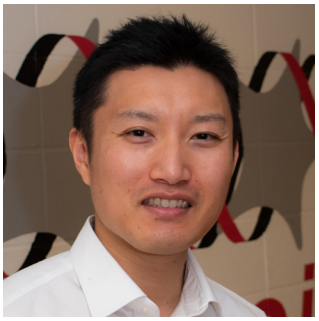
Wilfried O. Rossoll, PhD | Mayo Clinic Jacksonville

The project goal is to identify which proteins associate with tau protein aggregates may contribute to tau pathology in Alzheimer's. Researchers will precisely map the composition of insoluble protein aggregates in the context of living brain tissue via proximity labeling and proteomic analysis. This approach also is optimized for studying the tau transition from a physiological to pathological form in cultured neurons and brain tissue models of Alzheimer's.

Tau Treatment Targets for Alzheimer's Disease

Kristie Stefanoska, PhD | Flinders University of South Australia (Australia)
Mentor: Arne Ittner, PhD

The progression of Alzheimer's disease correlates with abnormal tau accumulation. Once modified, tau collects with other tau proteins and forms larger, abnormal structures in the brain. Disease-promoting sites on tau are essential in driving these modifications. Researchers will investigate how removing the disease-promoting sites on tau could reduce abnormal modification of tau and thus serve as a novel therapeutic approach to mitigate processes underlying Alzheimer's disease.



Clock-Driven Sleep Fragmentations in Tauopathy

Masashi Tabuchi, PhD | Case Western Reserve University School of Medicine

For this work, researchers will elucidate the role of inactivation states of voltage-gated sodium channels in regulating circadian rhythms and sleep in Alzheimer's disease and related tauopathies. Using comparative in vivo (*Drosophila*) and in vitro (induced pluripotent stem cells) assessments, they will test whether manipulating inactivation states of voltage-gated sodium channels in Alzheimer's disease leads to molecular and cellular changes and subsequent dysfunctional circadian rhythms, sleep alterations, and disease progression.

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

Susanne Wegmann, PhD | German Center for Neurodegenerative Diseases (Germany)

Proteins that form pores in the cell nucleus called Nups (for nucleoporins) can have aberrant interactions with the Alzheimer's disease protein tau. These interactions can interfere with normal movement of molecules in the cell, including into the nucleus. Researchers will identify the key players in these interactions in human neurons in association with Alzheimer's-related brain changes. They also will use cutting-edge techniques to screen for cellular molecules that can influence these aberrant interactions.

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 "translate" science into useful ways of diagnosing, treating, and managing Alzheimer's disease.

This translation can take many different forms, from using smartphone-based testing to monitor cognitive status, to finding ways to improve sleep and exercise, to promoting lifestyle activities associated with brain health as 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.

Understanding the Beneficial Role of Sleep in Cognitive Deficits

Christelle Anaclet, PhD | University of California, Davis
Co-Principal Investigator: Heinrich Gompf, PhD

Sleep is necessary for cognition, and cognitive deficits and sleep disruption are major symptoms of Alzheimer's disease. Using a unique mouse model, this team will test sleep enhancement as a way to reduce cognitive deficit in Alzheimer's. They will conduct the first investigations of the mechanism underlying sleep benefits for memory, providing new targets for pharmacological and interventional strategies to treat sleep and cognitive symptoms in Alzheimer's.

Washing Alzheimer's Disease Off the Brain

Michele Cavallari, MD, PhD | Brigham and Women's Hospital & Harvard Medical School

This team is studying a protective mechanism recently characterized in animal models. The mechanism involves drainage of potentially harmful Alzheimer's-associated toxins, such as amyloid-beta and tau proteins, outside the brain. Researchers are using data from two large international Alzheimer's studies for the first-in-human investigation of this mechanism in people at high risk for Alzheimer's-associated dementia. The findings could support development and testing of therapeutic approaches to prevent Alzheimer's dementia.

Understanding Early Effects of Amyloid and Tau in Different Memory Domains

Xi Chen, PhD | University of California, Berkeley
Mentor: William Jagust, MD

Older adults with normal cognition who present with Alzheimer's pathology will first undergo imaging to reveal activation differences among brain regions while viewing pictures of an object, a scene, and an object in a scene. Participants then will take a surprise memory test. Further imaging will characterize amyloid-beta and tau deposition to determine their specific effects on different memory performance domains and which brain regions are affected.

