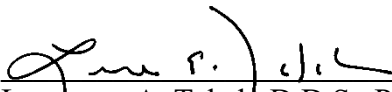


DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Alzheimer's Disease and Alzheimer's Disease-Related Dementias



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INTRODUCTION

The Joint Explanatory Statement accompanying the fiscal year (FY) 2024 appropriations for the U.S. Department of Health and Human Services (HHS) stated the following:

“The agreement includes an increase of \$100,000,000 across NIH for AD/ADRD research, including an increase of \$10,000,000 in NINDS and an increase of \$90,000,000 in NIA.

The agreement encourages NIA to increase support for research focused on mitigating immune dysfunction with precision inspired therapeutics for AD/ADRD and directs NIA and NINDS to provide a joint report to the Committees within 120 days of enactment of this Act on its progress in advancing these efforts; such report shall also be made available on the agency’s website.

In addition, the agreement continues to strongly urge NIA to prioritize resources toward new promising scientific research and notes with concern NIA’s plan to establish a Real World Data Platform (RWDP) multi-year project that is expected to cost significantly more than \$300,000,000. GAO has raised areas of concern with the RWDP including the reliability of the cost estimate and lack of coordination with other large-scale health data efforts. The agreement urges NIA to pause funding any awards for the RWDP until the GAO report is published and directs NIA to report to the Committees every 30 days after the date of enactment of this Act on any effort related to the RWDP.” (Conference Report, Page 42-43)

This report has been prepared by the National Institutes of Health (NIH), HHS, in response to this request.

BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disease that leads to a loss of memory and cognitive skills. More than six million Americans are currently living with AD, and it is predicted that more than 13 million will be living with the disease by 2060.¹ In addition, many people are living with other related forms of dementia, such as Lewy body dementia (LBD), frontotemporal dementia (FTD), and vascular contributions to cognitive impairment and dementia (VCID), or dementia with multiple underlying pathologies (also termed “mixed dementia”). The physical, emotional, and financial tolls inflicted by AD and AD-related dementias (ADRD) are immense, and research into underlying mechanisms driving these disease states is needed to deliver effective strategies for prevention and treatment.

Research discoveries of the last several decades have underscored that an array of factors may contribute to the onset and progression of Alzheimer's and related dementias (AD/ADRD). Since the discovery of AD, plaques and tangles in the brain have been understood to be hallmarks of the disease – and we now understand these plaques to be aggregates of the protein amyloid-beta ($A\beta$) and tangles to be deposits of the protein tau. In addition to these hallmarks, the field is also learning more about how the immune system, which is essential for maintaining and protecting the body, may play an important role in AD/ADRD. More specifically, new research suggests that dysfunction of immune processes could contribute to the development of AD/ADRD, including the buildup of plaques and tangles in the brain.

The National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) lead NIH and the Federal Government in strategically conducting and funding a broad range of basic, translational, and clinical AD/ADRD research. As part of the NIH AD/ADRD portfolio, NIH supports work to better understand how immune system dysfunction may be implicated in the onset and progression of these diseases. By studying the roles of each type of immune cell, understanding the signaling pathways in which these cells are involved, and identifying novel therapeutic targets, NIH researchers and grantees are aiming to advance the field's knowledge of the complex interactions of the immune system in AD/ADRD. NIH anticipates that these insights will inform the development of precision-inspired therapeutic approaches to mitigate immune dysfunction and potentially stop or slow disease onset and progression. In this report, we discuss the different immune cell types implicated in AD/ADRD, potential therapeutic targets, and cutting-edge clinical advances and issues in this field. We also describe NIH-funded scientific advances, activities, and projects that illustrate NIH's investments to understand and mitigate immune dysfunction in AD/ADRD.

IMMUNE CELLS, THEIR ROLES IN AD/ADRD, AND POTENTIAL THERAPEUTIC TARGETS

There is a myriad of cell types in the immune system, and those that affect brain function can be categorized into two groups: brain immune cells and peripheral immune cells. Brain immune cells, also called “*brain-resident* immune cells,” permanently exist within the brain and play crucial roles in maintaining brain health. Peripheral immune cells, on the other hand, circulate in the vasculature and exist throughout the rest of the body, but can move into the central nervous

¹ pubmed.ncbi.nlm.nih.gov/34043283/

system and affect the brain. In the healthy immune system, immune cells activate in response to infection, injuries, and other stimuli. Some immune cells, called innate immune cells, are activated in a fast and non-specific defense response against dangerous and foreign substances. Adaptive immune cells, however, engage in a slower targeted response against specific stimuli, providing the body with enhanced protection upon subsequent encounters to the same stimuli. Upon activation, these different immune cells work together to clear waste and foreign substances, and release inflammatory molecules, which sound the alarm to recruit help from other immune cells to collectively defend and protect the body. In a healthy body, the immune cells balance between activating and diminishing this inflammatory process. However, in instances where the immune system is dysfunctional or overwhelmed with an abundance of signals to activate, this alarm is less effective. If immune cells are unable to recruit others to help regulate the system, the body can move into a state of constant immune activation. This state is marked by chronic inflammation and an inability to effectively clear waste, which inevitably causes damage and death of neighboring cells, including neurons.

