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Is Immunotherapy a Transformative Paradigm for Neurodegenerative Diseases?

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Abstract

Neurodegenerative diseases represent one of the greatest unmet medical challenges of the twenty-first century. Despite decades of research, available treatments for most neurodegenerative conditions remain largely symptomatic, offering limited impact on disease progression. Immunotherapy of such diseases refers to those therapeutic strategies that harness or modify the immune system to prevent, slow, or reverse neurodegeneration… but still do not tackle the root cause of the disease. These approaches mainly target misfolded or aggregated proteins, neuroinflammation, or immune dysregulation. In this article, I will initially provide a brief primer on the brain immune system, its components and functions, dysregulations and disorders, and the neuroimmune communication. This background will be followed by a description of the four types of immunotherapies as they apply to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis. I will then survey the recent corresponding clinical trials with a summary timeline and meanings of the associated readouts. Lastly, I will outline the regulatory landscapes of the (U.S.) Food & Drug Administration and the European Medicines Agency, contrast their respective actions about each neurodegenerative disease, and conclude by projecting the potential impacts of future regulatory decisions.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ARIA: Amyloid-related imaging abnormalities; BBB: Blood-brain barrier; BDNF: Brain-derived neurotrophic factors; bmAb: Bispecific monoclonal antibodies; CJD: Creutzfeldt-Jakob disease; CSF: Cerebrospinal fluid; CSFBB: Cerebrospinal fluid brain barrier; CNS: Central nervous system; DAM: Disease-associated microglia; (EU) EMA: European Medicines Agency; EU: European Union; FDA: (U.S.) Food & Drug Administration; GF: Growth factor; HD:

Huntington's disease (HD); mAb: Monoclonal antibody; MS: Multiple sclerosis; MRT: Microglia replacement therapy; NDD: Neurodegenerative diseases; NGF: Nerve growth factors; NfL: Neurofilament light; NFT: Neurofibrillary tangles; NT: Neurotransmitters; PD: Parkinson's disease; pAb: Polyclonal antibodies; PET: Positron emission tomography; SLYM: Subarachnoid lymphatic-like membrane; TNF: Tumor necrosis factor; Treg: Regulatory T-cell; TREM2: Triggering receptor expressed on myeloid cells 2 (TREM2); WBC: White blood cells.

Vaccines & Drugs Cited

AADvac1; Aβ42/40; ACI-24060; ACI-35.030; ACI-7104,056 (vac Svn); Aducanumab; Cova-302; Donanemab; DRL-AB; Interleukin; JNJ-2056; Lecanemab; Leqembi; MEDII-341; Natalizumab; Ocrelizumab; Posdinemab; Prasinezumab; p-tau217; p-tau231; Renternetug; Semorinemab; UB-312.

Diseases Mentioned

Alzheimer's disease; amyotrophic lateral sclerosis; Creutzfeldt-Jakob disease; Huntington's disease; multiple sclerosis; Parkinson's disease.

Keywords

Alzheimer's disease; Amyotrophic lateral sclerosis; Huntington's disease; Immunotherapeutic strategies; Immunotherapy; Multiple sclerosis; Neurodegenerative diseases; Neuroimmune system; Parkinson's disease.

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Recently, I advanced the theory that Alzheimer's and other neurodegenerative diseases are but runaway autoimmune diseases and have also outlined a path to the cure of Alzheimer's disease (see Fymat 2018-2025). In this view, for example, the hallmarks of Alzheimer's disease (beta-amyloid plaques, neurofibrillary tangles) may only be symptoms or consequences of this runaway phenomenon that only evidence the mechanism(s) of the disease process not its root cause. It is gratifying, therefore, to note that the above theory is, as of late, taking root accompanied by further theoretical and experimental research. In this article, I review the immunotherapy of neurodegenerative diseases, which refers to those therapeutic strategies that harness or modify the immune system to prevent, slow, or reverse neurodegeneration… but still do not tackle the root cause of the disease. These approaches mainly target misfolded or aggregated proteins, neuroinflammation, or immune dysregulation that contribute to diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), multiple sclerosis (MS), and Creutzfeldt-Jakob disease (CJD).

Introduction

Neurodegenerative diseases represent one of the greatest unmet medical challenges of the twenty-first century. Disorders such as AD, PD, ALS, and related proteinopathies are characterized by progressive neuronal loss, synaptic dysfunction, and irreversible clinical decline. Despite decades of research, available treatments for most neurodegenerative conditions remain largely symptomatic, offering limited impact on disease progression. The growing global burden of aging populations has therefore intensified efforts to develop disease-modifying therapies that target the underlying biological mechanisms of neurodegeneration.