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

Claire Clelland, MD, PhD | University of California, San Francisco
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) share a genetic cause—a repeat expansion (GGGGCC) in the *C9orf72* gene. Using patient-derived cells, researchers will develop novel CRISPR-based therapeutic gene-editing technologies to reverse the cellular pathology resulting from repeat expansion. Results will advance use of CRISPR for therapeutic editing in FTD/ALS, inform understanding *C9orf72* gene regulation, and form the basis for investigating other repeat expansion and single gene disorders.

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

Yuval Dor, PhD | Hebrew University of Jerusalem (Israel)

Researchers will develop a liquid biopsy to monitor cell death in the brain and other key tissues during Alzheimer's disease development. Using cell type-specific DNA methylation patterns, the team will identify tissue sources of DNA released by dying cells into the blood. They will apply the assay to blood samples from individuals without Alzheimer's, those with mild cognitive impairment who develop Alzheimer's disease, and patients with established Alzheimer's.

This award is supported by the Sephardic Foundation on Aging.

Does Aß Drive Tau Spreading in Alzheimer's Disease?

Nicolai Franzmeier, PhD | Ludwig Maximilian University of Munich (Germany)

Amyloid pathology is assumed to trigger the spread of tau pathology across interconnected brain regions, and neuronal activity enhances tau spreading across connected neurons. For this project, researchers will address whether tau spreading across connected brain regions is specifically enhanced by amyloid-induced hyperconnectivity in patients with Alzheimer's. Using cutting-edge neuroimaging protocols, the team will determine whether early amyloid deposition in Alzheimer's is associated with neuronal hyperactivity that triggers tau spread.

Testing Sensitivity of New Markers of Brain Function for Alzheimer's Disease in People With Normal Cognition

Peter Fried, PhD | Beth Israel Deaconess Medical Center & Harvard Medical School

Working with healthy older adults, researchers will use a new blood test that can detect the Alzheimer's-related protein amyloid-beta and will collect data on brain activity relative to the amount of amyloid-beta. With more information about changes in the brain during preclinical Alzheimer's and how to measure them, researchers can develop new therapies to delay or prevent dementia.

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

William Korinek, PhD | Astrocyte Pharmaceuticals
Co-Principal Investigators: Theodore Liston, PhD; James Lechleiter, PhD, Astrocyte Pharmaceuticals & University of Texas Health Science Center

AST-004 is a promising therapeutic for traumatic brain injury (TBI) with significant efficacy across lab models, yielding reductions in cell death, edema, and markers of neuronal and astrocyte injury. In a repetitive TBI mouse model, AST-004 reduced long-term neurological deficits in motor coordination and anxiety. AST-004 also reduced edema and brain injury markers in a large animal TBI model and has shown preliminary efficacy with increased brain cell viability in two Alzheimer's mouse models. The project will support preclinical studies of AST-004 as well as the development of an oral formulation of the drug.

Jointly funded with the Medical Technology Enterprise Consortium.

Identifying Disease Mechanisms in Neurodegeneration Using Electrophysiology

Sanjeev Kumar, MD | Centre for Addiction and Mental Health (Canada)
Co-Principal Investigators: Tarek Rajji, MD, Daniel Blumberger, MD, Zafiris J. Daskalakis, MD, Nathan Herrmann, MD, Benoit H. Mulsant, MD, Bruce G. Pollock, MD & Reza Zomorrodi, PhD; Corinne E. Fischer, MD, St. Michael's Hospital (Canada)

Agitation and aggression affect most patients with Alzheimer's disease. Medications used to treat these symptoms are associated with many side effects. For this project, researchers will use magnetic brain stimulation and electroencephalography to understand the mechanisms of agitation and apply a noninvasive brain stimulation technique called transcranial direct current stimulation to treat it.

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

Stephanie Leal, PhD | William Marsh Rice University

The aim of this project is to use sensitive memory tasks that target the brain regions that are affected earliest in Alzheimer's. The tasks will be paired with state-of-the-art brain imaging techniques so that researchers can identify early cognitive and brain changes in Alzheimer's before clinical symptoms manifest. The findings could aid in the development of early interventions to prevent or slow Alzheimer's.

Circadian Regulation, Autonomic Function, and Alzheimer's Disease

Peng Li, PhD | Brigham and Women's Hospital & Harvard Medical School

Using novel, noninvasive wearable technology to assess circadian regulation and autonomic function, researchers will determine whether changes in these physiological functions can predict development and progression of Alzheimer's disease and cognitive decline in older people at early, prediagnosis stages. The results may provide new intervention targets for clinical studies and lay the groundwork for designing novel, unobtrusive, cost-efficient tools for long-term monitoring of cognitive impairment or risk for Alzheimer's.

