![BrightFocus Foundation | Alzheimer's Disease Research]

Today's investments, tomorrow's breakthroughs.

2024 Alzheimer's Disease Research Projects

Alzheimer's Disease Research

Meet the Next Generation of Innovators

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 aged 65 and older.
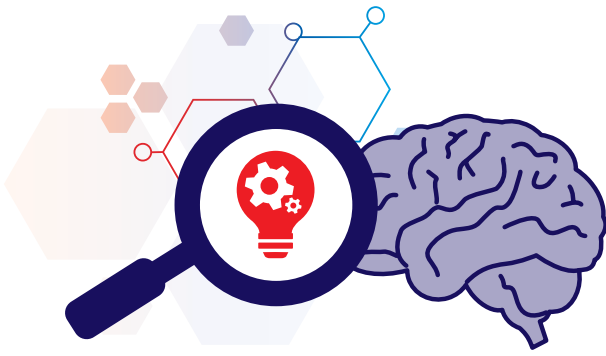
By providing initial funding for highly innovative experimental research and creative ideas, we spark revolutionary approaches and life-saving breakthroughs for this disease, the seventh-leading cause of death in the United States.

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

Explore all active grants:
brightfocus.org/ADRgrants

We're funding
112
active Alzheimer's research projects worldwide.

Since inception:
We've funded more than
$180M
in Alzheimer's research grants.

Since inception:
We've supported
**3,042**
scientists across 922 grants.

Our 360-Degree Approach

The exact causes of Alzheimer's remain unknown, but likely include a combination of age-related changes in the brain along with genetics, health, and lifestyle factors. This is why it is critical to explore a wide range of approaches spanning different areas of the brain and body.

As you'll see in the pages that follow, our funded research leaves no stone unturned, exploring the full range of scientific paths toward better treatments, prevention strategies, and ultimately a cure. With Alzheimer's Disease Research funding, scientists are testing hundreds of hypotheses regarding the disease's onset and progression, leading to the creation of novel treatments and improved earlier detection strategies.

We are deeply grateful to our donors, whose generosity empowers the next generation of researchers to pursue innovative, bold, and promising science, bringing us closer to tomorrow's cure.
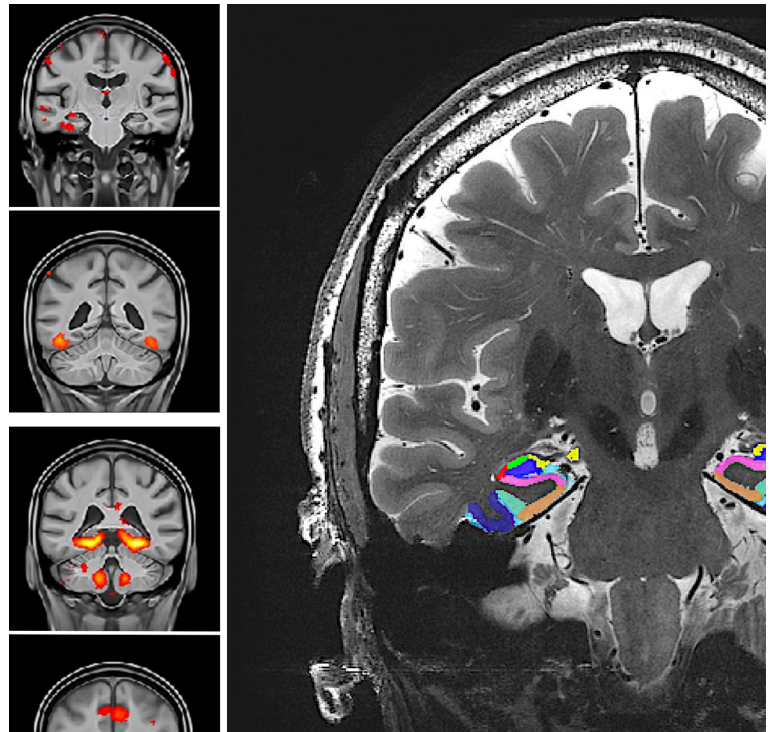
An MRI showing two distinct brain networks vulnerable to amyloid and tau Alzheimer's pathology (left) and subregions of the brain involved in memory processing (right) (Helena Gellersen, PhD).

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This portfolio reflects awarded grants as of July 3, 2024.

Amyloid-Beta

In Alzheimer's disease, amyloid-beta (Aβ) accumulates in the brain, forming toxic plaques that contribute to neurodegeneration, often in conjunction with the tau protein. Advances in technology now allow researchers to measure amyloid plaques in the brain and identify affected brain regions.

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.

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.
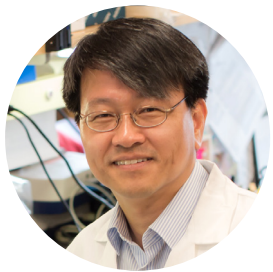
Increase of ADAM10 Protein Expression in the Brain as an Alzheimer's Disease Therapeutic

Jaehong Suh, PhD | Massachusetts General Hospital

ADAM10 is an enzyme that prevents the generation of amyloid-beta. Previous studies consistently showed that loss of ADAM10 function increases Alzheimer's

risk, suggesting that increasing ADAM10 expression can be a promising therapeutic target. This study will test if brain-selective modulation of ADAM10 expression affects Alzheimer's pathogenesis and will develop an experimental drug that increases ADAM10 expression for Alzheimer's treatment.