Immunotherapy, also known as 'biological therapy' or' biotherapy', encompasses a diverse set of therapeutic strategies to harness or modify the immune system to prevent, control, or eliminate disease. In its application to cancer, immunotherapy refers to treatments designed to stimulate or guide the immune system to recognize

and fight disease, often by enhancing or restoring immune responses to eradicate malignant cells while sparing healthy tissue. A broader definition of immunotherapy applies beyond oncology, including strategies to stimulate or suppress immune activity against other diseases such as autoimmune disorders, infectious diseases, and allergies.

Over the past decade, immunotherapy has emerged as a possibly transformative therapeutic paradigm in neurodegenerative disease research. Both passive immunotherapies, such as monoclonal antibodies directed against disease-associated proteins, and active immunotherapies, including peptide-based vaccines, have advanced into late-stage clinical trials—most notably in AD. Regulatory approvals of anti-amyloid antibodies have marked a turning point, validating biomarker-driven approaches while simultaneously highlighting limitations related to modest clinical benefit, safety concerns, and disease stage at intervention. More recently, attention has shifted toward tau-directed immunotherapies and immune-modulatory strategies that may more closely align with neurodegeneration and clinical progression across multiple disorders.

Immunotherapy includes both passive methods like monoclonal antibodies that mark abnormal cells for immune destruction, and active methods such as vaccines, immune checkpoint inhibitors, adoptive cell transfer, and cytokine therapies. Immunotherapy is being applied to a wider range of conditions, improving outcomes for many patients, though responses can vary depending on disease type, genetic background, and environmental factors.

A converging body of evidence has established that abnormal protein aggregation and chronic neuroinflammation are central pathological drivers across neurodegenerative disorders. Misfolded proteins—including amyloid-β and tau in AD, α-synuclein in PD, and mutant or misprocessed proteins in ALS—accumulate and propagate in a prion-like manner, contributing to synaptic toxicity and neuronal death. In parallel, sustained activation of innate and adaptive immune responses, particularly involving microglia, astrocytes, and peripheral immune cells amplifies neurodegeneration rather than resolves it. These insights have provided a strong biological rationale for immunotherapeutic strategies aimed at enhancing pathological protein clearance, limiting their spread, and modulating maladaptive immune responses within the central nervous system (CNS).

This article is a comprehensive overview of immunotherapeutic approaches in neurodegenerative diseases, focusing on recent clinical trial outcomes, evolving biomarker and regulatory frameworks, and emerging strategies beyond amyloid targeting. We discuss the successes and challenges of current immunotherapies, compare disease-specific applications across AD, PD, and ALS, and explore future directions including combination therapies, earlier intervention, and personalized immune-based treatments. Together, these advances suggest that immunotherapy—while still evolving—has the potential to fundamentally reshape the treatment landscape of neurodegenerative diseases.

The next section will provide a brief primer on the brain immune system. This background will contribute to a better understanding of immunotherapy in general and in its applications.

A brief primer on the brain immune system

The brain immune system (or neuroimmune system) is a sophisticated, multi-layered network that not only defends against pathogens but also actively shapes the brain's structural development and daily function. It involves specialized cells like microglia (which are resident immune cells) and other immune cells located in the brain’s protective barriers (meninges, choroid plexus) that work with the CNS to defend against

pathogens, clear debris, and maintain brain health. However, dysregulation of the system can lead to neuroinflammation, cognitive issues, and neuropsychiatric conditions. It is a complex communication network where the brain influences immunity and immune signals impact brain function, affecting mood, cognition, and behavior.

Key components and functions

The neuroimmune system includes five components: microglia, astrocytes, the meningeal interface, localized sources, and mast cells, as further elaborated below:

1. **Microglia** - The primary resident defenders: Microglia are the "sentinels" of the brain, clearing dead cells and pruning synapses. Their activation can harm neurons. Making up about 10% of all CNS cells, they fulfill multiple functions:

• **Dual Roles:** In a healthy state, they perform "synaptic pruning"—removing weak or unnecessary connections to refine neural circuits—and secrete growth factors like brain-derived neurotrophic factors (BDNF) (or abrineurin) to support learning and memory. In humans, BDNF is a protein that is encoded by the BDNF gene. It is a member of the neurotrophin family of growth factors, which are related to the canonical nerve growth factors (NGF), a family which also includes NT-3 and NT-4/NT-5. Neurotrophic factors are found in the brain and the periphery.

• **Dynamic surveillance:** Their processes are in constant motion, scanning the environment for misfolded proteins (like amyloid-beta) or cellular debris to clear through phagocytosis.

• **Disease-associated microglia (DAM):** When faced with chronic injury or aging, microglia can shift into a "DAM" state, which can be neuroprotective initially but may become neurotoxic if over-activated, contributing to AD or PD.

• **Replacement therapy:** Emerging in 2026, microglia replacement therapy (MRT) is being tested in clinical trials to replace aged or genetically mutated immune cells with a fresh, healthy supply to treat neurodegenerative diseases.

