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Perspective

The evolving landscape of Alzheimer's disease therapy: From Aβ to tau

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https://doi.org/10.1016/j.cell.2025.11.033

SUMMARY

A marked evolution in Alzheimer's disease (AD) therapy research is ongoing. In this perspective, we highlight emerging outcomes of tau-targeting approaches with disease-modifying potential evidenced by PET-based slowing of tau accumulation and early signs of cognitive benefit. We outline how decades of iterative amyloid β (Aβ)-trial refinement leading to the recent successes of approved anti-Aβ therapies have set the stage for accelerated optimization of next-generation trials. We summarize key learnings from first-generation tau immunotherapies and how these paved the way for early achievements in tau trials, while many challenges remain. Finally, we discuss the back-translation of clinical outcomes into fundamental insights on human tau pathobiology, and we outline challenges and future directions for AD therapy development including combination therapy and targets beyond Aβ/tau. Together, this provides a framework for next-generation AD and tau-therapy development toward increasingly efficient disease-halting interventions.

INTRODUCTION

In this perspective, we first outline recent breakthroughs that opened a new era in Alzheimer's disease (AD) research and treatment. These include the recent US Food and Drug Administration (FDA) approvals of anti-amyloid β (Aβ) therapies—lecanemab and donanemab—resulting from decades of setbacks yielding incremental success in Aβ trial optimization. Emerging outcomes of tau trials are fast following the Aβ successes, showing slower tau accumulation (measured by tau PET [positron emission tomography]) and early signs of cognitive benefit. While primary endpoints were not met, and corroboration in multiple, large future trials will be critical, these outcomes represent first proof of concept in humans of biological disease halting and present an important step forward for tau therapeutic agents. We here provide an integrated analysis of the tau trial outcomes alongside lessons learned from Aβ trials, which yield a roadmap for therapy optimization. We also discuss clinically validated insights in light of fundamental tau pathobiology and remaining challenges. Looking forward, we discuss opportunities for Aβ-tau combination therapies, as well as therapeutic strategies targeting other factors. Together, this provides a roadmap to guide accelerated, next-generation AD and tau-therapy development.

EVOLUTIONS IN AD THERAPY: FROM Aβ TO TAU

AD and other tauopathies

AD is the most frequent tauopathy and prevalent dementia, with an unmet medical need for therapy. Globally, AD accounts for approximately 32 out of 57 million dementia cases,[1–3] which are expected to climb to 153 million by 2050, posing a major health and socioeconomic challenge.[2] The AD brain is characterized by the presence of Aβ pathology (A), tau pathology (T), and neurodegeneration (N), as pathological hallmarks[4–9] that serve as a clinical-biological framework[10,11] of AD (Figure 1).

Both Aβ and tau represent key therapeutic targets. Accumulating evidence supports an initiatory role for Aβ in AD, while tau is proposed to have an executive role in the

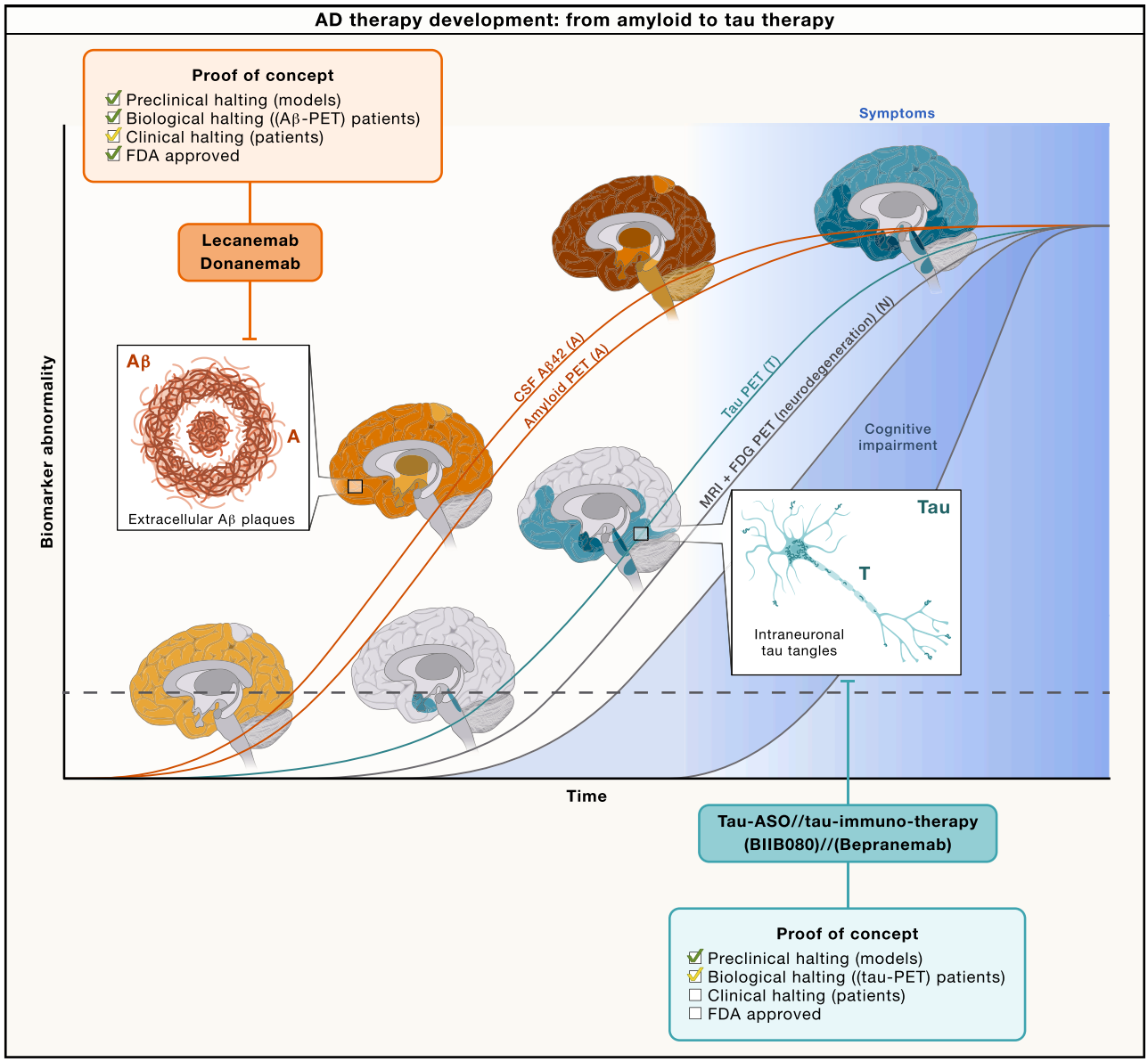

Figure 1. Evolutions in AD therapy—From Aβ to tau therapy

AD is characterized by the aggregation of Aβ (A) as extracellular Aβ plaques followed by aggregation of hyperphosphoryated tau (T) as intraneuronal neurofibrillary tangles. Aβ is considered the initiator of the disease process and tau the executor of the disease process, with tau aggregation strongly correlating with symptom progression. Recent developments led to FDA-approved anti-Aβ immunization therapies (lecanemab and donanemab), while emerging data indicate early signs of biological halting based on tau PET measured slowing of tau pathology for tau-immunization (bepranemab, E2814) and antisense oligonucleotide (ASO)-based therapy (BIIB080). The clinical-biological framework for AD, based on the presence of ATN-pathologies (A, Aβ pathology; T, tau pathology; N, neurodegeneration; and I, inflammation), provided a critical—biological—framework enabling accelerated trial optimization toward clinical efficacy and approved therapies (schematic presentation of ATN framework, based on and modified from Jack et al.[9] and Jucker and Walker[12]).

