THE NEUROIMMUNE SYSTEM AND ALZHEIMER'S DISEASE

Cure Alzheimer's FUND
20 years of breakthrough research

Cure Alzheimer's Fund is a nonprofit organization dedicated to funding research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

ALZHEIMER'S DISEASE AND THE NEUROIMMUNE RESPONSE

The neuroimmune system is a complex network that connects the nervous system and the immune system, working together to coordinate responses to maintain overall health and protect against infections, injuries and other pathogens.

— *The nervous system* includes the brain, spinal cord and nerves, and is responsible for transmitting signals throughout the body. This system controls motor functions, sensations and cognitive processes including thought, emotion and behavior.

— *The immune system* is the body's defense mechanism that cleans up regular debris, and identifies and neutralizes such pathogens as bacteria, viruses and other harmful agents.

— *The neuroimmune system* is the interface between the nervous and immune systems.

The responses from the neuroimmune system are essential for maintaining homeostasis and protecting the body from disease. However, if the coordination between the nervous and immune systems becomes dysregulated, it can contribute to neurodegenerative disease, including Alzheimer's disease. Identifying the causes of dysregulation are important for developing therapeutics to alter the course of Alzheimer's disease.

Understanding the neuroimmune dysregulation contributions to Alzheimer's disease also requires examining the structures that maintain different environments in the brain and the rest of the body. One such structure is the blood-brain barrier, a key protective element that regulates the movement of cells and molecules between the circulatory and central nervous systems.

We are currently in an exciting period of discovery of the mechanisms by which the immune cells of the brain and of the periphery communicate with one another in both health and disease. New discoveries have implicated previously unrecognized crosstalk across the structures—like the blood-brain barrier—that control the passage of cells and molecules in and out of the brain. When these structures lose their selectivity with age and disease, neuroinflammatory factors and peripheral immune cells can inappropriately enter the brain and cause neurodegenerative damage. CureAlz is bringing diverse expertise, innovative scientific thinking and multi-lab coordinated efforts to bear on this high-priority area of emerging research.

The Main Elements of the Pathology of Alzheimer's Disease

Scientists hypothesize that a combination of genetic, behavioral and environmental factors influence if and when the pathology of Alzheimer's begins, how it progresses and how the neuroimmune system responds to it. Many molecular and cellular changes occur in the brain of a person with Alzheimer's disease.

Content in this section reprinted from information provided on the website of the National Institute on Aging/National Institutes of Health. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease.

AMYLOID PLAQUES

The beta-amyloid protein involved in Alzheimer's is formed from the breakdown of a larger protein called the amyloid precursor. It comes in several different molecular forms that collect between neurons. The beta-amyloid 42 form is thought to be especially toxic. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that disrupt cell function.

NEUROFIBRILLARY TANGLES

Neurofibrillary tangles are abnormal accumulations of a protein called tau that collect inside neurons. Healthy neurons are supported internally in part by structures called microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites. In healthy neurons, tau normally binds to and stabilizes microtubules. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons.

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and beta-amyloid proteins and several other factors. It appears that abnormal tau accumulates in specific brain regions involved in memory. Beta-amyloid clumps into plaques between neurons. As the level of beta-amyloid reaches a tipping point, there is a rapid spread of tau throughout the brain.

CHRONIC INFLAMMATION

Research suggests that chronic inflammation may be caused by the buildup and harmful secretions of malfunctioning glial cells. Healthy glial cells help keep the brain free of debris. A type of glial cell called microglia engulfs and destroys waste and toxins in a healthy brain. When microglia fail to clear away waste, debris, and protein collections, including beta-amyloid plaques, Alzheimer's can develop.