2. **Astrocytes** - The immune coordinators: Historically viewed as support cells, astrocytes are now recognized as active immune effectors. Their functions are:

• **Maintenance of barriers** - blood-brain barrier (BBB) and cerebrospinal fluid -brain barrier (CSFBB): These crucial barriers regulate what enters the brain, with immune cells strategically positioned at these interfaces. They help regulate the permeability of the BBB, ensuring a shielded environment for neurons.

• **Neuroinflammation control:** They release cytokines and chemokines that direct microglial activity and can even act as "atypical" antigen-presenting cells to signal other parts of the immune system. Cytokines are any of several substances, such as interferon, interleukin, and growth factors (GF), which are secreted by certain cells of the immune system and influence other cells. Chemokines (or chemotactic cytokines) are a family of small cytokines or signaling proteins secreted by cells that induce directional movement of leukocytes as well as other cell types, including endothelial and epithelial cells. In addition to playing a major role in the activation of host immune responses, chemokines are important for biological processes, including morphogenesis and wound healing, as well as in the pathogenesis of diseases like cancers.

• **Phenotype switching:** Like microglia, they can adopt pro-inflammatory (A1) or anti-inflammatory (A2) phenotypes depending on the brain's needs.

3. **Meningeal interface** - The brain’s "border patrol": The meninges (membranes surrounding the brain) are the most immunologically diverse region of the brain, housing T-cells, B-cells, macrophages, and mast cells. These immune cells reside in the meninges (brain's covering) and dural sinuses, scanning for threats and responding to signals. Their functions include:

• **Immune surveillance:** These cells sample the CSF for antigens as it washes out of the brain.

• **Meningeal lymphatics** - lymphatic drainage: The meningeal lymphatics is a fluid system draining metabolic waste that also signals the immune system about infections. It signals antigens to the deep cervical lymph nodes, allowing the body's peripheral immune system to monitor brain health.

• **SLYM (subarachnoid lymphatic-like membrane):** A recently discovered fourth layer of the meninges, it acts as a physical barrier and a critical niche for immune cells to monitor fluid between the brain and the skull.

4. **Localized sources –** The skull bone marrow: Direct communication exists between the bone marrow in the skull and the brain via microscopic channels. Its function is to provide:

• **Emergency response:** This allows the brain to receive a rapid supply of immune cells (monocytes and neutrophils) during inflammation without waiting for them to travel through the general bloodstream.

5. Mast cells - The neuroimmune "bridge": Mast cells are located at the BBB and serve as rapid responders to both internal signals (like cytokines) and external allergens.

• **Cognitive modulation:** They release histamine, which influences social behavior, motivation, and wakefulness.

• **Cross-talk:** They communicate directly with microglia through tunneling nanotubes, allowing for instantaneous "alarm" signaling during an immune threat.

Neuroimmune communication

The above components of the neurosystem work together (so-called "neuroimmune communication") through the following processes:

• **Protection:** The system detects pathogens, initiates inflammation, and repairs damaged neurons.

• **Regulation:** Immune cells (like macrophages) in the meninges monitor brain fluids and alert the systemic immune system.

• **Brain-to-immune signaling:** The brain sends signals (e.g., through stress hormones or neural pathways) that can prime or suppress the immune system.

• **Immune-to-brain signaling:** Immune signals (cytokines, neurotransmitters) influence mood, sleep, cognition, and behavior, potentially leading to "brain fog" or neuropsychiatric symptoms.

Dysregulations & disorders

When neuroimmune communication defaults, the following dysregulations and disorders occur:

1. **Neuroinflammation:** Chronic or excessive immune activation in the brain, often triggered by injury, infection (like viruses), or chronic stress can damage neurons and impair function.

2. **Neuropsychiatric conditions:** Immune system signaling imbalances are linked to depression, anxiety, fatigue, and cognitive dysfunction.

3. **Neurodegenerative diseases:** Dysfunctional microglia and immune responses contribute to these diseases.

Immunotherapeutic Strategies

Immunotherapeutic strategies target the core pathological mechanisms of the neurodegenerative diseases of interest. Here, the emphasis is on approaches that have progressed to clinical development.

For example, in the case of AD, we will consider both passive immunotherapies, such as monoclonal antibodies directed against amyloid-β and tau, and active immunotherapies, including peptide-based and conformational vaccines designed to elicit endogenous antibody responses. In addition, we examine immune-modulatory approaches that target microglial activation, innate immune signaling pathways, and peripheral immune contributions to Alzheimer's pathology. While acknowledging the importance of genetic and non-immune therapeutic strategies, these are discussed only insofar as they intersect with immunological mechanisms or combination treatment paradigms.

