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PERSPECTIVE

Exploring the role of T cells in Alzheimer's and other neurodegenerative diseases: Emerging therapeutic insights from the T Cells in the Brain symposium

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Abstract

This proceedings article summarizes the inaugural "T Cells in the Brain" symposium held at Columbia University. Experts gathered to explore the role of T cells in neurodegenerative diseases. Key topics included characterization of antigen-specific immune

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responses, T cell receptor (TCR) repertoire, microbial etiology in Alzheimer's disease (AD), and microglia–T cell crosstalk, with a focus on how T cells affect neuroinflammation and AD biomarkers like amyloid beta and tau. The symposium also examined immunotherapies for AD, including the Valacyclovir Treatment of Alzheimer's Disease (VALAD) trial, and two clinical trials leveraging regulatory T cell approaches for multiple sclerosis and amyotrophic lateral sclerosis therapy. Additionally, single-cell RNA/TCR sequencing of T cells and other immune cells provided insights into immune dynamics in neurodegenerative diseases. This article highlights key findings from the symposium and outlines future research directions to further understand the role of T cells in neurodegeneration, offering innovative therapeutic approaches for AD and other neurodegenerative diseases.

KEYWORDS
Alzheimer's disease, amyotrophic lateral sclerosis, brain, central nervous system, clinical trials, conference proceedings, epilepsy, immunotherapy, major histocompatibility complex peptidome, Parkinson's disease, single-cell RNA sequencing, spinal cord, T cell receptor repertoire, T cells, viral infection

Highlights

- Researchers gathered to discuss approaches to study T cells in brain disorders.
- New technologies allow high-throughput screening of antigen-specific T cells.
- Microbial infections can precede several serious and chronic neurological diseases.
- Central and peripheral T cell responses shape neurological disease pathology.
- Immunotherapy can induce regulatory T cell responses in neuroinflammatory disorders.

1 | INTRODUCTION

Basic and translational neuroimmunology research continues to evolve rapidly, driven by technological innovations and interdisciplinary collaborations including immunologists, immunoengineers, biochemists, computational biologists, geneticists, and clinicians. One of the forefront areas of investigation within this field is the exploration of T lymphocytes and their role in neurological diseases, including Alzheimer's disease (AD),[1] Parkinson's disease (PD),[2] amyotrophic lateral sclerosis (ALS),[3] and epilepsy.[4] In particular, there is a growing recognition of the importance of antigen-specific T cells in modulating immune responses within the central nervous system (CNS). Traditionally, the brain was considered an immune-privileged organ, but emerging evidence suggests that T cells play a crucial role in both neuroprotection and neuroinflammation.[5] Previous studies investigating neurodegenerative diseases have extensively examined the reactivity of T cells toward suspected immunogenic aggregated proteins found within the brain, such as amyloid peptides in AD,[1,6] α-synuclein in PD,[2] and TAR DNA-binding protein 43 (TDP-43) in ALS.[7] With advanced single-cell RNA and T cell receptor (TCR) sequencing (scRNA/TCR-seq) technology, recent efforts have used unbiased approaches to unravel antigen-specific T cell responses in neurodegenerative diseases.[3,8,9] Understanding the dynamics of T cell phenotype and clonality within the CNS microenvironment is essential for elucidating the complex interplay between the immune system and neurologic diseases.

Recently, there has been a concerted effort to apply techniques developed for oncology and autoimmune disease research to neuroimmunology. This includes the development of novel high-throughput and multiplex technologies for screening T cell reactivity to self- and non–self-antigens and characterize their functional properties. By leveraging advanced sequencing technologies and scRNA/TCR-seq,[10] researchers are now able to identify and profile T cell populations with unprecedented precision (Figure 1). Furthermore, there is ongoing research aimed at modulating T cell responses for therapeutic purposes in neurologic diseases. Immunotherapy is now being explored as a potential treatment strategy for neurodegenerative disorders.[11,12] The engineering of T cells to target specific antigens or modulate immune pathways may alleviate neuroinflammation in conditions such as AD, PD, and ALS.

Against this backdrop, the "T Cells in the Brain" symposium, held at Columbia University in January 2024, provided a platform for leading experts in the field to convene and discuss the latest advancements in T cell research in neurologic diseases (Figure 1). This article aims to summarize the key insights and discussions from the symposium,