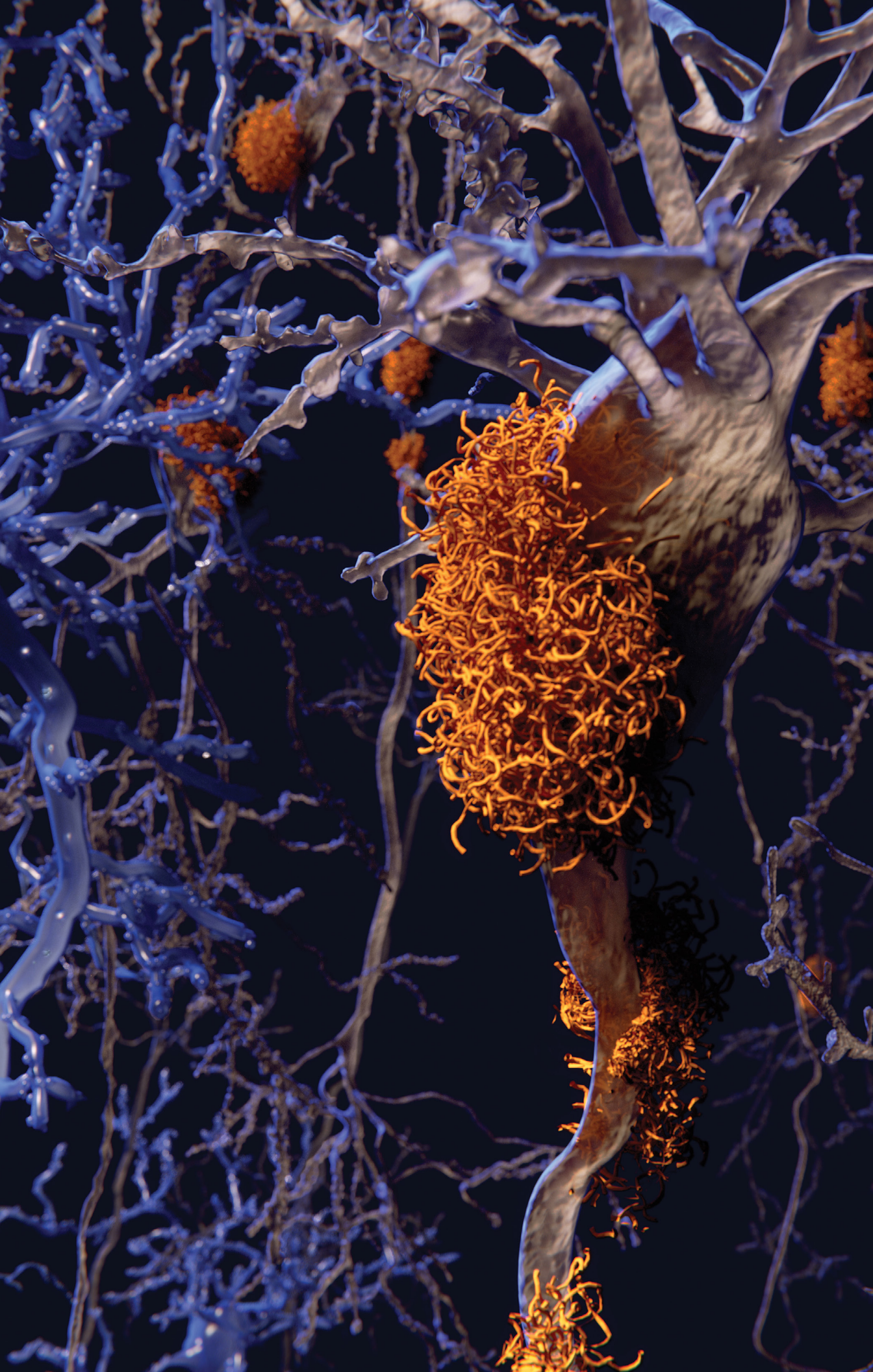
VASCULAR CONTRIBUTIONS TO ALZHEIMER'S DISEASE

People with dementia sometimes simultaneously experience a number of vascular issues—problems that affect blood vessels, such as beta-amyloid deposits in brain arteries, atherosclerosis (hardening of the arteries), and mini-strokes—a combination that can negatively affect brain health. Cardiovascular problems such as high blood pressure, diabetes, and stroke can damage blood vessels and reduce the flow of oxygen and nutrients to brain tissue, resulting in compounded damage and increased risk of vascular forms of dementia.