As poor waste clearance and chronic inflammation in the brain have been characterized as features of AD/ADRD, researchers have begun to explore the potential significant role of the immune system in the onset and progression of these diseases. The role(s) of innate and adaptive immune cells in the brain and the rest of the body are of specific interest. Some NIH funding opportunities are specifically scoped to spur advances in our understanding of immune dysfunction in AD/ADRD; several of these opportunities, and the projects funded in response to them, are described below in the relevant categories. NIH also welcomes the submission of investigator-initiated applications to research these topics through broad funding opportunities. This enables researchers to propose creative work beyond the scopes and timelines of specific solicitations. NIH has supported a number of investigator-initiated projects focused on immune dysfunction in AD/ADRD. The findings from NIH-funded projects have already revealed useful information about the links between the immune system and AD/ADRD, which offer opportunities for drug target identification and future drug discovery efforts.

Brain immune cells

Brain immune cells are subsets of glial cells, which encompass a diverse array of cell types that reside within the brain. In addition to their broader roles in maintaining neuronal communication and brain function, two glial cell types – microglia and astrocytes – are major components of the brain immune system. In this capacity, these cells non-specifically clear waste as part of the innate immune system. In AD and other neurodegenerative conditions, the ability of these cells to clear debris appears to decrease, and they seem to contribute to the initiation of chronic neuroinflammation. In order to gain insight into how and why this happens, NIH has made investments to better understand the role of glial cells in AD/ADRD, including awards made in response to a 2019 funding opportunity (RFA-AG-21-010, “Glial Plasticity in the Brain”) that encouraged investigators to propose projects to study how different types of glia may contribute to mechanisms of vulnerability and resilience to aging and AD/ADRD.² Select examples of projects funded through RFA-AG-21-010 and funding opportunities for investigator-initiated projects are described below.

² grants.nih.gov/grants/guide/rfa-files/RFA-AG-21-010.html; reporter.nih.gov/search/Ps2mPs1xsU-vpudLe6LRYg/projects

Microglia

In the healthy brain, microglia engulf and clear waste, including amyloid-beta ($A\beta$). Research has suggested that in AD, microglia are activated by the presence of $A\beta$, which they migrate to and clear. However, prolonged activation of microglia in AD has been found to impair their ability to properly function, ultimately leading to failure to clear away waste, debris, and accumulated proteins. Researchers are working to understand why microglia fail to perform this vital clearance function in AD and to test pathways for potentially restoring microglial activity. This research includes studying the genes involved in microglia function and alterations in microglia behavior during the onset and progression of disease.

NIH has a history of funding research to identify the robust associations between susceptibility to AD/ADRD and variants of genes that are expressed in microglia.³ The gene *APOE* is well-recognized as playing a critical role in AD and related dementias, with the variant *APOE4* serving as one of the most significant genetic risk factors for dementia.⁴ Researchers have studied the mechanism by which the APOE protein, encoded by the *APOE* gene, can mediate microglia function and influence disease onset and progression. Recently, NIH-funded scientists determined that APOE4 promotes lipid buildup in microglia, and stopping this buildup mitigates tau pathology and neuroinflammation in mouse models of AD.⁵ Additionally, when a group of NIH-funded researchers blocked the APOE protein from binding to a protein receptor called LILRB4 located on the surface of microglia, they observed a reduction in $A\beta$ plaques and AD-associated risk-taking behavior in mouse models of AD.⁶ Their findings suggest that a therapeutic that targets this interaction could potentially allow microglia to better clear $A\beta$ plaques and ameliorate symptoms associated with AD. Furthermore, a rare variant of *APOE* – *APOE3ch* – was found to confer resilience to AD (i.e., protect against the disease) in a single family. NIH-funded researchers have started to uncover how this variant may protect an individual from AD by studying mouse models with the variant.⁷ Affected mice appear to have enhanced microglial activity and reduced tau tangle formation, suggesting a possible role for microglia in the disease process. Understanding how rare variants promote dementia resilience opens new avenues for developing treatments. As one example, *APOE3ch*-inspired antibodies are already being developed as a potential AD therapeutic.⁸ Collectively, these results suggest that microglia dysfunction is associated with *APOE* and the protein for which it codes, and more work is needed to understand how different genetic variants can alter microglia activity involved in the onset and progression of AD.

Researchers have also identified additional genes of interest involved in microglial dysfunction in AD/ADRD. Notably, NIH-funded investigators have linked a gene expressed in microglia, *TREM2*, with AD risk. In the healthy brain, the TREM2 protein, which the *TREM2* gene codes

³ pubmed.ncbi.nlm.nih.gov/34493870/; pubmed.ncbi.nlm.nih.gov/31727856/; pubmed.ncbi.nlm.nih.gov/37248328/; pubmed.ncbi.nlm.nih.gov/35931864/; pubmed.ncbi.nlm.nih.gov/37774680/; pubmed.ncbi.nlm.nih.gov/37735198/; pubmed.ncbi.nlm.nih.gov/28714976/; pubmed.ncbi.nlm.nih.gov/37061460/; pubmed.ncbi.nlm.nih.gov/34731000/; reporter.nih.gov/search/HiMY2lcCZUyB0wUd_rkuWg/project-details/10468712; reporter.nih.gov/search/vSbTol7f-0qSk5_duBv8jA/project-details/10900992

⁴ nia.nih.gov/health/genetics-and-family-history/alzheimers-disease-genetics-fact-sheet#:~:text=APOE%20%CE%B54%20increases%20risk%20for,to%205%25%20carry%20two%20copies.