neurodegenerative process downstream of Aβ, including Aβ-independent roles.[5–8,13–19] Indeed, tau pathology closely correlates with symptom progression.[18–24] Besides AD, progressive tau aggregation characterizes a family of various neurodegenerative disorders, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), which represent primary tauopathies and additional unmet medical needs.[16,25,26] Genetic tauopathies with autosomal dominant mutations in the *MAPT* gene unequivocally identify tau as a causal, driving factor in the neurodegenerative process in tauopathies.[16,17,25–31]

Anti-Aβ immunotherapies: Recent breakthrough successes

Therapeutic strategies targeting Aβ, including anti-Aβ immunization, have been intensively pursued to inhibit the initiation of the

AD pathogenic process.[5,14,32–38] Aβ-targeting therapies underwent a long "unsuccessful" phase, often casting doubt on the underlying amyloid cascade hypothesis.[35,36] This optimization track finally converged on the recent breakthrough in anti-AD therapies with FDA approvals of anti-Aβ immunization therapies for lecanemab and donanemab.[33,34,37,39–43] Both show marked, near complete clearance of Aβ plaques in a drug dose-dependent manner, accompanied by a moderate slowing of cognitive deterioration.[33,34,40,41] In the phase 3 randomized, placebo-controlled CLARITY AD trial, anti-Aβ immunotherapy using lecanemab significantly reduced Aβ plaques, improved biomarker levels, and slowed cognitive decline by 27% in patients with early AD (Figures 1 and 2).[41] Lecanemab received first accelerated and subsequently full FDA approval in June 2023. Similarly, promising results followed from the TRAILBLAZER-ALZ 2 phase 3 trial of donanemab, showing fast and efficient Aβ clearance and a 29% reduction in disease progression overall (CDR-SB [clinical dementia rating-sum of boxes]), which was up to 40% in patients with low to intermediate tau levels (Figures 1 and 2).[40] These results highlight the efficacy of Aβ-targeting immunotherapies, while not yet obtaining full clinical halting.[33,34,40,41]

Lessons from anti-Aβ clinical trials

The long iterative optimization of Aβ-targeting therapies, not only converged on FDA-approved drugs but also provided a framework for accelerated AD therapy development. It took several decades on a path of setbacks and incremental partial successes to attain near complete clearance of Aβ pathology—reducing high Aβ PET to normal or low levels (from 70–120 centiloids to below 24 centiloids)—and concurrent moderate but significant clinical efficacy, now achieved with lecanemab and donanemab as FDA-approved therapies (Figures 1 and 2).[33,40,41] Proof of anti-Aβ immunization to clear Aβ plaques was delivered for the first time in 1999 in preclinical models.[43] The availability of preclinical models robustly mimicking AD pathologies provided the crucial basis for this breakthrough. This preclinical proof, shown consistently and in different models, was followed by the first successful clearance of Aβ pathology in patients enrolled in anti-Aβ immunization trials, showing biological slowing of AD (first active and later passive immunization trials)[37,39,44,45] (Figures 1 and 2). This landmark was however not immediately associated with effective halting of clinical symptoms[37,39,44,45] and was also associated with serious adverse effects.[37,39] Subacute meningoencephalitis in a subset of AD patients after active Aβ42 immunization[46,47] resulted in a more intensive pursuit of passive immunization approaches, which were considered safer.[48] However, the latter, including lecanemab and donanemab, are also not fully devoid of side effects, as Aβ-related imaging abnormalities (ARIA) are observed in subsets of patients and requires close mitigation, monitoring, and patient selection[33,34,40,41,48] Furthermore, the initial lack of clinical effect, despite indications of biological slowing, highlighted the need for further optimization of targeting strategies and trial design.

A variety of anti-Aβ passive immunization strategies have been tested in clinical trials with incremental success. This included the testing of multiple antibodies targeting different Aβ epitopes (various N-terminal or mid-region epitopes), and with different affinities for smaller to larger aggregates (including, non-exhaustively, bapineuzumab, solanezumab, crenezumab, gantenerumab, aducanumab, lecanemab, and donanemab),[33,34,44,45,48] on a path toward increasing insights into antibody mode of action (MoA) and more effective trials (Figure 2 and comprehensively reviewed in Boxer et al. and others[33,34,40–42]). Failures in meeting primary endpoints not only resulted from non-optimal epitopes or targeting strategies, but also from a combination of different factors, including initiating treatment too late in the disease course, sub-optimal patient selection (clinical endpoint-based instead of biomarker-based), patient heterogeneity, and disregarding advanced tau status as an independent driver of disease progression. Furthermore, insufficient Aβ clearance—not reaching threshold for clinical benefit—and adverse effects halting trials might also have contributed to the lack of clinical benefit in Aβ trials.[33,34]

However, these initial trial failures did pave the way for the definition of a biological framework of AD, based on ATN pathologies[7–11] and groundbreaking biomarker development[4,8,22–24,49–57] to monitor biology. In particular, the development of AD and tauopathy biomarkers, i.e., Aβ and tau PET, cerebrospinal fluid (CSF)- and blood-based biomarkers[7,49–63] provided an unprecedented window into AD processes in the brain. This biological monitoring and biomarker advances have been crucial to transform AD trials across four domains: (1) accelerated optimization of targeting strategy (N-terminal epitope/Aβ aggregate conformation, immunoglobulin G [IgG] isotype, and MoA) vs. clinical outcomes and target engagement; (2) optimized patient stratification and defined an optimal window of intervention based on tau burden, co-pathologies, co-morbidities, genetics (e.g,. apolipoprotein E [*APOE*] genotype), disease stage, and progression rate; (3) delivered rapid and sensitive measures of treatment efficacy, defining thresholds and dosing regimens to achieve the biological modification required for clinical benefit[32–34]; (4) balanced safety and efficacy with biomarker-informed stratification of patients at risk of adverse effects (reviewed in Boxer et al.,[33] Jucker and Walker,[34] and Brody and Holtzman[48]). The use of biological readouts and optimizing biological halting toward clinical efficacy was pivotal for developing approved therapies with clinical effect—lecanemab and donanemab—(Figure 2) resulting in significant but not yet complete disease halting.

From Aβ to tau therapy

Although anti-Aβ immunotherapies can almost completely clear Aβ pathology in most individuals over 12–18 months, they only partially normalize tau biomarkers (e.g., CSF and plasma tau, tau PET).[40,41] One potential explanation is that tau pathophysiology may become or develop Aβ-independent, with tau pathology propagating in the brain independent of Aβ, as demonstrated in the primary tauopathies.[30,31] Thus, the removal of the initial Aβ trigger may not sufficiently halt tau propagation in AD, highlighting the need to pursue anti-tau therapies, particularly in view of the unmet clinical need for effective, preferably complete halting of disease progression.