Vascular problems may lead to reduced blood flow and oxygen to the brain, as well as a breakdown of the blood-brain barrier, which usually prevents harmful substances from getting into the brain while allowing in glucose and other necessary molecules. In a person with Alzheimer's, disruptions to specialized transporter proteins in the blood-brain barrier may keep glucose from reaching the brain and prevent toxic beta-amyloid and tau proteins from being cleared away. This leads to inflammation, which may further worsen pathological changes in the brain. Recent studies have underscored the connection between glucose metabolism in the brain and multiple aspects of Alzheimer's, including gender differences in risk and the severity of the disease.

LOSS OF NEURONAL CONNECTIONS AND CELL DEATH

In Alzheimer's, as neurons are injured and stop working properly throughout the brain, connections among networks of neurons may break down, and many brain regions begin to shrink. By the final stages of Alzheimer's, this process—called brain atrophy—is widespread, resulting from significant cell death and causing the loss of brain volume.



Glossary of Scientific Terms

APOE4:
One of the variants of the APOE gene, the presence of the APOE4 gene is the second-highest risk factor for developing Alzheimer's disease after age 65 (termed sporadic Alzheimer's and representing approximately 95% of all cases) for most ethnicities. The highest risk factor is old age.

BLOOD-BRAIN BARRIER:
"Blood vessels are critical to deliver oxygen and nutrients to all of the tissues and organs throughout the body. The blood vessels that vascularize the central nervous system possess unique properties, termed the blood–brain barrier, which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain." *(National Institutes of Health—National Library of Medicine)*

GENE:
The basic unit of inheritance, passed from parents to offspring; a gene contains specific physical and biological traits.

GLIAL CELLS:
Support cells that hold neurons in place and have a variety of functions, including facilitating neurotransmission and immune response.

MICROGLIA:
A type of glial cell that acts as the primary line of defense and immunity for the brain.

NEURONS:
Specialized impulse-transmitting cells that are the fundamental working units of the brain and nervous system.

PATHOLOGY:
Structural and functional changes that result in disease.

PROTEIN:
Biomolecules made of chains of amino acids with numerous functions in cells, tissues and the body.

SPORADIC ALZHEIMER'S:
This is the most common form of Alzheimer's disease and, unlike the less common familial form, does not have a clear pattern of inheritance within families.

THE CURE ALZHEIMER'S FUND NEUROIMMUNE CONSORTIUM

For decades, neurons were the focus of Alzheimer's research. After all, they die off in large numbers over the course of the disease and are considered the primary cells for memory and other cognitive brain activity. However, when large-scale genetic sequencing of Alzheimer's patients became possible, the field discovered that the genetics of neurons are not common risk factors for most cases of Alzheimer's.

Of the common genes with variants that affect risk of sporadic Alzheimer's disease, more than half are made by microglia, astrocytes and peripheral myeloid cells — not neurons. These cells are the primary immune cells of the central nervous system and they continuously monitor the brain, quickly responding to pathological changes. They play a crucial role in maintaining brain homeostasis by isolating and clearing out cell debris, pathogens and cellular byproducts, including amyloid beta plaques. However, under certain conditions, these immune cells can start to malfunction, even degrading healthy synapses and neurons. This is thought to contribute to the neurodegeneration and cognitive decline observed in Alzheimer's disease.

Neuroinflammation has long been recognized as a hallmark of Alzheimer's disease, dating back to Dr. Alois Alzheimer's observations of reactive glial cells in the brain. Modern research suggests that this inflammatory response plays a more active role in disease progression than previously thought. The researchers within the neuroimmune consortium already have identified several genes in microglia important for the development of Alzheimer's-related pathologies, and demonstrated how these genetic changes can influence peripheral signaling, such as cytokine and hormone responses. Now, the consortium is investigating how inflammation outside the brain may directly impact Alzheimer's pathology. This bidirectional communication between the brain and the body is crucial for maintaining normal brain function and, when disrupted, may contribute to both the onset and progression of Alzheimer's disease.

The consortium includes experienced investigators with a track record of collaboration and highly complementary expertise across methods, species, cell types, and in brain and peripheral systems.

