

REVIEW ARTICLE

APOE and immunity: Research highlights

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Abstract

INTRODUCTION: At the Alzheimer's Association's APOE and Immunity virtual conference, held in October 2021, leading neuroscience experts shared recent research advances on and inspiring insights into the various roles that both the apolipoprotein E gene (APOE) and facets of immunity play in neurodegenerative diseases, including Alzheimer's disease and other dementias.

METHODS: The meeting brought together more than 1200 registered attendees from 62 different countries, representing the realms of academia and industry.

RESULTS: During the 4-day meeting, presenters illuminated aspects of the cross-talk between APOE and immunity, with a focus on the roles of microglia, triggering receptor expressed on myeloid cells 2 (TREM2), and components of inflammation (e.g., tumor necrosis factor α [TNF α]).

DISCUSSION: This manuscript emphasizes the importance of diversity in current and future research and presents an integrated view of innate immune functions in Alzheimer's disease as well as related promising directions in drug development.

KEYWORDS

Alzheimer's disease, amyloid beta, APOE, astrocytes, biomarkers, dementia, inflammation, microglia, neurodegeneration, neuroglia, neuroinflammation, tau, TREM2

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1 | INTRODUCTION

The two well-established hallmark pathologies of Alzheimer's disease (AD)—extracellular plaques of aggregated amyloid beta ($A\beta$) and intraneuronal tangles of hyperphosphorylated, aggregated tau—characterize all cases of AD and have been shown to play a direct role in AD-related neurodegeneration.^{1–3} However, there is evidence that the precise mechanisms that lead to the development of characteristic AD pathology may differ among individuals. Less than 1% of individuals who develop AD have an early-onset form of the disease that is solely due to mutations in genes involved in $A\beta$ processing, including amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2).^{4,5} In an effort to discover mechanisms that lead to AD in the remaining 99% of individuals who have a sporadic form of the disease that most often results in late-onset AD (LOAD), researchers have used genome-wide association studies (GWASs) and whole genome/whole exome sequencing (WGS/WES) studies to identify more than 30 AD-related risk loci.⁶ Among gene variants that are associated with an increased risk for LOAD, more than half are linked to immune cell function. To date, the strongest known genetic risk factor for LOAD is the apolipoprotein E (APOE) $\epsilon 4$ variant,^{7–9} which, during the past decade, has been hypothesized to play a role in AD largely through its immunomodulatory functions.¹⁰ The triggering receptor expressed on myeloid cells 2 (TREM2), which is expressed by microglia in the central nervous system (CNS), likely plays a significant role in the immunomodulatory functions of APOE, and genetic studies show that rare *TREM2* variants are among important risk factors for AD. In turn, microglia play a principal role in the neuroinflammation that accompanies the accumulation of $A\beta$ during earlier stages of disease, as well as immune dysregulation that modulates disease progression throughout the course of AD.¹¹ Building on a foundation of established and strongly suspected roles of APOE, *TREM2*, microglia, and immune changes in AD, current research focuses on understanding these roles while identifying new intricately linked biological/pathophysiological mechanisms and pathways, with the goal of determining how the modulation of one or more of these components might be effectively targeted in drug development. (Supporting Information)

2 | APOLIPOPROTEIN E BIOLOGY

Apolipoprotein E (apoE) is the primary transporter of lipids and cholesterol in the brain and plays critical roles in both the metabolism of lipoproteins and the redistribution of cholesterol. Because of these functions, apoE has long been a focus of research related to atherosclerosis and cardiovascular disease.¹² Outside of the CNS, apoE is generated primarily by the liver, whereas in the brain, apoE is produced mainly by astrocytes. In the brain, microglia and neurons also are capable of generating apoE during times of stress.^{13,14} Although a primary function of apoE is to reduce intracellular cholesterol levels by effluxing lipids, it also plays integral roles in the overall health of the brain and in the progression and development of Alzheimer's disease (or AD).

Three apoE isoforms affect the extent to which its functions are executed, and are characterized by varying risks for the development of

RESEARCH IN CONTEXT

Systematic Review: The role of the apolipoprotein E gene (APOE) and immunity in neurodegenerative diseases, including Alzheimer's disease and other dementias, is an active and growing area of research. The authors of this article report updates and advances in research presented at the APOE and Immunity virtual conference, held in October 2021.

Interpretation: There have been strides in research identifying the cross-talk between APOE and immunity, with a special focus and emphasis on the roles of microglia and components of inflammation, emphasizing the importance of diversity in current and future research, and presenting an integrated view of innate immune functions in Alzheimer's disease as well as related promising directions in drug development.

Future Directions: Research and advances into understanding both APOE and immunity in neurodegenerative diseases is needed to improve our understanding of brain diseases. These and other topics will be explored in two individual conferences, Immunity and APOE, both hosted in March 2023.

AD. APOE $\epsilon 3$, which is present in $\approx 78\%$ of the general population, is the most common of the three and is considered the standard “baseline” or “control” allele in AD research.¹⁵ The APOE $\epsilon 4$ allele, which is present in $\approx 14\%$ of the general population, significantly increases the risk of developing AD relative to APOE $\epsilon 3$, such that APOE $\epsilon 4$ homozygotes are known to have the greatest risk for AD, with an estimated 10- to 15-fold increase in risk in Caucasian populations (risk varies by race and ethnicity). The APOE $\epsilon 2$ allele, which is present in $\approx 9\%$ of the general population and in about 5% of all individuals with AD, is associated with a lower risk of the development of AD compared with the APOE $\epsilon 3$ allele,¹⁶ and also is associated with increased longevity.¹⁷

Compared with APOE $\epsilon 3$, APOE $\epsilon 2$ has a decreased affinity with low-density lipoprotein receptor (LDLR) and is associated with a type-3 hyperlipoproteinemia that is observed in individuals carrying the APOE $\epsilon 2$ allele. APOE $\epsilon 4$ is associated with an increased ability to bind lipids, but because of reduced proteolytic activity can lead to an increase in lipoproteins and cholesterol.^{15,18} A growing body of literature points to the $\epsilon 4$ allele as a driver of many types of AD-related neuropathology, including impaired regulation of cholesterol and fatty acid levels in the brain, damage to blood–brain barrier integrity, reduced cerebral glucose uptake, and impaired insulin signaling in the brain.^{19–22}

2.1 | APOE genotype and glucose metabolism

Metabolic disorders, such as insulin resistance and type 2 diabetes, increase the risk of dementia and have in common with AD a wide range of pathologic features, including inflammation, increased oxidative stress, and vascular dysfunction.²³ Many studies suggest that APOE

$\epsilon 4$ may reduce insulin signaling, in part by impairing the recycling of the insulin receptor.¹⁹ APOE status plays an important role in cerebral glucose metabolism during aging, even in the absence of neuropathology. Glucose metabolism is reduced in individuals with at least one copy of APOE $\epsilon 4$ compared with noncarriers.^{21,22} Changes in cerebral glucose metabolism that occur in APOE $\epsilon 4$ carriers begin many years before the emergence of AD-related symptoms, as evidenced by reductions in cerebral glucose utilization on fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, which reflect decreased neuronal activity and/or synaptic dysfunction.²⁴ More recent studies indicate that brain glucose hypometabolism is associated with impaired glycemic control in the periphery in cognitively healthy subjects.²⁵ In carriers, increased levels of glucose during midlife are linked to more severe AD-related pathology at autopsy, particularly with regard to neurofibrillary tangles in the medial temporal lobe.²⁶