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)*

The apolipoprotein E (*APOE*) gene is a risk factor in Alzheimer's disease due to its production of the APOE protein, which metabolizes and transports fats in the body. Scientists are trying to better understand the *APOE4* (ε4) variant, the most prevalent genetic factor associated with late-onset Alzheimer's, whose impact varies by genetic makeup, race, and ethnicity.

The Effects of Peripheral APOE2 on Alzheimer's Disease Pathology and Pathways

Guojun Bu, PhD | Hong Kong University of Science and Technology (China)

Researchers are working to develop safe and effective therapies to prevent or cure Alzheimer's disease. The *APOE* gene is a strong genetic risk factor, with *APOE2* reducing risk. This project will study the protective effect of *APOE2* using new model systems and advanced technologies to address how APOE2 in the blood affects brain cognition and Alzheimer's disease pathology. Findings should provide insights on APOE targeting for Alzheimer's disease therapy.

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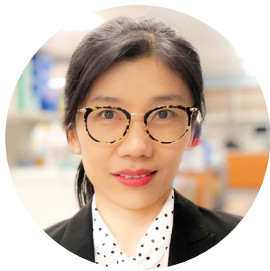
The Influence of Lifestyle Change and the *APOE* Gene in Aging and Alzheimer's Disease

Na Zhao, MD, PhD | 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. Researchers will investigate how diet or exercise affects brain health using animal models of aging or Alzheimer's, with and without the *APOE4* gene.

Biomarkers

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 disease stages. The best hope of stopping Alzheimer's is to identify it as early as possible.

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.

Shining a Light on How Early Tau-Related Brain Changes Affect Memory Loss

Martin J. Dahl, PhD | Max Planck Institute for Human Development (Germany)
Mentor: Ulman Lindenberger, PhD

This project investigates previously understudied brain regions that are the starting point of Alzheimer's-related tau accumulation and how their changes contribute to memory loss. Using innovative brain imaging techniques, blood-based biomarkers, and memory assessments collected over a decade from many participants, this project improves our understanding of the time course of neural changes in later life and their mechanistic role in the earliest stages of Alzheimer's development.

Identifying New Memory and Brain Markers for Early Alzheimer's Disease

Helena Gellersen, PhD | German Center for Neurodegenerative Diseases (Germany)
Mentor: David Berron, PhD

Identifying individuals in the early stages of Alzheimer's, monitoring their progression, and understanding disease subtypes is critical to tailor treatment approaches and maximize potential benefits. This project will develop new cognitive and neural markers sensitive to the early effects of Alzheimer's. These can be used to detect subtle memory changes, classify by subtype, and identify healthy brain signatures to clarify how an experimental treatment in early-phase clinical trials changes memory.

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.

Staging Alzheimer's Disease Using Blood Samples

Gemma Salvadó, PhD | Lund University (Sweden)
Mentor: Oskar Hansson, MD, PhD

Researchers will develop an Alzheimer's staging model based on plasma biomarkers to characterize people across different disease stages. To better understand the complex biological processes that occur during the disease, the study will also investigate how multiple protein levels change across these stages. The staging model may eventually help clinicians decide, in an easy and cost-effective way, who would benefit from an Alzheimer's treatment and empower them to provide more personalized care.

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

The human brain has an estimated 100 billion neurons, each with long axons forming connections called synapses with another neuron, creating a circuit for brain signaling. In Alzheimer's disease, neuron death disrupts these circuits, leading to symptoms like memory loss. Scientists are studying the brain's many cells and circuits, looking for ways to preserve neural 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.

Supported by the Luminescence Foundation.

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

Samuel Barnes, PhD | Imperial College of Science, Technology, and Medicine 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.

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 Brainwide Network Disruptions That Underlie Alzheimer's Disease

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

The main aim of this work is to identify brainwide 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.

Targeting Brain Cell Miscommunication to Restore Memory in Alzheimer's Disease

Amira Latif Hernandez, PhD | Stanford University

The brain's ability to adapt and change, known as synaptic plasticity, requires the expression of specific genes and proteins in different brain cells, including interneurons and astrocytes, which are affected in brain disorders like Alzheimer's. To find potential therapeutic strategies to recover synaptic plasticity and cell communication and improve memory in Alzheimer's, researchers will use advanced electrophysiology and transcriptomic techniques in mouse models and lab-grown mouse cultures with Alzheimer's-like pathology. Results will contribute to the development of improved treatments for people with synaptic dysfunction.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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.

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.

Does Alzheimer's Disease Accelerate Brain Aging?

María Llorens-Martín, PhD | Spanish National Research Council (Spain)

The hippocampus, a brain region crucial for learning and memory, generates new neurons throughout life. This process is damaged in Alzheimer's disease, but the cause is unknown. Researchers will use human brains and cutting-edge methodologies to assess the environmental toxicity surrounding new neurons. Study findings will identify novel mechanisms responsible for hippocampal changes in Alzheimer's and generate novel resources for faster, more accurate diagnosis of this condition.

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.

