

**MICROBIAL
PATHOGENESIS IN
ALZHEIMER'S DISEASE
GRANTEE RESEARCH
OUTCOMES**



PREVENTION



DIAGNOSIS






TREATMENT

Year Published:
2024

Grantee Cycles
2018-2022

Potential Study Outcomes (n=42)

Prevention	Diagnosis	Treatment	TOTAL
 38	 8	 22	67*

*Some grants are counted with multiple potential outcomes

Studies by Research Area (n=42)

Research Area	Number of Studies
Infection and Inflammation	17
Herpes	8
Oral Bacteria	3
Gut Microbiome	10
Other Novel Pathogenic Approaches	4
TOTAL	42

Note: The scientific results were originally submitted to IDSA as part of the grantees' progress reports. These summaries were translated into layman's terms using the artificial intelligence text chatbot ChatGPT and then edited by IDSA staff. The summaries were then verified by individual researchers for accuracy.

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Introduction

The Infectious Diseases Society of America (IDSA) is a community of over 13,000 physicians, scientists and public health experts who specialize in infectious diseases. Our mission is to improve the health of individuals, communities, and society by promoting excellence in patient care, education, research, public health, and prevention relating to infectious diseases.

Alzheimer's Disease (AD) is a progressive brain disorder that can affect memory, thinking, and behavior and currently impacts 6.6 million Americans, 65 years of age and older and 47 million individuals worldwide. The idea that bacteria, viruses, or other infectious pathogens may play a role in ID was first proposed over 30 years ago. Since then, the idea has encountered considerable resistance in the research community. In recent years, the intersection of microbial pathogenesis and neurodegenerative diseases has emerged as a promising area of research, offering potential insights into conditions like AD. Recent studies have increasingly implicated microbial agents —bacteria, viruses, and fungi—in the pathogenesis of AD, challenging conventional views that regarded it solely as a consequence of aging and genetic factors.

The link between infectious diseases (ID) and AD is both promising and underrepresented in the research space. IDSA's Microbial Pathogenesis in Alzheimer's Disease Grant (MPAD) program exists to enhance research on the correlation between infectious agents or microbial communities with AD; to promote novel research in the field of microbial triggers for AD; and to advance research and ultimately provide a cure to AD. In 2018, IDSA began the MPAD Program with 3 grant applicants and \$100,000 in funding. To date the program has received 261 applications and proudly funded \$5.6 million through 46 awards ranging from \$30,000-\$250,000 to 43 international recipients.

This report provides brief summaries of the findings from MPAD - funded research studies. The outcomes of these studies underscore the possible role of infections in disease onset and progression and demonstrates the potential implications for prevention, treatment, and diagnosis of the disease. We are excited for the potential to revolutionize our understanding and treatment of AD in the years to come.



PREVENTION/DIAGNOSIS

Allison E. Aiello, PhD

*University of North Carolina - Chapel Hill
and Columbia University,
Mailman School of Public Health*

THE ROLE OF DEMENTIA-ASSOCIATED PATHOGEN BURDEN IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Funded in 2019



The main goal of Dr. Aiello's project was to understand how infections might be linked to dementia. The study aimed to uncover how multiple infections, but especially cytomegalovirus (CMV), and other factors like inflammation, stress and socioeconomic

disadvantage might contribute to problems with memory and cognition, particularly in the context of Alzheimer's disease.

Dr. Aiello and her fellow researchers found that CMV plays a significant role in causing problems with memory and cognition. Specifically, they found that people infected with CMV had up to a 6-point lower score in cognitive function, based on a study of older adults in the U.S. This suggests that CMV might be a crucial factor in predicting cognitive decline and problems with cognitive function. Another finding involves inflammation and cognitive function. The researchers discovered that certain inflammation-related substances in the body (like IL-6 and tumor necrosis factor (TNF)) are linked to how well people perform cognitively. Cortisol, a stress hormone, seems to interact with TNF, increasing the risk of cognitive problems. This is the first time such a connection has been reported. The research found that factors like lower socioeconomic status and stress hormones can strengthen the impact of infections on cognitive function. Understanding these connections could help us identify new ways to explain why some people are at greater risk for Alzheimer's disease.



PREVENTION

Maria Eugenia Ariza, PhD

Ohio State University

ROLE OF THE HERPESVIRUS DUTPASE PROTEINS IN LATE-ONSET ALZHEIMER'S DISEASE

Funded in 2020



In this study, Dr. Ariza evaluated the potential mechanism(s) by which herpesvirus dUTPases and Apolipoprotein E (APOE) promote late onset Alzheimer's disease pathology. She and her colleagues found that the production and release of certain

substances (IL-1 β , IL-6 and TNF- α) were significantly increased in special types of human brain cells. These substances are found at higher levels in people with Alzheimer's disease and can damage the protective barrier of the brain.

They also found that certain processes were activated that reduced the activity of important genes in brain cells. These genes are related to the cell's waste removal and energy production systems. Problems in these systems are linked to Alzheimer's disease and are believed to be among the early signs of the disease's development. The research suggests that certain viral components might play a role in causing brain inflammation, energy production issues and memory or thinking problems in Alzheimer's disease.

The study also confirmed that the herpesvirus dUTPases induce mitochondrial fragmentation, providing evidence for the potentially direct role of various herpesvirus dUTPases in alteration of mitochondrial architecture. Validation of this work could lead to small molecule inhibitors of dUTPases.



PREVENTION

Iliia V. Baskakov, PhD

University of Maryland School of Medicine, Baltimore

THE ROLE OF INFECTIOUS ETIOLOGY OF LATE-ONSET ALZHEIMER'S DISEASE

Funded in 2021



Dr. Baskakov is exploring a different idea about what might cause Alzheimer's disease (AD). Instead of focusing on the buildup of a protein called amyloid, he and his colleagues are investigating whether viral or microbial infections in the brain .

could be a significant factor, especially in late-onset AD

They are particularly interested in the role of herpes simplex virus 1 (HSV-1), a common virus. They have created a new mouse model that mimics late-onset AD, and their first goal is to see if there is a direct link between HSV-1 infection in the brain and the development of Alzheimer's.

The researchers are also checking if different strains of HSV-1 have varying effects on the risk of Alzheimer's. They are conducting experiments on mice, infecting them with HSV-1 through different methods and studying how it interacts with the genes associated with a higher risk of AD.

In their experiments, the researchers found that in mice with pre-existing A β plaques (a hallmark of Alzheimer's), the presence of these plaques did not protect the mice from HSV-1 infection. Also, HSV-1 did not seem to trigger the formation of A β plaques.

Dr. Baskakov and his team are continuing their investigation to understand if HSV-1 infection has a direct role in causing AD, especially in mice genetically modified to be more susceptible to the disease. The overall goal is to gain insights that could help settle the ongoing debate in the scientific community about what really causes Alzheimer's disease.



PREVENTION

Martin Blaser, MD

Rutgers, The State University of New Jersey

ROLE OF THE PERTURBED EARLY-LIFE MICROBIOME IN ALZHEIMER'S DISEASE PATHOGENESIS

Funded in 2022



For the past 20 years, Dr. Blaser has been studying the community of microorganisms living inside the human body, particularly how the community develops from early life. He and his colleagues have found that antibiotics can disrupt this community, and these changes can have long-term effects

on health, even years later. They have also discovered that the types of microorganisms present early in life can impact the risk of diseases later on. Because of this, Dr. Blaser and his colleagues decided to investigate how giving antibiotics early in life, which disrupts the microorganisms in the body, affects the development of Alzheimer's disease in mice.