We place special emphasis on biomarker-driven trial design, including amyloid and tau positron emission tomography (PET), CSF and plasma biomarkers, and their evolving role in regulatory decision-making. Preclinical mechanistic studies are referenced selectively to support clinical observations, but the primary focus remains on translational relevance, clinical efficacy, safety, and regulatory implications. By integrating biological rationale with clinical outcomes, we aim to provide a critical assessment of where immunotherapy currently stands and where it is most likely to advance.

Rationale

Neurodegenerative diseases share three common pathological features:

• Accumulation of misfolded proteins (e.g., amyloid-β, tau, α-synuclein).
• Chronic neuroinflammation mediated by microglia and astrocytes.
• Breakdown of immune tolerance and impaired clearance mechanisms.

Consequently, immunotherapy aims to:

• Enhance clearance of toxic protein aggregates.
• Reduce neuroinflammation, including halting prion-like spread.
• Modulate harmful immune responses while preserving protective ones.

Types of immunotherapies

There are essentially four types of immunotherapies, as further described below:

Passive immunotherapy (monoclonal antibodies)

A monoclonal antibody (mAb) is an antibody produced from a cell lineage made by cloning a unique white blood cell (WBC). All subsequent antibodies derived this way trace back to a unique parent cell. Monoclonal antibodies are identical and can thus have monovalent affinity, binding only to a particular epitope (the part of an antigen that is recognized by the antibody). In contrast, polyclonal antibodies (pAb) are mixtures of antibodies derived from multiple plasma cells lineages which each bind to their particular target epitope. Artificial antibodies known as bispecific monoclonal antibodies (bmAb) can also be engineered to include two different antigen binding sites on the same antibody. It is possible to produce monoclonal antibodies that specifically bind to almost any suitable substance - they can then serve to detect or purify it. This capability has become an investigative tool in biochemistry, molecular biology, and medicine. Monoclonal antibodies are used in the diagnosis of illnesses such as cancer and infections; they are also used therapeutically in the treatment of cancer and inflammatory diseases including importantly neurodegenerative diseases.

Passive immunotherapy consists in the administration of antibodies that target pathological proteins. Key examples of neurodegenerative diseases to which it has been applied include:

• Alzheimer's disease (AD):

o Anti-amyloid-β antibodies (Aducanumab, Lecanemab, Donanemab).
o Anti-tau antibodies (e.g., Semorinemab – investigational).

• Parkinson's disease (PD):

o Anti–α-synuclein antibodies (Prasinezumab – investigational).

• Amyotrophic lateral sclerosis (ALS) & Huntington's disease (HD):

o Antibodies targeting mutant proteins (largely experimental).

The advantages are precise targeting and dose control. The associated limitations are blood–brain barrier (BBB) penetration, amyloid-related imaging abnormalities (ARIA), and high cost and repeated dosing.

Active immunotherapy (vaccines)

Active immunotherapy stimulates the patient's immune system to produce antibodies. Examples are:

• Amyloid-β and tau vaccines in AD (e.g., AADvac1).
• Anti-α-synuclein vaccines in PD.

The challenges facing active immunotherapy are the risk of autoimmune reactions and the variable immune response in elderly patients.

Immune modulation and anti-inflammation

These approaches target innate and adaptive immune responses rather than specific proteins. They include:

• **Microglial modulation:** For example, TREM2 (triggering receptor expressed on myeloid cells 2) which is a protein that in humans is encoded by the TREM2 gene. TREM2 is expressed on macrophages, immature monocyte-derived dendritic cells, osteoclasts, and microglia, which are immune cells in the CNS. TREM2 has anti-inflammatory activities. It might therefore be a good therapeutic target.

• **Cytokine inhibition (TNF-α, IL-1β):** Tumor necrosis factor (TNF), formerly known as TNF-α, is a chemical messenger produced by the immune system that induces inflammation. TNF is produced primarily by activated macrophages but also in several other cell types (T-cells, B-cells, dendritic cells, and mast cells). It induces inflammation by binding to its receptors on other cells. It is a member of the tumor necrosis factor superfamily, a family of transmembrane proteins that are cytokines, chemical messengers of the immune system. Excessive production of TNF plays a critical role in several inflammatory diseases, and TNF-blocking drugs are often employed to treat these diseases. TNF is also implicated in the pathology of several diseases including cancer, liver fibrosis and, importantly, AD. However, TNF inhibition has yet to show definitive benefits.

• Regulatory T-cell enhancement.
This strategy is especially relevant in AD, PD, and ALS.

Cell-based immunotherapy

It employs regulatory T-cell (Treg) therapy to suppress neuroinflammation and stem cell–based immune modulation. While still largely experimental, cell-based immunotherapy is promising for diseases with strong inflammatory components.