In a study published in 2017, Nielsen and colleagues explored the extent to which peripheral APOE levels affect cognition, gray matter volume (GMV), and cerebral glucose metabolism in an isoform-dependent manner. During the study they discovered important sex-related differences, such that women had higher plasma levels of total apoE and apoE $\epsilon 4$ compared with men.²⁷ They also found that higher ratios of apoE $\epsilon 3/\epsilon 4$ were negatively associated with cerebral metabolic rate of glucose (CMRgl) and GMV. Their findings pointed toward a potentially important role of peripheral apoE levels with regard to modulating brain health, and also offered potential insights into the higher risk for AD among women.²⁷

In a more recent study (of the same cohort) conducted by Edlund and colleagues, plasma insulin and glucose levels were obtained for the previously studied 128 cognitively healthy apoE $\epsilon 3/\epsilon 4$ individuals to determine the extent to which apoE is linked to peripheral glucose metabolism, and in turn to glucose metabolism in the brain.²⁸ The investigators determined that lower plasma apoE $\epsilon 3$ levels were associated with higher plasma glucose but not with insulin in men and in individuals with a body mass index (BMI) greater than 25. Negative correlations were found between plasma glucose and CMRgl in the left prefrontal and bilateral occipital regions of the brain. The authors suggested that these associations may have functional implications because glucose levels were in turn negatively associated with neuropsychological test scores. They concluded that plasma apoE $\epsilon 3$ but not apoE $\epsilon 4$ may be involved in insulin-independent processes that govern plasma glucose levels. They noted that higher plasma glucose, which has a deleterious effect on brain glucose metabolism, was associated with lower plasma apoE levels in APOE $\epsilon 3/\epsilon 4$ individuals. An important implication is that higher plasma glucose and lower apoE levels may be a potentially harmful combination that may lead to an increased risk for AD.²⁸

2.2 | Relationship between APOE $\epsilon 4$ status and C-reactive protein in AD

Inflammation has been observed consistently in brain tissue from patients with AD [see 3.0 Inflammation]. Evidence of inflammation has

been indicated by the presence of morphologically active microglia and astrocytes and increased extracellular complement factors, as well as cytokines and other inflammatory proteins, and elevated levels of inflammatory proteins both inside the brain as well as outside in individuals with AD. C-reactive protein (CRP), for example, plays a key role in the systemic response to inflammation, and plasma CRP has been evaluated as a potential biomarker for AD.²⁹ However, elevated blood CRP level is associated with an increase in AD risk only in APOE $\epsilon 4$ carriers.^{30,31}

In a recent study, Tao and colleagues examined the interactive effects of both plasma CRP and APOE genotype on cognition and a range of AD biomarkers.³² The study used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including APOE genotype, plasma CRP concentrations, diagnostic status (diagnosis of mild cognitive impairment [MCI], and dementia related to AD), Mini-Mental State Examination (MMSE) scores, Clinical Dementia Rating (CDR) score, cerebrospinal fluid (CSF) concentrations of A β 42, total tau (t-tau) and phosphorylated tau (p-tau), and amyloid (AV45) PET imaging. Among 566 ADNI participants, 274 (48.4%) did not have an $\epsilon 4$ allele, 222 (39.2%) had one $\epsilon 4$ allele, and 70 (12.4%) had two APOE $\epsilon 4$ alleles. Tao and colleagues found that elevated CRP was associated with lower MMSE scores at baseline and at 12-month follow-up, but only among participants who had two APOE $\epsilon 4$ alleles. They also found that two APOE $\epsilon 4$ alleles and elevated plasma CRP together were associated with increased CSF levels of t-tau and p-tau. Among ADNI individuals who had no APOE $\epsilon 4$ allele, elevated CRP was associated with reductions in CSF t-tau and p-tau, and these effects were more pronounced at 12-month follow-up. The authors concluded that CRP released during peripheral inflammation could be a mediator of APOE $\epsilon 4$ -related AD neurodegeneration and could, therefore, potentially serve as a drug target for AD.

2.3 | APOE and neuroinflammation

In an effort to explore some of the underlying mechanisms by which APOE $\epsilon 4$ affects AD risk, and to expand on previous findings regarding its role in impaired inflammatory responses, a recent study examined the effect of APOE genotype on inflammatory profiles in AD brains.¹¹ The study's investigators analyzed frozen brain tissue from the superior and middle temporal gyrus from APOE $\epsilon 3/\epsilon 3$ and APOE $\epsilon 4/\epsilon 4$ participants with AD pathology, and APOE $\epsilon 3/\epsilon 3$ participants without AD pathology to examine how apoE isoforms affect the neuroinflammatory state of the brain both with and without AD.¹¹ The NanoString Human Neuroinflammation Panel was used to determine the transcript levels of 757 inflammatory related genes, and immunohistochemistry of P2RY12 was performed to assess microglial activation. The study found that pathways related to neuroinflammation were impaired in APOE $\epsilon 4/\epsilon 4$ individuals with AD compared with APOE $\epsilon 3/\epsilon 3$ individuals with AD, and that the expression of genes related to microglial activation (SALL1), motility (FSCN1), epigenetics (DNMT1), and others showed altered expression in the former group. The study's findings suggest that APOE $\epsilon 3$ can become responsive to pathology and brain

changes, although it can result in a potentially harmful long-term inflammatory response, whereas APOE ϵ 4 causes a weakened response to pathology. Overall, the study indicated that apoE isoforms do appear to modulate the immune response to AD-type pathology in the brain.¹¹

3 | NEUROINFLAMMATION AND CELLS MEDIATING CNS IMMUNE SURVEILLANCE

Neuroinflammation is a response of the innate immune system in the CNS which involves the activity of microglia and astrocytes in combination with their secreted cytokines, chemokines, and altered homeostatic functions, which together play a central role in an early phase of AD pathogenesis.³³ The primary mediators of inflammatory mechanisms associated with AD are microglia and astrocytes—cells that also are responsible for neural transmission and critical synaptic remodeling.³⁴

A number of longitudinal studies showed that microglial activation and AD-related inflammation in the CNS occur years before the onset of AD-related symptoms.^{35,36} Other studies have demonstrated a durable link between neuroinflammation and amyloid and tau accumulation in the brains of individuals with AD.^{37,38} Although neuroinflammatory responses of microglia and astrocytes may precede A β plaque deposition, these responses are exacerbated with the accumulation of A β during the pathogenesis of AD and also modulate later stages of the disease, at turns either ameliorating disease or exacerbating it, in a complex, dynamic process. One study suggested that neuroinflammation may even precede amyloid aggregation, as older APOE ϵ 4 carriers with normal AD biomarkers had increased CSF levels of proteins associated with inflammation.³⁹ A fluctuation between pro- and anti-inflammatory states typically occurs in patients during early stages of AD, and it has been hypothesized that as the disease progresses, the inflammatory phenotype becomes more homogeneous.^{40,41} Neuroinflammation also occurs during normal aging.⁴² However, chronic neuroinflammation is capable of inducing neuronal injury and/or death by producing toxic substances such as reactive oxygen species (ROS) and nitric oxide (NO), or by promoting the phagocytosis of neurons by activated microglia. Activated microglia can engage in cross-talk with astrocytes, and provoke reactive astrocytes to directly kill neurons by means of secreted neurotoxic factors—as recently reported these include long-chain saturated fatty acids that are trafficked in apoE-containing lipoparticles.⁴³ Both microglia and astrocytes, the two primary components of the innate immune system, also have various effects on the accumulation of A β and tau pathology, in addition to their direct effects on neuronal viability.