⁵ pubmed.ncbi.nlm.nih.gov/37995685/

⁶ pubmed.ncbi.nlm.nih.gov/38569016/

⁷ pubmed.ncbi.nlm.nih.gov/38086389/

⁸ pubmed.ncbi.nlm.nih.gov/37791598/

for, tells the microglial cells to clear A β plaques and help fight inflammation in the brain.⁹ Variants of the *TREM2* gene are particularly associated with late onset AD, in which symptoms first appear in individuals ages 65 or older.¹⁰ NIH-funded researchers have found that an AD mouse model that lacks *TREM2* has more spreading of the tau protein around plaques as compared to AD mouse models that have *TREM2*.¹¹ The collective work in this field suggests that when TREM2 does not function normally, A β plaques build up between neurons, potentially leading to abnormal tau buildup and the onset of disease. Given these findings, NIH is exploring TREM2 as a viable therapeutic target in AD/ADRD. For example, NIH-supported investigators found that when mouse models of AD were treated with an antibody to activate the TREM2 protein, the treatment reduced damage to neurons as well as some behavior changes associated with AD.¹² NIH continues to fund this research group to explore how different dosages of TREM2 antibodies may affect AD pathology and symptoms in the mouse model.¹³ Furthermore, NIH funded a first in-human phase I clinical trial testing a variant of this TREM2 antibody in humans; results indicate it was well-tolerated and may be a promising clinical candidate for treating or slowing the progress of AD.¹⁴

As described above, research has confirmed that microglia play an important role in AD/ADRD, but it is not fully clear what types of microglia lead to beneficial or detrimental effects. In response to injury or infection, it is known that microglia become “activated” and their primary role (in the healthy immune system) is to clear debris. However, more advanced cellular profiling techniques have recently shown that microglia exist in more disparate “states,” with varying shapes, functions, and gene expression. Recently, NIH-funded researchers characterized the diversity of microglial states in humans using multiple advanced sequencing techniques on postmortem brain tissue from individuals with AD pathology and no AD pathology. These researchers defined 12 microglial states, including several that were associated with AD.¹⁵

Although AD-associated microglial states are believed to be an important feature of disease progression, the field is still working to define how and why microglia transition between distinct states during disease.¹⁶ To this end, a NIH-funded research team conducted *in vitro* cell culture experiments to identify genes influencing the state of microglia-like cells.¹⁷ The team observed a spectrum of microglial states in cell culture and employed targeted gene editing techniques to manipulate the expression of key genes and shift cells between states. These findings give insight into how potential therapies targeting genes that govern microglia states could help to prevent and treat disease. Additionally, NIH is funding research with individuals living with AD to understand how the relationship between microglial states and the disease translates beyond cell culture experiments. One such project is an NIH-funded longitudinal study using positron emission tomography (PET) imaging to measure microglial activity and understand its relationship with disease progression.¹⁸ In another project, using post-mortem

⁹ pubmed.ncbi.nlm.nih.gov/30617257/; pubmed.ncbi.nlm.nih.gov/36306735/; pubmed.ncbi.nlm.nih.gov/36219197/;
pubmed.ncbi.nlm.nih.gov/36368315/; pubmed.ncbi.nlm.nih.gov/34916658/

¹⁰ pubmed.ncbi.nlm.nih.gov/23150908/; pubmed.ncbi.nlm.nih.gov/23150934/; <https://pubmed.ncbi.nlm.nih.gov/26076170/>

¹¹ pubmed.ncbi.nlm.nih.gov/34100905/

¹² pubmed.ncbi.nlm.nih.gov/32579671/

¹³ reporter.nih.gov/search/TmodJXlib02XXnQKNwnq7g/project-details/10212020

¹⁴ pubmed.ncbi.nlm.nih.gov/32579671/

¹⁵ pubmed.ncbi.nlm.nih.gov/37774678/

¹⁶ reporter.nih.gov/search/hzLNHoYaSEK4RNNpyXU7-A/project-details/10032850; reporter.nih.gov/project-details/10596517

¹⁷ pubmed.ncbi.nlm.nih.gov/35953545/

¹⁸ reporter.nih.gov/search/vSbTol7f-0qSk5_duBv8jA/project-details/10633128

brain tissue, NIH-funded researchers identified a microglial state that was enriched in AD patients with two copies of the *APOE4* gene variant.¹⁹ This state was defined by the presence of a protein called ACSL1, which has a role in lipid metabolism. These same researchers conducted *in vitro* cell culture experiments using human microglia-like cells and determined that A β exposure resulted in increased expression of the *ACSL1* gene (which codes for the protein), increased lipid accumulation, and release of neurotoxic factors. Interestingly, these downstream changes were exacerbated in cells with the *APOE4* variant. Although further research is needed, these promising findings suggest a link between genetic risk factors for AD with changes in microglia state that may lead to neuronal death, offering potential therapeutic targets to treat disease.

Furthermore, NIH-funded researchers are exploring the relationship between changes in microglial state and non-genetic risk factors for AD/ADRD, including traumatic brain injury (TBI). In contrast to other risk factors, the timeline of exposure to the risk (i.e., injury) is often known and can be well-characterized, allowing for potential better examination of how disease may progress.²⁰ To this end, NIH-funded researchers are using experimental models of TBI in mice to study how microglia change after injury and whether interventions can prevent harmful TBI-induced microglial states.²¹

As researchers continue to build foundational knowledge on how microglia participate in disease onset and progression, NIH also supports complementary research on new techniques to study and target microglia. For example, one group of NIH-funded researchers developed a novel *in vitro* brain organoid model to study microglia, in which these cells behave much like they would in a human brain.²² Additionally, NIH is supporting a project to develop gene therapy methods that selectively target microglia.²³ Collectively, current research is poised to advance the field's understanding of immune processes involving microglia and how to potentially modulate them in AD/ADRD.