Table 1 summarizes the above immunotherapeutic approaches in the case of NDDs:

Immunotherapy	Examples	Disease application	Medicines	Notes
Passive (monoclonal antibodies) **Advantages:** **- Precise targeting** **- Precise dose control** **Limitations: - BBB penetration - ARIA - High cost - Repeated dosing**	o Antiamyloid-β antibodies o Anti-tau antibodies o Anti–α-synuclein antibodies o Antibodies targeting mutant proteins	o **AD** o **AD** o **PD** o **ALS, HD**	- *Aducanumab* - *Lecanemab* - *Donanemab* - Semorinemab - Prasinezumab	Investigational Investigational Largely experimental
Active (vaccines) **Disadvantages:** **-Risk of autoimmune reactions** **-Variable immune response in elderly patients**	o Amyloid-β vaccines o Tau vaccines o Anti-α synuclein vaccines	o **AD** o **AD** o **PD**	- AADvac1 - AADvac1	
Immune modulation & anti-inflammation	o Microglial modulation o Cytokine inhibition o Regulatory T-cell enhancement	o **AD, PD, ALS** o **AD, PD, ALS** o **AD, PD, ALS**	o TREM2 o TNF-α, IL-1β	
Cell-based	o Treg cells o Stem cell			Largely experimental

Table 1: The four types of immunotherapies for neurodegenerative diseases

Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ARIA: Amyloid-related imaging abnormalities; BBB: Blood-brain barrier; PD: Parkinson's disease; TNF: Tumor necrosis factor; Treg: Regulatory T-cells; TREM: Triggering receptor expressed on myeloid cells.

Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ARIA: Amyloid-related imaging abnormalities; BBB: Blood-brain barrier; PD: Parkinson's disease; TNF: Tumor necrosis factor; Treg: Regulatory T-cells; TREM: Triggering receptor expressed on myeloid cells.

Disease-specific highlights

Alzheimer's disease

- Most advanced immunotherapy field.
- Anti-amyloid antibodies show modest slowing of cognitive decline.
- Tau immunotherapy may better correlate with disease progression.

Parkinson's disease

- Focus on preventing α-synuclein spread.

• Clinical benefits remain unproven so far.

Multiple sclerosis

• Most successful immunotherapy application.

• Includes monoclonal antibodies (e.g., Natalizumab, Ocrelizumab).

• Primarily targets immune-mediated demyelination rather than protein aggregation.

Amyotrophic lateral sclerosis & Huntington's disease

• Early-stage research.

• Immune modulation rather than direct antibody therapy may be more beneficial.

Key challenges

• Blood–brain barrier penetration.

• Timing of intervention (earlier is better).

• Balancing immune activation vs neurotoxicity.

• Patient heterogeneity and biomarkers for response.

Future directions

• Combination therapies (immunotherapy + gene therapy).

• Personalized immunotherapy based on biomarkers.

• Targeting prion-like protein propagation.

• Improved antibody engineering for CNS delivery.

In sum, immunotherapy represents a transformative but still evolving approach to neurodegenerative diseases. While clear disease-modifying success has been achieved mainly in MS and partially in AD, ongoing advances in antibody design, immune modulation, and early diagnosis may substantially expand its effectiveness across other neurodegenerative conditions.

Update on recent immunotherapy clinical trials on selected neurodegenerative diseases

The following is an update of recent clinical trials (2025-early 2026) on immunotherapy for selected neurodegenerative diseases, focusing on AD, PD, and ALS. These include vaccines, monoclonal antibodies, and immune-modulating therapies in various phases of development.

The following is an update of recent clinical trials (2025-early 2026) on immunotherapy for selected neurodegenerative diseases, focusing on AD, PD, and ALS. These include vaccines, monoclonal antibodies, and immune-modulating therapies in various phases of development. Many trials are moving into earlier disease stages (preclinical or early clinical) where immunotherapies might have greater impact before significant neurodegeneration has occurred. Active vaccines have generally shown acceptable safety in early trials, but long-term data remain limited. FDA Fast Track designations (e.g., for tau immunotherapies) reflect urgency due to unmet treatment needs.

Immunotherapies

Alzheimer's disease

Anti-tau active immunotherapies:

• **ACI-35.030 (JNJ-2056):** An active immunotherapy targeting pathological phosphorylated tau.

– Phase 1b/2a data published showed robust antibody responses and good safety/tolerability.

– This candidate is now being advanced into an ongoing Phase 2b "ReTain" trial in preclinical AD (tau pathology present but no symptoms).

• **Posdinemab:** A tau-targeting monoclonal antibody in Phase 2b "AuTonomy" study for early symptomatic AD.

– It and JNJ-2056 have both received U.S. FDA Fast Track designations—a regulatory pathway to speed development due to high unmet need.