NEUROIMMUNE CONSORTIUM: FUNDED RESEARCHERS

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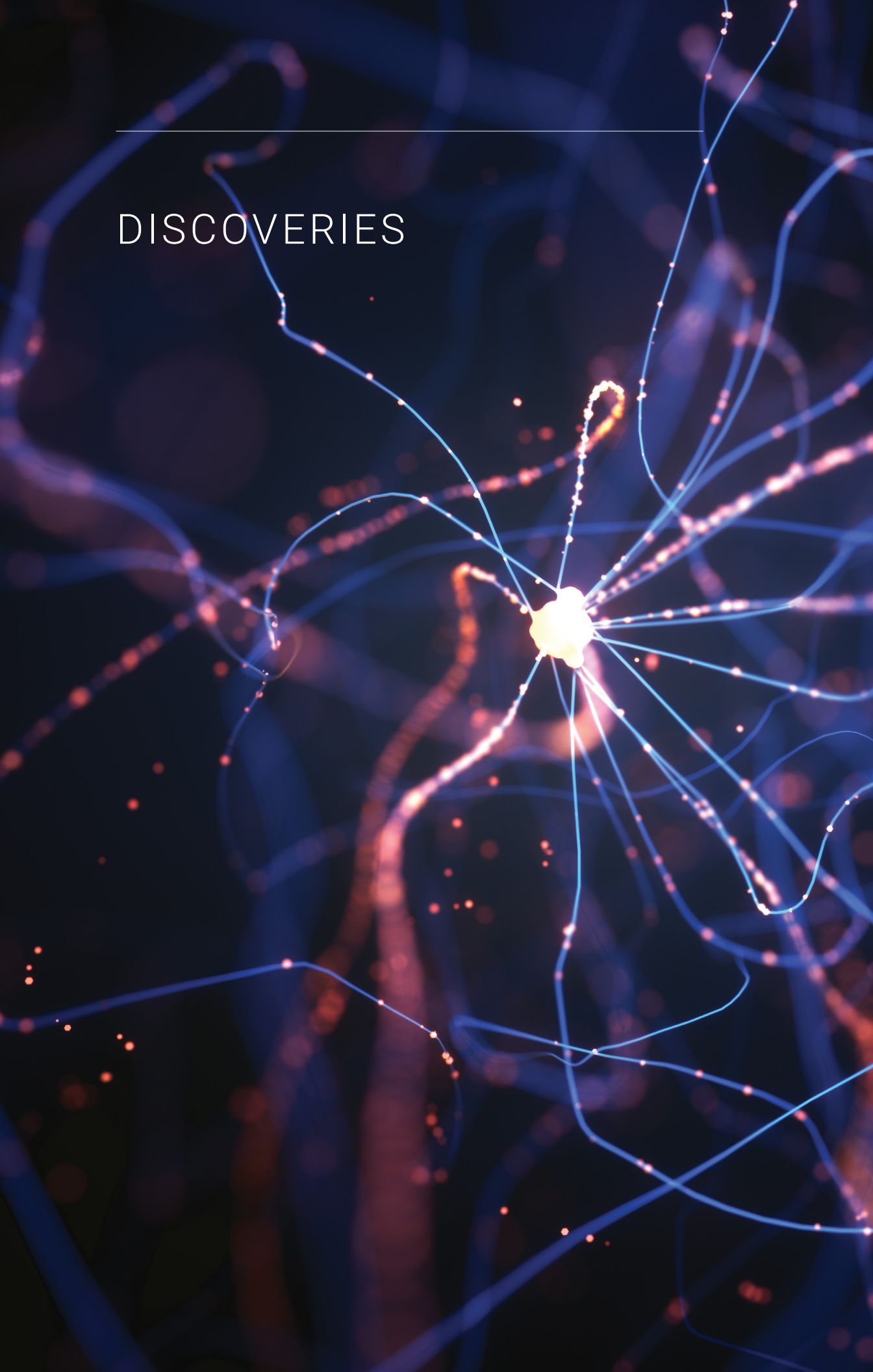
Find out more:
https://curealz.org/the-research/consortia/

DISCOVERIES



The Role of T Cells in Alzheimer's Disease Identified

The accumulation of abnormal tau in the brain is a key factor in the development of Alzheimer's disease. Microglia, the brain's resident immune cell, plays a vital role removing debris and unwanted particles throughout our lives. However, as we age and cell damage increases, microglia can shift from protective to destructive. A study of mice with brain shrinkage caused by tau pathology, similar to what is seen in Alzheimer's, found an increase in destructive T cells within the brain, drawn in by the altered microglia. These findings suggest that understanding the involvement of T cells in neurodegeneration could open new avenues for therapeutic strategies.