Astrocytes

Astrocytes, another subtype of glial cells, are responsible for supporting neuronal health, responding to degenerating cells, and maintaining the integrity of the vascular system in the brain (termed “neurovascular system”). Similar to microglia, astrocytes can be activated to participate in the innate immune system to help clear the buildup of A β and other cellular debris, with activated astrocytes (also known as “reactive astrocytes”) taking on different gene expression patterns and shapes. Reactive astrocytes, commonly found next to A β plaques in the brains of individuals with AD, release inflammatory signals which can damage neurons and other neighboring cells.²⁴ NIH-funded researchers recently showed that astrocyte activation may in fact be a link between two hallmarks of AD – i.e., A β plaques and tau pathology.²⁵ Researchers are building on these findings to deepen the field's understanding of the exact roles of these cells in the onset and progression of AD/ADRD.

¹⁹ pubmed.ncbi.nlm.nih.gov/38480892/

²⁰ liebertpub.com/doi/10.1089/neu.2022.0514

²¹ reporter.nih.gov/project-details/10661552; reporter.nih.gov/project-details/10806735

²² pubmed.ncbi.nlm.nih.gov/37172564/

²³ reporter.nih.gov/project-details/10587795

²⁴ pubmed.ncbi.nlm.nih.gov/2531723/

²⁵ pubmed.ncbi.nlm.nih.gov/37248300/

As mentioned earlier in this report, the gene *APOE* is deeply implicated in the biology of dementia. Astrocytes are known to be a key producer of the APOE protein, which is encoded by this gene, so researchers have long suggested APOE function in astrocytes may be important in AD/ADRD. Recently, a NIH-funded research group reported that selectively deleting *APOE4*, a variant of *APOE*, in astrocytes lowered inflammation and neuron damage in mice.²⁶ Thus, targeting astrocytes in ways that reduce APOE or its downstream effects could be a treatment strategy for AD.

NIH has supported research efforts to further our knowledge of astrocytes in AD/ADRD through multiple grant solicitations. In 2021, NIH released a funding opportunity (PAR-22-037 – “Role of Astrocytes in Degeneration of the Neurovascular Unit in AD/ADRDs”) to further understand the role of astrocytes in AD/ADRD.²⁷ In response to this solicitation, NIH is funding a project investigating a signal involved in astrocyte activation, with the goal of understanding its impact on the integrity of the neurovascular system in the brain.²⁸ Additionally, NIH is funding a project through RFA-AG-21-010 (“Glial Plasticity in the Brain”) to deepen the field’s understanding of how astrocytes supply nutrients to neurons and how disease affects this process in animal models.²⁹ Furthermore, a separate NIH-funded study, funded through a broader funding opportunity (PAR-19-070, “Research on Current Topics in Alzheimer’s Disease and Its Related Dementias”), is investigating the potential role of astrocytes in inflammation, neurovascular dysfunction, and cognitive dysfunction in VCID.³⁰ NIH also supported an investigator-initiated project that sought to understand whether strokes can initiate disease processes in astrocytes to cause long-lasting decreases in blood flow and contribute to dementia.³¹ Altogether, these projects will further define the role of astrocytes in AD/ADRD and potentially identify targets in astrocytic function as a treatment strategy to protect or preserve brain function in the context of dementia.

Peripheral immune cells

In addition to the brain’s glial cells, there is growing evidence that the immune cells that typically reside *outside* of the brain (i.e., peripheral immune cells) may play a role in brain health and AD/ADRD as well. These peripheral immune cells include B cells, T Cells, and peripheral monocytes/macrophages, but the exact role these cells play in AD/ADRD is still not fully understood.

The entry of peripheral immune cells and their downstream signaling molecules into the brain is limited and tightly controlled by a specialized brain vasculature system called the blood brain barrier (BBB). BBB dysfunction is a feature of AD/ADRD, characterized in part by increased BBB permeability to harmful toxins, cells, and other molecules that are normally prevented from entering the brain. Additionally, NIH-funded research suggests that peripheral immune cells and their signaling molecules may also enter the brain via the lymphatic system, which consists of a

²⁶ reporter.nih.gov/search/h125M0B-0kiqzOIY2e--5A/project-details/9881454; pubmed.ncbi.nlm.nih.gov/33831349/

²⁷ grants.nih.gov/grants/guide/pa-files/par-22-037.html

²⁸ reporter.nih.gov/search/gTScVcRUTUCJCWHqHcplcA/project-details/10562131

²⁹ reporter.nih.gov/search/Ps2mPs1xsU-vpudLe6LRYg/project-details/10393048

³⁰ grants.nih.gov/grants/guide/pa-files/par-19-070.html; reporter.nih.gov/search/_otUt5DJf0-l-eTbwluQBA/project-details/10054775

³¹ reporter.nih.gov/search/uJD055xd30O15Xjyg942_w/project-details/10774128

series of vessels that carry immune cells and cellular debris to lymph nodes.³² The lymphatics surrounding the brain, called meningeal lymphatics, were characterized by an NIH grantee and have also been implicated in the clearance of A β .³³ While the complete understanding of how these peripheral immune cells interact with the brain still eludes the field, it is evident that they likely play a role in the onset and progression of AD and related diseases.

To advance the field's understanding of the peripheral immune system's role in AD/ADRD, NIH released a funding opportunity (RFA-AG-22-017, "Role of Adaptive Immunity in Etiology of AD/ADRDs") in 2021.³⁴ The same year, NIH also released a funding opportunity to call for new partnerships between neuroscientists and immunologists (PAR-22-023, "Multi-Disciplinary Collaborations to Understand Mechanisms of Systemic Immune Signaling and Inflammation in ADRD and its Progression"), a strategic step toward expanding the understanding of systemic/peripheral immune responses and inflammation in AD/ADRD.³⁵ Select projects funded through RFA-AG-22-017, PAR-22-023, and other NIH funding opportunities are described further below under the relevant cell types under investigation.