Progranulin as a Potential Therapeutic Target for Alzheimer's Disease

Andrew D. Nguyen, PhD | Saint Louis University
Co-Principal Investigator: Susan Farr, PhD

Previous studies suggest that progranulin confers a protective effect on Alzheimer's disease in mouse models and in humans, but several important gaps in knowledge exist. This project aims to determine how progranulin exerts its effects in the central nervous system to enhance memory and to test if pharmacologically increasing progranulin levels can protect against Alzheimer's disease.
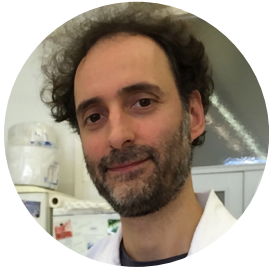
Targeting Memory Circuits as a Therapeutic Strategy in Alzheimer's Disease

Carlos Saura, PhD | The 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.

Mechanisms of Inhibitory Neuron Vulnerability to Alzheimer's Disease

Emiliano Zamponi, PhD | Columbia University
Mentor: Franck Polleux, PhD

Inhibitory interneurons, one of the key players in human cognitive processes, are among the first neuronal populations affected by Alzheimer's disease onset. The research team proposes their elevated energy consumption rates make these interneurons more vulnerable to Alzheimer's. Using multiple innovative approaches, Dr. Zamponi will investigate three fundamental aspects underlying inhibitory interneuron vulnerability to Alzheimer's, which could lead to new insights into the pathological basis of the disease and contribute to novel therapeutic approaches.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.
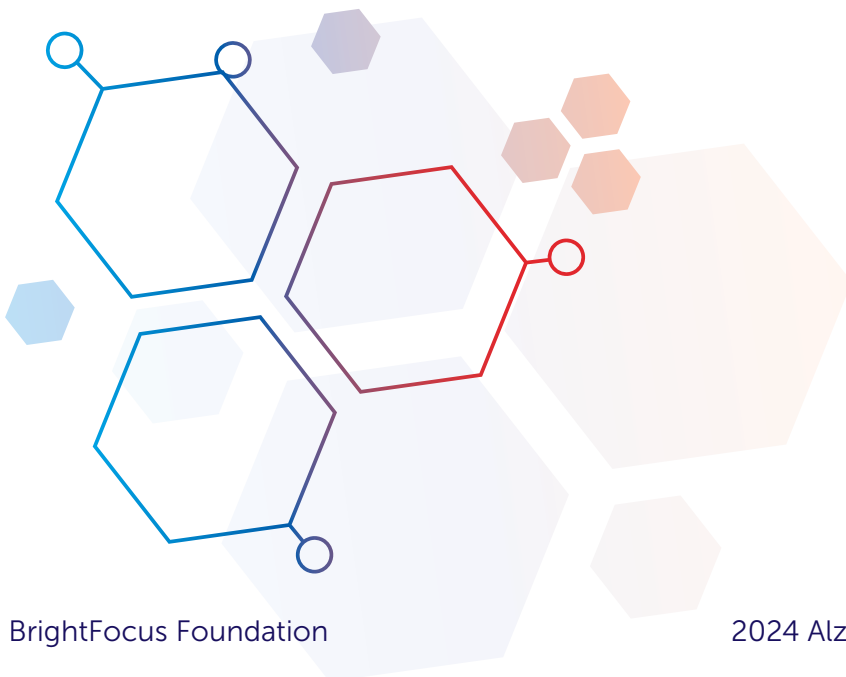
Genomics: DNA Blueprint for Alzheimer's

Genes carry the instructions that cells use to make proteins, which build and repair tissue. Even slight changes to these instructions can affect the risk of Alzheimer's. While early-onset Alzheimer's is linked to specific gene mutations (10% of cases), the remaining 90% involve genetic risk variants. Researchers are using advanced technologies to study the triggers of Alzheimer's disease, how genes interact with the environment and lifestyle factors to influence risk, 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.

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 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.

Validating the Receptor PILRA as an Alzheimer's Therapeutic Target

David 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.

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 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.

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.

Decoding Alzheimer's Disease Genomes With Deep Learning

Tatsuhiko Naito, MD, PhD | Icahn School of Medicine at Mount Sinai
Mentor: Towfique Raj, PhD

Dr. Naito's research aims to unravel the genetic complexities of Alzheimer's disease. This project will develop a pipeline to predict the impact of genetic mutations on RNA processing in brain cells using machine-learning technologies. Researchers will then apply this pipeline to huge genomic data to determine potential effects on individuals with Alzheimer's. A better understanding of genetic associations of Alzheimer's will aid in developing new treatments and identifying biomarkers.

Uncovering How Gene Regulators Protect Neurons Against Alzheimer's

Raffaella Nativio, PhD | Imperial College of Science, Technology, and Medicine (UK)

This study will focus on understanding how epigenetic factors, especially transcriptional repressors, influence gene expression in neurons and contribute to Alzheimer's disease. The research aims to identify how these transcriptional repressors protect neurons from Alzheimer's-related stress, potentially leading to new treatments for enhancing brain resilience against Alzheimer's.