Find out more: https://bit.ly/3U8yP74

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Discovering ACE Points: The Hidden Pathways for Maintaining Brain Health

Scientists only recently discovered that the brain is not perfectly isolated from the rest of the body's natural defense mechanisms and actually benefits from the immune system's support. The glymphatic and meningeal lymphatic systems together monitor the brain for toxins and other unwanted byproducts that collect in cerebrospinal fluid, and provide an exit path for brain debris. In the brain, small openings called arachnoid cuff exit (ACE) points allow cerebrospinal fluid carrying waste to drain into an outer area rich in immune cells. The ACE points act as sentinels and allow limited exchange of the cells and molecules back into the brain.

One of the most intriguing implications of this discovery is its potential connection to Alzheimer's disease. Preliminary data suggests that ACE points become clogged with amyloid beta plaques, interfering with the removal of these harmful proteins and waste from the brain. The clogged ACE points also may prevent immune cells from accessing the brain to remove more amyloid beta or damaged cells.

This study provides an understanding of how the brain accommodates the immune surveillance and clearance of waste, offering new insights into neuroinflammatory conditions and overall brain health.

Find out more: https://bit.ly/3ZVAyRL

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The Interplay of the Gut Microbiome and Estrogen in Alzheimer's Disease

"Our gut harbors a complex community of over 100 trillion microbial cells which influence human physiology, metabolism, nutrition and immune function. The human intestinal tract harbors a diverse and complex microbial community which plays a central role in human health. It has been estimated that our gut contains in the range of 1000 bacterial species and 100-fold more genes than are found in the human genome." *(National Institutes of Health, NIH.com)*

Women are more likely to be afflicted by Alzheimer's disease when compared to men and there are nuanced differences in how male and female brains develop and respond to Alzheimer's pathology. While women, on average, live longer than men — and age is the most significant risk factor for sporadic Alzheimer's — longevity alone does not account for the disparate impact of the disease on women. A study reveals unexpected insights into how the gut microbiome and female hormones may work together: that estrogen may suppress the activity of microglia, the brain's innate immune cells, allowing more amyloid plaque pathology.

Find out more: https://bit.ly/3Nd9shH

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How the APOE4 Gene Compromises Brain Defense in Women

Researchers have pinpointed a new mechanism that may explain why women with the APOE4 gene are at even greater risk for Alzheimer's disease than are male carriers. The discovery centers on neutrophils, a type of white blood cell that normally helps the body fight off infections. In female APOE4 carriers, these neutrophils interact with microglia, the brain's immune cells, in a way that interferes with the microglia's ability to protect the brain. This interaction is linked to increased plaque buildup in the brain and cognitive decline. By blocking the interaction in animal models, scientists were able to restore microglial function and improve cognitive performance, offering the hope of a future treatment tailored to female APOE4 carriers.

Find out more: https://bit.ly/3ZUa9Ux

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The Gut Microbe Bacteroides Fragilis May Be Connected to Alzheimer's Disease

The gut microbiome plays a key role in modulating the immune system. An imbalance in gut bacteria can lead to inflammation, which is linked to various neurological disorders, including Alzheimer's disease. The composition of the gut microbiome changes with age as well as with disease. Alterations in the gut microbiome of Alzheimer's patients have been linked to the buildup of amyloid plaques in the brain. A new study has found that gut microbe Bacteroides is linked to reduced clearance of amyloid beta, leading to buildup of amyloid plaque in the brain. Although there are more than 30 species of Bacteroides in our gut, many with important and beneficial roles, one species — Bacteroides fragilis — affected amyloid clearance. The findings could pave the way for the development of innovative microbiome-based therapies aimed at targeting these specific microbes.

Find out more: https://bit.ly/3XZr31o

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A New Compound Reduces Alzheimer's Disease Pathology in Male Mice

Scientists from two labs conducting independent investigations found that altering gut bacteria with a drug derived from seaweed could impact the progression of Alzheimer's disease. These studies showed that sodium oligomannate (GV-971) reduced amyloid plaques and brain inflammation in mouse models of Alzheimer's disease, but only in male mice. The compound, which changed the gut microbiome, demonstrates a critical link between the gut and Alzheimer's disease pathology, underscoring the importance of gut health in neurological diseases and the development of sex-specific therapies.