B Cells

B cells are adaptive immune cells that make specialized proteins called antibodies, that can bind to foreign substances such as toxins or other harmful invaders and trigger a neutralizing response. As such, B cells and their antibodies are key components of the adaptive immune system, which facilitates a faster and more effective immune response following re-exposures to foreign substances. Interestingly, NIH-funded researchers found that depleting B cells with a therapeutic molecule improved many aspects of AD, including memory deficits, in mouse models.³⁶ These findings suggest that B cells may play an important role in AD progression in mice, though the precise mechanism is not fully understood. NIH-funded researchers are continuing to work with AD mouse models to further decipher the role of B cells and elucidate mechanisms by which B cell depletion can reverse the progression of AD.³⁷ Understanding these underlying mechanisms, and strategies for targeting and clearing B cells in the brain, may help to develop a new therapeutic strategy for AD/ADRD.

T Cells

T cells are part of the adaptive immune system and protect the body by selectively killing infected and cancerous cells in a targeted fashion, while also modulating the activity of other immune cells. However, in neurocognitive disorders, some findings suggest that T cells may contribute to progression of disease.³⁸ NIH has funded, and continues to fund, efforts to understand the roles of T cells in AD/ADRD and their mechanism of action.³⁹

Several studies have suggested a detrimental role for T cells in AD/ADRD. For example, an NIH-funded study identified a pathway by which T cells may send chemical signals to the brain

³² pubmed.ncbi.nlm.nih.gov/26030524/; pubmed.ncbi.nlm.nih.gov/37580702/

³³ pubmed.ncbi.nlm.nih.gov/30046111/

³⁴ grants.nih.gov/grants/guide/rfa-files/RFA-AG-22-017.html

³⁵ grants.nih.gov/grants/guide/pa-files/PAR-22-023.html

³⁶ pubmed.ncbi.nlm.nih.gov/33846335/

³⁷ reporter.nih.gov/project-details/10913115

³⁸ pubmed.ncbi.nlm.nih.gov/19167499/; pubmed.ncbi.nlm.nih.gov/36890231/

³⁹ reporter.nih.gov/search/vSbTol7f-0qSk5_duBv8jA/project-details/10685434; reporter.nih.gov/search/ectFchAhGkKtTJ7uAetgeA/project-details/10693931; reporter.nih.gov/project-details/10913097

and contribute to cognitive impairment.⁴⁰ Another mechanism of T cell dysfunction under active investigation is the process of energy production in T cells. For example, a project funded through RFA-AG-22-017 (“Role of Adaptive Immunity in Etiology of AD/ADRDs”), is exploring how genes and signaling pathways involved in energy production affect T cell activity in AD mouse models.⁴¹ These researchers hypothesize that differences in energy production can help regulate the different roles of T cells and thus mediate their responses to AD disease progression. Additionally, NIH is funding efforts to elucidate how T cells may influence meningeal lymphatic vessels, which is a pathway for debris clearance in the brain, as described above. To start to answer this question, NIH is funding another project through RFA-AG-22-017 that investigates whether T cell signaling can negatively affect the integrity of the meningeal lymphatic vessels, which may subsequently lead to inadequate clearance of debris, such as A β .⁴²

There is also evidence that some populations of T cells can have a protective effect in AD/ADRD. Using mouse models of AD, NIH-funded scientists identified elevated levels of a subtype of T cells (termed “CD8+ T cells”) that may be important in restricting A β deposition and cognitive decline.⁴³ These CD8+ T cells appear to accumulate in an age-dependent manner and communicate with microglia in disease (see “Interplay of multiple immune cell types” section for additional details). Furthermore, NIH-funded researchers are also attempting to harness the potential for a subset of T cells, called regulatory T (Treg) cells, to treat disease. The primary function of Tregs is to monitor and inhibit the activity of other T cells, thereby suppressing excessive inflammation. These researchers engineered Treg to recognize A β , and strikingly, when these cells were transferred into an AD mouse model, they reduced A β and improved cognition.⁴⁴ Such findings suggest that certain types of T cells could help to protect the brain from cognitive decline, though additional research is needed to fully understand the complex roles for T cells in AD/ADRD.

NIH has also funded researchers to investigate the role of T cells in LBD, an ADRD associated with abnormal deposits of the alpha-synuclein protein in the brain.⁴⁵ These deposits, called Lewy bodies, affect brain function which, in turn, can lead to problems with thinking, movement, behavior, and mood. These researchers observed a specific type of T cell adjacent to Lewy bodies in postmortem brains and found T cells were more inflammatory when treated with alpha-synuclein *in vitro*. Altogether, these findings suggest a role for T cells in disease, but many questions remain regarding how T cells are involved and whether they can be targeted therapeutically to prevent or delay the onset of AD/ADRD.