Study of a Novel Genetic Risk Factor for Alzheimer's Disease

Giuseppina Tesco, MD, PhD | Tufts University

Dr. Tesco's lab discovered a novel genetic variant associated with late-onset Alzheimer's disease in African American families, called GGA3. Prior research demonstrated that GGA3 plays a critical role in the transport and regulation of BACE1, a key enzyme responsible for amyloid-beta production. The study aims to determine how this genetic variant leads to Alzheimer's. Results may increase understanding of genetic risk factors in the understudied African American population.

Immunity & Inflammation

One theory about Alzheimer's disease is that a breakdown in the brain's immune system plays a role. Microglia, the brain's primary immune cells, normally clear debris and respond to injuries, but in Alzheimer's, they release proinflammatory molecules that worsen the disease. Researchers are investigating the causes of this and how to support cells, including microglia, in fighting Alzheimer's.

Understanding TREM2 Signaling as an Alzheimer's Disease Target

Thomas Brett, PhD | Washington University 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.

Understanding Alzheimer's Risk and Immune Health in Heart Disease

Brittany Butts, PhD | Emory University
Co-Principal Investigator: Whitney Wharton, PhD

This study explores how the immune system relates to memory, cognition, and Alzheimer's risk in middle-aged adults with heart conditions. As heart problems surge in the under-65 population, connections to cognitive decline and Alzheimer's remain unclear. Surveys, blood tests, and memory assessments will clarify how factors like high blood pressure affect cognition and Alzheimer's risk. Insights into heart health, immunity, and Alzheimer's can benefit at-risk individuals and shape future treatments.

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.

The Role of the Immune System in Driving Cognitive Decline

Hannah Ennerfelt, PhD | Stanford University
Mentor: Katrin Andreasson, MD

During aging and Alzheimer's disease, certain inflammatory responses regulated by the immune system worsen the disease and contribute to impaired cognition and memory. This study will identify the machinery necessary for immune cells to amplify damaging inflammation in the body and brain. Using a novel method to target a specific immune cell mechanism, we will assess how impeding its associated inflammatory pathways can curb cognitive decline and Alzheimer's progression.

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.

Tracking Immune Cells in Alzheimer's Disease Brains

David Gate, PhD | Northwestern University Feinberg School of Medicine

In this project, researchers will develop molecular snapshots of proteins being made in samples from brains with and without Alzheimer's. The researchers expect to find specific immune proteins in the same places as misfolded Alzheimer's disease-related proteins, implicating the immune response to inflammation in Alzheimer's disease. Such links may present treatment targets to evaluate in future research.

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.

Defining the Impact of Cytokine Signaling in Alzheimer's Disease

Dong Kyu Kim, PhD | University of California, San Francisco
Mentor: Anna Molofsky, MD, PhD

Immune signals regulate brain homeostasis and are also a major driver of Alzheimer's disease pathology. This study aims to investigate how astrocyte-microglia crosstalk via IL-33 cytokine impacts Alzheimer's disease pathology and behavior. This work will determine the mechanistic impact of a key immune pathway in Alzheimer's pathology and brings forth the novel hypothesis that ECM disruption is linked to disease pathology.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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.
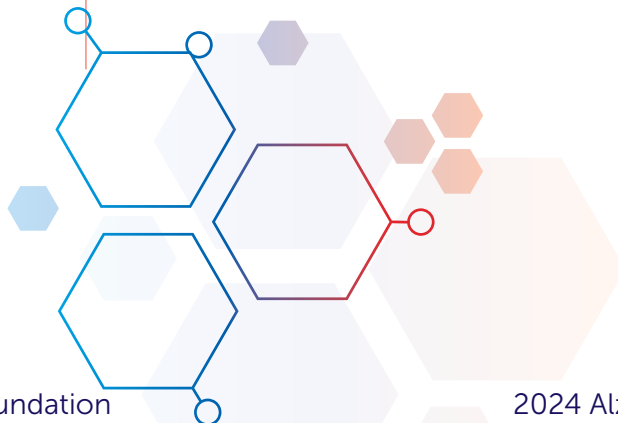
The Role of Immune Cells' Interaction in Alzheimer's Disease Pathology

Emanuela Pasciuto, PhD | Flanders Institute for Biotechnology (Belgium)

Researchers know little about how adaptive immune cells interact with amyloid plaques. MHCII is a microglia-associated Alzheimer's risk gene that mediates interaction with T cells. The relevance of the microglia-T cell interaction in Alzheimer's is unknown. This project will test a T cell-based immunotherapy in Alzheimer's mice lacking MHCII. Study findings will build toward more precise therapies targeting the immune system to protect against the progression of Alzheimer's.

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.

The Role of the Immune System in Alzheimer's Disease

Paula Sanchez-Molina, PhD | Oregon Health & Science University
Mentor: Bahareh Ajami, PhD

It is known that a specific type of brain immune cell, called microglia, plays a crucial role in the pathogenesis of Alzheimer's disease. This project aims to understand how immune cells from the blood impact microglia and contribute to the development of Alzheimer's. The characterization and validation of a peripheral immune mechanism that contributes to Alzheimer's pathology could offer important biomarkers for disease diagnosis and the design of new therapies.

Regulation of Microglia Phenotypes in Alzheimer's Disease

Johannes Schlachetzki, MD | University of California, San Diego

Alzheimer's disease is defined by the accumulation of harmful proteins in the brain. Microglia, the immune cells of the brain, play a key role in this process, but the molecular mechanisms that lead to distinct phenotypes are unclear. This study will use advanced techniques to isolate and analyze microglia, revealing how they contribute to disease and identifying new targets for developing effective treatments.