This study involves three groups of mice: one group will receive antibiotics early in life, another group will receive antibiotics as young adults, and a third group will not receive any antibiotics (the control group). There are both normal mice and mice genetically engineered to develop Alzheimer's disease in each group, with an equal number of male and female mice.

This study will sacrifice some mice at different ages to examine their brains and other tissues for signs of Alzheimer's disease and other abnormalities. The researchers will analyze brain sections to look for signs of Alzheimer's disease and study the changes in the microorganisms inside the mice's bodies over time.



PREVENTION

Elizabeth Bradshaw, PhD

Columbia University

PATHOGEN DRIVEN EPIGENETIC CHANGES IN MICROGLIA

Funded in 2021



In this study, Dr. Bradshaw proposes a “pathogen hypothesis,” suggesting that infections could affect the immune system in the brain, specifically a type of cell called microglia. Microglia are like the immune cells of the brain and seem to be involved in Alzheimer’s disease.

The study looked at how microglia respond to different infectious agents by activating them in a lab setting. They observed that these microglia-like cells showed distinct patterns of inflammation when exposed to various infectious agents. The researchers also created a model to understand how the memory of these microglia-like cells works. They stimulated the cells, let them rest and then stimulated them again later. They found that, especially with a bacterial stimulus, the cells produced more inflammation when stimulated a second time.

Dr. Bradshaw and her colleagues are now investigating the changes that occur in the genetic material of these cells (epigenetic changes) after the first stimulation with different infectious agents. This research aims to understand how infections might affect the immune system in the brain and contribute to the development of Alzheimer’s disease.



PREVENTION

Angela Brown

PhD, Lehigh University

ESTABLISHING THE ROLE OF ORAL BACTERIAL OUTER MEMBRANE VESICLES IN ALZHEIMER’S DISEASE

Funded in 2023



The goal of Dr. Brown’s project is to understand how outer membrane vesicles (OMVs) produced by periodontal pathogens transport bacterial components, including certain enzymes, to the brain. Derived from the bacterial membrane, OMVs resemble the surface of the parent

bacterium. Recent evidence has demonstrated the presence of certain molecules from periodontal pathogens in the brains of patients with Alzheimer’s disease, but the process by which these molecules cross the blood-brain barrier is unknown. Dr. Brown and her colleagues hypothesize that OMVs, which can cross the blood-brain barrier, enable this transport. The researchers studied the mechanism by which OMVs cross this barrier and the interactions between pathogenic proteins, including amyloid beta and tau, and the vesicle surface. Ultimately, we anticipate that by studying the role(s) of OMVs in Alzheimer’s disease, this work will lead to the identification of novel therapeutic and diagnostic targets.

There’s growing evidence suggesting that one of the roles of amyloid beta is to act like a defense peptide against microbes. These peptides interact with the surface of bacterial cells. This project hypothesizes that because bacterial vesicles have a similar surface to the bacteria they come from, amyloid beta might bind to these vesicles after they enter the brain. If this hypothesis is correct, it is expected that the amyloid beta will bind to the vesicles and potentially disrupt them.

These interactions are being studied in two ways:

1. Testing how well amyloid beta binds to “model vesicles” by using liposomes with different surface charges. Preliminary results indicate that amyloid beta binds more strongly to liposomes with higher surface charges.
2. Examining whether amyloid beta can disrupt the integrity of vesicle membranes. Initial experiments with liposomes without surface charges showed no disruption, and the experiments are now being repeated with liposomes that have more surface charges.

The next step is to redo these experiments using vesicles produced by specific bacteria from the mouth, namely *Aggregatibacter actinomycetemcomitans* and *P. gingivalis*.



PREVENTION/TREATMENT

Catherine Butler, PhD

University of Melbourne

BACTERIAL MEMBRANE VESICLES IN ALZHEIMER'S DISEASE

Funded in 2022



Existing evidence suggests a type of bacteria called *Porphyromonas gingivalis*, which causes gum disease, might play a role in the progression of Alzheimer's disease, especially in people who already have gum disease. In Dr. Butler's recent study with mice, she found parts of this

type of bacteria in their brains after they were given the bacteria by mouth for more than 12 weeks. These mice also showed signs of Alzheimer's disease in their brains.

With current funding, Dr. Butler wanted to study if certain parts of this type of bacteria, called outer membrane vesicles (OMV), alone can cause Alzheimer's-like changes in the brain. This will be done by removing the whole bacteria from the mice, then using these OMVs to see if they cause similar problems and also comparing them to OMVs from another type of bacteria found in the mouth, called *Neisseria oralis*. These OMVs will be tagged with a fluorescent marker and injected into mice, and researchers will watch where they go in the body and how long they stay there. The researchers will examine the mice's brain tissue under microscopes to see if it shows Alzheimer's-like changes and check for changes in the mice's genes.

This study will help researchers understand if Alzheimer's-like changes in the brain can happen without the bacteria directly infecting the brain and if these changes are specific to certain types of bacteria.



PREVENTION/TREATMENT

Jingchun Chen, PhD

University of Nevada, Las Vegas

THE IMPACT OF COVID-19 ON ALZHEIMER'S DISEASE, FOCUSING ON SHARING GENES AND PATHWAYS IN IMMUNE CELLS

Funded in 2022



Researchers have been studying how viruses might cause Alzheimer's disease (AD) for a long time. Recent studies show that older people, especially those with AD, are more likely to get very sick or die from COVID-19. Dr. Chen is studying whether

findings suggest that people who are genetically more susceptible to COVID-19 are also more likely to have AD, even after taking account of age, sex and the apolipoprotein E (APOE) gene (a gene known to influence AD risk). Dr. Chen hypothesizes that both diseases share some genetic risk factors, particularly in immune cells and inflammation pathways.

Dr. Chen and her colleagues have gathered data from genetic studies on both COVID-19 and AD and are analyzing them to see which genes and pathways they have in common. They have presented some of their initial findings at conferences and applied for a grant to further support their research.

In the future, Dr. Chen will be analyzing data from single-cell RNA-seq (scRNA) to understand how genes are regulated in COVID-19 and AD. This may lead to the exploration of potential drugs for both diseases, which is crucial because the majority of treatments for AD fail in clinical trials.



PREVENTION/TREATMENT

Alberto Costa, MD, PhD

Case Western Reserve University

ROLE OF PORPHROMONAS GINGIVALIS IN THE PATHOLOGY OF ALZHEIMER'S DISEASE

Funded in 2019



Dr. Costa's project aimed to determine if a substance called A β peptide, which is a major component in Alzheimer's disease plaques, plays a role in protecting the brain from infection caused by a bacterium called *P. gingivalis*. T

he researchers conducted experiments using mice, testing two hypotheses: 1) Mice without the gene that produces A β peptides would have a higher and more severe brain infection when exposed to *P. gingivalis*, and 2) Mice without the A β peptide gene would also experience increased infection when the bacteria were directly introduced into their brains.

The results showed that mice lacking one copy of the A β gene started losing weight, and some died after being exposed to *P. gingivalis* through their gums. On the other hand, normal mice did not experience these problems during the experiment, supporting the idea that A β peptide is important in preventing the spread of *P. gingivalis* infection in the brain.

The researchers were unable to complete the experiments with mice lacking both copies of the A β gene due to disruptions caused by the COVID-19 pandemic. However, during the pandemic, they discovered that non-contact infrared thermometers, commonly used to measure body temperature, were reliable and consistent compared to the specialized laboratory thermometer they originally intended to use.