3.1 | Other immune cells of the CNS

Although it is well established that disease progression in AD involves inflammation associated with the activation of innate immune cells, the role of adaptive immunity in AD is less well understood. In recent years, animal studies involving the depletion of B cells, T cells,

and NK cells have strongly suggested that adaptive immunity exerts an important influence on AD progression.^{44,45} These studies have revealed that there is significant cross-talk among cells involved in innate immune responses—primarily mediated by microglia in the CNS—and cells involved in adaptive immunity, which until recently were believed to be derived primarily from peripheral circulation.⁴⁶ The loss of cells from adaptive/peripheral immune cell populations by means of genetic ablation, for example, has been shown to alter the activation of microglia, increase neuroinflammation, and hasten amyloid pathogenesis.⁴⁴ Findings from other studies have suggested, in contrast, that B-cell depletion might be used therapeutically.⁴⁵

Because a better understanding of the function of all cells involved in CNS immune surveillance, in both the physiological and pathological states, may facilitate the discovery of new therapeutic targets for the treatment of neurological diseases, recent research has sought to provide detailed answers to questions regarding the origin and development of different types of immune cells in the brain.^{46,47} One such study led to the surprising finding that the mouse meninges contain a source of B cells that are supplied not by the blood but from bone marrow in the skull.⁴⁷ Using sophisticated techniques involving parabiosis and bone marrow chimeras, Brioschi and colleagues⁴⁷ discovered a lymphopoietic niche in the meninges—a reservoir for B cells that originate in skull bone marrow and travel to the meninges by means of tiny vascular corridors in the bone. These B cells, which have never had contact with peripheral blood, reside in such reservoirs until they are needed in response to injury or neuroinflammation. By means of single-cell RNA sequencing, investigators were able to determine that a wide range of B cells at various stages of maturity were located in the meninges, including immature cells that express the immunoglobulin M (IgM) receptor on their cell surfaces. Such findings suggest that the meninges may be an area where immature B cells can be uniquely “educated” by CNS antigens, in contrast to B cells from the periphery, which might be inclined to attack brain-specific antigens. In similar research also conducted at Washington University, Kipnis and colleagues discovered that skull bone marrow is also a key source of CNS immune cells that determines when and to what extent immune cells in the brain are derived from these sources,⁴⁶ how such cells may differ functionally from blood-derived cells, and how the source of immune cells in the brain may change during aging or in the context of various CNS diseases.

4 | MICROGLIA, ASTROCYTES, AND AD-RELATED NEURODEGENERATION

Microglial cells, myeloid cells that arise from early embryonic yolk-sac progenitors, are the primary macrophages of the brain and play a critical role in neuroinflammation in the CNS.⁴⁸ Microglia survey the brain in an effort to detect disruptions from homeostasis (e.g., injury, infection, disease, and so on) and subsequently work to clear debris and resolve disruptions, and in turn maintain an optimal microenvironment. Microglia can respond to virtually all foreign entities in the brain, most of which have been categorized as danger-associated

molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs).⁴⁹ In the presence of A β , microglia become activated, surround plaques, and attempt to phagocytose A β and prevent further spread of plaques.⁵⁰ An excessive accumulation of A β can lead to microglial cell death, and can increase inflammation and lead to the recruitment of more microglia, thus perpetuating an inflammatory cascade.⁴⁷ In addition, reactive microglia can release molecules such as tumor necrosis factor- α (TNF α) and interleukin 1 β (IL-1 β) among many other cytokines and complement components that can either directly recruit additional microglia to cause damage to surrounding tissue,⁵¹ alter neuronal function, or act as a seed to drive reactive inflammatory responses in adjacent cells like astrocytes.^{52,53}

A number of recent studies have demonstrated that, when in the disease-associated state, microglia can increase the expression of APOE.^{54–57} Accordingly it is important to explore whether microglial apoE may be a major source of amyloid-plaque-associated apoE,⁵⁷ and whether efforts to induce a disease-associated state in microglia may possibly increase plaque-associated apoE and in turn A β aggregation.⁵⁸

4.1 | Using single-cell technologies to identify diverse reactive glia phenotypes in AD

In AD and in other neurodegenerative diseases, many heterogeneous sub-states of reactive microglia and astrocytes have been observed in the brain. Traditionally, attempts were made to classify these cells into binary types: proinflammatory phenotype, involving a reduction in the release of neurotrophic factors and an exacerbation of inflammation and cytotoxicity; and anti-inflammatory phenotype, characterized by displays of anti-inflammatory cytokines, an increase in the expression of neurotrophic factors, and a range of signals involved in protection or repair processes. However, the advent and application of high throughput single-cell sequencing technologies in recent years has found a binary definition of reactive microglia/astrocytes to be incorrect and that many sub-states exist. In addition to heterogeneity within and across different disease/injury contexts, evidence from experimental studies suggest that phenotypic switching can occur in response to various stages of disease and/or degrees of disease severity.⁵⁹

Single-cell RNA-sequencing technologies are being used to improve our understanding of microglia and astrocytes and to ascertain their changing gene-expression profiles, their involvement in various pathways, and the epigenetic mechanisms that may be driving these cells—with the goal of improving future efforts to modulate disease by targeting these entities. A rapidly expanding collection of new tools are now available that enable rapid and cost-effective sequencing of individual cells, and new approaches for isolating, targeting, and establishing cultures of these cells in vitro.^{60–63} These new tools are providing novel insights into the functions of microglia and astrocytes during normal development, as well as during the early initiation and later progressive stages of many chronic neurodegenerative diseases. A key aim is to create models that integrate both cell types, and to reveal how they communicate and are able to integrate functions throughout the brain. Accordingly, current efforts are underway to

obtain microglia and astrocyte surface proteomes and secretomes and to integrate these data with other multi-omics data sets (e.g., involving transcriptomics, epigenetics, and proteomics).

Efforts to identify more diverse subtypes/profiles of microglial cells are pointing increasingly to far greater complexity in human cells compared with animal cells^{64–66}; however, only the most subtle of differences are reported across species for astrocytes. Although astrocyte isolation and culture have been successful in both rodents⁶³ and humans, similar successes with microglia have been limited. An important challenge has stemmed from the observation that removing microglia from the CNS microenvironment leads to rapid alterations in gene expression,^{67–69} and the creation of an ex vivo state of microglia has been particularly problematic.⁶² In some studies, for example, researchers have accidentally assigned a biological relevance to microglial states that do not exist in situ. This was historically a problem for the in vitro study of astrocytes/microglia as well, because early methods for culture relied on serum addition, which has been reported to irreversibly alter the gene expression and function of both astrocytes and microglia; however, recent serum-free methods have circumvented this problem.^{53,61,63,67} It is important to note that cholesterol, which is likely trafficked in apoE-containing lipoparticles in vivo.⁶⁷ Caveats still remain, however, as microglia and astrocytes grown in culture, even in the absence of reactivity-inducing serum components, are likely not fully recapitulating their in vivo counterparts (e.g., morphologies of culture astrocytes are very basic and lack the complex bushy tertiary and quaternary processes seen in vivo). One should not discount the power of such culture-based systems, however, as the high fidelity investigation of single functional interactions, or the role of cell–cell communication in homogeneous populations (either of homeostatic or reactive sub-states) is difficult to the level of impossible in vivo, due in large part to the extreme heterogeneity of both cell types at both homeostatic^{62,70–72} and AD-associated reactive states.^{65,73,74} What remains a bottleneck for the understanding of cellular heterogeneity is twofold: a lack of sub-state-specific culture systems to study the functional changes that occur; and second, a lack of genetic diversity in functional testing to determine if apoE isoform may alter not only gene expression differences but also key homeostatic functions like lipid delivery, synaptogenesis, and phagocytosis, among others. The investigation of these putative altered functions will be particularly important moving forward—as the astrocyte–microglia communication in AD seems particularly altered given the APOE-TREM2 interactions already reported by many groups.