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.

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 Alzheimer's risk, this project will suppress an *APOE4* risk signal and clarify 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.

Oxysterols in Innate and Adaptive Immunity in a Tauopathy Mouse Model

Danira Toral-Rios, PhD | Washington University in St. Louis
Mentors: Anil Cashikar; PhD, David Holtzman, MD &
*   Steven M. Paul, PhD*

Neuronal loss in Alzheimer's disease is linked to brain infiltration of blood-derived immune cells in a neurotoxic cascade of tau protein accumulation and inflammation in the brain. Preliminary studies show evidence for altered brain cholesterol metabolism in mediating tau pathology and infiltration of blood immune cells into the brain. This project aims to investigate this pathway with the long-term goal of pharmacological intervention to block neuronal loss in Alzheimer's.

Metabolism Driving Cell Death and Inflammation in Alzheimer's Disease

Larissa Traxler, PhD | University of California, San Diego
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.

Dysregulated Astrocyte P38, Brain Inflammation, and Alzheimer's Pathology

Linda Van Eldik, PhD | University of Kentucky Research Foundation

Astrocytes, the most abundant glial cell type in the brain, become abnormally activated early in Alzheimer's disease and can lead to detrimental brain inflammation and nerve cell damage. The p38 MAPK drives inflammation in microglia but its role in astrocytes is understudied. This project will use novel mouse models and well-characterized human biospecimens to define the potential linkage between astrocyte p38, neuroinflammation, and Alzheimer's neuropathologic change, providing new insight into how abnormal astrocyte activation in Alzheimer's contributes to disease progression.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

The Role of DYRK1A Kinase in Alzheimer's Disease Microglia Differences

Frances Wiseman, PhD | University College London UK
Co-Principal Investigator: Selina Wray, PhD

Down syndrome is a genetic condition caused by an extra copy of chromosome 21 and is associated with an increased risk of developing early-onset dementia caused by Alzheimer's disease. Recent research has demonstrated the brain's immune response to Alzheimer's disease pathology differs in people with Down syndrome; this may contribute to the development of dementia. The team will test their hypothesis that the chromosome 21 gene, DYRK1A, may contribute to this using a new cellular model of Alzheimer's disease.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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*

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.
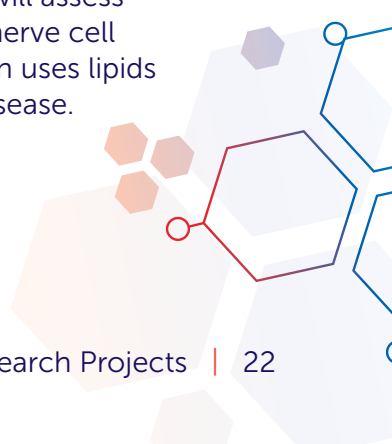
Metabolism & Bioenergetics

The brain consumes 20% of the body's energy and relies on efficient glucose metabolism, which declines with age and in Alzheimer's disease. This metabolic dysregulation affects cognition and processing speeds, with dysfunctional mitochondria (known as the "power plants" of cells) contributing to a neurotoxic environment.
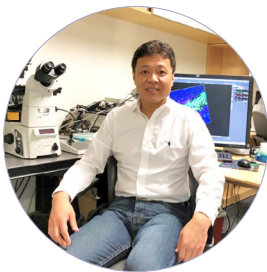
Mitochondrial Calcium Deregulation and Memory Loss in Alzheimer's Disease

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 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.

Cancer-Like Metabolic Changes in Alzheimer's Disease Neurons

Jerome Mertens, PhD | University of California, San Diego

This research focuses on how metabolic changes impact gene expression and protein modifications in Alzheimer's disease. Using neurons from

Alzheimer's patients, researchers have identified disruptions in metabolic pathways leading to abnormal gene processing. This study aims to understand how these changes contribute to key Alzheimer's features, such as tau tangle formation. By understanding upstream metabolic pathways of Alzheimer's pathology, they aim to identify potential intervention targets to rescue the loss of synaptic function and prevent neuronal cell death.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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 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*

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.

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.
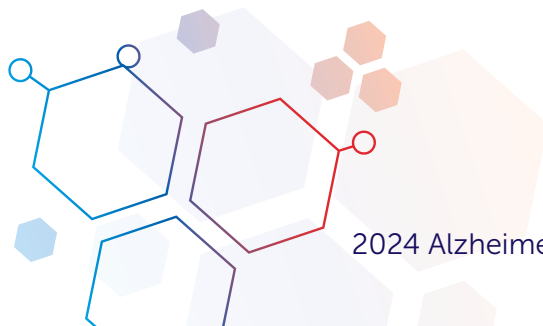
Other Misfolded Proteins

Most dementia in people over 80 is of mixed etiology, involving multiple diseases or causes. Misfolded proteins from conditions like ALS, Parkinson's, and vascular dementia interact, worsening cognitive impairment in people with Alzheimer's. Clinically distinguishing between dementias is important for therapies that target specific proteins.