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

Brad Manor, PhD | Hebrew Rehabilitation Center
Co-Principal Investigator: Alvaro Pascual-Leone, MD, PhD

Memory loss and executive dysfunction are hallmarks of Alzheimer's disease that map onto spatially distinct brain networks. Researchers will deliver two types of transcranial current stimulation (tCS) to provide multisymptom relief for older adults with mild Alzheimer's. With this dual, simultaneous stimulation and assessment of individual therapeutic benefit, this work will support development of tCS interventions with maximal impact on daily life function for this population.

Identifying a Disease-Modifying Treatment for Alzheimer's

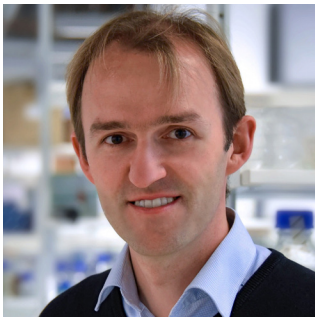
Courtney Marshall, PhD | University of Pennsylvania School of Medicine
Mentor: Virginia Y.M. Lee, PhD

Researchers will test a clinically approved anticancer drug targeting a protein that is increased in Alzheimer's disease. Researchers will use samples from people with Alzheimer's to test the drug, a CK2 inhibitor, in mouse models of the disease. Because CK2 inhibitors have already cleared safety tests in cancer trials, this drug has potential to go straight to clinical testing for Alzheimer's disease if results are positive.

Measuring Brain Aging in Early-Onset Alzheimer's Disease

Peter Millar, PhD | Washington University School of Medicine in St. Louis
Mentor: Eric McDade, DO

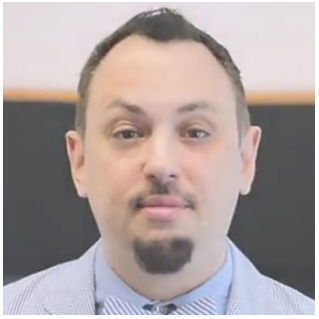
In symptomatic Alzheimer's disease, brains appear older than chronological age would predict. Investigators will assess people with a rare genetic mutation related to early-onset Alzheimer's disease to test if their brains show signs of relatively more aging as predicted dementia onset nears. Researchers also will assess whether clinicians can use this "brain age" approach to identify people with very early Alzheimer's pathology and predict Alzheimer's risk.



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

Dominik Paquet, PhD | Ludwig Maximilian University of Munich (Germany)

Researchers will develop a human model of tau-related dementias, such as Alzheimer's and frontotemporal dementia. Tau regulation in human nerve cells differs from that of mouse models, the currently used lab models. Using brain cells derived from adult human stem cells and genome editing with CRISPR, investigators will generate brain tissue with genetic alterations in the tau gene that lead to dementia in patients as a model for studying human disease mechanisms.



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

Carlos Roncero, PhD | Baycrest Centre for Geriatric Care (Canada)

Transcranial direct current stimulation (tDCS) shows potential for improving quality of life for people living with Alzheimer's disease. For this project, researchers will test a new intensity level of tDCS that may produce stronger results in people with Alzheimer's disease. The team also will collect participant information to identify who best responds to tDCS. These results will support optimization and tailoring of tDCS for people with Alzheimer's disease.

Preclinical Testing of a CRISPR-Based Alzheimer's Gene Therapy

Subhojit Roy, MD, PhD | University of California, San Diego

In this work, researchers plan to take a gene-editing-based therapy for Alzheimer's disease to the clinic. Broadly speaking, their approach restores the normal balance of the amyloid pathway, decreasing neurotoxic protein fragments while promoting neuroprotective protein fragments. The results could yield the first CRISPR-based therapeutic for any neurologic disease.

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

Quincy Samus, PhD | Johns Hopkins Bayview Medical Center

This grant supports a partnership with the University of Maryland Baltimore County, Jade Gong & Associates LLC, and Johns Hopkins Home Care Group, with support from the Maryland Primary Care Program, Maryland Medicaid, and Johns Hopkins Alliance for Patients. The aim is to advance incorporation of John Hopkins University's comprehensive, evidence-based dementia care MIND at Home model within Maryland's new primary care program to achieve greater care coordination and value for a vulnerable patient population.