5 | TREM2 AND APOE

Research focused on the microglial receptor known as triggering receptor expressed on myeloid cells 2 (TREM2) has increased recognition of the importance of microglia in AD, particularly because a number of mutations in TREM2 increase the risk for AD.⁷⁵ TREM2 is present on myeloid-derived cells such as microglia, macrophages, and osteoclasts and responds to a wide range of entities including apoptotic cells, A β , and lipoproteins. In individuals without AD pathology,

this receptor protein enhances the rate of phagocytosis in microglia and macrophages, and regulates inflammatory signaling, as well as myeloid cell number, proliferation, and survival. TREM2 plays a role in the pathogenesis of AD by modulating microglial functions, such as the production of inflammatory cytokines, in response to A β plaques and tau tangles. When TREM2 is absent, amyloid pathology is enhanced during the early stages in models of AD, and during the later stages this tendency is increased further with the loss of the ability to clear A β through phagocytosis. TREM2 variants contribute to AD pathogenesis in part by decreasing the phagocytic ability of microglia, and by interfering with the proinflammatory response of these immune cells.

In AD, TREM2 appears enriched in microglia that surround neuritic plaques. In mouse models that lack TREM2, microglia are unable to move toward A β plaques. Growing evidence suggests that the timing of TREM2 expression is key—a finding that likely has important implications for drug development [see 8.1]. Studies have indicated that although TREM2 is critical for the clearance of early A β plaques and the slowing of cognitive decline during early stages of AD, expression of TREM2 during later stages of disease progression could have disadvantageous long-term consequences.

5.1 | APOE and TREM2 interactions

In a recent study, Fitz and colleagues investigated how APOE and TREM2, two major genetic risk factors for AD, affect microglial response to A β .⁷⁶ First, by applying shotgun lipidomics they compared the phospholipid content of human brain and native mouse apoE lipoproteins and established that there is an apoE isoform-specific phospholipid signature. Overall, the native apoE e3 lipoproteins were more lipidated and had a higher level of negatively charged phospholipids compared to apoE e4, which may represent differences in potential lipid-activation signals. Using preclinical AD mouse models, they demonstrated that apoE e3 lipoproteins, in contrast to apoE e4, prompted faster microglial migration toward injected A β , facilitated A β uptake, and ameliorated damaging effects of A β on cognition. In vivo two-photon imaging of mouse brains clearly demonstrated that the apoE e3 lipoproteins caused microglia to gravitate toward A β and surround the injection site more robustly compared with the apoE e4, which can act as a protective mechanism decreasing the spread of A β . This observation is in agreement with the authors' previous publication.⁷⁷ Here they showed in *ApoE* ϵ 3 expressing AD model mice, microglia establish a more complete barrier around small senile plaques, which restricted plaque growth compared to *ApoE* ϵ 4 expressing and *Trem2*^{-/-} mice. This emphasizes the importance of the early response by microglia to amyloid pathology, which is apoE isoform as well as Trem2 status dependent.⁷⁷ Bulk and FACS sorted RNA-sequencing demonstrated that, compared with cortical infusion of apoE e4, infusion of apoE e3 lipoproteins led to the upregulation of higher proportion of genes linked to activated microglia response. This upregulation was most pronounced in microglia that have engulfed A β , suggesting that apoE e3 could initiate a stronger response by microglia to A β than apoE e4. In single-cell RNA-sequencing analysis, microglia

of wild-type (WT) versus *Trem2*^{-/-} injected with apoE e3 or e4 lipoproteins were grouped in homeostatic and activated microglia clusters. Overall, for all active clusters, they observed a higher number of differentially expressed genes between WT versus *Trem2*^{-/-} in the mice injected with apoE e4 rather than with apoE e3. This suggests that apoE e4 lipoproteins compared to apoE e3 are less prepared to withstand TREM2 deficiency particularly in the presence of A β . Again, this is similar to their previous findings, where they observed twice as many differentially expressed genes when comparing *ApoE* ϵ 4 versus *ApoE* ϵ 3 AD model mice than their *Trem2*^{-/-} counterparts, even with increased amyloid pathology in both *ApoE* ϵ 4-expressing mice.⁷⁷ The authors also showed that, in vitro, the lack of TREM2 decreases A β uptake only by APOE e4-treated microglia, thus suggesting an important interaction between TREM2 and apoE isoform. Their results support the hypothesis that the phospholipid signatures of native apoE e3 lipoproteins trigger a more rapid phenotypic and transcriptional response of microglia to A β than apoE e4 in ameliorating the deleterious effects of A β .

6 | BIOMARKERS

Current research aims to discover the impact of a range of factors that may affect AD pathology, such as APOE genotype and measures of inflammation/inflammatory proteins, and how such factors may influence disease progression, possibly long before the emergence of clinical symptoms. Further investigation of such factors, including the associations between AD biomarkers and fluid levels of apoE (in plasma),⁷⁸ may reveal new information about the sequence of events that leads to AD, may provide more detailed information about the influence of gender and racial differences on disease progression [see 7.0 DIVERSITY], and in turn may improve the ability to identify targets for effective therapies.

Building on earlier studies that have demonstrated that apoE plays a role in modulating concentrations of CSF A β 1-42 (A β 42) in patients with AD-related cognitive decline, recent studies evaluated how the effect of apoE on CSF A β 42 varies by age and also aim to understand the potential association between apoE and the onset of preclinical AD.⁷⁹ In one study that examined a large cohort of cognitively healthy individuals from nine clinical research centers, APOE genotypes and CSF A β 42 concentrations were obtained for cognitively healthy individuals between the ages of 17 and 99.⁷⁹ The investigators found that CSF concentrations of A β 42 were lower in APOE ϵ 4 carriers compared with non-carriers in a gene dose-dependent manner, and that the effect of apoE e4 on CSF A β 42 was age dependent. Homozygous APOE ϵ 4 carriers showed a steady decline in CSF A β 42 concentrations with increasing age throughout the entire age span examined in the study. The study showed that individuals with the APOE ϵ 4 allele start to exhibit a decrease in CSF A β 42 concentration almost a decade before APOE ϵ 4 non-carriers. Homozygous APOE ϵ 4 carriers were believed to deposit A β 42 during all of the ages examined in the study. The authors suggest that there may be an APOE ϵ 4-dependent period of early alterations in amyloid homeostasis, when amyloid slowly

accumulates, which several years later, in conjunction with other downstream pathological events, such as tau pathology, may translate into cognitive decline. Another study found no effect of APOE genotype on CSF A β 42 concentration in people younger than 35 years of age, corroborating that the associations observed are not due to any direct effects of apoE isoforms on CSF concentrations of A β 42, but are more likely explained by earlier onset of A β accumulation in APOE ϵ 4 carriers.⁸⁰

With the availability of a growing number of plasma biomarker tests, an important question is whether APOE genotype might be used to improve the performance of fluid biomarkers for AD pathologies. Studies that examined this question so far had conflicting results or found that APOE genotype information does not improve the predictive value of robust CSF biomarkers.^{39,81} For plasma A β 42/A β 40 ratio, however, information on age and APOE genotype improves the diagnostic performance of the test. To date, researchers have proposed that an ideal biomarker should accurately measure changes in AD pathology (e.g., A β or tau) regardless of APOE status.

6.1 | Using CSF proteomics to examine roles of apoE and components of immunity in AD

One avenue by which researchers are attempting to better understand heterogeneity among individuals with AD is through the application of CSF proteomics. Because CSF contains thousands of proteins, the concentrations of which can vary considerably among individuals with neurodegenerative disease, CSF proteomics have been used in efforts to detect AD subtypes that reflect individual differences in pathophysiological processes across the AD disease spectrum.