Find out more: https://bit.ly/4gRPwyn

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The Choroid Plexus Synergizes with Immune Cells During Neuroinflammation

The choroid plexus, a small but essential structure in the brain, is best known for producing cerebrospinal fluid and acting as a barrier between the brain and the body. The choroid plexus also acts as a hub of immune activity. In mouse studies, when brain inflammation occurs, the epithelial cells lining the choroid plexus trigger an immune response. These cells

not only recruit immune cells, but also temporarily open the barrier between the blood and the cerebrospinal fluid, allowing immune cells to enter the brain. The epithelial cells then support these immune cells as they fight off the infection. Once the job is done, epithelial cells reseal the barrier, restoring the brain's protective layer. This discovery is the first evidence that the choroid plexus plays a role in immune defense.

Find out more: https://bit.ly/4dDH7fh

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New Brain Atlas Reveals Vulnerable Neurons in Alzheimer's Disease

In an effort to understand how the pathology of Alzheimer's disease spreads through the brain, scientists meticulously mapped the genetic activity of 1.3 million cells across six regions of the brain.

Their findings identify subtypes of neurons in the entorhinal cortex and hippocampus that are particularly susceptible to Alzheimer's disease — a discovery that helps explain why these regions consistently develop Alzheimer's pathology earlier than do other regions. This project also identified specific cellular pathways, including the Reelin pathway, as possible influencers in the progression of the disease. The research also revealed the protective role of astrocytes in fostering cognitive resilience against Alzheimer's. By mapping cellular changes associated with disease progression across the brain, the project yielded new insights into how this causal chain could someday be interrupted therapeutically.

Find out more: https://bit.ly/3TXKFBQ

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Why are Some People Resilient to Alzheimer's Disease?

Some individuals develop significant levels of amyloid beta plaques and tau tangles in their brains but never show clinical symptoms of dementia. The leading hypothesis to explain these resilient brains is that their neuroimmune system responds to Alzheimer's-related pathology with lower levels of neuroinflammation, which is common in symptomatic cases of the disease. However, the factors triggering excessive neuroinflammation remain unclear.

Neuroinflammation is a healthy response to debris and pathology in the brain, but this response must be appropriate in level and duration or it can become damaging rather than protective. The pathology that leads to Alzheimer's disease starts to develop many years before symptoms appear. Amyloid beta accumulates in the brain as plaque bundles, followed by the formation of tau tangles. Synapses are the points of communication between neurons and are essential for memory and cognition. Severe loss of synapses and neurons — neurodegeneration — thus disrupts the circuitry that encodes thought and memory. The neuroinflammatory response to Alzheimer's-related pathologies is a more direct driver of the loss of neurons and their synapses than are the pathologies themselves. Understanding how the neuroimmune response in resilient people differs from that of people who develop clinical Alzheimer's disease could allow the development of therapies designed to replicate this resilience in all people.

Find out more: https://bit.ly/49leqfN

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The Role of Skull Channels in Neuroimmune Communications

The central nervous system (CNS), made up of the brain and spinal cord, has a specialized neuroimmune system that historically has been considered isolated from the immune system that serves the rest of the body. However, recent research has challenged this idea by demonstrating an intricate relationship between the two. Newly discovered skull channels connect bone marrow within the skull to the protective layers surrounding the brain, suggesting that bone marrow can contribute white blood cells to guard the CNS. This discovery has helped overturn the previous belief that the blood-brain barrier always keeps peripheral immune cells from entering the CNS, and highlights a specialized form of neuroimmune communication. The exact mechanisms of this interaction and its implications for CNS health and disease still are being determined, but the presence of these channels signifies a major advance in our understanding of neuroimmune interactions.

Find out more: https://bit.ly/49GmfBT

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Boosting Microglia to Remove Sticky Amyloid Plaque Bundles

Immune cells named microglia reside in the brain to perform housekeeping and protective functions. Signals from neurons, astrocytes and other brain cells inform microglia when there is material to be addressed and how aggressive that response should be. Microglia can thus recognize that the sticky bundles of amyloid beta that accumulate in Alzheimer's disease do not belong in a healthy brain, and so they surround and clear them away. In Alzheimer's disease, the microglia do not perform adequately, allowing the amyloid plaque bundles to continue to accumulate.