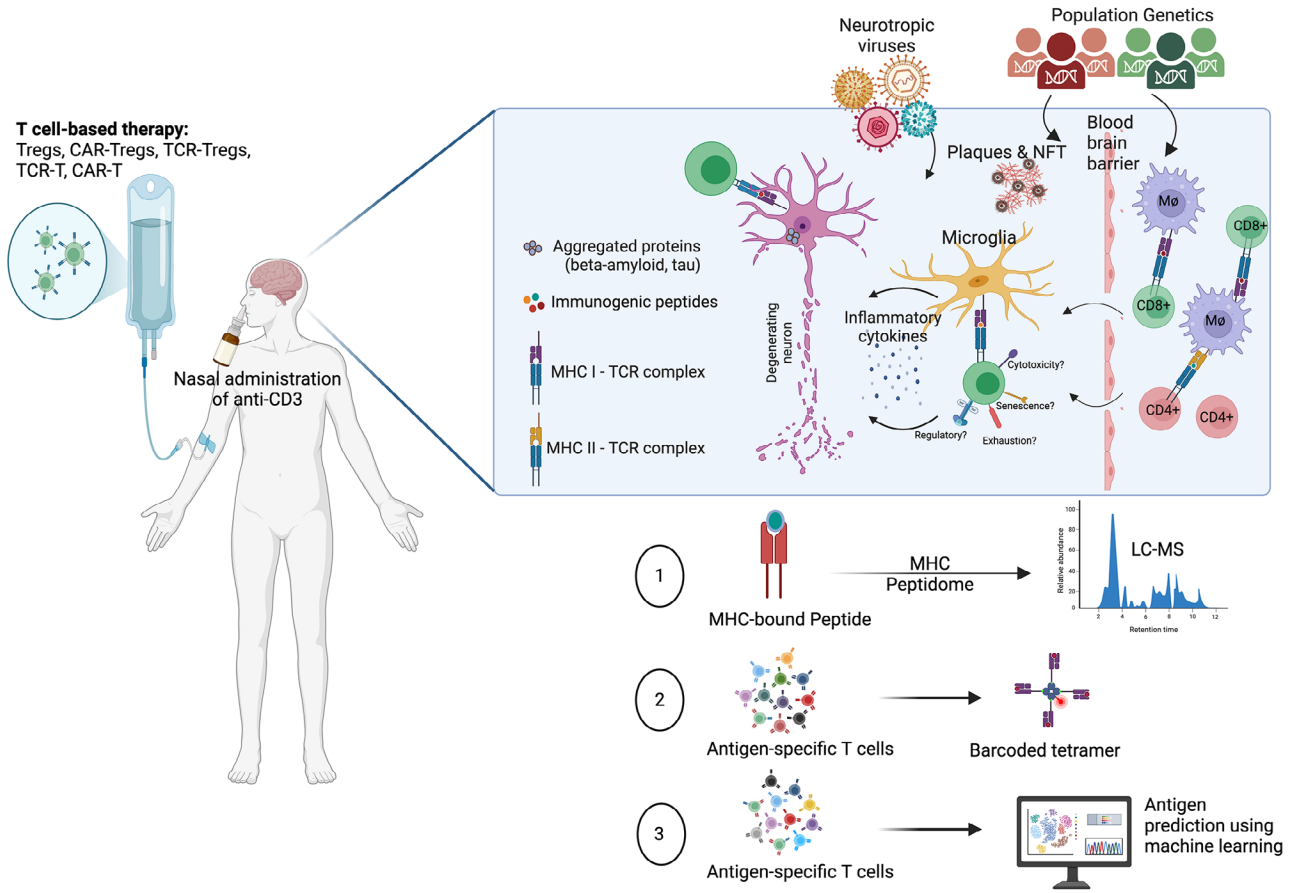

FIGURE 1 Schematic illustration of research topics presented at the T Cells in the Brain 2024 symposium, highlighting the discovery of antigens presented on MHC class I and II molecules in the context of neurodegenerative diseases, and the identification of clonally expanded T cells, their phenotypes, and antigen specificity using single-cell RNA/TCR sequencing (scRNA/TCR-seq) and TetTCR-seqHD. Studies cover two antigen types: (1) self-antigens potentially derived from aggregated proteins, such as amyloid beta and tau in AD, alpha-synuclein in PD, and TDP-43 in ALS; and (2) non–self-antigens, including microbial antigens such as herpesviruses (e.g., HSV-1, associated with AD) and bacteria (e.g., Porphyromonas gingivalis, also linked to AD). These antigens are processed by brain-resident cells expressing MHC molecules: microglia, which express both MHC class I and II, and neurons, which predominantly express MHC class I. Antigen presentation leads to the recruitment of peripheral T cells to the brain border and parenchyma, where they undergo clonal expansion and activation. The cascade is modulated by genetic variants, particularly within the MHC locus, which impact immune surveillance and antigen processing. Finally, therapeutic approaches targeting T cells are discussed, including the use of regulatory T cells (Tregs) and nasal administration of anti-CD3 monoclonal antibody (foralumab) to promote immune tolerance and potentially modulate neuroinflammation in neurodegenerative diseases. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CAR, chimeric antigen receptor; HSV-1, herpes simplex virus 1; LC-MS, liquid chromatography mass spectrometry; MHC, major histocompatibility complex; PD, Parkinson's disease; TCR, T cell receptor; TDP-43, TAR DNA-binding protein 43.

highlighting the potential implications for health-care delivery, disease management, and patient outcomes in the context of neuroimmunology. Owing to the continued growth in this field, the symposium has become an annual event (see http://tcellsbrain.org) to capture the latest progress in identifying T cell phenotypes in neurological diseases.

2 | ADVANCED METHODS FOR ANALYZING ANTIGEN-SPECIFIC T CELLS

A distinct feature of T cells is their ability to rearrange and recombine segments of TCR genes to generate a vast repertoire of potential protein sequences. This allows T cells to recognize virtually any foreign pathogen. Each T cell is engineered to recognize a specific antigen, usually a peptide fragment bound to the major histocompatibility complex (MHC) on an antigen-presenting cell. Profiling the TCR repertoire, therefore, theoretically opens the door to interrogate an individual's lifetime infection and exposure history, which may be especially relevant for understanding immune system involvement in AD and other neurodegenerative diseases. In AD, antigen-specific T cell responses could contribute to neuroinflammation and interact with hallmark proteins like amyloid beta (Aβ) and tau. Unfortunately, antigen specificity for the majority of TCR sequences is currently unknown.[13]