Whether tau therapies can be successful for AD remains to be seen, but there are several arguments supporting tau as a key driver and target in tauopathies. These include (1) tau genetic mutations in tauopathies indicating tau dysfunction as a process sufficient to drive neurodegenerative symptoms[16,21,25,26]; (2) progressive spatio-temporal tau aggregation characterizing all

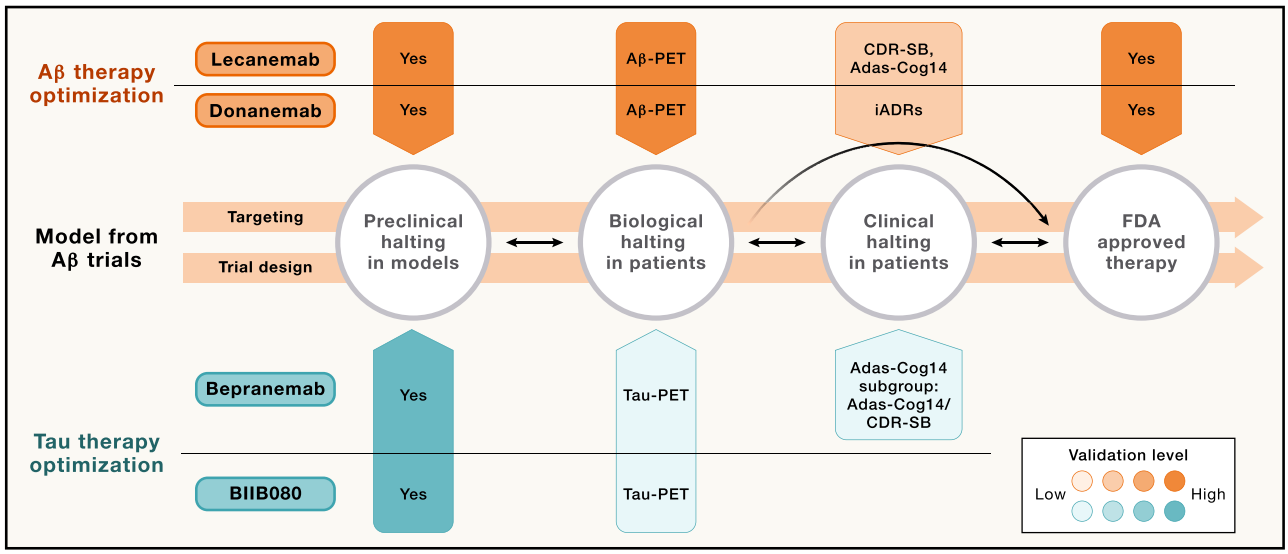

Figure 2. Lessons from anti-Aβ clinical trials: Roadmap for accelerated trial optimization from preclinical to biological and clinical halting for regulatory agency therapy approval

Lessons from the long and incremental learning path from anti-Aβ trial optimization toward approved anti-Aβ therapies, provided a roadmap for accelerated trial optimization for anti-Aβ therapies, tau therapies, and combined Aβ-tau therapies. The roadmap encompasses toggling back and forth, to move from optimal preclinical halting to obtaining optimal biological halting toward improved clinical efficacy and regulatory agency-approved therapies. The stage for current therapies and trial outcomes for Aβ (lecanemab and donanemab) and tau (bepranemab and BIIB080) along the roadmap are indicated. The Aβ and tau trial and therapy optimization show different levels of validation and different levels of efficacy of achieved preclinical, biological, and clinical slowing of the disease process (as discussed). This roadmap enables accelerated development of increasingly effective therapies with controlled side effects, through continuous targeting optimization and trial design optimization.

tauopathies in association with symptoms and symptom progression[3–11,13–19]; and (3) propagation of tau pathology between cells as a potential targetable process, contributing to pathogenetic processes.[12,64–66] While some open questions and challenges remain, tau targeting is a straightforward approach with recent emerging data supporting its potential feasibility and safety.

The learnings from the anti-Aβ trials generated a validated roadmap for accelerated trial optimization toward more clinically effective therapies with fewer side effects. The roadmap includes toggling back and forth from (1) preclinical validation to (2) proof of biological halting in patients, to increased (3) clinical efficacy, and (4) approved therapies (based on biological or clinical efficacy), by continuous optimization of targeting strategy and trial design (Figure 2), a roadmap now useful for tau-targeting therapies.

TAU THERAPIES

Tau pathobiology and tau therapies: Challenges and opportunities

Tau is a microtubule-binding protein mainly expressed in neurons and limited in glia in the adult human brain, which exists in 6 different isoforms that differ in the number of inserts (0, 1, or 2) in the N-terminal domain and number repeat domains (3 or 4) in the microtubule-binding region (MTBR)[25–29,67,68] (Figure 3). As an intrinsically disordered protein, tau exerts its physiological functions, while in pathological conditions tau aggregates strongly correlate with progressive neurodegeneration and clinical symptoms in tauopathies.[24–28]

In tauopathies, tau monomers aggregate into various oligomers and filaments, with different molecular and structural characteristics depending on the respective tauopathy[69,71,72] but sharing a large MTBR region in their aggregate core. Tau aggregation is markedly accelerated by templated tau seeding, i.e., pre-aggregated tau inducing fast aggregation of physiological unfolded tau. Intercellular transmission of tau seeds then provides a compelling mechanism for the fast progressive development of tau pathology in tauopathies (Figure 3). Templated seeding and intercellular propagation of tau pathology has been shown *in vitro* and *in vivo* in preclinical models,[64,65,73–75] and is supported by accumulating evidence in humans, while clinical validation is still missing.[76–79] This process, discussed in detail below, encompasses an extracellular phase of pre-aggregated tau, which is potentially important in the context of tau immunization.

Tau undergoes a variety of post-translational modifications (PTMs), including phosphorylation, glycosylation, acetylation, as well as truncation[16,25,28,29] (Figure 3). Hyperphosphorylation is an important and intensively studied PTM in tauopathies, causing tau to detach from microtubules and facilitating tau aggregation. Tau can also be cleaved and secreted from neurons mostly as N-terminal fragments that can be measured in biofluids but are not prone to aggregate.[80] Conversely, tau fragments containing the MTBR region may misfold and seed tangle pathology and can also be released as MTBR tau fragments, detectable in biofluids albeit in lower quantities.[49,58,63] MTBR-containing tau, full length or fragments, can serve as a substrate for tau aggregation, a process that also involves full-length tau containing both N- and C-terminal sequences, while full-length

tau seems more rarely released from neurons.[80] Besides fibrillar tau aggregates, oligomeric tau forms are particularly considered as toxic agents in the disease process.[81,82] Furthermore, targeting tau based on pathogenic PTMs may leave physiological tau unaffected and functional but may also only target a subpopulation of pathological tau, leaving other toxic subpopulations untargeted. In the context of passive immunization, truncated tau species are of particular interest as epitope choice might define the targeting of total or a subset of tau pools (Figure 3).

Tau is hence a complex molecule forming a variety of tau species and polymorphs (3R/4R, PTMs, structure, and aggregation state), with physiological and pathological roles in tauopathies. While pathognomonic tau aggregates mainly accumulate intracellularly, in contrast to extracellular Aβ plaques, various tau forms are detected both intra- and extracellularly. These tau forms may contribute differently to physiological and pathogenic processes, including progressive tau pathology and/or tau-associated neurodegeneration, which are not necessarily identical processes and remain to be understood in detail.[28,29] Based on this pathobiology, tau targeting presents with specific challenges and opportunities.