Anti-amyloid therapy:

• **Lecanemab:** Real-world data (post-Phase 3) presented at AD/PD 2025 reinforce:

– Safety and efficacy in clinical practice.

– Results consistent with earlier Phase 3 (CLARITY-AD) findings showing reduction in amyloid and slowed cognitive decline.

In summary, tau-targeted immunotherapies are now in mid-stage trials, with regulatory acceleration, while anti-amyloid therapy continues to demonstrate real-world benefit.

Parkinson's disease

Active immunotherapy against α-synuclein:

• **ACI-7104.056 (VacSYn):** A phase 2 active immunotherapy vaccine targeting pathological α-synuclein in early PD.

– Interim data show strong immunogenicity, good safety, and stable CSF α-syn levels, which may reflect reduced pathological spread.

– Some interim biomarker and clinical signals suggest potential slowing of progression—supporting future pivotal trial planning.

Other PD immunotherapy approaches:

• Early funding and preparatory regulatory work are underway for immunomodulatory approaches focused on neuroinflammation and blood-brain barrier effects, though clinical trials are still planned rather than recruiting.

In summary: PD immunotherapy is still in phase 2, with encouraging interim biomarker signals but no late-phase registration data yet.

Amyotrophic lateral sclerosis

Immunomodulatory combination trials:

• COYA 302 (Phase 2b ALSTARS):

– Combines low-dose interleukin-2 (LD IL-2) and DRL-AB to enhance regulatory T-cell function and suppress neuroinflammation.

– This immunotherapy approach aiming to re-balance immune responses is now actively recruiting ~120 participants in the U.S. and Canada.

In summary: ALS immunotherapy is being tested in larger Phase 2 trials focused on immune regulation rather than protein-targeted vaccines or antibodies.

Table 2 summarizes the above key trials:

Disease	Therapy	Target	Phase	Key update
AD	ACI-35.030 / JNJ-2056	Tau	2b	o Strong immunogenicity o Ongoing registration-enabling trial
AD	Posdinemab	Tau-mAb	2b	o Fast track designation o Enrolling
AD	Lecanemab	Amyloid-β	Post 3	Real-world efficacy & safety data
PD	ACI-7104.056	α-synuclein vaccine	2	Interim biomarker & safety results
ALS	COYA 302	Immune modulation	2b	o Recruiting o Regulatory sites in US/Canada

Table 2: Summary of key clinical trials

Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; PD: Parkinson's disease.

Timelines and trial readout schedules

Below is a clear timeline and trial readout schedule for major immunotherapy programs in neurodegenerative diseases, highlighting when key results are expected and how these milestones fit into the broader landscape (AD, PD, ALS):

Alzheimer's disease

• ACI-35.030 (Anti-Tau active immunotherapy) — Phase 2b (ReTain)

- Large trial in preclinical AD (~500 participants) focused on cognitive decline and tau pathology.
- Duration: ~4 years of treatment with annual biomarker/PET scans.
- Interim analyses: Planned during the study; potential support for accelerated FDA filing depending on results.
- Final readout: Likely 2027–2028 (given the 4-year design).

Primary endpoints include cognitive composite scores and tau PET changes.

• ACI-24.060 (Anti-Amyloid vaccine) — Phase 1b/2

- Early immunogenicity and safety trial.
- Key biomarker readouts in 2026:
- 6-month amyloid PET scans (expected H1 2024 in initial report) but continued follow-ups extend into 2026.

These data will inform advancement into larger, later-phase studies.

• Remternetug (Anti-Amyloid mAb) — Phase 3 TRAILRUNNER-ALZ-1

- Targets a specific pyroglutamated form of amyloid-β.
- Completion: Expected by 2026.
- Outcomes to watch: Amyloid plaque clearance via PET; safety/tolerability, and time to complete plaque clearance metrics.

Positive results could lead to regulatory filings soon after.

• Other AD trials & approaches

- Some passive tau antibodies (e.g., Semorinemab) were discontinued due to negative Phase 2 results.
- Non-protein immunotherapies and immune modulators continue in development, but most are still in early phases.

Parkinson's disease

• ACI-7104.056 (Anti-α-syn active immunotherapy)

— Phase 2

- Designed to trigger antibodies against α-synuclein pathology.
- Safety/Immunogenicity update: Expected H2 2026 (per company guidance).
- Trial completion: Though final data may stretch into 2027–2028, interim biomarker results will inform later phase design.

• UB-312 and other α-syn vaccines — Phase Ib / II

- UB-312 (monoclonal peptide vaccine) is in a Phase Ib trial scheduled to complete by April 2025, but published data have not yet appeared.
- Expanded Phase II enrollment is planned, with completion timelines around 2028 based on adaptive trial design (conclusion projected January 2028).