This study suggests that A β peptide may play a role in protecting the brain from infection, particularly from *P. gingivalis*, and the findings could potentially guide the development of treatments for Alzheimer's disease in the future. The unexpected positive aspect of the pandemic was the discovery that non-contact infrared thermometers are effective for measuring temperatures in mice.



PREVENTION/TREATMENT

Laura M. Cox, PhD

Harvard Medical School, Brigham & Women's Hospital

INVESTIGATING STRAIN-SPECIFIC PATHOGENICITY FACTORS IN BACTEROIDES THAT INFLUENCE ALZHEIMER'S DISEASE

Funded in 2020



Dr. Cox's research focused on a specific gut microbe called *Bacteroides fragilis*, which tends to increase as people age and in those with Alzheimer's. By giving this microbe to mice with an Alzheimer's-like condition, Dr. Cox and her colleagues noticed more amyloid-beta plaques in the brain, a characteristic feature of Alzheimer's.

The challenge is that there are many different types of Bacteroides, and not all may contribute to Alzheimer's. The researchers discovered that *Bacteroides fragilis* can hinder the immune system's ability to clear amyloid-beta, a protein associated with Alzheimer's. They also found differences in how various strains of Bacteroides affect the uptake of amyloid-beta, with some strains from healthy individuals enhancing the process while strains from Alzheimer's patients do not.

Furthermore, they observed that *Bacteroides fragilis* affects the expression of certain genes in the brain's immune cells (microglia), making them less effective in clearing amyloid-beta. This effect is connected to a decrease in the production of a cytokine called GM-CSF, which usually enhances the microglia's ability to engulf and remove harmful substances.

In summary, this study suggests that certain strains of the gut microbe Bacteroides, specifically *Bacteroides fragilis*, may influence Alzheimer's disease by interfering with the immune system's ability to clear amyloid-beta from the brain. These findings have provided valuable information for future research and the development of potential treatments for Alzheimer's disease.



PREVENTION

Colette Cywes-Bentley, PhD

Brigham and Women's Hospital, Harvard Medical School

NEUROINFLAMMATORY IMPACT OF MICROBIAL MATERIAL IN ALZHEIMER'S DISEASE

Funded in 2018 and 2021



Dr. Cywes-Bentley's research aims to understand how a polysaccharide substance, called poly N-acetyl glucosamine (PNAG) and found in certain microorganisms, contributes to inflammation in the brain and affects

cognitive function. Dr. Cywes-Bentley and her colleagues are investigating whether antibodies to PNAG can help protect against cognitive decline in mice, and if the inflammation caused by PNAG-containing microbial material (PNAG-MM) plays a crucial role in nerve-related diseases. The study involves three main goals: examining the impact of PNAG-MM on brain inflammation, studying the effects of purified PNAG on nerve cell pathology and determining whether antibodies to PNAG, by removing PNAG-MM and reducing inflammation, can prevent the PNAG-MM from causing cognitive decline in mice.

The researchers found that vaccinating mice against PNAG prevented cognitive decline in tests. Brain tissues from these mice showed reduced inflammation, as well as reduced levels of PNAG associated with beta-amyloid proteins, compared to control mice. The study also discovered that PNAG-MM is linked to certain proteins and is engulfed by specific cells in the brain.

Additionally, PNAG-MM was found to influence the expression of certain proteins in brain tissues, suggesting a potential connection to inflammatory properties. In human neural stem cells exposed to PNAG-MM, there was evidence of increased production of certain proteins, such as beta-amyloid, associated with nerve-related diseases. This suggests that PNAG may contribute to inflammation in the brain independently of other factors.



PREVENTION/TREATMENT

Daniel Czyz, PhD

University of Florida

DECIPHERING THE EFFECT OF HUMAN MICROBIOTA ON ALZHEIMER'S DISEASE USING C. ELEGANS

Funded in 2020



Recent evidence suggests that an imbalance in the gut bacteria (gut dysbiosis) is linked to a higher risk and severity of Alzheimer's disease and related diseases. Understanding how these microbes affect protein stability

is crucial for developing effective treatments. However, the complexity of the human microbiota makes it challenging to understand the role of individual microbes in maintaining protein integrity.

To study how bacteria affect the integrity of human proteins, Dr. Czyz used tiny worms (*Caenorhabditis elegans*) that produce fluorescent markers that allow him to observe changes in protein folding caused by different bacteria. His team found that certain harmful bacteria in the worms' intestines disrupted the folding of proteins in other tissues. These harmful bacteria produced clumps of proteins that contributed to the disruption.

Interestingly, when the worms were colonized with beneficial bacteria or exposed to a substance called butyrate, the clumping was reduced, and the associated problems with protein folding were alleviated. The researchers analyzed various bacteria from the Human Microbiome Project to understand their impact on protein balance.

Ultimately, the study identified specific beneficial bacteria that could potentially protect against problems related to these protein imbalances. This research provides insights into the connection between gut bacteria and AD, paving the way for potential strategies to prevent or treat these conditions.



PREVENTION/DIAGNOSIS/TREATMENT

Gautam Dantas, PhD

Washington University in St. Louis

INVESTIGATING GUT MICROBIOME COMPOSITION AND FUNCTIONS DURING STAGES OF ALZHEIMER'S DISEASE

Funded in 2020



Recent research has shown that people with symptomatic Alzheimer's disease (AD) have different gut microbe communities compared to healthy individuals. These specific microbe groups are also linked to markers of AD in the cerebrospinal fluid and inflammation pathways.

Dr. Dantas and his team wanted to understand how the gut microbiome changes before AD appears. They believe that studying the gut microbes in individuals who are cognitively normal but have signs of preclinical AD (amyloid positive) can reveal differences in microbe composition and activity using samples from people without preclinical AD, those with preclinical AD and those with symptomatic AD.

By using advanced techniques to analyze the genetic material of these microbes, Dr. Dantas and his colleagues aim to confirm if there are unique features in the gut microbiome of people with preclinical and symptomatic AD. The goal is to find early markers in the gut that can help diagnose and predict AD, and possibly develop new interventions.

So far, the researchers have found that individuals with preclinical AD have distinct gut microbe profiles compared to healthy individuals. These microbial features are related to markers of AD, and specific microbe groups are associated with preclinical AD. Additionally, including information about the gut microbiome improves the accuracy of machine learning models for predicting preclinical AD status.



PREVENTION/TREATMENT

Martin Darvas, MD, PhD

University of Washington

THE ROLE OF PILRA IN THE MICROBIAL ETIOLOGY OF ALZHEIMER'S DISEASE

Funded in 2022



Dr. Darvas is currently studying how herpes simplex virus 1 (HSV-1) might affect Alzheimer's disease. Dr. Darvas and his colleagues have been using mice infected with HSV-1 and observing their brain tissue during

periods when the virus is inactive. They have observed some interesting changes in gene expression. They are also looking at how the virus affects amyloid levels, which are linked to AD, and testing the mice's behavior. The researchers used a special strain of mice for these experiments and started breeding them with their existing colony.

Dr. Darvas' team includes experts in analyzing different types of biological data, like genes and proteins, to understand how they work together. This team is focusing on a specific gene called PILRA, which might play a role in protecting against AD. They are using a special type of mouse that has both AD risk factors and a protective version of the PILRA gene.