Reducing Dietary Protein for the Prevention of Alzheimer's Disease

Timothy Sargeant, PhD | 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, can destroy amyloid plaques associated with Alzheimer's disease, but the system begins to falter with age. Drugs or specific nutrient restriction in the diet can activate autophagy. In mice, reducing protein levels in food decreases plaque accumulation in the brain. Researchers will assess whether reducing protein intake increases autophagy in humans, comparing findings with a mouse model of Alzheimer's disease administered a similar diet.

Unfolding Alzheimer's Tau Therapies: Near- and Long-Term Approaches

Paul Seidler, PhD | University of Southern California
Co-Principal Investigator: Daryl Davies, PhD

Researchers will assess the effectiveness of a commercial dietary supplement on slowing accumulation of tau tangles. The research team will synthesize small molecules that bear effective features of the supplement and test how well they prevent tau accumulation in tissue samples from Alzheimer's disease brains. The most effective small molecules will undergo further testing to analyze how their structure influences their activity against tau misfolding.

This grant is supported by Alzheimer's Los Angeles.

Imaging Probes for Precision Medicine in Alzheimer's Disease

Sahil Sharma, PhD | Memorial Sloan Kettering Cancer Center
Mentor: Gabriela Chiosis, PhD

The project aim is to build tools for imaging and selecting patients with Alzheimer's disease who are likeliest to benefit from a new experimental medicine with disease-modifying potential. This medicine, PU-AD, works by rebalancing cellular networks and brain circuits. In mouse models, PU-AD reversed cognitive dysfunction, and it is now in clinical evaluation for Alzheimer's and related disorders. Tools developed in this project thus have immediate translational potential.

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

Annabelle Singer, PhD | 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.

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

Aristeidis Sotiras, PhD | Washington University in St. Louis

Researchers will develop artificial intelligence tools based on deep learning to identify individuals showing 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. These tools also 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.

Advancement of Drugs to Treat Repeated Mild Traumatic Brain Injury

Patrick Sullivan, PhD | 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 the 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.

Jointly funded with the Medical Technology Enterprise Consortium.

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

Peter Tessier, PhD | University of Michigan
Co-Principal Investigator: Colin Greineder, MD, PhD

A drawback of monoclonal antibodies is that they poorly penetrate the blood-brain barrier, greatly limiting their use in Alzheimer's disease. This team has developed the novel solution of attaching a small protein to antibodies that can facilitate their entry. For this project, researchers will 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.

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

Saul Villeda, PhD | University of California, San Francisco

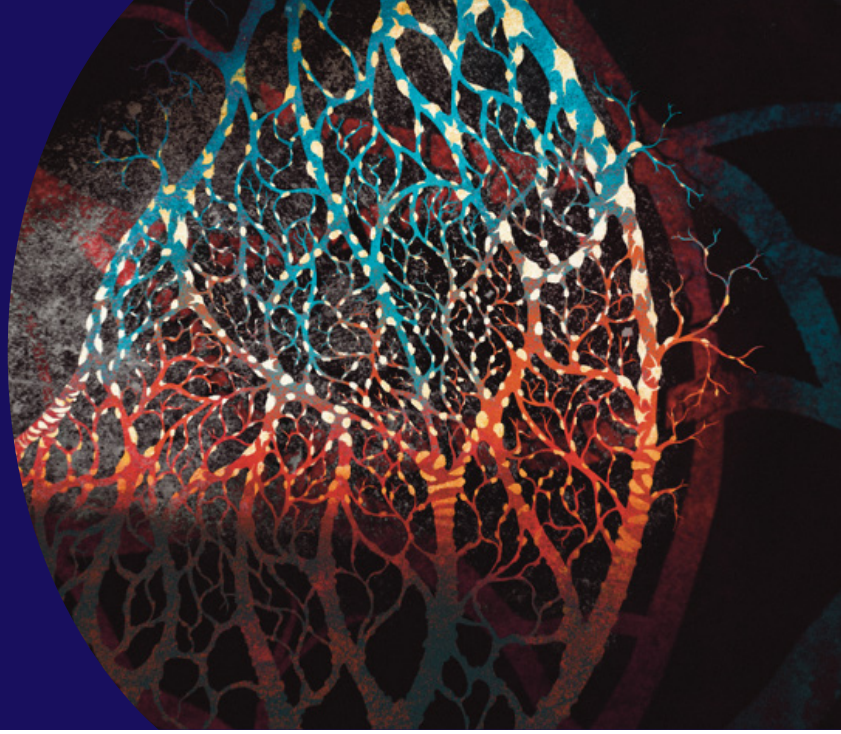
Factors in young blood may potentially reverse age-related brain impairments. For this project, researchers will assess the therapeutic potential of young platelets and platelet-derived circulating factors to reverse neurodegenerative phenotypes in a mouse model of Alzheimer's and elucidate their downstream mechanisms of action. The results are expected to identify blood-based therapeutic intervention to restore functions related to cognitive impairments in Alzheimer's disease and broadly counter dementia-related neurodegenerative diseases.