Decoding the Role of an Alzheimer's Causal Gene in Distinct Brain Cell Types

Willem Annaert, PhD | Flemish Institute for Biotechnology (Belgium)

Research has focused on the major causal genes of early-onset familial Alzheimer's disease, PSEN1 and the amyloid precursor protein, ignoring the rare PSEN2 mutations. This project will provide a comprehensive picture with unprecedented insights in the contribution of PSEN2 in Alzheimer disease pathology. This work could identify novel therapeutic strategies to tackle these rare cases of PSEN2-associated Alzheimer's disease.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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.

Evaluating the Role of the TDP-43 Protein in Alzheimer's Disease Pathogenesis

Mercedes Prudencio, PhD | Mayo Clinic Jacksonville
*Co-Principal Investigator: Yongjie Zhang, PhD*

TDP-43 proteins abnormally accumulate in up to 70% of brains with Alzheimer's disease and are associated with worse memory and greater volume loss. This proposal will characterize TDP-43 dysfunction in Alzheimer's pathogenesis. Studies will evaluate whether TDP-43 dysfunction heightens Alzheimer's symptoms and pathology and examine the relationship between disease factors and TDP-43. Research outcomes will explore the potential of TDP-43 pathology for therapeutic targeting and biomarker design.

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

Sandra O. Tomé, 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.
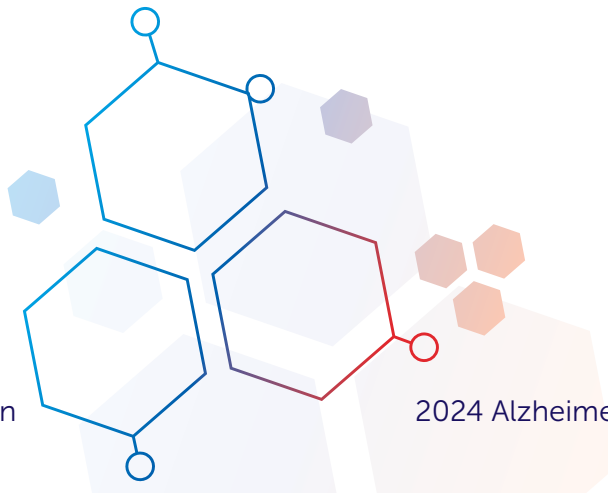
Research Tools & Resources

Having the right preliminary information and tools is crucial for the success of research projects, particularly in understudied areas. Alzheimer's Disease Research supports the development of resources for high-quality dementia research, including shared data and tissue repositories, and collaborative projects to accelerate knowledge, disease models, and interventions.

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.

Exploring Rural Health Disparities in Alzheimer's Disease

Justin Miller, PhD | University of Washington School of Medicine

Emerging evidence shows that older adults living in rural communities are at increased risk for Alzheimer's disease; however, rural communities have been severely underrepresented in Alzheimer's research, and the factors that may contribute to these urban-rural disparities are unclear. The team's goal is to fully characterize cognitive aging and validate Alzheimer's-specific biomarkers among rural-dwelling older adults. This project will enrich the biomarker characterization of a rural cohort and identify the most viable blood markers for use in rural-dwelling older adults.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

Sex-Based Differences

Women are disproportionately affected by Alzheimer's and account for two-thirds of Alzheimer's-related diagnoses. While their longer life expectancy compared to men was once thought to explain this, recent research has revealed additional sex-based differences in genetics, immunity, hormones, and underlying risk factors such as higher depression rates.

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.

Sleep & Circadian Rhythm

Chronic sleep disruption impacts Alzheimer's disease by impairing the brain's ability to clear waste and toxins, including misfolded proteins, and break down and dispose of amyloid-beta plaques present in early Alzheimer's. Changes in sleep patterns often occur in early Alzheimer's. Researchers are investigating 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.

The Effect of Alzheimer's Disease on Neurons Across the Sleep/Wake Cycle

Md. Joynal Abedin, PhD | Massachusetts General Hospital
Mentor: Ksenia Kastanenka, PhD

In Alzheimer's disease, the buildup of amyloid beta (Aβ) can result in sleep disturbances. Dr. Abedin and his team will investigate the activity of specific neuronal types in a genetically engineered mouse model of Alzheimer's disease to understand how Aβ affects neuronal activity during the sleep/wake cycle. This research could pave the way for therapeutic development to restore abnormal neuronal activity and potentially lead to a cure for Alzheimer's disease.

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.

Treating Insomnia in Mild Cognitive Impairment

Peter Fried, PhD | Beth Israel Deaconess Medical Center

Many people with mild cognitive impairment (MCI) experience symptoms of insomnia, such as difficulty falling or staying asleep, which can speed cognitive decline and worsen quality of life. The team proposes to test a novel intervention to improve sleep and cognition in persons with MCI that combines noninvasive neuromodulation with transcranial magnetic stimulation with an Internet-delivered cognitive behavioral therapy for insomnia program. If successful, this approach will meet the need for an efficacious, non-pharmacologic, and accessible therapy.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

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

Christopher 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.