Peripheral Monocytes and Macrophages

Peripheral monocytes are innate immune cells of the periphery, which circulate in the blood and are often recruited to sites of inflammation. Once recruited, peripheral monocytes become a more specialized type of cell called macrophages, which ingest and degrade bacteria, recycle dead cells, and clear away debris such as A β . One NIH-funded study has found that peripheral monocytes are enriched in areas surrounding the brain in AD mouse models compared to control

⁴⁰ pubmed.ncbi.nlm.nih.gov/38049579/

⁴¹ reporter.nih.gov/search/O9kWCTBGmUWGc8w5ZeyLOA/project-details/10698034

⁴² reporter.nih.gov/search/9qsMKNCBcUSQqoH84CTqVw/project-details/10684836

⁴³ pubmed.ncbi.nlm.nih.gov/37679549/

⁴⁴ pubmed.ncbi.nlm.nih.gov/38111016/

⁴⁵ pubmed.ncbi.nlm.nih.gov/34648304/

mice.⁴⁶ When these researchers reduced the number of peripheral monocytes from the AD mice, they saw an increase in amyloid plaques. A change in monocytes in AD brains translates to humans as well. In a study partly funded by NIH, researchers assessed monocytes found in blood samples of individuals with subjective memory complaints, mild cognitive impairment, and AD and found that monocytes are most activated in patients with mild cognitive impairment and least activated in individuals with AD.⁴⁷ This work may offer insight into how monocyte activation could serve as a biomarker of disease and the timing of monocyte activation in disease onset and progression. Researchers are also seeking to understand how macrophages may affect debris clearance in the brain. NIH-funded scientists identified a subtype of macrophages near the brain as key regulators of cerebrospinal fluid flow, which could be targeted to alleviate brain clearance deficits associated with AD in mouse models.⁴⁸ The mechanistic links between monocytes, macrophages, and AD/ADRD is still unclear, but these studies suggest a potential role for peripheral monocytes and macrophages in targeting and clearing amyloid plaques.

NIH continues to fund studies to deepen our understanding of these cells, including a project to investigate the role of peripheral monocytes in AD and HIV-associated neurocognitive disorder, aimed at identifying shared neuropathologic mechanisms and novel therapeutic candidates for both neurodegenerative conditions.⁴⁹ Additionally, NIH is funding work to investigate the role of monocytes in FTD, which is caused by a group of disorders that gradually damage the brain's frontal and temporal lobes, resulting in changes in thinking and behaviors. Mutations in the *GRN* gene are among the leading causes of FTD, and the encoded protein has been implicated in inflammation. To investigate the impact of monocyte-mediated inflammation in FTD, NIH is supporting research, through PAR-22-023, to study the potential role that monocytes play in neurodegeneration using *in vitro* cell culture experiments and animal models of FTD.⁵⁰ This study may provide insight into whether activation of monocytes contribute to neuroinflammatory and neurodegenerative processes in FTD.

Interplay of multiple immune cell types

NIH-funded research has implicated the aforementioned types of immune cells in AD/ADRD and examined them separately in disease onset and progression, yet the immune system's complexity arises from its dynamic interactions between immune cells. Accordingly, NIH-funded research is also exploring the interplay of multiple immune cell types in these diseases.

As one example of dynamic interaction in AD/ADRD, NIH-funded researchers have found that altering communication between microglia and other immune cells can affect disease progression in mouse models.⁵¹ For instance, researchers identified a signaling pathway linking microglia and CD8+ T cells that can dampen inflammation, and disruption of this pathway resulted in increased A β aggregation in mouse models of AD.⁵² In another study, researchers

⁴⁶ pubmed.ncbi.nlm.nih.gov/35511433/

⁴⁷ pubmed.ncbi.nlm.nih.gov/34154615/

⁴⁸ pubmed.ncbi.nlm.nih.gov/36352225/

⁴⁹ reporter.nih.gov/search/zSPHSRf2o0mjhA32-zfEuQ/project-details/10899788

⁵⁰ reporter.nih.gov/project-details/10514263

⁵¹ pubmed.ncbi.nlm.nih.gov/33902708/; pubmed.ncbi.nlm.nih.gov/37679549/

⁵² pubmed.ncbi.nlm.nih.gov/37679549/

found direct evidence that depletion of microglia in AD mouse models prevented T cell entry into the brain, and a loss of T cells in the brain ameliorated inflammation and brain atrophy.⁵³

To further understand the interconnectedness of these cells in AD/ADRD, NIH is driving research into this field through various funding opportunities, including RFA-AG-22-017 (“Role of Adaptive Immunity in Etiology of AD/ADRD”) and PAR-22-023 (“Multi-Disciplinary Collaborations to Understand Mechanisms of Systemic Immune Signaling and Inflammation in ADRD and its Progression”), both described above.⁵⁴ Through these opportunities, NIH is funding several projects to identify and quantify the proportions of multiple immune cells in older adults and understand how these immune profiles relate to levels of AD biomarkers, dementia status, and blood brain barrier integrity.⁵⁵ These studies will help build a more holistic understanding of how the immune system and brain interact.

As discussed above, chronic inflammation has a detrimental impact on brain health, and NIH research has provided evidence for the involvement of multiple immune cell types in triggering the inflammation process in AD/ADRD. Recognizing inflammation as a critical process in disease onset and progression, NIH is funding projects across the research continuum – from basic, to translational, to clinical – with the aim of identifying and testing potential therapeutics that target inflammation in AD/ADRD.⁵⁶ For example, NIH-funded researchers have identified a new signaling pathway involved in neurodegeneration and neuroinflammation and are testing newly developed preclinical antibodies that block this pathway in an AD mouse model.⁵⁷ Additionally, through PAR-22-023, NIH supports a project exploring effects of systemic inflammation on brain health using AD mouse models.⁵⁸ This research group will investigate the impact of sepsis, which involves systemic inflammation, on A β and tau in these animal models. Sepsis is known to accelerate cognitive decline in individuals with AD and this work may help the field understand the mechanism by which systemic inflammation exacerbates neurobehavioral impairment and progression of AD. Similarly, NIH-funded researchers tested the therapeutic potential of TNF α , a key signal in inflammation, and found that lowering levels of TNF α in the brains of mice could lessen excessive inflammation and thereby improve memory and thinking ability and cellular changes associated with AD.⁵⁹ NIH-funded researchers are also actively investigating the role of chronic inflammation on A β plaque pathology, immune cell infiltration, and behavioral outcomes in a mouse model of AD.⁶⁰