Recent advancements in immunology have ushered in a new era of precision and depth in the analysis of antigen-specific T cells. Cutting-edge methods such as scRNA/TCR-seq,[9] MHC peptidome,[14] mass cytometry, and high-dimensional flow cytometry[15] enable researchers to dissect the heterogeneity and functional profiles of T cell

populations with unprecedented resolution. These techniques can identify rare antigen-specific T cell subsets, elucidate their dynamics within complex immune landscapes, and offer invaluable insights into their role in health and disease. In this context, startups like TScan Therapeutics and 3T Biosciences leverage TCR repertoire data to advance immunotherapy for cancer with a robust pipeline of TCR-engineered T cell therapies (TCR-T).[16] By integrating cutting-edge TCR sequencing technology with machine learning and bioinformatics, both companies aim to harness the full potential of the TCR repertoire, creating personalized, potent, and safe immunotherapies and transforming the treatment landscape for patients with cancer and inflammatory diseases.

2.1 | Deciphering the MHC peptidome in neurodegenerative diseases: insights from the human brain

The MHC system, known as the human leukocyte antigen (HLA) in humans, has been linked to susceptibility for a number of neurodegenerative diseases, including AD, PD, and ALS.[17] The proteins encoded by the MHC present antigens to T cells. It is now possible to comprehensively profile the collection of MHC-binding peptides, known as the MHC peptidome, in specific tissues or cell types. In research carried out by Dr. Stern and others,[14,18] MHC peptidome studies have emerged as powerful tools for uncovering the repertoire of antigens targeted by T cells in various diseases including neurodegenerative diseases. For instance, clonally expanded T cells that infiltrate the CNS and contribute to neuroinflammation have been reported in AD and other neurodegenerative diseases. Recent fine-mapping studies of the HLA locus have revealed a protective association of the HLA-DRB1*04 subtype with AD, PD, and possibly ALS. This HLA subtype was linked to fewer neurofibrillary tangles and lower cerebrospinal fluid (CSF) tau levels, and its preferential binding to the aggregation-prone acetylated K311 tau PHF6 peptide suggests that an adaptive immune response against aggregated tau could be protective against neurodegenerative diseases.[10] Studies of the MHC peptidomes of inflamed brain tissue from AD, PD, and ALS patients, in addition to islet cells in human type 1 diabetes and liver cells in a mouse model of metabolic disease, were presented that identified many new disease-associated T cell epitopes, including several non-mutational neoantigens resulting from tissue-specific physiological changes[18] (Stern et al., unpublished data).

2.2 | High-throughput and high-dimensional profiling of antigen-specific T cells

High-throughput and multi-dimensional tetramer screening techniques enable the rapid, sensitive, and comprehensive identification of antigen-specific T cells within patient samples. Recently, clonally expanded T cell subsets have been identified in several neurodegenerative and inflammatory diseases including ALS[8] and inclusion body myositis (IBM)[19] that are unseen in healthy controls. The antigen specificity of these cells has not yet been characterized, and the full nature in which these cells contribute to disease pathogenesis and progression remains a mystery. A shared pathological hallmark across ALS and IBM is the mis-location and aggregation of TDP-43.[20] Recent studies have shown that the dysfunction of TDP-43, a ubiquitously expressed RNA-binding protein involved in repression of cryptic exons, results in the expression of a set of de novo proteins that are unique to TDP-43 proteinopathies and missing in healthy controls.[21] These cryptic peptides become plausible targets for clonally expanded CD8+ T cells. Dr. Jiang's laboratory used a high-throughput and a multidimensional single cell profiling approach, TetTCR-seqHD,[22] to comprehensively profile the T cell populations specific to cryptic exon epitopes resulting from TDP-43 dysfunction from ALS and IBM donors. They identified several activated and clonal CD8+ T cell populations that could recognize cryptic epitopes and be functionally stimulated by them (Chizari et al., unpublished data).

2.3 | Prediction of T cell epitopes using fine-tuned protein structure prediction networks

Prediction of TCR specificity from sequence alone is a grand challenge problem in computational immunology. State-of-the-art approaches trained on databases of TCR–epitope pairings are able to recognize new TCRs that bind to characterized epitopes, but these approaches have not demonstrated robust generalization to unseen epitopes not present in the training data.[23] A major obstacle to generalizable prediction with machine learning methods is the current scarcity of experimentally validated TCR–epitope pairings. 3D structural modeling of TCR–epitope interactions represents an alternative to sequence-based prediction that leverages recent advances in protein structure prediction networks[24] and may require less training data. Indeed, Dr. Bradley's laboratory has found that a fine-tuned variant of the AlphaFold[24] network has significant predictive power for TCR epitope assignment.[25] With continued advances in protein structural modeling,[26] we are optimistic that it may become possible to infer the antigen specificity of individual T cells from their TCR sequences, providing valuable insights into the antigenic targets driving immune responses in human diseases. A more detailed understanding of antigen-specific T cell responses may aid in precision medicine approaches for autoimmunity, cancer, age-related chronic conditions, and more.