• Passive α-syn mAbs

-MEDI1341 (monoclonal antibody) Phase II in multiple system atrophy (MSA) scheduled to conclude by August 2025, but results may emerge late in 2025–early 2026.

It should be noted that PD immunotherapies often use biomarkers (CSF α-syn levels, imaging, digital measures) rather than purely clinical endpoints early on, so readouts may be informational rather than definitive initially.

Amyotrophic lateral sclerosis

• COYA-302 (Immune Modulation Trial) — Phase 2b

- Combines low-dose IL-2 with DRL-AB to enhance regulatory T cell function and reduce neuroinflammation.
- Recruitment status: Active in U.S./Canada, but definitive outcome data are not yet available (trial still recruiting).
- Estimated completion: Likely late 2026–2027 based on enrollment targets and treatment duration.

It must be noted that ALS immunotherapy tends to focus on immune regulation rather than antigen targeting, and thus biomarker changes (e.g., T-cell function, inflammatory markers) will likely be earliest readouts before robust clinical efficacy data.

Table 3 summarizes the trials timelines and key readout to watch:

Year	AD trials	PD trials	ALS trials
2025	Remternetug Phase 3 completion expected	Some passive α-syn mAb data (e.g., MEDI1341)	UB-312 Phase Ib completion
2026	Safety/biomarker signals for ACI-24.060 continuing Remternetug full analysis likely	ACI-7104.056 immunogenicity update expected H2	ALS immune modulation data emerging (if enrollment completes)
2027-2028	Major efficacy readout for ACI-35.030 (Phase 2b)	ACI-7104.056 Phase 2 final data (projected)	ALS Phase 2b completion anticipated

Table 3: Clinical trials' summary timeline and key readouts

Readouts meanings

Early biomarker results

• Many trials first report changes in PET imaging, CSF biomarkers, or antibody titers — these are critical early indicators of target engagement before clinical outcomes.
• Biomarker shifts often occur months to years sooner than symptomatic improvement.

Clinical vs. biomarker endpoints

• Trials in preclinical AD (e.g., tau vaccine in cognitively normal individuals) aim primarily to show slowing or prevention of disease progression, which requires long follow-up.
• PD and ALS immunotherapy trials often focus on

safety, immune response, and disease biology before definitive efficacy.

Regulatory context

FDA Fast Track or accelerated programs may allow interim biomarker readouts to support early approval decisions if they strongly predict clinical benefit. Below is a regulatory-focused summary of how major agencies like the (U.S.) FDA and the European Medicines Agency (EMA) are approaching immunotherapies for neurodegenerative diseases — especially Alzheimer's — and what key decisions or pathways to watch over the next few years:

(U.S.) FDA Regulatory pathways

• Fast track & priority review:
The FDA has been actively using expedited pathways for immunotherapies that show promise in serious conditions with unmet need:

-Posdinemab (anti-tau mAb) and JNJ-2056 (anti-tau vaccine): Both received Fast Track designation, meaning the FDA will expedite review and increase interaction with developers to potentially speed approval if benefit is shown. Fast Track is designed for serious diseases and helps firms get important therapies to patients sooner if early data are promising.

• Maintenance dosing approvals:

- **Leqembi® (lecanemab-irmb):** This monoclonal antibody targeting amyloid-β has additional FDA approval for a once-every-four-weeks IV maintenance dosing regimen after initial intensive treatment.

- **Biologics:** The FDA has also accepted a supplemental Biologics License Application for a potential subcutaneous (weekly) version of Leqembi, with a decision expected by August 31, 2025 — which could make treatment more accessible and easier to administer outside of infusion centers.

• Accelerated approval trend for AD:
- The FDA has demonstrated regulatory flexibility by permitting approvals of amyloid-targeting antibodies based partly on biomarker evidence (amyloid reduction), although there is ongoing debate about how well these translate into clinical benefit.

In summary, the FDA is actively using Fast Track, accelerated or priority review mechanisms to move immunotherapies forward in neurodegenerative diseases, especially AD. Continued engagement and possibly additional accelerated approvals are expected if surrogate biomarkers (like amyloid PET or tau measures) correlate with clinical slowing.

(EU) European Medicines Agency (EMA) regulatory landscape

• Approvals & opinions:

- **Leqembi:** The EMA's CHMP issued a positive opinion recommending its approval for early AD and the product has been approved in several EU countries, marking an important regulatory milestone in Europe.
- **Donanemab:** This other amyloid-targeting antibody faced initial refusal by CHMP but was later authorized in the EU after re-examination in 2025 — illustrating that European regulators may have stricter review standards but can eventually align with U.S. approvals.

• Guidance updates:
- EMA has updated clinical trial guidelines for PD to modernize how progression-modifying therapies should be investigated, which could affect how future PD immunotherapy trials are designed and reviewed.