Tau therapies: Proof of concept in patients

Different strategies for halting pathological tau progression and its executive role in neurodegenerative tauopathies have been developed and are being pursued.[15,17,27,70,83–86] Preclinically, small molecules as well as biological approaches are being explored at various stages of the development pipeline, including decreasing tau expression by antisense oligonucleotide (ASO) and small interfering RNA (siRNA) therapies, altering tau PTMs (e.g., phosphorylation, acetylation, glycosylation, and truncation), active tau vaccination, passive tau immunization, promoting tau degradation via proteolysis targeting chimera (PROTAC), tau aggregation inhibition, and O-GlcNAcase enzyme inhibitors.[15,17,27,61,70,83–86] Emerging outcomes for tau-directed ASO and "second-generation" tau-immunization therapies are showing the first signs of disease-modifying effects, based on slowing PET-assessed tau pathology progression and early signs of cognitive benefit.

Proof of concept for tau-directed ASO as a therapeutic strategy was first demonstrated in preclinical models, showing decreased tau pathology and tauopathy-induced neurodegenerative changes[87,88] without major side effects. siRNA approaches for reducing tau expression have also been developed and tested preclinically in a murine tauopathy model.[89] Development of ASO tau therapy was built on and encouraged by early successes using ASO against mutant *SOD1* in genetic amyotrophic lateral sclerosis (ALS), which showed treatment-induced lowering of CSF and plasma concentrations of neurofilament light chain (NFL), an established biomarker for neurodegeneration intensity expected to translate into clinical benefit. On this basis, the FDA-approved tofersen for mutant *SOD1* ALS (FDA).[90,91] ASO- or microRNA-based therapies also present promising clinical results in other neurodegenerative diseases (Huntington's disease [adeno-associated virus (AAV)-based gene therapy][92] or spinal muscular atrophy[93,94]).

Several ASO-based clinical trials aimed at reducing tau expression are ongoing (BIIB080 [in AD], NIO752 [in AD and PSP], and LY3954068 [in AD]). Highly interesting and promising results emerged from a phase 1b trial of tau-directed ASO BIIB080 (NCT03186989), currently being evaluated in a phase 2 clinical study (CELIA study: NCT05399888). In the phase 1b study, a 36-week multiple-ascending-dose trial followed by a 64- or 71-week open-label long-term extension in 46 participants with mild AD, BIIB080 dose-dependently reduced soluble total-tau and p-tau in CSF and aggregated tau pathology measured with tau PET. Tau PET showed reduced tau accumulation in BIIB080 versus placebo arms at week 25 (n = 13), and at 100 weeks versus baseline across all regions assessed in the BIIB080 arm (n = 12).[95,96] The result in the BIIB080 arm was associated with suggested favorable trends in cognitive outcomes[95,96] (Alzforum ADPD 2023, CTAD 2023[97]); BIIB080 was fast-tracked by the FDA in April 2025. The successful biological slowing of tau pathology with the tau-targeting ASO therapy, BII080, is an important breakthrough, reminiscent of the Aβ field (Figures 1 and 2), while follow-up studies are required.

Promising results are also emerging from second-generation passive tau immunotherapies[98] (Alzforum),[99–101] following first-generation tau immunotherapies that failed to show clinical efficacy. In these latest trials, passive tau immunotherapy with bepranemab now successfully slowed tau pathology progression (tau PET; slowing tau accumulation by 33%–58% versus placebo after 80 weeks of treatment) and cognitive decline (Alzheimer's disease assessment scale-cognitive subscale 14-item version [ADAS-Cog14]; reduced by 21%–25% versus placebo) as secondary endpoints (TOGETHER-trial n = 466; Alzforum).[98–101] Although primary endpoints were not met in the whole study population, this trial now shows biological slowing of tau pathology (tau PET) associated with significant, moderate cognitive benefit (ADAS-Cog14) for tau-directed trials (Figures 1 and 2).

Along the same lines, the second-generation tau antibody E2814 slowed tau pathology progression, measured by PET imaging, albeit only in a few patients, and reduced CSF concentrations of MTBR-tau243, a tau fragment strongly correlated to tau PET, in a larger sample. Phase 2 data with additional second-generation tau antibodies are expected by the end of 2025 (E2814/etalanetug, posdinemab, BMS-986446, and MK-2214) and will be important to generate new insights for future trial development, including defining optimal targeting strategies, optimal biomarker-based patient selection, endpoints, and others further discussed below.

Together, these results provide now evidence of biological disease modification of tau pathology (bepranemab, E2814, and BIIB080) and emerging functional benefits (bepranemab) by tau-directed ASO therapy and passive tau-immunization therapies. While corroboration of the outcomes in multiple and large future clinical trials will be critical, these pave the way for tau trial optimization and development of increasingly effective therapies.

Anti-tau immunotherapies: Optimization of tau targeting and clinical trial design

The recent achievements of tau-immunization trials built on learnings in therapy development by optimizing targeting efficacy and trial design. Despite intracellular accumulation of tau aggregates