2.4 | Polyspecific CD8+ α/β T cells responding to multiple viral antigens

Recent studies have identified T cells expressing TCRs that can respond to multiple unrelated viral antigens.[27] These T cells are believed to serve as a first line of defense against infections, providing a crucial time window for the development of a more specific and efficient T cell response against pathogens.[27] However, due to their broad response spectrum, these TCRs may also recognize autoantigens, potentially

contributing to autoimmune diseases. This is especially pertinent to brain autoimmunity, as CNS T cells drain via meningeal lymphatics to cervical lymph nodes (LNs),[28] which are also involved in responses to oropharyngeal infections. This connection is particularly relevant in conditions such as multiple sclerosis (MS) and pediatric autoimmune neuropsychiatric disorders (PANDAS), which are associated with Epstein–Barr virus (EBV) or streptococcal infections that cause major oropharyngeal inflammation. Notably, Dr. Klatzmann's laboratory has recently demonstrated that relapses in MS are preceded by the expansion of these polyspecific T cells (Klatzmann et al., unpublished data). Further research should investigate how viral reactivation of polyspecific T cells might trigger or exacerbate immune-related brain diseases.

3 | MICROBIAL INFECTIONS AS A RISK FACTOR FOR AD

In recent years, mounting evidence has suggested a potential role of infectious agents in the pathogenesis of several neurodegenerative diseases including AD.[29] The exploration of neurotropic viruses, bacteria, and parasites as potential etiological factors has gained significant attention, offering new insights into the complex interplay between infectious agents and neurodegeneration. Recent advances in genomic sequencing and bioinformatics have enabled researchers to characterize the virome and microbiome of the CNS with unprecedented depth and resolution.[30,31] Metagenomic sequencing of brain tissue and CSF samples has revealed the presence of diverse microbial communities, providing valuable insights into the composition and diversity of neurotropic microbes in health and disease.[32] Understanding the complex interactions between infectious agents and the host immune system is crucial for elucidating disease mechanisms and identifying novel therapeutic targets.

3.1 | Pathogens, microglia, and AD

Studies have implicated various neurotropic viruses, including herpesviruses (such as herpes simplex virus type 1 [HSV-1] and human herpesvirus 6), as well as neurotropic bacteria (such as Chlamydia pneumoniae) and parasites (such as Toxoplasma gondii), in the pathogenesis of AD (Figure 2). These microbes have been detected in *post mortem* brain tissue, CSF, and peripheral blood of AD patients, suggesting their potential involvement in disease pathology. The immune system protects the brain from neuroinvasive infectious agents which increase susceptibility to AD, including HSV-1.[33] In vivo murine studies have demonstrated that microglia are the main protectors of the CNS by producing a type I interferon response.[34] Interestingly, epidemiological studies demonstrate an interaction between AD genetic associations and HSV-1 in susceptibility to AD.[33] Mutations in apolipoprotein E (*APOE*) and paired immunoglobulin-like type 2 receptor α (*PILRA*), genes highly expressed in microglia and implicated in microglia metabolism have been shown to modulate the association of HSV-1 and AD.[35] This pathogen genetic variation interaction may be useful in the personalization of therapeutics for AD.

The potential implications of neurotropic microbes in the pathogenesis of AD extend beyond direct neuronal damage to include neuroinflammation, immune dysregulation, and disruption of synaptic function. Infectious agents may trigger aberrant immune responses and chronic inflammation within the CNS, contributing to the accumulation of Aβ plaques and tau tangles, hallmark features of AD pathology. Moreover, microbial infections have been implicated in the disruption of blood–brain barrier integrity, facilitating the entry of peripheral immune cells and exacerbating neuroinflammatory processes. Further research by Dr. Bradshaw and others into the infectious etiology of AD holds promise for the development of targeted interventions aimed at preventing or slowing disease progression.

3.2 | The role of advanced age in recovery from neurotropic coronavirus infection

The contribution of CD8+ T cells to cognitive function after viral infection has been an area of increasing interest, especially in the wake of the COVID-19 pandemic.[36] Although primarily a respiratory infection, patients infected with SARS-CoV-2, as well as other epidemic and seasonal coronaviruses, often present with neurologic symptoms, some continuing long after viral clearance as a persistent symptomatic phase termed "long COVID." Advanced age increases the risk of severe acute disease, as well as incidence of long COVID. Dr. Funk presented research from her lab using a murine coronavirus, mouse hepatitis virus strain A59 (MHV-A59), which was inoculated intranasally to produce a respiratory infection that disseminated to the brain. Results showed that aged animals harbored more activated CD8+ T cells within their brains but reduced viral specificity of those CD8+ T cells. This correlated with spatial learning impairment in aged animals, which also showed increased neuronal cell death and reduced neuronal regeneration in the aged hippocampus. Using primary cell culture, data showed that activated CD8+ T cells induce neuronal death, independent of antigen specificity. Together, these results support the evidence that CD8+ T cells in the brain directly contribute to cognitive dysfunction after coronavirus infection in aged individuals.[37]

3.3 | Antiviral therapy: valacyclovir treatment of AD trial

In AD patients, the presence of HSV-1 in the brain is notably higher compared to those with normal cognitive function, correlating with cognitive decline.[38] Studies in neuronal cultures have shown that HSV-1 infection prompts the formation of Aβ and tau proteins, processes mitigated by antiviral drug administration.[39] Ongoing clinical trials led by Dr. Devanand, namely Valacyclovir Treatment of Alzheimer's Disease (VALAD, a 78-week trial in AD) and Valacyclovir Treatment for Mild Cognitive Impairment (VALMCI; a 52-week trial for mild cognitive impairment [MCI]), are underway to evaluate the efficacy of