Development of Synthetic Gene Feedback Circuits to Prevent Tau Aggregation

Benjamin Wolozin, MD, PhD | Boston University
Co-Principal Investigator: Ahmad Khalil, PhD

This proposal uses a radically novel approach, synthetic biology, which leverages 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 then 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.

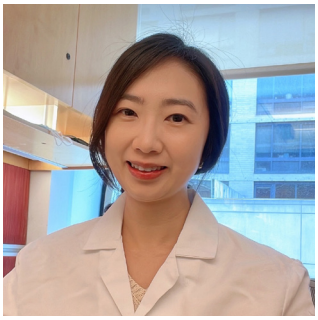
Vascular Contributions to Dementia



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. Image courtesy of Andrew Yang, PhD, University of California, San Francisco.*

Vascular dementia is the most common condition co-occurring with Alzheimer's disease. 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. 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 by a 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.



Do Tau Deposits Affect Blood Oxygen Supply to the Brain?

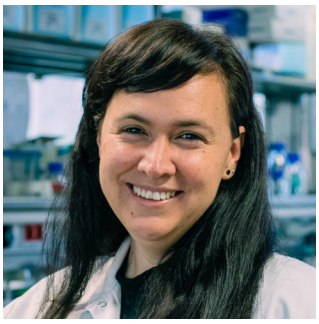
Sung Ji Ahn, PhD | Weill Cornell Medicine

This project will address whether tau accumulations affect blood flow in the brain, depriving cells of oxygen and nutrients. With this information, researchers will examine whether oxygen treatments change these patterns for the better. Improvements could signal an opening to related therapies that counteract brain dysfunction related to tau accumulation.

Cerebral Blood Flow Dysfunction in Alzheimer's Disease

Antoine Anfray, PhD | Weill Cornell Medicine
Mentor: Costantino Iadecola, PhD

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



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

Marta Cortes-Canteli, PhD | 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 older age, and cardiovascular disorders and Alzheimer's disease appear together in symptomatic stages. The diseases share risk factors and have long subclinical phases. Researchers will analyze what happens in the 10-20 years before the symptoms of either disease appear. These studies will decipher whether unhealthy lifestyle patterns in the sixth decade of life have negative consequences for the brain and contribute to memory problems a decade later.

This award is supported by the Sephardic Foundation on Aging.

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

Scott Counts, PhD | Michigan State University
Co-Principal Investigators: Timothy Collier, PhD & Roxana Carare, MD, PhD, University of Southampton (UK)

The contribution of cerebral amyloid-beta angiopathy (CAA) and cerebrovascular pathology to Alzheimer's disease progression is gaining renewed interest. Expanding on preliminary data, researchers will test whether degeneration of the locus coeruleus and cholinergic basal forebrain projection systems contribute to cognitive impairment by damaging intramural periarterial drainage of amyloid-beta and contributing to Alzheimer's disease and CAA. If successful, this work will support targeting these interactions as a disease-modifying strategy.

Neurovascular Changes During Midlife Hypertension and Alzheimer's Disease

Christian Crouzet, PhD | University of California, Irvine
Mentors: Bernard Choi, PhD & David Cribbs, PhD

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

Understanding How Newly Approved Anti-Amyloid Drugs Affect Blood Vessels

Kate Emily Foley, PhD | Indiana University School of Medicine
Mentor: Donna M. Wilcock, PhD

This study will assess a metallopeptidase, MMP9, for its role in the development of amyloid-related imaging abnormalities, or ARIA, which can arise with newly approved anti-amyloid-beta antibody treatments. Researchers will work with mouse models and with postmortem tissue samples to assess how MMP9 affects the brain's blood vessels. The results are expected to generate important information about pathways that could be targeted in cells to slow or prevent ARIA in people receiving antibody therapy.