Circadian Rhythm Disruption and Alzheimer's Disease

Ashish Sharma, PhD, MPharm | Washington University in St. Louis
Mentor: Erik Musiek, MD, PhD

This study investigates how disruptions to circadian rhythms, common in aging and Alzheimer's disease, impact disease progression using a mouse model of chronic jetlag (CJL). Researchers aim to understand how CJL affects Alzheimer's markers—amyloid plaques and tau protein accumulation. Investigating the connection between circadian disruption, glial function, and Alzheimer's-related changes may reveal therapeutic strategies, offering novel approaches to disease prevention.

Supported by an Innovative Seed Funding Program grant by an anonymous foundation.

Tau

Tau, a protein crucial for transporting nutrition and waste in and out of the brain, becomes misshapen and collects in messy tangles in Alzheimer's disease. Unlike amyloid plaques, which can precede symptoms by years, tau tangles signal rapid disease progression. Researchers are studying how misfolded tau and amyloid-beta interact and contribute to Alzheimer's spread in the brain.

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.

Assessing the Impact of Blood-Brain Barrier Dysfunction in Alzheimer's Disease

Joshna Gadhavi, PhD | Emory University
Mentor: Nicholas Seyfried, PhD

Blood-brain barrier (BBB) breakdown has been observed in various neurodegenerative diseases including Alzheimer's disease. In a healthy brain, the BBB does not allow transportation of proteins or large molecules into the brain. However, due to BBB dysfunction, enhanced permeability

of plasma-derived proteins can be observed in different parts of brain regions, and may lead to neurotoxicity, neuroinflammation, and oxidative stress. This project will identify novel biomarkers and key targets for BBB breakdown and explore how it may contribute to Alzheimer's diagnosis and progression.

Identifying the Mechanisms That Underlie Tau Aggregation and Neurotoxicity

Sarah Kaufman, MD, PhD | University of California, San Francisco
Mentors: Martin Kampmann, PhD, University of California, Los Angeles & William Seeley, MD

Alzheimer's disease and frontotemporal dementia feature the accumulation of tau protein in neurons that are eventually lost to the disease. The mechanisms underlying tau misfolding and accumulation, and their associated neurotoxicity, are not known. This project employs whole-genome screening techniques to identify the cellular pathways that regulate tau aggregation and toxicity. Study findings will provide critical insight into tau-associated disease mechanisms and identify potential therapeutic targets for these diseases.

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
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, MD, PhD | 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.

Unlocking Tau's Secrets: Human Brain Cells in the Mouse Brain

Wenhui Qu, PhD | Weill Cornell Medicine
Mentor: Li Gan, PhD

Dr. Qu has pioneered modeling tau buildup in human neurons using stem cells derived from skin biopsy. This study proposes transplanting both neurons and microglia—the brain's immune cells—to generate a groundbreaking chimera

human-mouse model that develops tau accumulation. Using this model, the study will also examine how specific molecular pathways might affect the disease's progression. This research could lead to breakthroughs in understanding and treating Alzheimer's and other tau-related diseases.

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

Joost 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.

Tau Treatment Targets for Alzheimer's Disease

Kristie Stefanoska, PhD | The 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 form 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.

Translational Research & Clinical Interventions

Translational research aims to move basic science knowledge from the lab or research setting into practical treatments and interventions for Alzheimer's disease. This can include innovations like smartphone-based cognitive tests, promoting brain-healthy activities, and improving lifestyle factors. Clinical trials and studies are essential for testing and advancing new drugs and interventions for people living with Alzheimer's today and those at risk in the future.

Neurostimulation to Improve Depression and Memory in Dementia

Davide Cappon, PhD | Hebrew Rehabilitation Center

This project combines two types of transcranial electrical stimulation, a noninvasive technology that modulates brain network activity to address depressive and memory symptoms in older adults with depression and Alzheimer's dementia. By using cutting-edge technology to study targeted brain circuits and delivering the intervention at home, this study will help develop a scalable, noninvasive intervention with the greatest impact on alleviating depression and Alzheimer's symptoms.

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 beta-amyloid 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.

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.

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.

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

Stephanie Leal, PhD | University of California, Los Angeles

This project will 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

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.

Measuring Brain Aging in Early-Onset Alzheimer's Disease

Peter Millar, PhD | Washington University School of Medicine
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.
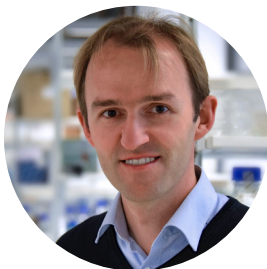
A Human Stem Cell-Based Model of Tau-Related Dementias

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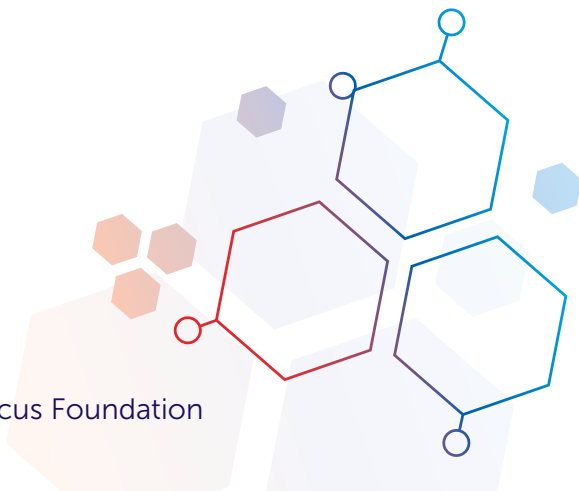
Preclinical Testing of a CRISPR-Based Alzheimer's Gene Therapy

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.