PREVENTION/TREATMENT

Gagan Deep, PhD

Wake Forest University Health Sciences

ROLE OF GUT-DYSBIOTIC BACTERIAL METABOLITE

L-HISTIDINOL IN ALZHEIMER'S DISEASE

Funded in 2022



Researchers have found a substance produced by bacteria in the gut that changes when there's a problem with the balance of bacteria in the gut, and this might be important in causing Alzheimer's disease. With their research

grant, Dr. Deep and his colleagues want to see how much of this substance is in people who are healthy compared to those who have memory problems. They also want to see if tiny structures (bacterial extracellular vesicles) released by bacteria in the gut can carry this substance to the brain. Scientists know that there's a connection between the gut and the brain in various diseases, but they don't fully understand how it works. Dr. Deep's team wants to determine if these tiny structures play a role in how the gut affects the brain and other parts of the body.

They have two main goals for their study:

1. They want to see if two substances, called L-histidinol and L-histidine, could be used to inform whether Alzheimer's disease is getting worse. To do this, they'll look at samples from 100 people who are normal, have minor memory problems or have Alzheimer's disease. They'll use a special machine to measure the levels of these substances in the samples and see if they match up with how well the people can think, what their brain scans look like and other tests.
2. They want to understand how these tiny structures carry L-histidinol from the gut to the brain. They plan to find out what proteins are on the surface of these tiny structures and see where they go in the body, especially in the part of the brain called the hippocampus, which is important for memory.

They've already made good progress by doing experiments with these tiny structures using fluorescent-labelled microRNA and testing new ways to see where they go in the body.

Overall, the researchers are working hard to understand how problems in the gut might lead to problems in the brain, and they're using advanced techniques to do it.



TREATMENT

Eran Elinav, PhD

Weizmann Institute of Science, Systems Immunology Department, Rehovot, Israel

ENCODING MICROBIAL SPECIES AND PRODUCTS

MODULATING ALZHEIMER'S DISEASE - TOWARDS

PRECISION PROBIOTICS AND POSTBIOTICS TREATMENT

Funded in 2020



Dr. Elinav and his colleagues are exploring the connection between Alzheimer's disease (AD) and the bacteria in our gut, known as the gut microbiome. They believe that changes in the composition and function of the gut microbiome could play a role in the development and progression of AD.

They are investigating how alterations in the gut microbiome may influence AD and are particularly interested in understanding if certain types of bacteria or their byproducts could affect the brain and contribute to the development of Alzheimer's. To do this, they are studying mice that are raised without any germs (germ-free mice) and comparing them to mice with a normal microbiome.

Dr. Elinav's team found that germ-free mice and mice treated with antibiotics showed improved cognitive performance compared to mice with a normal microbiome. The analysis of the brain also revealed unique gene expression patterns and changes in chromatin and histone modifications in germ-free mice.

They also observed differences in the microbiome composition of Alzheimer's mice over time. However, interventions to change the microbiome in germ-free mice did not affect their cognitive abilities.

Additionally, they identified potential candidate molecules in the blood that might be involved in the communication between the gut microbiome and the brain in the context of Alzheimer's disease. Overall, the research aims to better understand how the gut microbiome influences Alzheimer's and whether targeting specific aspects of the microbiome could be a potential therapeutic approach.



PREVENTION

Pinghui Feng, PhD

University of Southern California

COLLATERAL DAMAGE OF IMMUNE EVASION IN HSV-1-INDUCED NEURODEGENERATION

Funded in 2021



Alzheimer's disease (AD) is a condition that causes gradual loss of cognitive function in the brain. Researchers are urgently looking into the main causes and potential treatments for AD. There is growing evidence that infections caused by certain microbes, particularly

herpes simplex virus 1 (HSV-1), might speed up the formation of harmful substances called amyloid beta plaques in the brain, which are associated with AD. In this study, Dr. Feng discovered a specific enzyme called NAMPT that normally helps limit the replication of HSV-1. This enzyme works by modifying certain proteins of the virus, preventing them from being properly included in new virus particles. However, the virus fights back by changing the NAMPT enzyme through a process called deamidation, making it less effective in synthesizing NAD⁺, which is important for cell function.

Dr. Feng hypothesizes that this alteration in the NAMPT enzyme might lead to a decrease in the production of NAD⁺, which impairs neuronal function. They believe that this process could contribute to the accelerated brain degeneration seen during aging and in mice infected with HSV-1, shedding light on a potential mechanism linking herpes infections, aging and neurodegenerative diseases like AD.



PREVENTION

Kristen Funk, PhD

University of North Carolina, Charlotte

ROLE OF APOBEC3 IN MHC-I ANTIGEN PRESENTATION AND NEURONAL SYNAPTIC STABILITY IN VIRAL NEUROINFLAMMATION AND ALZHEIMER'S DISEASE

Funded in 2021



Dr. Funk is looking at how infections – specifically neurotropic infections like West Nile virus – might affect the connections between brain cells (synapses) and contribute to cognitive problems seen in Alzheimer's disease. This research is focusing on a protein called APOBEC3,

which normally helps protect against West Nile virus infection. The researchers want to understand how APOBEC3 influences expression of the immune protein MHC-I on brain cells during healthy conditions as well as during acute infection and following clearance of infection. Specifically, Dr. Funk and her colleagues want to understand how these proteins may affect connections between brain cells that are important for their communication.

Dr. Funk and her colleagues have observed that APOBEC3 is increased in the brains of both humans and mice with AD and neurotropic infections.

They have two main objectives:

1. To examine how APOBEC3 influences the expression of another protein called MHC-I in brain cells.
2. To understand the impact of APOBEC3 on the connections between brain cells and overall brain function under different conditions – normal, during infection and after infection.

The results of the study will help explain how MHC-I functions in the brain, both in maintaining connections between cells and in the immune response.

The researchers also found that APOBEC3 protects against West Nile virus infection by limiting the virus's ability to replicate in the brain. Additionally, when APOBEC3 is reduced, it affects the activation of immune cells in the brain and the retention of certain immune cells, which may contribute to the severity of the infection.



TREATMENT

Bhanu (Priya) Ganesh, PhD

The University of Texas Health Science Center at Houston

ENHANCE MICROBIOME-DERIVED TRYPTOPHAN METABOLITES IN THE GUT TO IMPROVE THE CENTRAL IMMUNE FUNCTION AND REDUCE A β BURDEN

Funded in 2022



Research suggests that as people age, problems with memory and thinking are often caused by brain damage from both nerve and blood vessel issues. One particular problem is called cerebral amyloid angiopathy, where a harmful protein called amyloid- β builds up in the

blood vessels of the brain, leading to memory problems and sometimes causing bleeding in the brain.

Dr. Ganesh's study focuses on how changes in the gut (specifically, an imbalance in homeostatic bacteria) can affect inflammation in both the body (peripheral organs) and the brain. She found that in mice with amyloid- β pathology, problems in gut barrier function can lead to more inflammation in the body and brain, which worsens memory.

Dr. Ganesh and her colleagues hypothesize that a receptor in the body called the aryl hydrocarbon receptor (AHR), which is affected by the bacteria in the gut, might help control this inflammation. They found that in older mice, there's less of this molecule in the brain, and they also found that, with age, there is a decrease in the bacteria in the gut that produce small molecules to activate the AHR. Additionally, they found that these active molecules from the gut can pass through the blood-brain barrier and interact with brain immune cells and neurons. These molecules seem to play an important role in neurodevelopment and immune maturation.

Their research has two main goals:

1. To see if fixing the gut problems in older mice, by giving them gut bacteria from younger mice, can improve their memory and reduce brain damage.
2. To investigate if certain molecules produced by helpful gut bacteria can reduce inflammation in the brain and slow down the buildup of harmful proteins with advanced age.

Overall, this research seeks to understand if fixing gut problems and introducing beneficial gut bacteria molecules can help improve memory and brain health in aging mice with amyloid- β pathology.