In a recent study examining data from two large independent AD cohorts, the European Medical Information Framework for Alzheimer's Disease Multimodal Biomarker Discovery (EMIF-AD MBD) and the Alzheimer's Disease Neuroimaging Initiative (ADNI), investigators found 705 proteins (77% of 911 tested) whose concentrations differed in individuals with AD, compared with controls (who were defined as having normal CSF amyloid and tau and normal cognition).⁸² Using these proteins, it was possible to identify three distinct AD subtypes with characteristic patterns of pathophysiology, one of which had a distinct pattern of innate immune system activation. This subtype was characterized by higher levels of proteins that—in both cohorts—pointed to involvement of the innate immune system, as well as oligodendrocyte development. Individuals comprising the subtype 2 population had, for example, high levels of proteins associated with complement pathway activation, which may play a role in neuronal injury in AD, because complement proteins can accumulate at synapses and tag these for phagocytosis by activated microglia. The authors noted that biological processes that characterize subtype 2 seem to be associated with activated microglia, which may contribute to neuronal dysfunction, or may be associated with the activation or dysregulation of astrocytes. The team concluded that subtype 2 individuals may potentially benefit from therapeutic strategies that target microglia and astrocyte activation.

6.2 | A hypothesis-driven approach to pro- and anti-inflammatory proteins in Alzheimer's disease

Neuroinflammation has been strongly associated with AD, and as such, efforts have been made to obtain discrete CSF measures of inflammatory proteins for both diagnostic and prognostic purposes; however, such discrete measures may fail to account for overlapping disease pathways and the relationships between them. In recently published work by Hu and colleagues, 15 CSF proteins that reflect microglial and T-cell functions were measured across diagnostic categories in 382 participants from ADNI, as well as for participants from two independent cohorts. The researchers demonstrated that higher levels of proteins related to soluble tumor necrosis factor receptor 1 (sTNFR1) are associated with a reduced risk of conversion to dementia in people with MCI related to AD, whereas higher soluble TREM2 levels are associated with a slower decline in the dementia stage of AD. The team demonstrated that these inflammatory proteins are capable of providing prognostic information independent of established AD markers.⁸³

An important implication of this research is that CSF-based prognostic biomarkers might complement core AD diagnostic biomarkers in the very early stages of AD and provide additional prognostic information at an early stage of disease. The authors note that other investigators also examined CSF inflammatory proteins in AD, including sTNFR1, sTNFR225, and TREM2. With the large sample size drawn from ADNI and two additional cohorts, the team was able to detect extraordinarily consistent principal components (PCs) and PC families across all cohorts, even when biomarkers within the same PC were derived from different cell types.

7 | ENSURING DIVERSITY IN APOE AND OTHER AD-RELATED RESEARCH

Research that examined interrelationships among APOE, cognitive performance, morbidity, and mortality has focused mainly on populations with European ancestry.^{84–86} However, conclusions drawn from such studies do not adequately reflect the diversity of individuals who may be at risk for AD. A recent examination of the international distribution of APOE alleles drawn from public databases around the world, as well as ancient DNA samples, for example, provided a number of insights into the nature of human longevity that also shed light on the importance of ensuring diversity in AD research.⁸⁷ This study emphasizes the importance of exploring APOE variability, as well as the variability of other longevity and AD-related genes, with vital consideration of population-specific cultural and ecological traits to “disentangle” the pathway from genotype to phenotype for the purpose of improving the interpretation of APOE-related data in different populations. In an effort to learn more about overlooked contributions to AD phenotypes, a number of studies in recent years examined the effects of APOE alleles and other AD-associated genetic variants on cognition, with an emphasis on potentially important implications related to differences in race/ethnicity and sex/gender among study participants.^{88,89}

7.1 | Examining AD-related sex and gender differences

Building on the knowledge that sex can be a key modifier of neurological disease outcomes,^{90,91} a number of recent studies have more closely examined sex-specific influences on neurodegenerative diseases. In a recent study of sex-specific differences, for example, Kodama and colleagues examined differences in microglial response to tau pathology that exist between male and female mice.⁹² Because previous studies revealed that sex differences in microglial gene expression and functions could be observed in young adult mice, were likely more pronounced in the aging brain, and that microRNAs (miRNAs) regulate immune networks in microglia, the authors determined whether microglial miRNAs are expressed in and function in a sex-specific manner. After performing miRNA sequencing (miRNA-seq) on microglia isolated from brains of adult mice and inducing and evaluating changes in the transcriptomes of male and female microglia, the authors found that they expressed different miRNA patterns, both at baseline and in the context of tauopathy. Furthermore, they discovered that the loss of miRNAs resulted in sex-dependent consequences on the microglial transcriptome and tau pathogenesis. The authors concluded that microglial miRNAs are key contributors to sex-specific phenotypes and noted that a better understanding of microglial miRNA function could aid in the identification of novel molecular networks that may contribute to neurological diseases.

In a recent study exploring sex differences in humans with regard to associations between APOE and CSF measures of tau, Babpour-Mofrad and colleagues built on earlier research that revealed stronger associations between APOE ϵ 4 and CSF tau levels among women compared with men, and suggested that APOE may play a role in modulating risk for neurodegeneration in a sex-specific manner, particularly in amyloid-positive individuals.⁹³ Mofrad and colleagues obtained CSF A β 42, t-tau, and p-tau at threonine 181 (p-tau 181) levels from 1801 participants with probable AD dementia ($n = 937$), MCI ($n = 437$), and subjective cognitive decline ($n = 427$). The authors found that among APOE ϵ 4 carriers, sex differences in CSF p-tau, that is, higher levels in females, are more apparent during early stages of disease, but that for APOE ϵ 4 non-carriers, females are more evident in advanced disease stages. Based on their findings, the authors concluded that the effect of APOE ϵ 4 on sex differences in CSF biomarker levels vary depending on disease stage in individuals with AD.⁹⁴

These and other recent studies examining sex differences (biological differences such as chromosomal gonadal or hormonal differences) and gender differences (psychosocial and cultural differences between men and women, including access to education and occupation) suggest that both sex and gender play an important role in the development and progression of neurodegenerative diseases, including AD. Continued investigation and understanding of both sex- and gender-specific risk factors, as well as factors that may be protective for AD, will be essential for developing and evaluating successful individualized interventions for the prevention and treatment of AD.⁹⁵

7.2 | Examining differences in race/ethnicity

A growing body of research is examining the established and suspected differences in risks for AD and related dementias (ADRDs) among various racial and ethnic populations to better understand the diagnostic and prognostic implications of these differences, as well as implications for treatment, future research, and for the design of clinical trials. An important goal is to determine the degree to which elevated risk for and incidence of ADRD in various populations can be explained by genetic differences, or by psychosocial/environmental differences, racism, or by complex interactions between environmental and genetic factors.

A recent study,⁹⁶ for example, examined psychosocial contributors to ADRD risk among non-Latinx Black older adults, who are known to have an elevated risk of ADRDs compared with non-Latinx White adults.^{97,98} The study examined data obtained from 221 non-Latinx Black older adults who were participants in the Washington Heights-Inwood Columbia Aging Project [WHICAP],^{98,99} a longitudinal, community-based study of aging and dementia in northern Manhattan. Participants completed multiple measures of discrimination at a single time point and structural magnetic resonance imaging (MRI) scans at two time points. Both everyday discrimination and lifetime discrimination were assessed, and MRI outcomes included both hippocampal and white matter hyperintensity volumes. This information was used to estimate associations between the measures of discrimination and each MRI outcome over a period of 4 years. The study's investigators found that lifetime racial discrimination was associated with lower initial hippocampal volume, and that everyday racial discrimination was associated with a faster increase in white matter hyperintensity volume over time. The investigators concluded that racial discrimination is likely detrimental for brain aging among non-Latinx Black older adults, and that it may contribute to the disproportionate dementia burden among this population.