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.

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.

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.
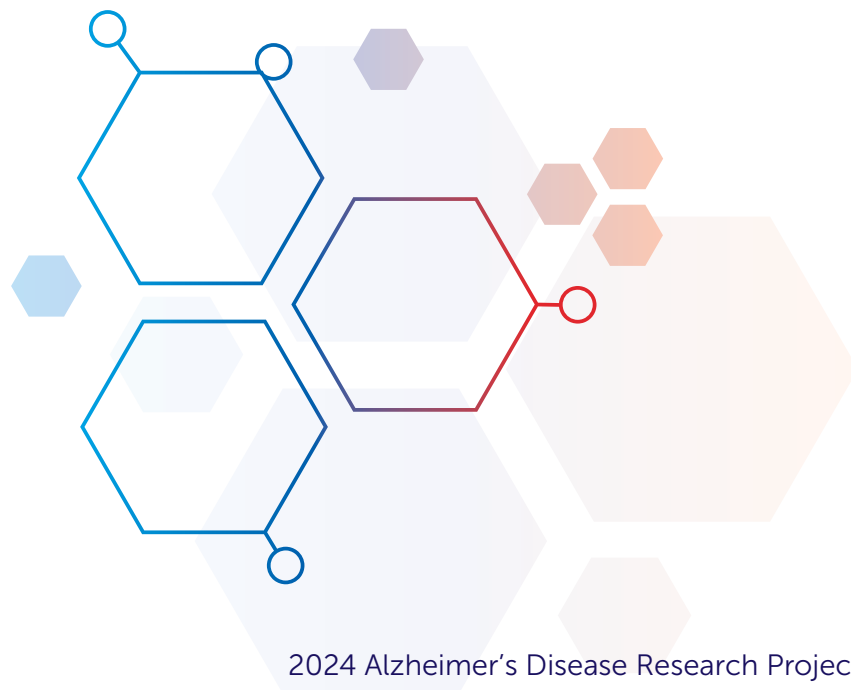
Vascular Contributions to Dementia

Vascular dementia is the most common condition that co-occurs with Alzheimer's disease, as the brain's neurons rely on a complex vascular system to deliver oxygen and glucose. This system, stretching about 60,000 miles, is protected from the rest of the body by the blood-brain barrier, which prevents harmful substances from entering. Both 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, MD

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.

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 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.

The Role of the Brain Vascular-Immune Processes in Alzheimer's

Julie Ottoy, PhD | Sunnybrook Research Institute (Canada)
Mentors: Sandra Black, MD and Maged Goubran, PhD, University of Toronto

Damage to the brain's blood vessels can triple Alzheimer's disease risk, and overactive immune cells may further exacerbate this damage. This study examines how vascular-immune responses affect Alzheimer's progression by analyzing brain scans and blood samples from 500+ individuals over time. Outcomes will provide unique insights on key and understudied mechanisms driving Alzheimer's, empowering conversations on personalized biomarkers and treatment strategies targeting the vascular system, brain immune cells, and Alzheimer's.

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 "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

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.

Waste-Clearance Mechanisms

In addition to immune-mediated clearance duties of the microglia, cells use self-eating, or autophagy, to remove old or misprocessed proteins and optimize health and function. Abnormalities in the endo-lysosomal pathway, an early feature of Alzheimer's, relate to genetic risk factors. The brain's lymphatic system, which drains fluid and immune cells, may contribute to Alzheimer's pathology if impaired, making it a potential target for therapeutic interventions.

Characterizing Factors That Induce Waste Clearance in Microglia

Anna Podlesny-Drabiniok, PhD | Icahn School of Medicine at Mount Sinai
*Co-Principal Investigator: Alison Goate, DPhil*

Researchers have identified potential factors that may boost the ability of microglia to dispose of accumulated waste during Alzheimer's. This project aims to validate computational predictions and characterize two factors of human microglia at baseline and with amyloid proteins. Additional investigation will also occur in microglia from people carrying two copies of *APOE4*. Study outcomes will explore potential novel therapeutic strategies aiming to induce waste clearance processes in microglia.

Understanding Tau Seeds: The Role of Protein Clumps on Membranes in Alzheimer's Disease

Sankalp Shukla, PhD | University of California, Berkeley
Mentor: James Hurley, PhD

In Alzheimer's disease, protein clumps build up and spread from one part of the brain to another, damaging the brain. These protein clumps can interact and disrupt the membranes that contain and destroy them, which causes protein clump leakage and spread. This project aims to understand the underlying cause of membrane leakage for therapeutic development to counteract protein clump escape by promoting the repair of damaged membranes.
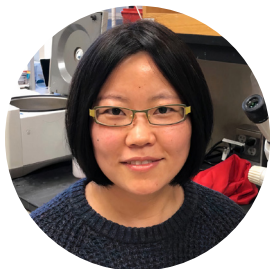
Identification of Protein Biomarkers for Aging and Alzheimer's Disease

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 goal of the project is to identify new protein biomarkers of aging and Alzheimer's disease and provide new treatment targets.

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