PREVENTION/TREATMENT

Jason Grayson, PhD

Wake Forest School of Medicine

USING MACHINE LEARNING TO DETERMINE THE ROLE OF HERPESVIRUS-SPECIFIC CD8+ T CELLS IN ALZHEIMER'S DISEASE

Funded in 2019



Recent studies show that infections from viruses (like herpes), bacteria and parasites might be linked to Alzheimer's disease (AD).

These infections happen early in life and stay in the body. When the immune system is not working well (due to factors like aging or certain treatments), these infections can become active again and cause more inflammation.

To understand how the immune system affects AD, Dr. Grayson studied 40 people with cognitive issues. He and his team found that those with amyloid plaques in their brains had changes in their immune system. People with mild cognitive problems had different immune cells compared to those without amyloid, and those with normal cognition but amyloid had more of a specific type of immune cell.

This study suggests that the immune system plays a role in AD. Boosting certain immune functions might be a way to help treat or prevent the disease.



PREVENTION/DIAGNOSIS

Eric Hamlett, PhD

Medical University of South Carolina

CAN BRAIN-DERIVED EXTRACELLULAR VESICLES REVEAL MICROBIAL SHEDDING WITH ALZHEIMER'S DISEASE?

Funded in 2022



Dr. Hamlett's hypothesis is that tiny particles called EVs, which come from the brain and are found in the blood, might contain certain signs of how the body's increased response to germs in people with Alzheimer's disease compared to those without the disease who are the same age.

He and his colleagues are examining whether the signs we find in these EVs are different from what we see in the brain itself, and if they can help us tell the difference between early and late onset Alzheimer's disease. To do this, Dr. Hamlett and his colleagues are collecting blood and brain samples from donors with Alzheimer's disease and those without it. They will use these samples to isolate the EVs and study them.

Additionally, they are interested in studying whether a specific type of fat called Omega 3 is found more in EVs from the brain, as the brain has more Omega 3 compared to other parts of the body.



PREVENTION

Catherine Helmer, PhD

Bordeaux University

VIRAL INFECTIONS IN ALZHEIMER'S DISEASE

Funded in 2019



Despite our growing knowledge of Alzheimer's disease (AD), we still don't fully understand what causes it. However, finding out what triggers the brain changes seen in AD could help us prevent it.

Some research suggests that infections, like viruses, might play a role in causing these brain changes. Dr. Helmer is investigating this idea further. Instead of focusing on just a few viruses, as in previous studies, she is using a technology called VirScan to look at over 200 different viruses and 1,000 strains.

By studying over 1,000 people over many years, Dr. Helmer hopes to see if people who have been exposed to certain viruses are more likely to develop cognitive decline and AD. Her team also wants to determine if some people are more susceptible than others to the harmful effects of these viruses. This could help us better understand how viruses might contribute to AD and who might be at greatest risk.



PREVENTION/DIAGNOSIS

Mark Hicar, MD, PhD

University at Buffalo

USE OF SHARED ANTIBODY RESPONSES AMONGST ALZHEIMER'S DISEASE PATIENTS TO REVEAL AN INFECTIOUS DISEASE ETIOLOGY

Funded in 2021



The goal of Dr. Hicar's research is to understand how our immune system fights infections and how that relates to Alzheimer's disease. By studying antibodies in different people, Dr. Hicar and his colleagues hope to find common traits called "public clonotypes" in the antibodies that

can lead to new ways of diagnosing and possibly treating Alzheimer's. So far, they've discovered some interesting patterns in these antibodies that could be important for future research.

Over 1.4 million heavy chain variable sequences were retrieved from public biorepositories for 43 healthy people and 205 people with HIV. By examining a large number of antibody sequences from both healthy individuals and those with HIV, Dr. Hicar and his colleagues found that a small percentage of these sequences were shared among multiple people. Certain parts of the antibody genes were more commonly used than others, and shorter versions of a specific part of the gene were particularly common among these shared sequences.



PREVENTION/DIAGNOSIS

Bert Jacobs, PhD

ASU, Foundation for a New American University

THE ROLE OF MICROBE-INDUCED NECROPTOTIC DEATH IN TAUOPATHY

Funded in 2020



Scientists believe that a process called necroptosis, which is a type of cell death, might play a role in the death of brain cells in Alzheimer's disease. They think that a specific molecule in cells, called DAI, could sense certain types of stress in the brain, like viral infections or oxidative stress, and

trigger this cell death process.

Dr. Jacobs and his colleagues are testing if blocking DAI can reduce brain cell death caused by a protein called tau, which is known to build up in Alzheimer's disease. They also want to see if inducing this cell death process in mice with Alzheimer's-like symptoms makes the disease worse. Overall, they hope this research will help increase understanding of how infections could potentially lead to Alzheimer's disease.

Thus far, they have observed that mice without the ability to undergo necroptosis have less brain cell death caused by tau. Additionally, they've seen signs of the necroptosis process in the brains of people who had Alzheimer's disease after they died.



PREVENTION/TREATMENT

Shuqi Li, PhD

Harvard Medical School and Brigham and Women's Hospital

DOES THE MEDITERRANEAN DIET SUPPRESS PATHOGENIC FUNCTION IN THE GUT MICROBIOTA IN ALZHEIMER'S DISEASE?

Funded in 2022



Dr. Li's study aims to understand how certain harmful bacteria in the gut can affect the brains of people with cognitive impairments, and how changes in diet might help. Dr Li's hypothesis is that following a Mediterranean diet could

improve Alzheimer's disease by reducing harmful gut bacteria and their byproducts.

The study has two main goals:

1. To find out which bacteria and their functions are affected by the Mediterranean diet and how they are related to the buildup of amyloid-beta proteins in the brain.
2. To identify specific substances in the gut, blood and brain that change when following the Mediterranean diet and are linked to amyloid-beta protein buildup.

This study has organized the experimental mice into 12 groups based on their diet, sex and genetic background. They were bred from specific parent mice to ensure consistency in their gut bacteria. The mice were then assigned to different cages based on factors like age, sex, genotype and diet. A Western diet was also included in the study to compare with the Mediterranean diet. Longitudinal data collection includes weighing the mice and collecting fecal samples. Behavior tests will also be conducted when the mice reach eight months of age to ensure they have been on their respective diets for a full six months and to observe any differences in behavior between the different groups of mice. Upon completion of sample collection, they will be sent for sequencing in batches.



PREVENTION/TREATMENT

Xueyi Li, PhD

Massachusetts General Hospital

VPS35 AND HERPETIC VIRUS INFECTION SYNERGY IN ALZHEIMER'S DISEASE

Funded in 2021



Over 30 years ago, a microbe infectious cause of Alzheimer's disease (AD) was proposed. One germ, called herpes simplex virus 1, seems to be particularly harmful and linked to AD. It was recently discovered

that a certain gene mutation called VPS35, which is missing in the brains of people who had AD, makes it harder for Herpes Simplex Virus (HSV1) to replicate. This gene usually helps move certain molecules around in cells, including one called tetherin that fights viruses. Tetherin is also important in stopping the spread of other viruses, like the one causing COVID-19, which sometimes affects the brain and causes problems with thinking.

Dr. Li and his colleagues are examining whether HSV1 and the COVID-19 virus might both affect the brain in similar ways. Dr. Li is studying how HSV1 affects the movement of certain molecules in brain cells and how it might be related to Alzheimer's. They are also looking at how the COVID-19 virus behaves in brain cells and what effects it might have.