Detecting Leaky Vessels in Cerebral Amyloid Angiopathy

Whitney Freeze, PhD | Leiden University Medical Center (The Netherlands)
Mentors: Louise van der Weerd, PhD; Susanne van Veluw, PhD, Massachusetts General Hospital

Researchers will combine state-of-the-art imaging with detailed postmortem examinations to explore associations of brain-blood barrier leakage, subtle hemorrhagic brain pathology, and cognitive functioning in patients with cerebral amyloid angiopathy. A successful outcome is expected to result in a new tool to predict risk of hemorrhages in dementia at an early stage. This ability will be pivotal in selecting patients for amyloid-modifying therapies and developing new drugs to prevent bleeds.

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

Shannon Macauley-Rambach, PhD | Wake Forest University

Overactive neurons are thought to drive Alzheimer's disease pathology, and identifying new ways to reduce brain excitability is an important strategy for treating Alzheimer's. For this work, researchers will explore how targeting the brain's vasculature with a repurposed Food and Drug Administration-approved drug might dampen overactive neurons and decrease Alzheimer's pathology.

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

Melanie Samuel, PhD | Baylor College of Medicine
Co-Principal Investigator: Joshua Wythe, PhD

Comorbidities, such as vascular disease, can significantly accelerate cognitive decline in people with Alzheimer's disease. Alterations to neuron and blood vessel communication may drive these outcomes. The aim of this study is to generate an understanding of how Alzheimer's disrupts energy homeostasis and neurovascular coupling through specialized vascular structures called pericyte nanotubes.

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

Susanne van Veluw, PhD | Massachusetts General Hospital

In cerebral amyloid angiopathy (CAA), amyloid builds up in the brain's blood vessels, which can cause bleeding and dementia. Removing amyloid with immunotherapy carries a high bleeding risk that is further increased with the *APOE4* genotype. Removing APOE, which is co-deposited with amyloid, could be a safer alternative. Whether removing APOE improves CAA and protects blood vessels is unclear and will be tested in mouse models in this project.

How Aging Damages the Blood Vessels in Cerebral Small Vessel Disease

Xiaowei Wang, PhD | University of California, San Francisco
Mentors: Douglas Gould, PhD & Tyson Kim, MD, PhD; Scott Earley, PhD, University of Nevada

Researchers will develop novel characterizations of age-dependent cerebrovascular malfunctions in the Col4a1 mutant mouse model of cerebral small vessel disease. The completion of the proposed research will provide mechanistic insight into the age-dependent changes in cerebrovasculatures. Additionally, researchers will test the efficacy of therapeutic strategies originating from these mechanistic studies, which could impact treatment options for vascular dementia.

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

Cheryl L. Wellington, PhD | University of British Columbia (Canada)

Circulating high-density lipoprotein (HDL) particles ("good" cholesterol) can prevent amyloid-beta from sticking to blood vessel walls as the protein moves from brain to blood. The 6% of HDL particles that contain APOE are especially effective. Researchers will use a new method to measure APOE-HDL in ~2,000 blood samples from people with and without dementia and use additional approaches to study how APOE-HDL acts on the brain's small blood vessels.

Studying Vascular Dysfunction of Cerebral Perforating Arteries in the Pathogenesis of VCID/Alzheimer's Disease