When an antibody that blocks APOE from binding to a receptor molecule on microglia, called LILRB4, was used, microglia resumed their normal function, engulfing and clearing the amyloid bundles. This study highlights the potential role of future immunotherapies in treating Alzheimer's disease.

Find out more: https://bit.ly/3XUzNpy

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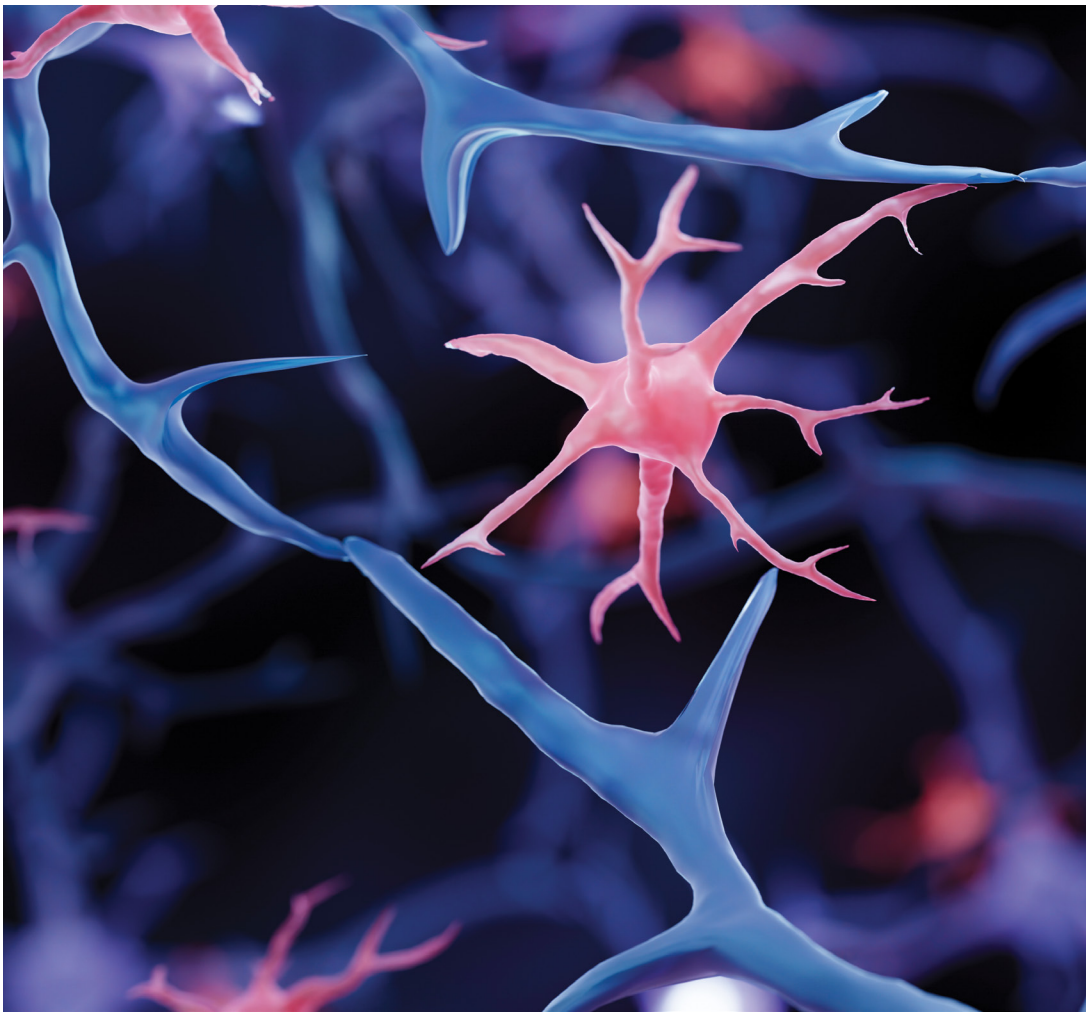