So far, the following observations have been made: HSV1 infection causes a buildup of a certain molecule called APP in abnormal structures in brain cells. This infection also reduces how much APP and another molecule called VPS35 are found together. When the surface of brain cells was examined, they found that HSV1 infection changed the levels of several proteins compared to cells treated with inactive virus. Additionally, they found that the COVID-19 virus's protein interacts with and moves along with the VPS35 molecule in brain cells.



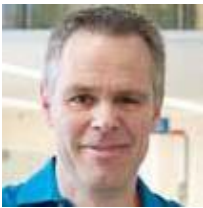
PREVENTION/TREATMENT

Roger Lippé, PhD

University of Montreal & Research Center of the Sainte-Justine University Hospital

INFECTIOUS ETIOLOGY OF ALZHEIMER'S DISEASE: MOLECULAR LINKS BETWEEN HSV-1 AND APP

Funded in 2022



Dr. Lippé's lab has found that a protein from the herpes virus (HSV-1) interacts with a human protein called BRI2, which is linked to Alzheimer's disease (AD). This interaction helps the virus spread.

Their study has three main goals:

1. They are investigating how the virus affects BRI2 and another protein called APP, which is also involved in AD. They've confirmed the interaction between the virus and BRI2 in non-neuronal cells and are now planning to repeat the experiments in neuronal cells, which are more physiologically relevant.
2. They are examining how the virus affects the levels and processing of BRI2 and APP. Both proteins are processed into different fragments within cells, so they're testing various antibodies to detect these fragments. They've found that the virus also interacts directly with APP.
3. They are researching if the virus affects the formation of amyloid-beta oligomers, which are implicated in AD. They've created a mutant virus without the specific gene and are working to detect these oligomers in cell cultures.

Additionally, Dr. Lippé's lab has started collaborating with other IDSA-funded researchers to test ideas in animal models of AD and to access human brain tissues affected by AD, which could provide valuable insights into this area of research.



PREVENTION/TREATMENT

Melissa Lodoen, PhD

University of California, Irvine

REDUCTION IN AMYLOID PLAQUE BURDEN BY TOXOPLASMA GONDII INFECTION OF AD MICE

Funded in 2022



Dr. Lodoen's project focuses on understanding how an infection caused by the parasite *Toxoplasma gondii* affects Alzheimer's disease (AD). AD is known for the

buildup of harmful substances called amyloid plaques in the brain, leading to brain damage and memory loss. While genes play a role in AD, it's unclear how external factors like infections might contribute.

Toxoplasma gondii is a parasite that infects many people worldwide, usually through contaminated food. Studies show that infecting mice with *T. gondii* reduces amyloid plaques in their brains and improves their memory. However, we don't fully understand how this happens.

The project has two main goals:

1. Understand how *T. gondii* infection reduces amyloid plaques in AD mice
2. Study how the immune cells derived from stem cells of AD patients respond to *T. gondii* infection.

The researchers started by infecting AD mice with *T. gondii* and examining their brains at different time points after infection. They observed increased immune cell activity in the brains of infected mice, along with a decrease in amyloid plaques. Specifically, they found that immune cells in the brain called microglia were better at clearing amyloid in infected mice.

The researchers investigated a gene called TREM2, known to be involved in regulating immune responses and linked to AD risk. They found that mice lacking this gene showed reduced activation of protective microglia during *T. gondii* infection, suggesting that TREM2 plays a role in the beneficial effects of the infection.

Overall, these findings suggest that *T. gondii* infection activates immune responses in the brain, leading to improved clearance of amyloid plaques, possibly through the TREM2 pathway.



PREVENTION

Kamada Lwere, MD

Islamic University in Uganda

THE GUT MICROBIOME AND IMMUNOPATHOGENESIS OF ADRD IN A UGANDAN POPULATION

Funded in 2022



Dr. Lwere is conducting a study in Uganda to understand Alzheimer's disease and related dementias, or ADRD, in older African individuals. He and his colleagues are looking at bacteria in the gut and related inflammatory substances in the body that might be linked to these diseases.

As part of this study, they have collected DNA from rectal swabs and measured certain substances in the blood.

They have screened 122 older people in two villages in Uganda to see how common dementia is there. They used tests and interviews to collect information about dementia and other factors. Now, they're analyzing these data to see what might be causing dementia in these communities.

Their main goals are:

1. To see what types of bacteria are in the gut of people with ADRD compared to those without;
2. To measure certain inflammatory substances in the blood and see how they relate to the bacteria in the gut of people with ADRD compared to those without.

Additionally, they are reviewing existing research. Ultimately, this study has the potential to increase the understanding of the development of dementia in the Ugandan population and how to better detect cognitive disorders early on.



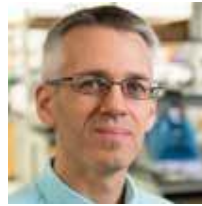
PREVENTION/TREATMENT

Ashley Moseman, PhD

Duke School of Medicine

INFECTIOUS INFLUENCE: USING FATE MAPPING TO DETERMINE HOW SITES OF HISTORICAL VIRAL INFECTION IMPACT ALZHEIMER'S DISEASE INITIATION

Funded in 2020



Within the upper respiratory tract, the olfactory epithelium (OE) is a specialized mucosal barrier dedicated to scent detection. A unique anatomical arrangement within the OE allows olfactory sensory neurons to directly link the upper airway (URT) with the central nervous system (CNS). Some viruses (such as herpesviruses, influenza viruses and coronavirus) that infect our URT can also infect the CNS.

Dr. Moseman's hypothesis was that sites of previous viral infection serve as initiators for disease-associated pathologies. His research was to see if these viruses could have a role in diseases such as Alzheimer's disease and to investigate the role of olfactory viral infection on seeding or accelerating AD. He and his team used special viruses in mice to see where infections happened and if they caused Alzheimer's-like issues.

The researchers found that parts of the brain infected by the virus didn't have Alzheimer's-related plaques and that infection didn't exacerbate memory problems in the mice. Surprisingly, they also found that infected mice actually showed better memory in the long term.

Rather than universally detrimental, it appears that certain types of CNS infections might lessen Alzheimer's associated memory deficits.



PREVENTION/TREATMENT

Ravinder Nagpal, PhD

Florida State University

KLEBSIELLA PNEUMONIAE AS A MICROBIAL TRIGGER FOR ALZHEIMER'S DISEASE: FROM MICROBIAL PATHOGENESIS TO NEUROPATHOGENESIS

Funded in 2021



Dr. Nagpal's research is focused on Alzheimer's disease (AD) and its potential connection to gut bacteria. The researchers in this study found that people at risk of AD with mild memory problems have dysbiotic gut bacteria patterns, which seem to be related to the levels of certain biomarkers in

the brain associated with AD. Specifically, they found higher levels of a bacterium called *Klebsiella pneumoniae* (*Kpn*) in the intestines of these at-risk individuals. This bacterium is concerning because it's becoming resistant to antibiotics and has been linked to infections in hospitals, which have also been linked to sepsis, memory problems and dementia in older people.

Dr. Nagpal and his fellow researchers wanted to understand if the presence of *Kpn* in the gut could be causing or contributing to AD. To investigate this, they proposed a study using mice that have both AD-like symptoms and gut microbiome dysbiosis caused by *Kpn*.

Early findings suggest that, particularly under antibiotic-induced gut dysbiosis milieus that mimic hospital/ICU settings, *Kpn* can translocate from the gut into the bloodstream, potentially reaching the brain and triggering neuroinflammatory and cognitive impairments. This suggests that *Kpn* might play a causative role in worsening AD symptoms by causing inflammation in the brain.