NIH is also funding multiple clinical trials in humans that target inflammation in AD/ADRD. As of December 2023, NIA is actively funding one late-phase (Phase 2b) and eight early-phase (Phases 1 & 2a) clinical trials targeting inflammation.⁶¹ In fact, inflammation is the primary process targeted in early-stage NIA-funded AD/ADRD clinical trials. As one example, NIA

⁵³ pubmed.ncbi.nlm.nih.gov/36890231/

⁵⁴ grants.nih.gov/grants/guide/pa-files/par-19-070.html; grants.nih.gov/grants/guide/rfa-files/RFA-AG-22-017.html; grants.nih.gov/grants/guide/pa-files/PAR-22-023.html

⁵⁵ reporter.nih.gov/search/yszZ6pYPR0eb1fPTdwkAKg/project-details/10766210; reporter.nih.gov/search/GEVcIr1AkU-R1RyEHwtKhA/project-details/10688122

⁵⁶ reporter.nih.gov/search/aXmdY1nmOkCcmlXbBbGQ0A/project-details/10762833;

reporter.nih.gov/search/EpWF2LLQZEuEUkA0UnKI4A/project-details/10459119

⁵⁷ reporter.nih.gov/search/VuyJ2_bNyE6csbMsd66yzyw/project-details/10660332

⁵⁸ reporter.nih.gov/search/War0Pfd4U61M5vpE6dm4A/project-details/10513525

⁵⁹ pubmed.ncbi.nlm.nih.gov/35234334/

⁶⁰ reporter.nih.gov/search/iagWtpGrJ02RqdH9ov51kg/project-details/10914576

⁶¹ nia.nih.gov/research/ongoing-AD-trials

funded Neurokinine Therapeutics to test the compound MW150 in a Phase 2a clinical trial with individuals with mild-to-moderate AD.⁶² MW150 inhibits the p38alphaMAPK kinase protein with the intention of reducing inflammation and improving synaptic function in AD/ADRD. The Phase 2a study seeks to understand the safety and tolerability of MW150 and its effect on cognitive performance and activities of daily living.

These recent findings and ongoing research projects – across the whole research pipeline – demonstrate the integrated approach NIH is taking to understand the dynamic components and processes involved in immune system function and dysfunction in AD/ADRD.

CUTTING-EDGE CLINICAL ISSUES AND ADVANCES

While this report summarizes recent progress in understanding immune dysfunction in AD/ADRD, it is important to recognize that this research builds on knowledge that many other factors and systems contribute to the onset and progression of AD/ADRD. An individual's disease risk and/or resilience differs due to a combination of factors, including one's sex, genetics, environmental exposures, social determinants of health, comorbidities, and more. As such, researchers have recognized the need to apply a precision medicine approach to diagnosing, preventing, and treating these diseases — that is, a “participant-centric” strategy that results in each person getting the right treatment and at the right time. To that end, NIH supports work to identify and develop precision-inspired therapeutics for various immune dysfunction targets, prioritizing individual considerations and incorporating the latest scientific findings and techniques. In this section, we will describe three exciting areas of research into immune dysfunction and precision-inspired therapeutics for AD/ADRD. These research areas are (1) Exploring the connections between immune dysfunction in Down Syndrome and AD, (2) Understanding the role of immune cells in Amyloid Related Imaging Abnormalities, and (3) Testing the potential of Chimeric Antigen Receptor immune cell therapy in AD/ADRD.

Exploring the connections between immune dysfunction in Down Syndrome and AD

People living with Down syndrome (DS) have a high risk of developing AD, attributed to the fact that they are born with an extra copy of chromosome 21. This chromosome carries a gene that produces a specific protein called the amyloid precursor protein. Having an extra copy of this gene leads to a buildup of A β plaques in the brain. Accordingly, almost all adults living with DS have AD-related brain changes by age 40.⁶³ Researchers believe that neuroinflammation and immune dysfunction may be key causative factors in the pathogenesis of AD in DS.⁶⁴

NIH-funded research has provided insights into the role of immune cells in DS, including the finding that individuals with DS and AD had more abnormally shaped microglia compared to individuals without DS or AD.⁶⁵ While more work is needed to understand the significance of

⁶² reporter.nih.gov/search/BQJl1Jlw70qaeAYFilqbmw/project-details/10402417; clinicaltrials.gov/study/NCT05194163

⁶³ cdc.gov/aging/publications/features/down-syndrome-alzheimers-risk.html

⁶⁴ pubmed.ncbi.nlm.nih.gov/34687637/

⁶⁵ pubmed.ncbi.nlm.nih.gov/33088896/

these abnormally shaped microglia and how they relate to the aforementioned microglial states, this work reinforces the potential role of immune dysfunction in DS and AD. Additionally, NIH is currently supporting research to elucidate the mechanisms by which neuroinflammation controls progression of DS and AD. As part of this project, the researchers plan to test a potential therapeutic that targets a protein called Reelin, which has been implicated in inflammation, using a mouse model of DS and identify its effects in AD.⁶⁶ Identifying the role of the immune system and key mechanisms involved in DS may help identify therapeutic targets that could slow or stop the progression of AD in individuals with and without DS.