Lirong Yan, PhD | Northwestern University

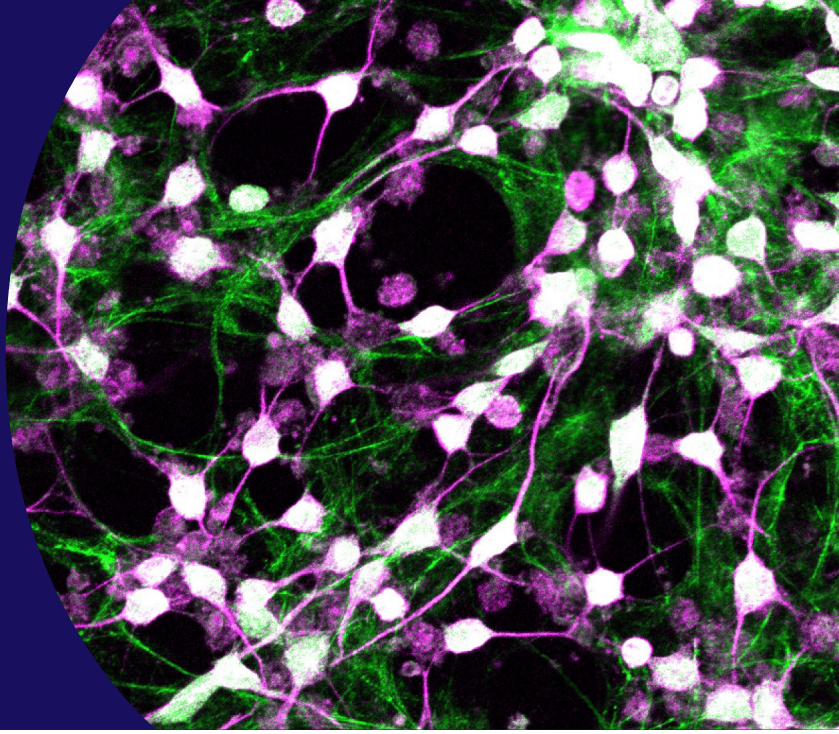
Small vessel disease arising from dysfunction of cerebral perforating arteries is a frequent vascular pathology in vascular cognitive impairment and dementia (VCID), which shares risk factors with Alzheimer's disease. Researchers will use state-of-the-art MRI to image the cerebral perforating arteries directly. They will optimize two high-resolution MRI techniques to quantitatively characterize the structure and flow function of cerebral perforating arteries and study dysfunction of these arteries in the pathogenesis of VCID/Alzheimer's.

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

Andrew Yang, PhD | University of California, San Francisco
Mentor: Saul Villeda, PhD

Elucidating the functions of the many risk variants associated with late-onset Alzheimer's disease is critical to inform treatments but remains challenging, in part because the vascular portion of human brain cell types has eluded powerful single-cell assays. Researchers will use a new vascular-capturing VINE-seq technique to identify 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.

Waste-Clearance Mechanisms



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

Along with the immune-mediated clearance duties of the 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.

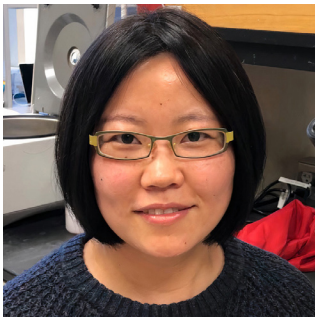
Endosomes and lysosomes are cellular compartments responsible for breaking down and recycling or removing waste. Endolysosomal pathway abnormalities are an early Alzheimer's disease feature and are closely related to genetic risk factors.

The brain has its own lymphatic system associated with its membranes, or meninges. The meningeal lymphatics drain 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.

Studying Lysosomal Vulnerability in Aging and Alzheimer's Disease

Ching-Chieh Chou, PhD | Stanford University
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. For this project, researchers will reprogram human skin cells into brain cells (neurons) to determine how and why clearance mechanisms are disrupted in Alzheimer's.



Identification of Protein Biomarkers for Aging and Alzheimer's Disease

Xiaojing Sui, PhD | Northwestern University
Mentor: Richard Morimoto, PhD

For this study, researchers 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 ultimate goal of the project is to identify new protein biomarkers of aging and Alzheimer's disease and provide new treatment targets.

Catalyzing Life-Changing Breakthroughs

For the past 50 years, BrightFocus Foundation has funded the boldest research and what-if ideas to get us closer to cures for Alzheimer's disease, macular degeneration, and glaucoma, resulting in the novel treatments and diagnostic tools in use today. We also raise awareness and empower people with these diseases and their loved ones by sharing expert resources and information.

Alzheimer's Disease Research Milestones

Alzheimer's Disease Research

1985

Alzheimer's Disease Research, a BrightFocus Foundation program, is established.

1993

Our grantees are the first to identify the apolipoprotein E (*APOE*) gene as a major risk factor for late-onset Alzheimer's.

2003

Following their discovery that Alzheimer's can be detected in the lens of the eye, an Alzheimer's Disease Research-funded team develops new optical tests to better diagnose and monitor the disease from its early stages.

2020

The first blood test to identify early signs of Alzheimer's disease becomes commercially available in the U.S., bolstered by critical early Alzheimer's Disease Research funding.

2021

With our support, a team of scientists develop the first-ever driving test to predict Alzheimer's disease.

Explore more breakthroughs: **brightfocusbold.org/breakthroughs**

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