The ongoing research is looking at mechanisms via which *Kpn* affects and exploits the gut microbiome and how it might travel from the gut to the brain via the gut-blood-brain barrier, as well as how it influences inflammation and memory problems in mice with AD-like symptoms. Ultimately, through their recently established project REMIND, or "Role of Enteric Microbial Infections in Neurodegenerative Disorder," they hope to better understand the relationship between gut pathogens, particularly *Kpn*, and Alzheimer's disease.



PREVENTION/DIAGNOSIS

Mujeeb Salaam, PhD, MHP, MSc

Islamic University in Uganda, Kampala

HIV/AIDS, SYPHILIS AND CARDIOVASCULAR DISEASES AS PREDISPOSING FACTORS AMONG DEMENTIA PATIENTS ATTENDING SELECTED REFERRAL HOSPITALS IN UGANDA

Funded in 2020



Dementia is a clinical syndrome that affects memory, thinking, behavior and everyday activity. Dementia results in cognitive decline and behavioral problems that lead to difficulties in carrying out of daily activities. Many patients are undiagnosed as most

health care providers are not aware of laboratory tests using biochemical markers in the blood that can guide a diagnosis of dementia.

The goal of Dr. Salaam's study is to see if HIV/AIDS, syphilis and heart problems could be factors that make people more likely to develop dementia. The study involves 50 older patients diagnosed with Alzheimer's dementia from five hospitals in Uganda. Blood samples were taken to check for certain markers, and participants filled out questionnaires about their health and cognitive abilities. The data are being analyzed using software to determine if there's a connection between these diseases and dementia.

So far, the study has found that HIV infection is more common among dementia patients, but syphilis doesn't seem to be related to Alzheimer's disease and dementia. The study did not show a strong significance of demographic factors playing a role in dementia, but more research is needed. Overall, the results indicate that people with higher rates of infections may be more likely to have dementia.



PREVENTION

Marvin Schulte, PhD

Idaho State University

LINK BETWEEN VIRAL INFECTIONS, SPECIFIC VIRAL PROTEINS AND THE DEVELOPMENT OF ALZHEIMER'S DISEASE

Funded in 2019



Dr. Schulte's research explores an exciting new connection between viral infections and Alzheimer's disease. His work has focused on the ability of viruses to mimic naturally occurring proteins and alter signaling between cells at the molecular level. This "viral mimicry" enables viruses to

alter the body's immune and inflammatory responses. This same ability appears to also enable the viruses to interact with nerve cells, altering their ability to conduct impulses.

This research has focused specifically on herpes virus, which was shown to inhibit neurotransmission via neurotransmitter receptors that are lost in Alzheimer's disease, and which are important to cognition, learning and memory. In addition to herpes virus, similar mimicry appears to be present in influenza and COVID-19, suggesting this may be a more common trait in viruses than was previously thought. Dr. Schulte's research has uncovered the molecular basis of these interactions and is working to develop novel drugs that will prevent these effects.

The link between viruses and central nervous system disorders is an extremely exciting and emerging area of research. This research may ultimately uncover new connections between viral infection and diseases such as Alzheimer's disease, autism and long COVID, along with uncovering opportunities for novel preventative therapies.



PREVENTION/DIAGNOSIS

Jason Tchieu, PhD

Cincinnati Children's Hospital Medical Center

INVESTIGATING THE IMPACT OF THE ENDOGENOUS RETROVIRUS HERV-K (HML-2) ON ALZHEIMER'S DISEASE

Funded in 2021



Studies have shown that certain viruses and pathogens might be responsible for causing Alzheimer's disease. Some studies have observed that these pathogens, like viruses (e.g., herpes viruses), are more commonly found in people with Alzheimer's disease. compared to those without the disease. However, whether these pathogens

are correlated with Alzheimer's or cause the disease is still a subject of intense debate because we do not fully understand the exact ways these pathogens might lead to Alzheimer's.

Human endogenous retroviruses (HERV) are genetic elements in our DNA that originally came from viruses that infected our ancestors. Normally, they're switched off (silenced), but they can be switched back on by certain factors, including other viruses.

One type of HERV called HERV-K (HML-2) is of interest because when it's activated, it seems to negatively affect the development of certain brain cells (cortical neurons) and brain structure (forebrain).

Dr. Tchieu's study investigates whether activating HERV-K (HML-2) might play a role in causing Alzheimer's disease. He and his colleagues use a method called CRISPR activation to switch on HERV-K (HML-2) in different types of brain cells grown in the lab from cells taken from patients with Alzheimer's and healthy individuals (controls). By studying how HERV-K (HML-2) activation affects these cells at a genetic level, they hope to understand if it contributes to Alzheimer's development.

The researchers have discovered that activating HERV-K (HML-2) in brain organoids (miniature brains grown in the lab) with genetic risk factors for Alzheimer's causes certain genes related to Alzheimer's to become more active. They've also found that this activation might be more powerful as a person ages. To explore this further, they plan to convert cells from older individuals into neurons in the lab and study how HERV-K (HML-2) affects them.

This study could show whether a specific type of genetic element, HERV-K (HML-2), when activated, might contribute to Alzheimer's disease development.



PREVENTION/DIAGNOSIS

Christoph Thaiss, PhD

University of Pennsylvania

MICROBIAL CONTROL OF AMYLOID PRECURSOR PROTEIN

Funded in 2020



Scientists are trying to understand how Alzheimer’s disease develops. They are looking at two main theories: One focuses on certain proteins in the brain called amyloid proteins, and the other looks at the potential role of microorganisms like bacteria or viruses.

Dr. Thaiss’ project aims to combine these two theories into one idea. He believes that microorganisms might influence how these amyloid proteins work in the brain, and this could be important in the development of Alzheimer’s disease. Dr. Thaiss and his colleagues are using a mix of techniques from microbiology, gnotobiology (the study of germ-free organisms) and neuroscience to figure out how microorganisms might be linked to the behavior of amyloid proteins.

So far, they’ve developed a new technology that helps them study how microorganisms affect amyloid precursor proteins. This technology lets them look at many different microbial genes and proteins at once to see how they affect things like how much amyloid precursor protein is made, how it’s shaped and how it’s broken down.

Initial results suggest that many different microbial features could be involved in these processes.



PREVENTION/TREATMENT

Richard Thompson, PhD and Nancy Sawtell, PhD

University of Cincinnati College of Medicine

IRON AND THE INTERSECTION OF HERPES SIMPLEX VIRUS INFECTION, THE HUMAN APOE4 ALLELE AND ALZHEIMER’S DISEASE

Funded in 2020/2021



Alzheimer’s disease (AD) is characterized by decreased cognitive function, accompanied by the accumulation of amyloid- β proteins in the brain and

neurofibrillary tangles, which lead to damage and death of nerve cells. The exact cause of late-onset AD remains elusive, although age and a specific gene variant called APOE4 are recognized as significant risk factors.

There is notable research in the overlap between HSV1 infection and the presence of the APOE4 gene variant affects a substantial portion of the global population.

To investigate how HSV1 may contribute to the development of AD, Dr. Sawtell and Dr. Thompson have developed a unique model using mice that possess the APOE4 gene variant and are infected with HSV1 over a prolonged period. Their findings suggest that HSV infection induces disturbances in iron levels in the nervous system, particularly evident within six days postinfection. This disruption in iron balance leads to oxidative stress, which is further exacerbated by the presence of the APOE4 gene variant, particularly as the mice age. Over a 15-month period, these mice develop cognitive impairments, accompanied by spatial memory deficits, tauopathy (the presence of abnormal tau protein) and the accumulation of amyloid deposits in the brain.