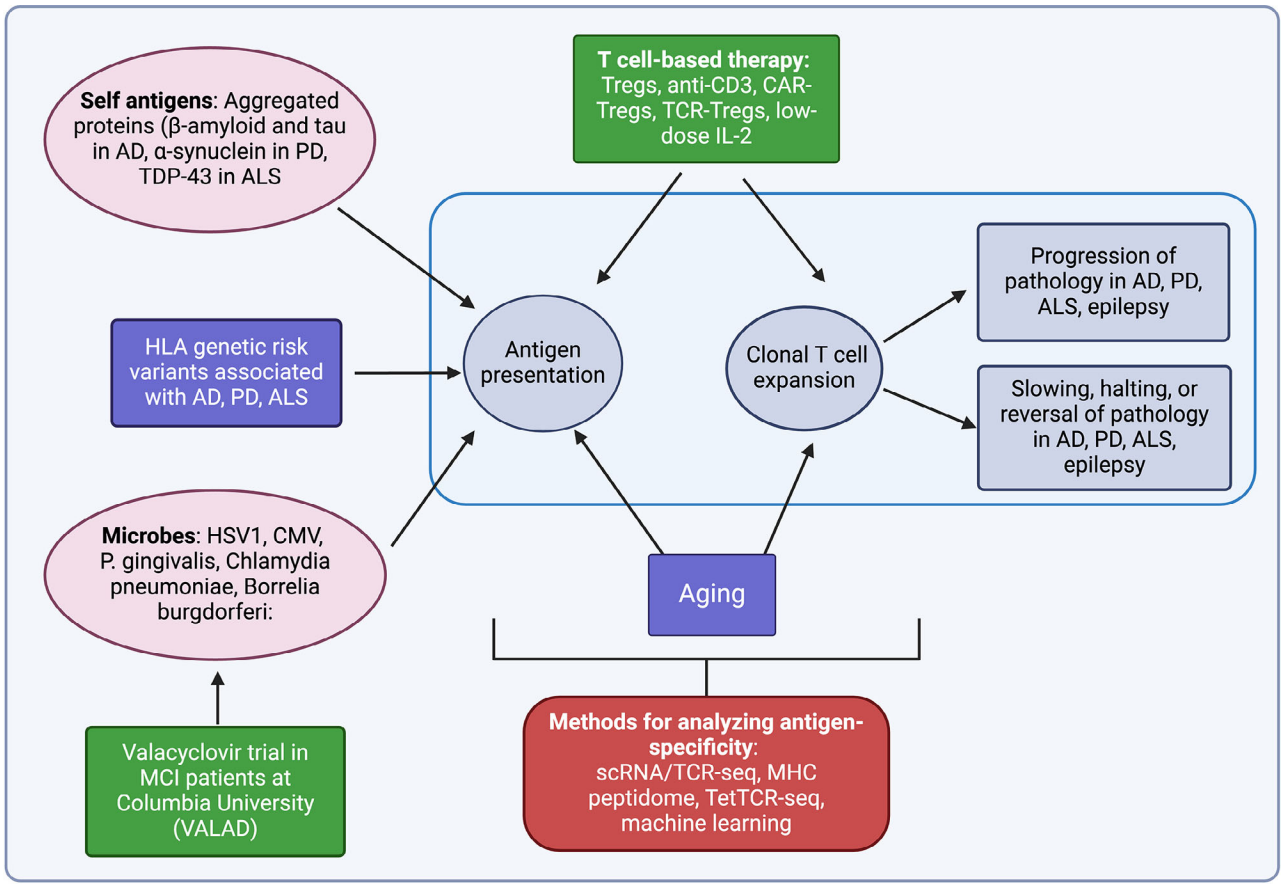

FIGURE 2 Schematic diagram of topics discussed at the T Cells in the Brain 2024 symposium. HLA genetic variants linked to neurodegenerative diseases, such as AD, PD, and ALS, modulate MHC molecules that play key roles in antigen presentation. These MHC molecules present disease-associated self-antigens (e.g., Aβ and tau in AD, α-synuclein in PD, and TDP-43 in ALS) as well as non–self-antigens, including microbial antigens from herpesviruses and other microbes, leading to T cell recruitment to the CNS and clonal expansion of disease-specific T cell phenotypes. Aging, a major risk factor for neurodegenerative diseases, exacerbates immune dysfunction and immunosenescence, further influencing T cell behavior in the CNS. To characterize T cell antigen specificity and phenotypes in these diseases, advanced techniques are used, including single-cell RNA sequencing (scRNA-seq) and T cell receptor sequencing (TCR-seq) for immune profiling, MHC peptidomics to identify CNS antigens, and tetramerized TCR sequencing (TetTCR-seq) to assess T cell reactivity. Clinical trials are underway to inhibit detrimental T cell responses, using strategies such as autologous and allogeneic Tregs, TCR-engineered Tregs (TCR-Tregs), CAR-Tregs, anti-CD3 monoclonal antibodies, and low-dose IL-2 to restore immune homeostasis. Specifically targeting microbial infections, Columbia University researchers are evaluating the efficacy of valacyclovir in the Valacyclovir Treatment of Alzheimer's Disease (VALAD) trial, a randomized, double-blind, placebo-controlled study, to assess whether antiviral treatment can mitigate neuroinflammation and slow disease progression. Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; HLA, human leukocyte antigen; MHC, major histocompatibility complex; PD, Parkinson's disease; TDP-43, TAR DNA-binding protein 43.

valacyclovir compared to a placebo in HSV seropositive patients with mild to moderate AD or MCI.[40] These trials will monitor changes in biomarkers such as Aβ and tau via positron emission tomography imaging to assess treatment outcomes in addition to assessment of changes in cognition and function (Figure 2).