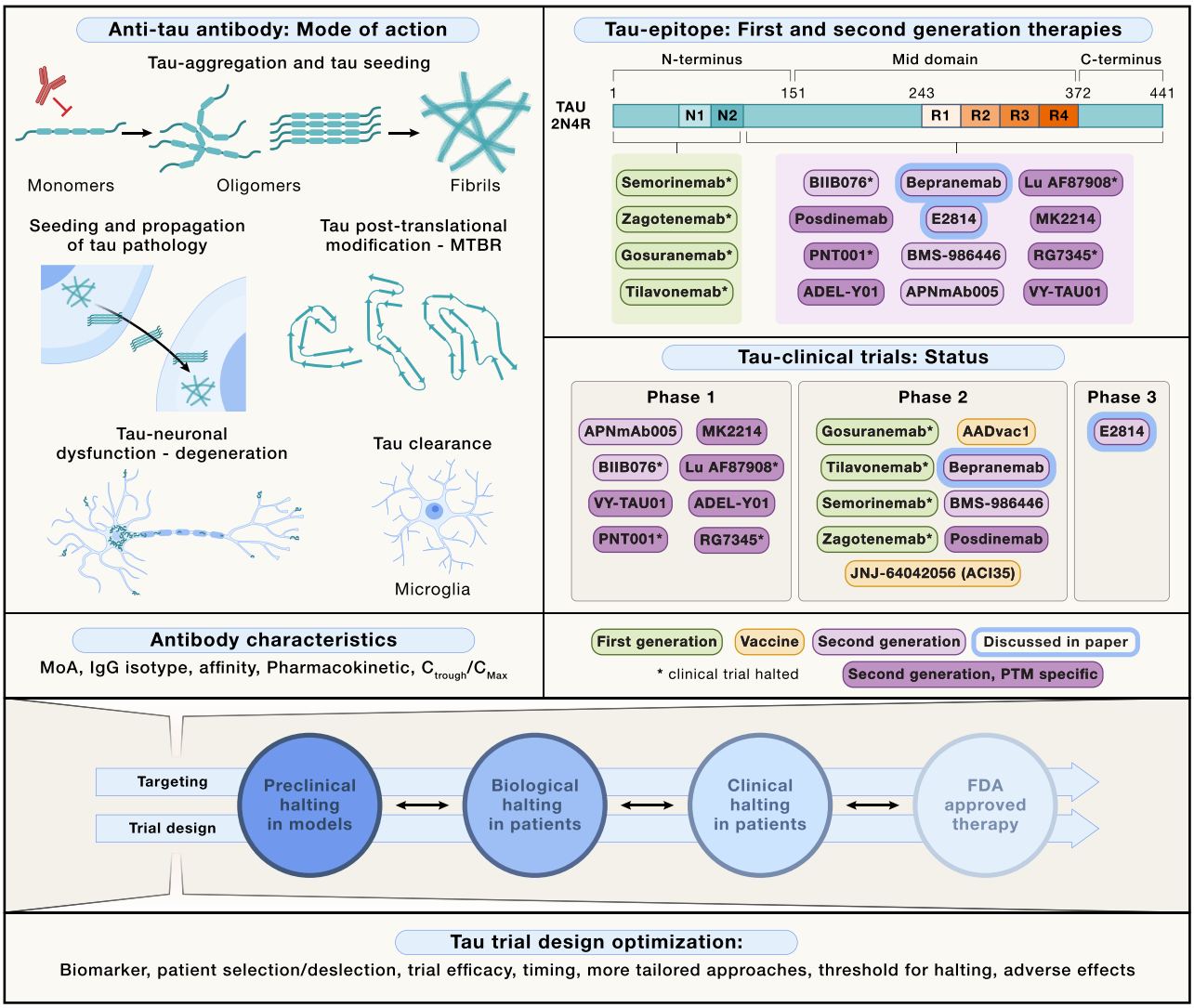

Figure 3. Lessons from anti-tau immunotherapies: Optimization of tau targeting and clinical trial design

Optimization of anti-tau immunotherapy is currently ongoing by continued targeting optimization and trial design optimization. A roadmap toggling between preclinical halting, to biological halting, to clinical efficiency is pursued. First- and second-generation therapies have been or are being developed, with first-generation therapies, targeting N-terminal tau epitopes. First- and second-generation antibodies display a variety of targeting epitopes, tau forms being targeted, antibody characteristics, as well as proven MoA of the antibody. Clinical trials are in different phases of development, and clinical trial design is being optimized based on biomarker use and specific parameters. (Schematic presentation of tau structures and tau propagation, based on and modified from Parra Bravo et al.[28] and Shi et al.,[69] tau clinical trials based on and modified from Cummings et al.[70]).

presenting an additional challenge, tau immunization was successfully and reproducibly shown to halt tau pathology in preclinical models.[27,102–107] This led to various trials pursuing tau immunotherapy pipeline including[27,102–106,108,109] passive and active (e.g., AADvac-1 and JNJ-64042056 [ACI-35]) immunization therapies. Here, we focus on the progress of passive tau-immunization trials. It is important to note that anti-tau antibodies may strongly differ in their MoA and target different tau-related pathogenic processes and forms. The MoA may include blocking tau cleavage, PTMs, and misfolding (chaperone-like), blocking oligomeric tau, stimulating microglial phagocytosis (opsonization), interfering with seeding and transcellular tau propagation (extracellular release and uptake), and blocking intracellular effects of tau, depending on the targeting strategy and the site of action (Figure 3).

First-generation anti-tau immunotherapies: N-terminal targeting of tau

First-generation passive tau immunotherapies targeted solely or partially the N-terminal domain of tau (Figure 3), including tilavonemab, gosuranemab, semorinemab, and zagotenemab.[85] However, they differ significantly in binding affinities (0.1 nM for gosuranemab; 3.8 nM for semorinemab; 20 nM for tilavonemab) and pharmacokinetic profiles (half-lives of > 550 h for gosuranemab and tilavonemab; 400 h for semorinemab). These very different properties led to varying target engagement in the brain for the same dose.[110] Furthermore, most

first-generation tau antibodies (gosuranemab,[111] semorinemab,[112] and tilavonemab[113]) were of the IgG4 isotype, while zagotenemab (registered as NCT03518073) was an IgG1. IgG1 binds with higher affinity to Fc gamma receptors than IgG4, leading to better phagocytosis of the antibody-antigen complex by macrophages in the periphery or microglia in the CNS, accompanied by pro-inflammatory cytokine release. It had been shown that both tau antibodies with IgG1 or IgG1 with Fc mutation leading to complete lack of Fc gamma receptor binding could be effective, suggesting that effector function is not required for efficacy,[114] while IgG1 might increase effector functions and intracellular uptake.[105,115] However, IgG1 can lead to pro-inflammatory cytokine release, which would increase the risk of neuroinflammation.[114] Therefore, it is important to consider the choice of IgG isotype, besides the tau epitope the antibody targets.[27]

First-generation tau trials unfortunately failed endpoints. Tilavonemab (N-terminal AA 25–30) was not effective in PSP, with its relatively weak affinity potentially requiring higher doses to achieve high target engagement in the brain.[113] Patient selection in this trial was based on clinical measures, without biologically confirmed tau pathology using biomarkers. Semorinemab (N-terminal AA 6–23) was not efficacious in AD, with a shorter half-life and medium affinity also potentially necessitating higher doses to attain high target engagement.[112] Patient selection included both clinical assessment and Aβ pathology positivity by PET or CSF biomarkers but not tau pathology biomarkers. Despite higher affinity, longer half-life, and target engagement in the CSF, gosuranemab (N-terminal AA 15–24) did not show positive effect on clinical outcomes or imaging biomarkers in PSP or AD,[111,116] leading to the conclusion that targeting N-terminal epitope tau may not be efficacious in PSP. In the AD trial, patients were selected based on clinical deficits and positive Aβ PET scan but not based on tau pathology. Despite a sub-nanomolar affinity, zagotenemab (N-terminal AA 7–9) had no effect on tau PET in a phase 2 trial of early symptomatic AD.[117,118] Interestingly, in this trial, patients were selected based on intermediate levels of brain tau on PET imaging.

Taken together, first-generation passive tau immunization did not achieve effects on tau pathology or efficacy with clinical endpoints. The most straightforward explanation could relate to the choice of N-terminal tau epitope, given that all first-generation anti-tau antibodies targeted this region of the protein. In view of the higher accessibility of N-terminal epitopes for antibodies compared with MTBR epitopes, their high immunogenicity, possibly less interference with the physiological role of tau, and the abundant presence of truncated tau encompassing N-terminal regions in biofluids, N-terminal tau targeting was a straightforward and valid strategy to initially pursue. Later on, however, a variety of truncations have been identified, including fragments with either N-terminal tau or MTBR-encompassing tau in human brain and in CSF.[62,63,119–121] In addition, N-terminal fragments are not prone to aggregate, and N-terminal tau-targeting antibodies were shown to be less effective at inhibiting seeding and propagation of tau pathology *in vitro* and *in vivo* when using human postmortem extracts.[103,107] Hence, the current data suggest that following tau truncation, it may not be efficacious to target non-MTBR-containing fragments of tau to prevent seeding and propagation of tau pathology.[62,63,74,75,122–125]

Second-generation anti-tau immunotherapies: Optimization of targeting and antibody design

In light of that, the second generation of passive tau immunization instead focused on epitopes closer to the aggregation- and seeding-prone MTBR region, which have the potential to block spread and seeding of tau pathology[62,63,74,75,103,107,122–125] (Figure 3). This second generation includes BIIB076,[126] bepranemab, E2814, BMS986448 (PRX005), posdinemab (JNJ-63733657), Lu AF87908, MK-2214, APNmAb005, ADEL-Y01, VY-TAU01 (likely now called VY7523) (Figures 1 and 3). Like the first-generation therapies, these antibodies are quite different from each other and the data generated with one may not necessarily apply to others.