In an effort to evaluate racial differences in TREM2, a key immune mediator in AD, another recent study examined the levels of CSF soluble TREM2 (sTREM2) and compared the frequency of associated genetic variants in groups of individuals who self-reported their race as African American (AA) or non-Hispanic White (NHW).⁸⁹ Data were obtained from 91 AAs and 868 NHWs who were participants in the Knight Alzheimer Disease Research Center (ADRC) cohort, which includes one of the largest groups of AA in AD research for which both CSF biomarker and genetic data have been collected. The cohort, which consists of community-dwelling older adults, includes participants both with and without cognitive impairment who are enrolled in research studies of memory and aging at Washington University in St. Louis. The study examined concentrations of CSF biomarkers, including sTREM2, as a function of race. The investigators found that CSF sTREM2 levels were lower in the AA group compared with the NHW group, and that AAs were more likely to have TREM2 coding variants, which were associated with lower CSF sTREM2. AAs also were less likely to carry the rs1582763 minor allele, located near MS4A4A, which was associated with higher CSF sTREM2. This study's findings were replicated in an independent cohort of 23 AAs and 917 NHWs.

The investigators concluded that the lower CSF sTREM2 levels among AAs compared with NHWs were likely related to the greater tendency for AAs to have genetic variants associated with lower CSF sTREM2 levels. These findings suggest that race may be associated with risk for genetic variants that influence AD-related inflammation, as CSF sTREM2 reflects TREM2-mediated microglial reactivity, a critical step in the immune response to amyloid plaques.⁸⁹

In response to findings from several publications that have revealed weak and inconsistent associations between *APOE* alleles and cognitive decline, MCI, and ADRDs in Latinx populations, despite higher rates of these disorders among Latinos compared with non-Latino Whites, a recent study determined whether these inconsistencies might be explained by ancestry-specific genetic effects.⁸⁸ The study's investigators examined associations between *APOE* alleles and significant cognitive decline, as well as MCI, in 4183 Latinos, comprising six distinct background groups—Cuban, Dominican, Mexican, Puerto-Rican, South-American, and Central American—and explored the degree to which continental genetic ancestry (e.g., European, African, or Amerindian) likely modified these associations. Participants were selected from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a population-based longitudinal cohort study of 16,415 U.S. Hispanic/Latino adults enrolled at four field centers (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California). Data obtained from the participants included anthropometry, biospecimens, information about AD-related risk/protective factors, and the results of four cognitive tests. The study found that *APOE* ϵ 4 was associated with an increased risk of significant cognitive decline, with the strongest association among Cubans. *APOE* ϵ 2 was associated with a decreased risk of MCI in Puerto Ricans. The study concluded that Amerindian genetic ancestry protects against the risk of significant cognitive decline conferred by the *APOE* ϵ 4 allele, and the study's authors indicated that future studies are needed to identify Amerindian genetic variants that may interact with the *APOE* ϵ 4 allele, as well as the nature of these interactions, with the goal of developing genetic measures for predicting significant cognitive decline and MCI in Latinos with mixed ancestry (of varying proportions).⁸⁸

7.3 | Examining diverse cohorts in AD prevention studies

Studies that have indicated higher rates of AD among AAs compared with non-Hispanic Whites (or nHw) have raised important questions regarding possible differences in etiology that may be responsible for these differences. In an effort to estimate the incidence of AD among AAs and NHWs across all available studies, Steenland and colleagues conducted a meta-analysis of six relevant population-based studies and based on their calculations found that the incidence of AD was 64% higher for AAs compared with NHWs.¹⁰⁰ They suggested that the higher incidence for AAs might be explained by a combination of biological, psychological, and socioeconomic influences.¹⁰⁰ The authors noted, for example, that AAs have higher rates of hypertension, obesity, and diabetes compared with NHWs, and that all of these

comorbidities have been linked to AD. The authors also cited studies indicating that vascular risk factors such as hypertension may activate neuroinflammatory responses and influence the levels of amyloid in the brain. Steenland and colleagues noted that these variables, as well as depression and stress, could be acting as confounders. The authors indicated the need for further research to confirm hypothesized biological, psychological, and socioeconomic factors, which may have important implications for the development of future treatments and for more accurate assessment of the public health burden of AD in the United States.

In related research conducted 1 year earlier, Wharton and colleagues designed a study to assess the effect of modulating the renin-angiotensin system (RAS) on the conversion to AD and cognitive decline in people with MCI, as well as effects of the permeability of the blood–brain barrier (BBB) and race on a potential relationship between the RAS and AD.¹⁰¹ The researchers followed individuals receiving antihypertensive medications who had MCI at baseline and who had cognitive assessments during at least two follow-up visits to assess conversion to AD as well as cognitive and functional decline. Among all participants, 488 were receiving RAS-acting antihypertensive medications. The team found that users of RAS-acting medications were less likely to convert to AD and also demonstrated slower decline on the CDR Sum of Boxes (CDR-SOB) and Digit Span Forward, compared with nonusers. BBB-crossing RAS-acting medications were associated with slower cognitive decline on the CDR-SOB, the MMSE, and the Boston Naming Test. The investigators found that RAS-acting medications were more likely to be associated with cognitive benefits among African Americans, compared with Caucasians. In addition to showing that people prescribed RAS medications were less likely to convert to AD, the study suggested that the BBB permeability of the medications may help explain cognitive benefit, and that African Americans are more likely to benefit from RAS modulation than Caucasians. The results of the study provided a strong rationale for trials investigating RAS modulation during prodromal stages of AD.

8 | TARGETED THERAPIES

Research in recent years that has examined the cross-talk between *APOE* and immunity has pointed to a number of promising directions for drug development. Of particular interest to AD researchers are early pathomechanistic alterations that occur along the AD continuum and contribute to the development of neuroinflammation, pathologic changes in immune signaling, and the progressive accumulation of A β and tau, which might be targeted for the prevention or early-stage treatment of AD.

8.1 | Modulation of protective TREM2-dependent microglial functions

A growing body of research ranging from human genetics and biomarker studies to human tissue/postmortem studies suggest the

value of investigating novel therapeutic strategies that enhance aspects of microglial function, such as innate immune signaling and immunometabolism, for the treatment of AD. In particular, GWASs and studies examining TREM2 signaling suggest that TREM2 may have beneficial functions in the CNS, that loss of TREM2 function increases the risk for AD, and that TREM2 modulation and/or activation might be used to prevent the onset or slow the progression of sporadic AD.^{102–104}

Among the best-described approaches to the modulation of TREM2 activity are those involving agonist antibodies that are capable of activating receptor signaling and enhancing the protective function of microglia. Four TREM2 agonistic antibodies—antibodies 1 and 2 (generated by R&D Systems and by Amgen, respectively), AL002c,¹⁰⁵ and 4D9³³—enhance survival of microglia and macrophages under low macrophage colony-stimulating factor (M-CSF) conditions.¹⁰⁶ These antibodies have a number of shared characteristics, including a tendency to bind in similar or overlapping sites within the stalk region of TREM2.¹⁰⁷ They also share the ability to stimulate both the proliferation and survival of myeloid cells. Moreover, all of these antibodies are characterized by dual mechanisms of action, such that each is capable of promoting TREM2 signaling by means of the cross-linking of surface TREM2, which stimulates phagocytosis and the removal of cellular debris, and also is capable of inhibiting TREM2 shedding.^{106,107}

Evidence that TREM2 plays a role in supporting the compaction of amyloid plaques and the clustering of microglia around amyloid plaques, which in turn helps to reduce plaque-associated neuritic pathology,^{106,108,109} suggests that TREM2 agonist antibodies might be used to successfully target amyloid accumulation. Indeed, the AL002c and 4D9 antibodies have been tested to determine whether they affect amyloid accumulation in the brain of transgenic AD mouse models.^{105,107,110} Although neither AL002c nor 4D9 has a tendency to increase clustering of microglia around amyloid plaques, 4D9 reduces the halo of amyloid plaques when administered to an APP knock-in mouse model. Two studies also established that both AL002a and 4D9 are capable of enhancing microglial phagocytosis of A β as well as of myelin debris.^{107,111}