It appears that the EMA tends to be more conservative than the FDA, often requiring robust evidence of clinical benefit beyond biomarkers. However, major immunotherapies like Leqembi and Donanemab have

eventually been authorized, showing regulatory alignment over time.

Potential impacts of future regulatory decisions (2025–2028)

• FDA:

- **Leqembi subcutaneous decision —** mid-2025 (PDUFA date: Aug 31, 2025); could shift care toward home-based therapy.

-Posdinemab, vaccines: Additional tau immunotherapies — potential end-of-Phase 2 advice and Breakthrough Therapy designations if early data are strong (not yet granted but possible).

- Continued review of amyloid & tau biomarkers as surrogate endpoints could shape *Accelerated Approval guidance broadly for dementia therapies.*

• EMA:

- Continued review and label expansion decisions for immunotherapies (e.g., maintenance dosing approvals).

EMA CHMP opinions will influence whether European labeling includes early/preclinical treatment populations — a key regulatory frontier.

Regulatory strategic differences

Table 4 outlines the regulatory strategic differences between the U.S. and the European Union:

Aspect	FDA (U.S.)	EMA (EU)
Use of biomarker surrogates	o More flexible and used for accelerated approvals, which are common o Accepts as surrogates	o More conservative, supportive only, often demands stronger clinical outcome data o Rare accelerated approvals
Fast Track / Breakthrough	Widely deployed	Similar mechanisms (e.g., PRIME) exist but are more stringent
Patient access	Often earlier with managed post-marketing commitments	Slightly slower but greater emphasis on risk-benefit balance
Designation timelines	Clear PDUFA dates (e.g., Lecanemab subcutaneous)	CHMP opinions guide national approvals

Table 4: Regulatory strategic differences between the U.S. and the European Union

Overall, the (U.S.) FDA's approach tends to be more permissive of novel surrogate endpoints (especially for first-in-class or seriously unmet needs), potentially leading to earlier approvals, whereas the EMA may wait for stronger clinical evidence before broad authorization.

Implications for future immunotherapy trials

• Regulatory guidance shapes trial design:

- Sponsors increasingly design confirmatory clinical outcomes alongside surrogate biomarker endpoints to satisfy both FDA and EMA requirements.

- Adaptive designs and early engagement with regulators (e.g., via Breakthrough or PRIME support) can accelerate development.

• For patients & clinicians:

-Regulatory decisions continue to expand treatment accessibility (e.g., easier dosing forms).

- Continued debate about clinical meaningfulness vs biomarker effects may lead to evolving policy over the next several years.

Table 5 summarizes the mandatory clinical endpoints as well as the biomarker employed, the corresponding regulatory roles, advantages/limitations and their main uses.

Biomarker	Measure(s)	Regulatory role	Advantages/ Limitations	Main usage
Amyloid-PET	Brain amyloid-β plaque burden	o Accepted by FDA as surrogate end-point o Basis for accelerated approvals	o Weak correlation with symptoms once dementia is established o EMA views amyloid reduction as necessary but not sufficient	o For early AD o Proof of target engagement
Tau-PET	Spread & NFT density	Viewed favorably because of strong correlation with cognitive decline, disease stage, neuronal loss	o Not yet a formal surrogate, but increasingly persuasive o Likely primary biomarker endpoint	Disease-modifying claims
CSF/Plasma	o p-tau217, p-tau231 o NfL o Aβ42/40 ratio	o Supportive evidence o Rarely sufficient alone for approval	o Minimally invasive o Good for monitoring response	Trial enrichment & monitoring
Mandatory clinical endpoints	**AD:** o CDRSB (primary) o ADAS-Cog o iADRS	**PD:** o MDS-UPDRS o Digital motor biomarkers (emerging)	**ALS:** o ALSFRS-R o Survival	No biomarker alone replaces clinical benefit for full approval (especially for EMA)

Table 5: Biomarkers and mandatory clinical endpoints

Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; CSF: Cerebrospinal fluid; NfL: Neurofilament light; NFT: Neurofibrillary tangles; PD: Parkinson's disease; PET: Positron emission tomography.

Further, the FDA accepts modest clinical meaningfulness, higher risk tolerance, and strong reliance on post-marketing commitments. By contrast, for the EMA, the clinical meaningfulness must be clear, the risk tolerance lower, and reliance on post-marketing commitments is lesser. In other words, regulators now accept biomarker-driven immunotherapy for neurodegenerative diseases, but long-term approval will depend on demonstrating that clearing pathology truly slows clinical decline — especially via tau-based strategies. What this means for the future is that tau immunotherapy is best positioned for next approvals, earlier intervention (preclinical disease) will equate higher success, the combination endpoints (PET + cognition) will dominate, and PD and ALS immunotherapies will need immune modulation + biomarkers, not just antibodies

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