Understanding the role of immune cells in Amyloid Related Imaging Abnormalities

In recent years, the AD/ADRD community has seen remarkable progress, marked by the U.S. Food and Drug Administration (FDA) approval of the use of specific antibodies against A β (termed “anti-A β immunotherapies”) for the treatment of early AD.⁶⁷ Generally, these anti-A β immunotherapies are thought to work by marking clumps of A β to be cleared by immune cells. During the clinical trials for anti-A β immunotherapy, however, MRI abnormalities were reported as an adverse treatment effect, termed “amyloid-related imaging abnormalities” (ARIA). Unfortunately, some patients have experienced severe side effects associated with ARIA, including a leaky blood-brain barrier, edema, brain hemorrhage, and death in rare cases.

The cause of ARIA remains a critical question. Recently, an Eli Lilly-supported study found that treating AD mice with a mouse version of an anti-A β immunotherapy led to activation of macrophages within the blood vessels and these mice had leakier blood vessels.⁶⁸ To better provide insight into who is at risk for these adverse side effects, researchers are continuing to investigate the role of immune cells engaged in these therapies. NIH is currently funding a project that tests whether mouse anti-amyloid immunotherapy triggers ARIA through inflammation in mouse models.⁶⁹ Furthermore, in 2023, NIH announced a funding opportunity soliciting applications designed to increase understanding of cellular and molecular mechanisms that can be targeted to protect the blood-brain barrier and associated blood vessels to prevent ARIA.⁷⁰ Additionally, in September 2023, NIA and NINDS held a workshop that brought together leading experts and researchers from around the world to identify scientific gaps and opportunities, including the efforts to understand the basic mechanisms behind ARIA.⁷¹ Participants discussed how anti-A β antibodies affect the immune system and the potential role of the brain and peripheral immune response in ARIA. The insights from this workshop, as well as the ongoing research, will help inform NIH as it identifies priority areas and research opportunities to better understand the role for immune cells in this critical adverse effect and ultimately reduce the risks associated with current AD treatments. Together, these research efforts, funding opportunities, and workshop discussions may pave the way for a stronger precision medicine approach to treating forms of dementia that include A β plaques in the brain.

⁶⁶ reporter.nih.gov/search/fHWZA_iFl06jXKOSf4XEPg/project-details/10760161

⁶⁷ nia.nih.gov/news/nia-statement-report-lecanemab-reducing-cognitive-decline-alzheimers-clinical-trial

⁶⁸ molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-023-00649-w

⁶⁹ reporter.nih.gov/project-details/10850128

⁷⁰ grants.nih.gov/grants/guide/pa-files/PAR-23-140.html

⁷¹ ninds.nih.gov/news-events/events/anti-beta-amyloid-passive-immunotherapy-alzheimers-dementia-and-amyloid-related-imaging

Testing the potential of Chimeric Antigen Receptor immune cell therapy in AD/ADRD

Chimeric Antigen Receptor (CAR) cell therapy is a novel immunotherapy approach used to treat cancer which involves engineering immune cells in the laboratory so they can specifically target and kill cancer cells. NIH is funding efforts to explore whether CAR-expressing immune cells can be customized as treatments for AD/ADRD. The currently available FDA-approved CAR therapies are used to treat certain types of cancer. CAR therapies are a prime example of precision medicine because they are made with cells, including T-cells and macrophages, from the patient and are engineered in the laboratory to become CAR-T cells and CAR-M cells, respectively. The CARs on these cells recognize and bind to specific target proteins, or antigens, and activate specific functions of the immune cell. After the engineered CAR-T or CAR-M cells are “expanded” into the millions in the laboratory, the cells are then infused back into the patient. If all goes as planned, the CAR-T or CAR-M cells multiply in the patient’s body, and with guidance from their engineered receptor, recognize and eliminate cancer cells and debris expressing the target antigen.

There is emerging evidence that this therapeutic approach could be translated to AD/ADRD. NIH-funded scientists demonstrated that CAR-M may be utilized to target and degrade unwanted materials, such as A β plaques in the brains of AD mice.⁷² NIH is currently funding projects exploring the therapeutic potential of CAR-T and CAR-M cells with specificity to A β in AD/ADRD.⁷³ Building on these existing projects, NIH also announced a funding opportunity (RFA-AG-24-046, “Chimeric Antigen Receptor (CAR) Approaches to AD/ADRD”) in August 2023 to further examine whether CAR therapies have promise as treatments for AD/ADRD.⁷⁴ The grants associated with this funding opportunity may be dispersed as early as November 2024.

CONCLUSION

Thanks to the substantial investment in AD/ADRD research over the past years, we now have a much better understanding of the multi-faceted role of the immune system in AD/ADRD. We understand that there are multiple immune cell types involved in AD/ADRD, and researchers are studying their individual roles in neurodegeneration as well as the interplay of these different cell types in disease onset and progression. NIH is investing in many complementary projects aimed at advancing the field’s understanding of the immune system’s role in AD/ADRD, with the goal of producing research findings that can eventually translate into targeted therapies. NIH will continue to leverage the agency’s research portfolio and longstanding expertise in therapeutics development to advance research and develop precision-inspired therapeutics to mitigate immune dysfunction in AD/ADRD.

⁷² pubmed.ncbi.nlm.nih.gov/38516884/

⁷³ reporter.nih.gov/project-details/10562093; reporter.nih.gov/search/TCRilhKs7k-i_IMtQ89Rbw/project-details/10633721

⁷⁴ grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-046.html