A growing number of studies suggest that sTREM2 in CSF also may be an important target for TREM2 agonist antibodies.¹¹² Studies of sTREM2 in CSF have provided insights into disease pathogenesis in AD through the examination of the sequence of microglia activation relative to A β deposition and tau aggregation.¹¹² Recent studies also suggest that sTREM2 may have non-cell autonomous protective functions and that changes in various physiological conditions and/or disease states can affect levels of sTREM2 in CSF.¹¹² For these reasons, sTREM2 is undergoing evaluation as a therapeutic biomarker as well as a target for TREM2 antibodies.^{105,112} One antibody, 4D9, efficiently binds sTREM2 in CSF when administered at high doses (50 mg/kg) in the periphery, which correlates with an increase in total TREM2 levels in the brain.¹⁰⁷ This finding suggests that 4D9 is capable of achieving target engagement in the CNS in vivo, although further research will be required to determine the exact mechanisms that mediates the increase of soluble or cell-surface TREM2 in the CNS. One hypothesis is that by blocking shedding activity, 4D9 may increase cell-surface TREM2, and in turn may prevent its degradation and clearance.

As TREM2 antibodies undergo further development, researchers will need to address a number of important safety considerations. Because TREM2 antibodies affect a wide range of microglial subpopulations and dynamic microglial states in the brain, it will be critical to ensure that therapeutic efforts achieve a balance between beneficial and harmful effects of immune activation. Current efforts to use profiling data obtained with single-cell and single-nucleus RNA-seq technologies to better understand the diversity of sub-populations of microglia and their functions may eventually enable more comprehensive assessments of all microglia-targeting therapies.¹⁰⁶ Also important will be efforts to determine the effects of TREM2 agonist antibodies on bone as well as on lung, liver, spleen, and peripheral adipose tissues. Further work will be required before an optimal therapeutic molecular signature and optimal functional outcomes of treatment with TREM2 agonistic antibodies can be determined.

8.2 | APOE-modifying therapies

A major current avenue of drug development research involves identifying and targeting the factors through which APOE and its variants influence the development of AD, with the aim of discovering whether the protective effects of some APOE genotypes might be used to reduce the probability or delay the onset of developing AD.

It is well established that APOE, the strongest risk factor among susceptibility genes for late-onset AD, has three common alleles (APOE ϵ 2, ϵ 3, and ϵ 4) that give rise to six genotypes (APOE ϵ 2/ ϵ 2, ϵ 2/ ϵ 3, ϵ 3/ ϵ 3, ϵ 2/ ϵ 4, ϵ 3/ ϵ 4, and ϵ 4/ ϵ 4). Particular APOE alleles, including APOE ϵ 2 and the recently described APOE Christchurch mutation, are associated with a reduced risk of developing AD and other neurodegenerative disorders.^{113,114} In contrast, and compared with the most common APOE ϵ 3/ ϵ 3 genotype, each copy of the APOE ϵ 4 allele is associated with a higher risk of AD dementia and with a younger age at dementia onset, such that APOE ϵ 4 homozygotes are subject to the greatest risk, whereas either one or two copies of the APOE ϵ 2 allele is associated with a lower risk of AD and an older age of dementia onset. APOE variants may have an even greater impact on the development and potential treatment and prevention of AD than previously thought—due in part to the likelihood that earlier studies underestimated the influence of the APOE genotype because they include neuropathologically misclassified cases and controls.^{115–117}

In one recent study, Reiman and colleagues established that APOE ϵ 2 homozygotes have an exceptionally low likelihood of AD dementia.¹¹⁴ The study demonstrated an exceptionally low likelihood of developing AD dementia among APOE ϵ 2 homozygotes in a large population of clinically and neuropathologically confirmed individuals and controls. Moreover, the investigators provided updated information for each of the six common APOE genotypes with regard to the differential risk for developing AD and demonstrated a stronger association of APOE genotypes on the development of AD dementia than previously estimated. The study further supported known effects of APOE genotypes on standard measures of neuritic A β plaque and tau tangle severity and suggested progressively protective effects on Braak stage for genotype

groups (such that $APOE \epsilon 3/\epsilon 4 < \epsilon 2/\epsilon 4 < \epsilon 3/\epsilon 3 < \epsilon 2/\epsilon 3 < \epsilon 2/\epsilon 2$) compared with $APOE \epsilon 4/\epsilon 4$ homozygotes.

Other recent findings further stressed the importance of clarifying factors through which $APOE$ and its variants account for differential risks for AD. In a recent study, Arboleda-Velasquez and colleagues, determined that a Colombian $PSEN1$ E280A mutation carrier who did not develop MCI until their mid-seventies (nearly three decades after the median age of MCI onset among these carriers) had two copies of the rare $APOE \epsilon 3$ Christchurch (R136S) mutation.¹¹³ This $APOE \epsilon 3$ Christchurch homozygote demonstrated resistance to ADAD despite having the highest amyloid plaque burden among members of her kindred (evidence of the overproduction of $A\beta 42$ for more than 20 years). Despite PET and CSF evidence of high $A\beta$ plaque burden, the same individual had PET evidence of limited tau tangle burden and neurodegeneration, which supports the idea that $APOE$ variants have effects on the development of AD that go beyond plaque burden. This idea is further supported by evidence in other human and animal studies that $APOE$ variants likely have differential effects other than amyloid plaque deposition, such as effects on $A\beta$ aggregation and plaque morphology, $A\beta$ -mediated neuroinflammatory changes, tau propagation, and neurodegeneration.

Although these studies strongly suggest that apoE and its associated molecular pathways may be particularly attractive therapeutic targets, additional research will be needed to clarify the mechanisms linking $APOE$ with risk for AD. It will be particularly important to determine whether $APOE$ variants contribute to differential AD risk due to a toxic gain of function, which might suggest the benefit of an $APOE$ gene silencing treatment, or due to a toxic loss of function, which might suggest the benefit of increasing apoE function. Reiman and colleagues have proposed early-phase trial strategies in which these possibilities might be tested in p-tau+ and NfL+ $APOE \epsilon 4$ homozygous (as determined by CSF or plasma).

Gene editing treatments, including gene-silencing antisense oligonucleotide and RNA interference treatments already in development, and apoE protein-reducing or -modifying treatments are among currently proposed strategies that might safely and sufficiently replicate the protective effects of $APOE \epsilon 2/\epsilon 2$ genotypes to prevent or delay the clinical onset of AD. A key challenge will be to inform the efficacy of AD-modifying treatments in early phase clinical trials with satisfactory endpoints. Among theragnostic endpoints that are currently considered promising for $APOE$ -modifying treatments are CSF and plasma p-tau (e.g., p-tau181, 217, and 231), which are indicators of $A\beta$ -mediated tau pathophysiology, and CSF and plasma neurofilament light (NfL), which are indicators of neuronal injury and/or degeneration.

8.3 | Targeting chronic inflammation and soluble TNF

Neuroinflammation is one of the earliest pathologic mechanisms that occurs during the development of AD, which typically begins decades before the onset of clinical symptoms [see 3.0 Neuroinflam-

mation]. Although clinical trials that investigated compounds with anti-inflammatory properties have failed to achieve primary endpoints, current studies point to a continued strong therapeutic rationale for pursuing such treatment strategies.