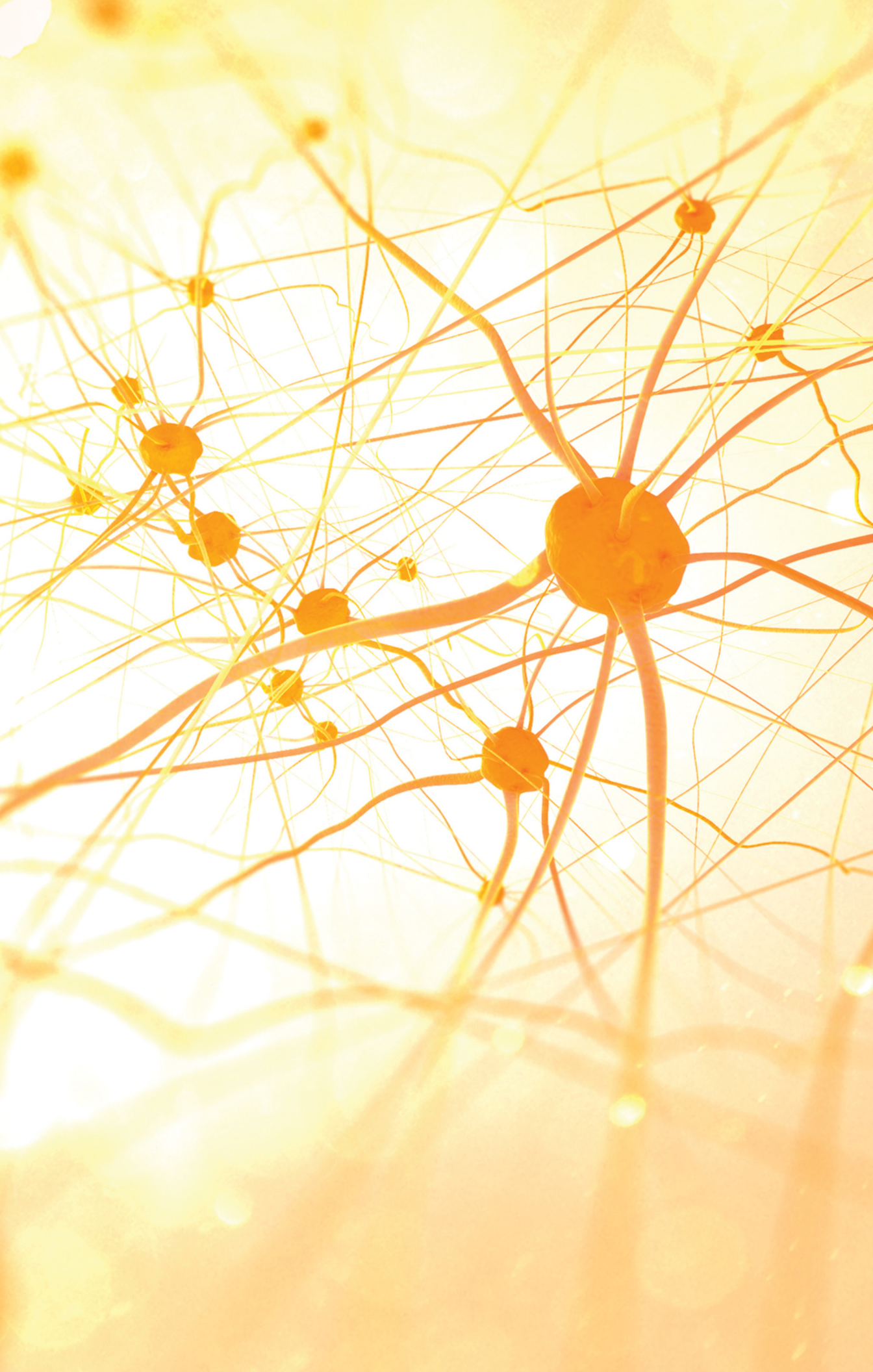

Ways to Donate

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TELEPHONE:
If you would like to make a contribution by credit card over the phone, please call us at 781-237-3800. Our business hours are 9 a.m. to 5 p.m. ET. If calling after hours, please leave a message and we will return your call the next business day.

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