Some of these antibodies target specific tau PTMs, such as phosphorylation (p217 for posdinemab, p396 and 404 for Lu AF87908, p413 for MK-2214, and acetylated K280 for ADEL-Y01) that may increase engagement of specific pathological tau forms, leaving physiological tau unaffected. APNmAb005 binds a conformational epitope in tau oligomers, and hence binds tau in synaptosomes and insoluble fractions in human brain extracts better than monomeric, cytosolic tau.[127] BIIB076 targets the middle domain of tau.[128] Both antibodies halt tau seeding and propagation of tau pathology in preclinical models. Last, VY-TAU01 binds a C-terminal epitope.

In addition, most second-generation tau antibodies are now IgG1 isotype (BIIB076, E2814, BMS986448, Lu AF87908, APNmAb005, posdinemab, and ADEL-Y01) with stronger effector function than IgG4 (bepranemab, VY-TAU01), but which, conversely, may potentially increase neuroinflammation and ARIA risks, if combined with anti-Aβ antibodies. In this respect, it must be noted that the MoA of immunotherapy may be very different for Aβ and tau. For Aβ, strong effector function (IgG1) is important for efficacy, since microglia engagement via the Fc gamma receptor is key for phagocytosing extracellular Aβ aggregates. The effect is an active mechanism for clearing Aβ via microglia and is antibody maximum (peak) bloodstream concentration (C_{max})-driven, i.e., once a sufficient antibody concentration is reached in the target organ (brain), microglia actively phagocytose the aggregated Aβ. A sustained presence of high antibody concentration may not be necessary for removing plaques and a pharmacokinetic profile with rapid brain penetration but a shorter half-life could be appropriate.[129] For tau, however, it was shown that anti-tau antibodies with or without effector function can both be efficacious in preclinical research.[114] The MoA may be related to blocking binding sites besides, or in addition to, opsonization and phagocytic uptake by microglia.

These trials are now at various stages, with some already ceasing clinical development. This is the case for BIIB076, which completed phase 1 trial (NCT03056729), and showed target engagement, based on reduced mid-region tau in CSF, 1 week after infusion, but whose side effects at the highest dose prompted trial termination. Lu AF87908 was in clinical development (NCT0414986) but is no longer listed in the Lundbeck portfolio; the reason for removing this antibody is unknown to us. Some antibodies are starting early clinical trials, such as VY-TAU01/VY7523 (NCT06874621), MK2214 (NCT05466422), APNmAb005

(NCT05344989), and ADEL-Y01 (NCT06247345), but no data are yet available regarding safety, pharmacokinetics, CSF target engagement, and efficacy. Some others have completed phase 1 trials, with safety and target engagement having been considered sufficient to move toward phase 2 proof-of-mechanism trials, E2814 (NCT04231513, NCT04971733, NCT05269394, NCT06602258, and NCT01760005), BMS986446 (NCT06084598 and NCT06268886), and posdinemab (NCT 05407818, NCT03689153, NCT04619420, and NCT03375697).

First outcomes are emerging for two antibodies with epitopes in or close to MTBR. The second-generation antibody E2814 (Alzforum 1, Alzforum 2) was shown to reduce early and late tau pathology biomarkers in a subset of patients with dominantly inherited AD with mild-to-moderate cognitive impairment (n = 7) that received E2814 in escalating doses (750–4,500 mg) during 6 to 26 months. Two years of treatment reduced CSF p-tau217 and tau-MTBR levels by 50% and 75%, respectively, compared with DIAN observational study data (Wildsmith et al., CTAD24). Study limitations included a small sample size, unblinded design, and lack of a placebo arm. Interestingly, a few patients stabilized with a trend toward reduced tau by PET. Together, the data support target engagement and slowed progression of tau pathology (tau PET and tau MTBR) in a limited number of patients. Currently, E2814 is also being tested in combination with anti-Aβ therapies, with a readout expected in 2027–2028, further discussed below.

Bepranemab is another second-generation, MTBR-region-directed tau antibody with phase 2 data in AD (TOGETHER-trial n = 466; CTAD 2024, Alzforum).[98,103,107] Bepranemab significantly slowed secondary cognitive (ADAS-Cog14) and tau pathology (measured by tau PET) endpoints in the whole trial population in a phase 2 double-blind, placebo-controlled trial with high (90 mg/kg) and low (45 mg/kg) doses (Alzforum).[98] This represents the first time that a tau antibody demonstrated an effect on cognitive and pathology endpoints. However, the effect was not statistically significant on the primary CDR-SB endpoint in the whole population, although it was statistically significant in a prespecified sub-analysis of subjects with low baseline tau or were *APOE4*-negative. Most interestingly, predefined sub-analyses in this clinical trial were formulated based on the hypothesis that (1) patients with low/medium- but proven-baseline tau burden would benefit more than patients with high tau burden, and (2) *APOE4* carriers may react differently to non-carriers. These findings may help select patients more likely to respond to tau immunotherapies in future trials.

Bepranemab's MoA was selected on and shown to prevent intercellular propagation of tau seeding in preclinical models. As an antibody with low effector function (IgG4), bepranemab's effects on tau PET and ADAS-Cog14 suggest that strong effector function is not necessary for the MoA of tau antibodies in humans, aligned with preclinical data.[114] Given bepranemab predominantly binds extracellularly released tau seeding species,[103,107] the effect of bepranemab is expected to be C_{trough}-driven, i.e. a high and stable antibody concentration in the target organ (brain) is needed to capture seeding species as they are released from cells, favoring a pharmacokinetic profile with longer, stable half-life. Of note, several promising immunization approaches with a distinct goal of increasing intracellular targeting of tau and its pathogenetic effects to halt tauopathies are also at various stages of development (e.g., intrabodies, liposomal antibody administration, and others).[27,86,104,115,130,131]

These emerging outcomes suggest that screening assays used to identify bepranemab and related tau-immunization strategies could translate to clinical effects, at least partially, and are providing insights into optimal tau-targeting epitopes (MTBR-encompassing domain and bepranemab/E2814) and antibody characteristics (IgG isotypes and pharmacokinetics) (Figure 3. In addition, emerging outcomes of various ongoing trials effectiveness in humans may further provide crucial insights about optimal tau-targeting strategies, as well as the exact pathogenic forms of tau and their role in tau pathology progression and tau-induced neurodegenerative processes.

Second-generation anti-tau immunotherapies: Optimization of clinical trial design

Clinical trial design is an important issue that, at least in part, may have contributed to the failure of first-generation anti-tau immunotherapies (Figure 3). However, adopting the framework provided by Aβ trials can help identifying critical parameters for optimal design of tau trials (Figures 1 and 2).