Numerous studies of animal models of AD, as well as longitudinal human studies, suggest that TNF is an attractive therapeutic because it plays an important role in early proinflammatory processes that take place during preclinical stages of AD.^{118,119} Many studies found that elevated TNF levels are associated with both MCI and AD.^{35,118} TNF is released throughout the course of AD, by reactive microglia and infiltrating peripheral immune cells, and to a lesser extent reactive astrocytes and stressed neurons. One suggested initiator of this TNF increase is increased levels of extracellular $A\beta$ ¹²⁰; however, given that TNF increases are reported in several neurodegenerative diseases without $A\beta$, it is also likely that other non-AD specific drivers of cytokine increase are equally responsible. TNF also can trigger γ -secretase activity, which causes an increased synthesis of $A\beta$ peptides, and in turn a further increase in the release of TNF.¹¹⁸ It has been hypothesized that this feedback loop contributes to excessive levels of TNF- α that in turn lead to $A\beta$ synthesis, the inhibition of phagocytosis of $A\beta$ by microglia, and neuronal loss.¹¹⁸ TNF, along with other cytokines released by immune cells under inflammatory conditions in the early stages of AD, can drive reactive astrocyte sub-states—either those that are neurotoxic,^{43,52} or some with putative protective functions.⁷⁰ TNF also increases insulin resistance and related cognitive decline in AD.¹²¹

Although insulin impairment and inflammation are characteristic features of both type 2 diabetes and AD, until recently the shared molecular and signaling interactions underlying these features were not well understood. Recently investigators explored the disruption of metabolite processing in both insulin impairment and neurodegenerative conditions such as AD.¹²² Specifically, they investigated how soluble tumor necrosis factor signaling (solTNF) affects the integration of peripheral immune signals and metabolic feedback signals in states of energy overload and insulin insensitivity. These researchers found that a high-fat, high-carbohydrate diet (HFHC) diet in wild-type C57BL6/J mice affects central insulin signaling and immune-metabolic interactions in a solTNF-dependent manner, which is accompanied by disruption in sociability and inflammatory gene networks in the brain. They also found that selective solTNF neutralization can reduce diet-induced insulin impairment, and identified solTNF as a potential target for therapeutic intervention for lowering AD risk in inflammatory states, findings that have implications for individuals with type-2 diabetes at higher risk for development of AD.

In November 2019, INmune Bio launched a phase 1b, proof-of-biology trial of a protein biologic, known as XPro1595, which targets and selectively neutralizes the soluble form of inflammatory cytokine TNF, in 18 patients with clinically diagnosed AD. Participants, who were required to have evidence of inflammation (elevated blood CRP, hemoglobin A1c, high erythrocyte sedimentation rate [ESR], or carry at least one $APOE \epsilon 4$ allele), received weekly subcutaneous injections of 0.3, 0.6, or 1.0, mg/kg XPro1595 for 3 months. In addition to reporting that the drug was safe, INmune Bio reported a dose-dependent

reduction in biomarkers of neuroinflammation and neurodegeneration across multiple measures and modalities at 12 weeks that continued to improve in the six patients who remained on drug for 6 to 12 months. A proof-of-concept Phase 2 study in mild AD patients with biomarkers of inflammation is currently underway to further explore whether these biological changes in response to treatment can lead to clinical improvement (ClinicalTrials.gov Identifier: NCT05318976).

9 | CONCLUSION

At the 2021 APOE and Immunity virtual conference, the APOE and Immunity research communities demonstrated an enthusiastic commitment to advancing the interrelated fields of APOE and Immunity. This meeting was marked by a strong collaborative spirit and dedication to deepening our understanding of all aspects of APOE and Immunity biology and their interconnected relationships.

The Alzheimer's Association is committed to supporting dementia researchers around the globe. Currently, the Alzheimer's Association has over \$310 million invested in 950 projects in 48 countries on 6 continents. The Association supports researchers across dementia science, including projects that advance our understanding of new treatment strategies, and that improve our understanding of AD, help to improve care and support for individuals with dementia and their families, and help further our knowledge of brain health and disease prevention.

In 2023, the Alzheimer's Association is hosting two conferences to build upon the momentum of this APOE and Immunity virtual conference. AAIC Advancements: APOE will be held in St. Louis Missouri in March of 2023; and AAIC Advancements: Immunity will be held in Boston, Massachusetts in March of 2023. It is hoped that both conferences will attract new talent and funding to the field, while fostering greater awareness of this high-impact research.

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London, Neurology Seminar, Inflammation/Immunity in Parkinson's; Mind, Mood, and Microbes Conference (Cork, Ireland/Virtual): Gut Inflammation: Lessons from Sporadic Parkinson's Disease; MJFF LRRK2 Industry Summit, LRRK2, Colitis & PD; AD/PD 2021 Virtual, RGS10 and experimental colitis promotes nigrostriatal degeneration; Pittsburgh Institute Neurodegenerative Disease, Gene-by-Immune Interactions in PD; Keystone Scientific Symposium, Neuroimmune Interactions Short-Talk: LRRK2, Colitis & PD; UF MD/PhD Symposium: Scientific Journeys-Lessons from Academia to Biotech and Back Again; NINDS/NIDDK Gut-Brain Axis Workshop in D.C.; NIA ADRC Biomarker Core Leaders Virtual Workshop, Technical and Practical Considerations for Measuring Inflammatory Biomarkers in ADCs; Alzheimer's Association ApoE-Immunity Virtual Conference, Targeting chronic inflammation & soluble TNF to reduce risk for Alzheimer's disease; St. Jude Children's Research Hospital, CMB, Targeting Chronic Inflammation in the Gut-Brain Axis to Reduce Risks for Neurodegenerative Diseases; Bright Focus ALZ FastTrack, Chronic inflammation and neurodegenerative disease: risks and therapeutic opportunities in the age of COVID19: Targeting Soluble TNF-dependent Chronic Inflammation; ISTAART Immunity and Neurodegeneration PIA "What are Fluid Immune Biomarkers Telling us about Alzheimer's Disease?"; University of Wisconsin, Madison Group of Women in Medicine and Science Symposium, Breaking Down Barriers; University of Tennessee College of Medicine, Pharmacology, Targeting chronic peripheral inflammation to lower risk for neurodegenerative disease; Walter and Eliza Hall Institute of Medical Research, Victoria Australia, New Healthy Aging Series, Targeting Chronic Inflammation in the Gut-Brain Axis to Reduce Risks for Neurodegenerative Disease; American Neurological Association SIG 2021 Series: Movement Disorders, Targeting Immune; Calico Life Sciences, In Vivo Science and Pharmacology, Dysfunction and Inflammation in Parkinson's Disease Targeting chronic inflammation and soluble TNF to lower risk for development of neurodegenerative diseases; Oxford Diagnostics, Peripheral and Central Inflammation in Parkinson's Disease: Biomarkers and Therapeutic Opportunities. In 2022: The Ohio State University, Targeting chronic peripheral inflammation to lower risk for neurodegenerative disease; Baylor College of Medicine, Neuroscience, Targeting chronic peripheral inflammation to lower risk for neurodegenerative disease; Alzheimer's Latinos 2022, Chronic inflammation and interplay of gene-environment interactions in age-related dementia; Parkinson's EXPO, The Gut-brain Connection And Importance Of Microbiomes In Detecting And Slowing The Progression Of Parkinson's Disease; Synuclein 2022, Leuven, Belgium, The role and neuroimmune interactions of alpha-synuclein and LRRK2 in the gut-brain axis in PD pathophysiology; 4th Neuroimmunology Drug Development Summit, Using Pre-clinical Models to Inform Clinical-Trial Design Targeting of Chronic Inflammation in Neurodegenerative Disease; Washington University Lysosome Working Group, LRRK'ing around at the lysosome: assessing the effects of LRRK2 and other PD-risk genes on lysosomal function in peripheral immune cells; MJFF Parkinson's Disease Research (PDRx) Series, Targeting LRRK2 in Colitis Models; NIH Medical Genetics Branch, Targeting chronic peripheral inflammation and soluble TNF to reduce risk for Alzheimer's disease; LRRK2

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [supporting information](#).

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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