4 | DECODING CENTRAL AND PERIPHERAL IMMUNE RESPONSES IN NEUROLOGICAL DISORDERS

The third session addressed the latest developments in single-cell transcriptomic analysis of immune cells and brain-resident cells. Our understanding of the spatial and temporal phenotype of immune cells in both health and disease has been revolutionized by advancements in single-cell genomic technologies, encompassing techniques such as scRNA/TCR-seq, B cell receptor (BCR) sequencing, assay for transposase-accessible chromatin with sequencing (ATAC-seq),[41] and other epigenetic analyses. These cutting-edge methodologies enable the high-resolution profiling of individual immune cells, unraveling the heterogeneity and dynamics of immune cell populations within complex tissues. By characterizing the gene expression profiles, receptor repertoires, chromatin accessibility, and epigenetic landscapes of immune cells at the single-cell level, researchers can dissect the functional states and lineage trajectories of immune cell subsets in response to physiological cues or pathological stimuli.

This comprehensive understanding of immune cell heterogeneity and plasticity provides valuable insights into the mechanisms underlying immune-mediated diseases, including cancer, autoimmune disorders, and infectious diseases, thereby paving the way for the development of targeted immunotherapies and precision medicine approaches (Figure 2).

4.1 | Human immunity in space and time

As immune cells travel through the body, they often encounter pathogens, cognate antigens, cytokines, chemokines, and other signals. These signals may encourage them to travel to target organs or areas of inflammation, or to undergo differentiation and development into unique, specialized populations. Aging is an important mediator of this process, and often involves accumulation of immune cells with memory, senescent, or late-differentiated phenotypes. Profiling immune cells at high resolution, in multiple organs and tissues, and across the lifespan helps us better understand the dynamic trajectory of immune cell function in health and disease. Dr. Farber has established a novel human tissue resource whereby her laboratory obtains multiple lymphoid and mucosal tissues from deceased human organ donors at the time of organ acquisition for lifesaving transplantation, through a collaboration with organ procurement organizations. Dr. Farber's laboratory has mapped the human immune system across multiple tissues and over age. For T cells, the majority subset in mucosal sites such as lungs and intestines is tissue-resident memory T cells (TRMs), which is also the predominant subset in the brain. TRMs exhibit distinct phenotypes and gene expression programs that enable their long-term maintenance and exhibit the capacity for both pro-inflammatory and regulatory functions along with site-specific functions and adaptations. TRMs are generated to site-specific pathogens and can also localize in lymphoid organs in response to vaccines. Over age, TRMs are maintained but lose in situ functionality in barrier sites. These results on human T cells in non-diseased sites can serve as a new baseline for interpreting disease pathologies in autoimmunity and for characterizing immune infiltration into inflammatory sites.

4.2 | The landscape of T cell immunity in PD

The progressive neurodegeneration in PD is characterized by regional heterogeneity. Recent evidence implicates the adaptive immune response in disease pathogenesis; however, how T cell pathology relates to the regional variability in neurodegeneration is unknown. Dr. Dalahmah's laboratory set out to explore the properties of T cells in the brain regions where neurons degenerate and analyzed the identities and interactions of T cells in PD using *post mortem* brain tissue. They used single-nucleus RNA sequencing (snRNA-seq),[41] spatial transcriptomics, and TCR sequencing. They identified that T cells in the substantia nigra of PD brain donors exhibit a CD8+ resident memory phenotype, increased levels of clonal expansion, and disease-associated cell–cell interactions involving T cells, astrocytes, and myeloid cells.[42] These findings nominate targeting disease-associated cell networks as a potential therapeutic strategy to block neurodegeneration in PD.

4.3 | Peripheral immune cell phenotypes in medically refractory epilepsy

Epileptic seizures are associated with blood–brain barrier disruption, which can induce infiltration of peripheral immune cells into the CNS and activation of circulating immune cells. These findings have been confirmed using epilepsy animal models, and by analysis of surgical specimens from human epilepsy patients. In a study led by Dr. Sarkis in collaboration with Dr. Elyaman's group, scRNA/TCR-seq was performed on peripheral blood mononuclear cells, including cells from medically controlled and medically refractory epilepsy. Sequencing was also performed on immune cells from resected brain tissue in several medically refractory patients. Epilepsy patients had lower proportions of several innate and adaptive immune cell types. Clonally expanded T cells, mostly CD8+ T effector memory, were found in the blood and brain tissue. Cell–cell interaction analysis showed stronger P-selectin signaling in epilepsy. Immune cell populations also were affected by common anti-seizure medications, confirming some of their immune-modulatory properties.

4.4 | Unraveling phenotypic variations and TCR profiles in sporadic versus familial ALS

ALS is a disease in which patients suffer continuous loss of neurons that control muscle, leading to an inability to voluntarily move, speak, chew, or breathe. More than 5000 people in the United States are diagnosed with ALS each year, but because of the fatal nature of this neurodegenerative disease, only ≈ 16,000 Americans are living with ALS at any given time. Currently there is no meaningful treatment for ALS. Human and experimental studies reported a detrimental role of the immune system in neurodegeneration observed in the ALS brain and spinal cord. Recent clinical trials in ALS, including our own expanded access program (EAP) at Columbia University Medical Center, are leveraging immune cell–based therapies using suppressor lymphocytes to treat sporadic forms of ALS (see section 5.1). While this approach is promising to tame exaggerated inflammation in the CNS of ALS patients, this approach may non-specifically compromise the patient's immune system and increase patients' susceptibility to infectious diseases and cancer. The ongoing research effort in Dr. Elyaman's laboratory focuses on characterization of the TCR repertoire and MHC peptidome in sporadic and genetic ALS patients to identify antigen-specific immune responses using peripheral and CNS-infiltrating immune cells. This technology will help identifying TCR clones and their cognate antigens to the end goal of engineering precision T cell–based therapies that target specifically proteins involved in ALS pathogenesis and pose a lower risk of general immunosuppression.