In terms of safety and adverse effects, tau immunotherapy seems to display a better safety profile compared to anti-Aβ immunotherapy. No ARIA has been described with any of the tau antibodies, and, more generally, no major safety concerns have been identified so far in non-human primate toxicology studies, nor in phase 1 or phase 2 studies of healthy volunteers, AD, or PSP patients with a variety of tau antibodies, apart from BIIB076 at high doses.

In terms of patient selection, using PET/CSF and/or blood-based biomarkers is pivotal to select patients more likely to respond to the treatment, define trial efficacy, set thresholds of biological effects that translate to functional outcomes, and shorten recruitment time. Successful outcomes in predefined bepranemab phase 2 sub-group analyses suggested that selecting patients positive for Aβ but lower, yet proven, baseline tau pathology or *APOE4*-negative (often with comparably lower tau pathology) is important for tau therapeutic antibodies. This is also being used now in other trials. In the TargetTau-1 trial for the tau antibody BMS986446, presence of tau pathology is part of the inclusion criteria. Moreover, for the AUTONOMY trial testing the p217-specific tau antibody posdinemab, plasma p-tau217 followed by intermediate (not high, not absent) levels of tau PET are inclusion criteria.

In AD and primary tauopathies, different biomarkers related to tau and Aβ are available. For tau, different tau forms can be measured in fluids yielding insight into different pathologies. For instance, p-tau may be more reflective of Aβ pathology while MTBR and "total" tau correlate with tau pathology, although the latter should be cautiously employed as not all tau species may be captured by antibodies or visible by mass spectroscopy. Blood biomarkers, such as plasma p-tau (e.g., p-tau-217) for Aβ-related tau phosphorylation[59] and eMTBR-tau243 for tau tangle pathology,[58] should facilitate easier and faster selection of patients with positive Aβ pathology and low/medium tau pathology using less invasive, cheaper, and readily available tests in larger number of centers. Additionally, glial fibrillary acidic protein (GFAP) and NFL, as well as other complementary markers

indicative of gliosis, neurodegeneration, and synaptic dysfunction (e.g., CSF neurogranin) can be useful in association with functional readouts.[132] For tau PET, reduction in baseline values, progression rate of tau pathology, and/or progression to different brain regions can be used. Overall, the use and continuous optimization of biomarkers, both blood- and CSF-based and PET imaging,[23,55,63] is of utmost importance in the context of patient selection.

Clearly, for all these biomarkers (imaging or biofluids), it will also be necessary to determine thresholds of biological effects that translate into symptom-slowing effects. Accordingly, among different anti-Aβ trials, increased biological effects on Aβ plaque clearance were associated with slowing of cognitive decline.[32,33] Reducing Aβ pathology to a threshold below 24 centiloids (on PET, ± 70% reduction) is considered necessary for clinical efficacy. Importantly, thresholds of biological effects for tau required for clinical efficacy may differ in AD compared with primary tauopathies.

Besides patient selection, another concern impacting trial outcomes is patient exclusion. Currently, patients are not excluded based on the presence of alpha-synuclein (aSyn) pathology, a co-morbid pathology in ∼30% of patients clinically diagnosed with AD.[133] aSyn by itself can induce cognitive deficits, and Lewy body dementia can be misdiagnosed clinically as AD, as well as affect AD clinical trajectories.[134] Clinically diagnosed AD patients with aSyn may not respond to tau antibodies, enhancing clinical trial variability and impacting absence of efficacy outcomes. Optimized patient stratification based on excluding non-AD or AD patients with high co-morbidities and/or co-pathologies that drive cognitive deficits and symptom progression can lead to improved clinical trial design and outcomes. Other factors may include APOE genotype, stage of tau pathology, type of tauopathy, mono or combination therapy. This exclusion will be particularly important in initial tau-therapy validation, while future combined therapies can potentially enable treatment of patients with co-pathologies (aSyn and TDP43, among others) or different subgroups of patients.

The choice of endpoints is critical for demonstrating effective disease modification in clinical trials. The best-suited clinical endpoint depends strongly on the trial stage, target population, and regulatory strategy. The CDR-SB and iADRS (the integrated AD rating scale) are the current endpoints of choice following their use in the lecanemab and donanemab trials,[40,41] respectively. The CDR-SB is widely accepted and recognized as a primary endpoint by regulatory agencies for its broad assessments of cognition and function. CDR-SB assesses six domains and is sensitive in early AD, showing dynamic range in early symptomatic stages (mild cognitive impairment [MCI] due to AD and mild AD dementia). However, it may be subject to inter-rater variability and has limited granularity. The iADRS is a composite measure of ADAS-Cog and Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-iADL), which offers an integrated view of cognitive and functional decline and was used to validate donanemab and recent anti-Aβ trials. The iADRS has enhanced sensitivity to change, with a good signal-to-noise ratio in early AD and MCI but may still lack long-standing regulatory recognition despite the growing momentum. Both endpoints are suitable for disease-modifying therapy trials, but neither are AD-specific nor directly confirm "disease modification," which requires additional biomarker evidence (e.g., Aβ or tau PET, CSF, or blood markers). Hence, current best practices for maximizing the success of AD trials may involve using CDR-SB or iADRS, supported with biomarker evidence to indicate disease modification. Preferentially, secondary measures such as CGIC/CaGIC (clinical/caregiver global impression of change), quality of life and caregiver burden should also be included.

Overall, targeted epitope, IgG isotype, PTM, and pharmacokinetic characteristics are important design features for tau antibodies. Additionally, key crucial trial design considerations include the use of biomarkers of target engagement and targeting efficacy, biomarker thresholds that translate to clinical efficacy, patient selection (who and when), as well as exclusion and a choice of endpoint critical for demonstrating effective disease modification.

Back-translating tau immunotherapy trials: Clinical validation tau pathology propagation and its mechanisms

Previous research demonstrated the concept of seeding and propagation of tau misfolding and pathology in preclinical tauopathy models.[12,25,64–66,73–76,123,135,136] Extracellular release of misfolded tau and its subsequent uptake seeds aggregation of physiological intracellular tau in the recipient cell. This process bypasses the long lag phase of tau aggregation, accelerating and propagating tau pathology throughout the brain in functionally connected brain regions (Figures 3 and 4).[12,25,64–66,73–76,123,135–139] Accumulating evidence showing the presence of seeding- and propagation-competent tau forms and tau seeds in human brains of patients with AD and primary tauopathies support these concepts.[12,34,64–66,73–75,79,140] In human tauopathy patients, imaging data, functional connectivity, rate of disease progression, and tau seed analysis further support propagation of tau pathology and its contribution to progressive tau pathology and disease progression.[30,31,51,78,79,141–143] However, clinical proof of propagation of tau pathology in human AD brains is now emerging from the effects of bepranemab on tau PET, and of E2814 on tau PET/MTBR-tau243, both designed to target seed-competent tau and its propagation in preclinical models. The current trial outcomes thereby support a role for tau-seed-based propagation of tau pathology as a clinically validated contributory mechanism to progressive AD in humans.