Key observations include the presence of iron deposits within neurons of the trigeminal ganglion, brain stem and hippocampus, particularly pronounced in the early stages of infection. Notably, regions displaying iron disturbances also exhibit elevated levels of toxic tau protein derivatives, which are associated with the propagation of AD-like pathology. Importantly, infected mice carrying the APOE4 gene variant demonstrate neurofibrillary tangles and tauopathy, phenomena not observed in uninfected mice or those lacking the gene variant. Additionally, the severity of iron imbalances and neurological damage increases over time postinfection and correlates with the degree of cognitive dysfunction observed in the mice.

These findings suggest a potential mechanism by which HSV infection, particularly in individuals with the APOE4 gene variant, may contribute to the initiation and progression of AD through disturbances in iron homeostasis and subsequent oxidative stress-induced damage in the brain and may provide valuable insights into potential therapeutic strategies for preventing or treating AD.



PREVENTION/DIAGNOSIS

Fred Turek, PhD

Northwestern University

DOES CIRCADIAN DISRUPTION-INDUCED DYSBIOSIS EXACERBATE COGNITIVE DYSFUNCTION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE?

Funded in 2022



Dr. Turek's research is focused on understanding if adjusting when mice eat can help delay or lessen the symptoms of Alzheimer's disease (AD). He and his colleagues have previously conducted similar studies that showed that feeding mice at certain times of the day can either

help or hurt their metabolic health, as well as having a major impact on body weight regulation.

Dr. Turek and his colleagues have gathered data from three groups of mice, including both male and female mice. During the 12-week study, they measured changes in their metabolism, sleep patterns and cognitive abilities. They found that female mice with AD-like symptoms spent more time awake and less time in deep and dreaming sleep. The timing of feeding also affected these patterns, showing that when mice eat at the wrong time, it interrupts their natural body rhythms.

In healthy mice, feeding time also impacted their sleep patterns, but not as much as in mice with AD-like symptoms. This suggests that AD affects the body's internal clock. Both types of mice with AD-like symptoms had trouble learning spatial memory tasks, but the timing of their meals made a difference in how well they learned.

Overall, mice with AD-like symptoms have sleep problems and struggle with learning tasks. The timing of their meals and whether they're male or female can impact the severity of these symptoms.

In the future, Dr. Turek will look at how these factors affect the microbes in the gut of the mice to understand more about how diet and genetics impact AD-like symptoms.



PREVENTION/TREATMENT

Kyle Walsh, PhD

Duke University

SEROLOGIC AND GENOMIC MODIFIERS OF BETA-AMYLOID LEVELS IN AN IMMUNO-COMPROMISED COHORT OF ADULT DOWN

Funded in 2020



Alzheimer's disease (AD) is a complicated brain condition where cells die off, leading to memory loss and other problems. It seems to involve changes in the immune system, how the body deals with fats and certain proteins in the brain. People with Down syndrome, who have an extra chromosome,

are more likely to get AD. Dr. Walsh is studying how the immune system works in people with Down syndrome to help understand why they are at higher risk.

Dr. Walsh's research found that certain genes linked to a higher risk of AD also affect things like how many platelets someone has, or their white blood cell count. Dr. Walsh and his colleagues looked at hundreds of genes that affect platelets and found that a few are also linked to AD. They also found that a protein called EGFR and a past infection with varicella (chickenpox) might together increase the risk of developing AD.

This research suggests that there might be a connection between the immune system, infections and certain genes that could help us understand and potentially treat Alzheimer's disease, especially in people with Down syndrome.



PREVENTION/TREATMENT

Panos Zanos, PhD

University of Cyprus

IDENTIFICATION OF VIRAL-MEDIATED PATHOGENIC MECHANISMS IN COMORBID ALZHEIMER'S DISEASE AND MAJOR DEPRESSION USING SYSTEMS BIOINFORMATICS

Funded in 2022



Alzheimer's disease (AD) is a brain condition that causes memory loss and thinking impairment and is the most common reason for dementia in older adults. Additionally, it can also lead to depression and trouble sleeping. Currently, there are no effective medicines

for treating AD, and having depression along with AD worsens the disease progress and prognosis.

Dr. Zanos' project aims to use advanced computer techniques to better understand how viral infections might facilitate the emergence of co-existing AD and depression. Their main goal is to determine which viruses might make people more likely to exhibit co-occurring AD and depression, and they also aim to understand whether infection with more than one virus at the same time worsens these conditions.

Dr. Zanos' team recently made some important progress:

1. They have identified specific ways by which certain viruses facilitate the development of co-existing AD and depression.
2. They have grouped the viruses into categories based on how they affect the body and found some common ways they might cause AD.
3. They looked into how being infected with more than one virus at once might worsen AD and depression progress. For example, when an individual gets infected with a new virus, such as the virus that caused the COVID-19 pandemic, it is possible for another virus the individual had been infected with previously (like the herpes virus) to reappear.

Dr. Zanos' team plans to further investigate these findings and explore potential medications for treating AD and depression caused by these viruses. They will also examine drugs that are already approved for the treatment of other conditions to assess their potential efficacy in addressing co-existing AD and depression.



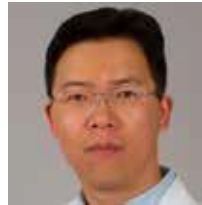
PREVENTION/TREATMENT

Zhen Zhao, PhD

University of Southern California

CGAS-STING INNATE IMMUNE RESPONSE MODULATES NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

Funded in 2022



Infections, aging and certain proteins in the brain can lead to immune responses that contribute to Alzheimer's disease (AD). Dr. Zhao is studying a specific immune pathway called cGAS-STING, which seems to play a crucial role in brain inflammation related to AD and infection.

Dr. Zhao and his colleagues are working to understand how the cGAS-STING pathway affects AD progression, especially in response to herpes virus infections, and testing if activating this immune pathway in brain cells (microglia) is a key factor in causing inflammation and worsening AD symptoms, particularly when both the herpes virus and Alzheimer's-related proteins are present. To do this, they have created special mouse models to mimic AD and microglia-specific cGAS-STING pathway changes. They're also using a humanized mouse model susceptible to herpes infection to study how the virus interacts with AD-related changes.

Initial experiments from this research suggest that herpes virus infection worsens inflammation and AD-related pathology in the brain. The researchers have also developed new methods to study subtle changes in AD at a single-cell level, which will increase understanding of how herpes infections impact the disease progression.



PREVENTION/TREATMENT

Kevin Zwezdaryk, PhD

Tulane University

**THE ROLE OF INFECTIOUS AGENT-DRIVEN
MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE**

Funded in 2021



Researchers are finding that certain infections, particularly those caused by microbes like viruses, may play a role in the development of Alzheimer's disease (AD). They're trying to understand how these infections, which can happen repeatedly over a person's lifetime, affect

the aging process of the brain and contribute to conditions like AD.

Dr. Zwezdaryk's research hypothesis is that these repeated infections might affect how our brains age by altering mitochondrial function and energy production, promoting neuropathology.

Dr. Zwezdaryk and his colleagues are researching how these infections impact cognitive function and the physical health of the brain, with the hope that this knowledge could lead to new treatments or ways to prevent cognitive decline as we age.

So far, Dr. Zwezdaryk's team has found that mice infected multiple times with cytomegalovirus show decreased cognitive function as they age, elevated mitochondrial function in certain brain cells, increased levels of oxidative stress (which is like rust for cells) and changes in how brain cells transport glucose (which is their fuel).