5 | REVOLUTIONIZING NEURODEGENERATIVE DISEASE TREATMENT: THE ERA OF IMMUNOTHERAPIES

Modulating immune cells as a treatment strategy was once reserved for diseases classically considered immune mediated. We now understand the role of the immune system in shaping the course of a variety of conditions, and immunotherapy has progressed accordingly. While the earliest examples of immunotherapy involved vaccination against pathogenic microbes, vaccine technology has found application in non-infectious diseases as well. Vaccination against Aβ remains an active area of research and clinical development, despite several failed clinical trials in the past.[43] Several recently approved AD immunotherapies are antibodies that bind to amyloid plaques. While effective in reducing amyloid buildup, these therapies can also lead to brain swelling that can become fatal.[44] This has led other companies to opt for a more conservative approach, such as targeting the microglial Trem2 receptor to potentiate immune responses to amyloid plaque in CNS-resident cells.[45] Checkpoint inhibition, an approach originally developed to prevent cancer cells from evading the immune system, may help potentiate the immune response to neurological conditions as well.[46] As multiple preclinical models and clinical trials have shown us, safe and effective immunotherapy must mount a sufficient response, but avoid excessive activation that can lead to damage.

The final session of the symposium, titled "Revolutionizing Neurodegenerative Disease Treatment: The Era of Immunotherapies," showcased the latest advances in using immunotherapies for the treatment of neurodegenerative diseases. Dr. Neil Shneider and Dr. Howard Weiner, two renowned experts in the field, presented data from ongoing clinical trials focusing on regulatory and anti-inflammatory T cells in patients with ALS and MS, respectively (Figure 2).

5.1 | Investigational new drug application for CK0803, a T regulatory cell therapy for ALS

Dr. Neil Shneider discussed encouraging early data from the Regulatory T Cells for Amyotrophic Lateral Sclerosis (REGALS) clinical trials, an ongoing multicenter study at the Eleanor and Lou Gehrig ALS Center at Columbia University Irving Medical Center (CUIMC), leveraging cord blood–derived regulatory T cells (Tregs) provided by Cellenkos, Inc. Tregs, known for their immunosuppressive capabilities, are being explored for their potential to counter neuroinflammation in ALS, a disease in which immune dysregulation is increasingly recognized as a key factor. REGALS is being conducted across Columbia University in New York, and the Michael E. DeBakey VA Medical Center and Baylor College of Medicine, both in Houston.

In the phase 1 REGALS trial (NCT05695521), a second cohort of patients with ALS are now receiving CK0803 Treg cell therapy, following a positive recommendation from the data safety monitoring board.[47] The study's primary goals are to establish the safety and tolerability of repeated doses of CK0803, alongside a combined assessment of function and survival (CAFS) based on ALS Functional Rating Scale-Revised (ALSFRS-R) scores and survival time. A secondary endpoint includes the measurement of neurofilament light chain levels in serum and CSF as a marker of preliminary efficacy.

Dr. Shneider presented preliminary data suggesting that Treg-based immunotherapies could help attenuate neuroinflammation and delay disease progression. While these results are promising, the therapeutic benefits of Tregs in ALS remain to be confirmed in larger studies. Limitations of this therapeutic approach include the challenges of achieving consistent therapeutic efficacy, given that allogenic Tregs may not persist long enough to provide sustained therapeutic benefits. Moreover, the long-term effects of allogenic Treg therapy are not well understood. There could be unwanted immune suppression that might increase susceptibility to infections or other immune-related complications. Nonetheless, these immunomodulatory therapies could provide a new avenue for addressing immune-related aspects of ALS and improving patient outcomes if further validated.

Tregs are also a potential therapeutic approach for AD due to their ability to modulate immune responses and reduce inflammation. In AD, chronic neuroinflammation is thought to contribute to neuronal damage and cognitive decline. Tregs may help mitigate this by suppressing pro-inflammatory immune activity in the brain, protecting neurons from inflammatory damage. Early AD mouse studies suggest that Treg-based therapies could help reduce amyloid plaque accumulation and neuroinflammation, key pathological features of AD.[48,49] However, other studies demonstrated that Tregs depletion is beneficial in AD mice.[50] More research is needed to determine the feasibility, safety, and efficacy of using Tregs to treat AD patients, especially given challenges in delivering Tregs effectively to the brain.

5.2 | Nasal Anti-CD3 mAb induces Tregs that dampen microglial activation and treat neurologic diseases including MS, AD, and ALS

In his presentation, Dr. Howard Weiner provided insights into the use of anti-inflammatory T cell therapies in patients with MS. MS is characterized by autoimmune-mediated demyelination and neuroinflammation, and strategies aimed at modulating T cell responses have emerged as promising therapeutic approaches. Dr. Weiner discussed ongoing clinical trials targeting anti-inflammatory T cell subsets, such as regulatory Th2 cells and Tr1 cells, to suppress autoimmune responses and promote tissue repair in MS patients. Preliminary data from these trials have shown encouraging results, including reductions in neuroinflammatory markers and improvements in clinical symptoms, suggesting that T cell–based immunotherapies could serve as effective, disease-modifying treatments. However, challenges remain, such as ensuring consistent efficacy across patients and avoiding side effects from non-specific immune modulation.

Dr. Weiner also briefly addressed the potential application of nasal anti-CD3 antibody therapy as an innovative approach to modulate T cell responses in neurodegenerative diseases, specifically AD. Anti-CD3 antibodies, when administered intranasally, can activate regulatory T cells peripherally, including within gut-associated lymphoid

tissue, without requiring direct CNS access. This activation of peripheral regulatory T cells has shown promise in preclinical studies for reducing neuroinflammation and Aβ plaque burden in AD mouse models, likely through the modulation of peripheral immune responses that indirectly influence the brain's inflammatory environment.[48,49] The intranasal delivery of anti-CD3 is a non-invasive method that could provide a safer alternative to direct CNS immunotherapy, as it minimizes the risks associated with crossing the blood–brain barrier. This approach is particularly appealing for AD, in which immune dysregulation and chronic neuroinflammation contribute to disease progression.

Overall, the presentations by Dr. Neil Shneider and Dr. Howard Weiner underscored the growing interest in harnessing the immunoregulatory properties of T cells for the treatment of neurodegenerative diseases. By leveraging the complex interplay between the immune system and the CNS, these innovative immunotherapies offer new avenues for combating neuroinflammation, preserving neuronal integrity, and ultimately improving clinical outcomes for patients with neurodegenerative disorders.

6 | FUTURE DIRECTIONS

The increased focus on how the adaptive immune system, particularly T cells, interacts with the nervous system has accelerated advances in our understanding of neurological diseases. Despite this, many questions remain unanswered, especially when it comes to identifying antigen-specific T cells within the brain. In AD, the discovery of disease-associated antigen-specific T cells could open the door to targeted immunotherapies. Technologies such as scRNA-seq, paired with TCR repertoire analysis, have become essential for identifying TCR sequences linked to specific antigens. These techniques allow for the examination of T cells at an unprecedented resolution, offering insights into their role in disease progression. One promising approach is TCR sequencing, which provides detailed information about the diversity and clonality of T cells in the brain. Paired with antigen discovery platforms like MHC peptidome or multiplex tetramer staining, researchers can now trace T cell specificity to particular CNS-derived antigens. This growing catalog of antigen–TCR pairs can be crucial for understanding whether T cells recognize self-antigens (e.g., tau, amyloid, synaptic proteins), or foreign pathogens. A deeper understanding of these specificities would greatly benefit the development of antigen-specific immunotherapies.

Another crucial method is spatial transcriptomics, which provides a map of T cell interactions with brain-resident cells such as microglia and astrocytes and the consequence on neuronal health. By spatially resolving gene expression, researchers can determine whether infiltrating T cells promote neuroinflammation or support tissue repair and regeneration.

In chronic neurodegenerative diseases, it remains unclear whether T cells are driving pathology or simply responding to ongoing damage. Answering this question will likely require further development of humanized mouse models that replicate human neuroinflammatory conditions, coupled with advanced imaging tools such as in vivo two-photon microscopy. These models will be critical for manipulating T cell activity and observing real-time effects on brain pathology. In human studies, coupling neuroimaging with periodic examination of T cell phenotypes in peripheral blood in a longitudinal study design will help us map a timeline of T cell dysregulation versus pathological changes in neurodegenerative disease.

The role of viral infections in neurodegenerative diseases, especially in the context of aging, further complicates the picture. T cells that combat viral infections may become senescent over time, leading to either ineffective viral clearance or a shift toward chronic, pro-inflammatory states. Studying this aspect will involve techniques like viral barcoding and epitope mapping, which allow researchers to trace T cell responses to viral pathogens within the brain.

Ultimately, refining our technological toolkit will be essential for therapeutic development. The ability to selectively modulate T cell function—using tools such as engineered TCRs or chimeric antigen receptor T cells—could lead to treatments that either dampen harmful T cell responses or enhance protective immunity in AD and other neurodegenerative diseases.

Advanced T cell phenotyping and detection of antigen-specific responses could provide powerful biomarkers for early diagnosis, disease progression, and therapeutic response in AD. Profiling distinct T cell populations and identifying AD-specific antigens may reveal immune signatures associated with the onset and progression of the disease, including interactions with hallmark proteins like Aβ and tau. Such biomarkers could improve our ability to detect AD before significant neurodegeneration occurs, track disease advancement more accurately, and monitor patient response to targeted therapies, ultimately aiding in the development of precision medicine approaches for AD care.

In conclusion, the symposium provided a platform for researchers, clinicians, and industry stakeholders to exchange knowledge, share best practices, and foster collaborations in the field of biomedical research. The sessions highlighted the transformative potential of emerging technologies and innovative approaches in advancing our understanding of disease mechanisms and improving patient care. Moving forward, continued investment in research and development will be crucial to translating these advancements into clinical practice and addressing unmet medical needs.

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CONFLICT OF INTEREST STATEMENT

D.P. Devanand serves on scientific advisory boards for Eisai, GSK, Acadia and a data safety monitoring board for BioXcel. All other authors have no conflicts to disclose. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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