Mechanistically, several cellular and subcellular mechanisms can contribute to pathological tau propagation in the brain.[28,144,145] Exosomes, tunneling nanotubes, unconventional secretion, extracellular vesicles, and multivesicular body release of tau seeds have been identified as mechanisms of tau release from cells.[28,146] Conversely, different molecular mechanisms have been identified for cellular uptake of tau seeds, including by interaction with (low-density lipoprotein receptor-related protein 1) LRP1 and heparan sulfate proteoglycans (HSPGs),[28,146–148] via MTBR region.[28,131,147,148]

In the bepranemab and E2814 trials, most of the antibody is anticipated to be present in the extracellular compartment, where it targets extracellular, freely available seed-competent tau, without—or with limited—access, to tau in tunneling nanotubes or extracellular vesicles. The successful slowing of progressive

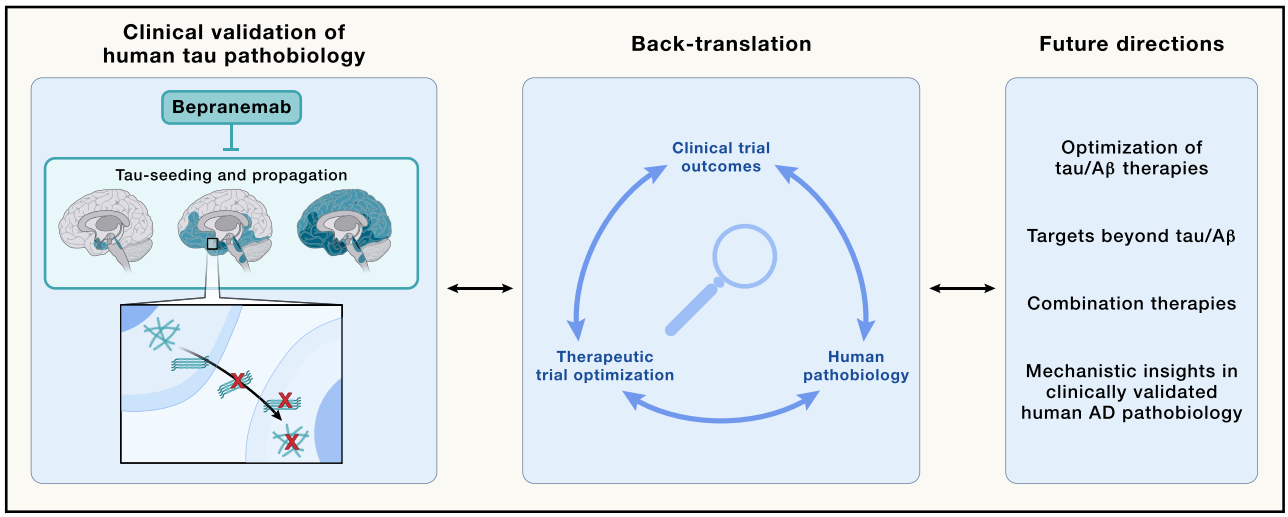

Figure 4. Back-translation to clinically validated insights in human tau pathobiology and future directions

Back-translation enables clinically validated human tau pathobiology insights useful for future development of tau-targeting therapies. Back-translation of clinical outcomes to human tau pathobiology and its mechanistic insights, is enabled by the specific, well-known and well-defined targeting epitope and MoA of passive immunization therapies. In general, back-translation of human AD and tauopathy pathology enable development of mechanism-based AD and tauopathy therapies toward increasingly effective trials for AD and tauopathies. Future trials extend to optimized trials for Aβ and tau, combination trials of Aβ/tau, and targets beyond Aβ and tau, including neuroinflammation and the neurodegenerative process (i.e., its hallmarks[19]) in AD and tauopathies (N). This optimization process is anticipated to lead to increasing insights into human pathobiology and increasingly effective trials with clinical efficacy. (Schematic presentation of tau propagation, based on and modified from Parra Bravo et al.[28]).

tau pathology in these trials suggests that a considerable portion of seed-competent tau is freely available in the brain parenchyma.[28,105,115] It is noteworthy that mechanisms of antibody internalization into neurons, and subsequent transfer to the cytosol, have been identified, and enhanced intracellular delivery is being therapeutically pursued, representing interesting alternative or additional approaches to target non-freely available seeds, or tau intracellularly.[104,115,130,149,150] For bepranemab however, neuronal cytosol levels depend on its uptake and subsequent lysosomal membrane rupture and are anticipated to be low compared with extracellular antibody levels.

The fact that these antibodies both target and bind the MTBR region, shown as necessary for tau seeding in preclinical models, suggests that targeting MTBR-encompassing tau forms and interfering with tau seeding presents a promising therapeutic strategy. However, consolidation of these insights will require confirmation of the disease-modifying effects in future trials. That no complete halting is yet obtained also indicates the need for further optimization.

Recent studies have identified similarities and differences in structure of mature tau aggregates in different tauopathies.[71,72,151] Therefore, tau antibodies that target different tau strains may need to be developed for different tauopathies.[71,72,151] Cryogenic electron microscopy studies have shown that the core structure of tau aggregates is composed of a subsegment of the MTBR domain (R3 and R4), while specific conformations vary according to the tauopathy type (Figure 4).[124,125] However, the common involvement of the MTBR tau domain again underscores its crucial role in tau aggregation. While progressive tau pathology strongly correlates with disease progression,[18–24] the executive tau polymorphs of the neurodegenerative process, driving clinical symptoms, still remain unidentified. Fully mature tau aggregates may not represent the main culprits, but rather oligomeric and intermediate soluble tau aggregates could be the toxic species.[81,82] Upcoming trial results from second-generation tau immunotherapies have the potential to shed light on specific tau forms and their respective contribution to the neurodegenerative process.

Despite the emerging insights, several questions regarding tau pathobiology remain. Although the bepranemab data provide clinical validation and insights into tau propagation, detailed mechanisms of tau uptake, clearance, and tau toxicity are still unclear. Furthermore, within the bepranemab's AD trial, APOE4 carriers displayed differential outcomes, which can suggest more aggressive biological processes, although this remains mechanistically poorly understood. Future trials may provide more insights into the differing tau pathogenetic processes dependent on APOE genotype. Similarly, differing mechanisms of tau pathogenetic processes in AD vs. primary tauopathies need to be clarified, as well as mechanisms of the progression and interaction of Aβ and tau co-pathologies in AD.

Taken together, the effects of bepranemab and E2814 on tau pathology (PET), cognitive endpoints (ADAS-Cog14), and some biofluid-based biomarkers for tau pathophysiology, provide the first proof of concept for an effect of tau antibodies in the clinic. They also support the concept of tau pathology propagation and spreading to different brain regions (Figure 4). Furthermore, these antibodies mostly have access to freely available extracellular tau, so their clinical effect suggests the contribution of this fraction to tau pathology propagation, while other pools (vesicles, nanotubes, and intracellular tau) may also contribute. Extracellular tau, and the epitope near the MTBR, targeted by these antibodies are considered to participate in the observed effects. Finally, the exact identity of the tau seeding and toxic tau

polymorphs remains unclear; in this respect, the cautiously promising results of bepranemab provide interesting insights, suggesting the antibody may target at least some seeding and toxic species. However, outcomes of ongoing and future tau trials—including postmortem analysis—will be critical to confirm and corroborate these early successes, as well as to gain in-depth insights into optimal targeting strategies and tau pathobiology in human subjects, to back translate the findings to research. This will be essential for the future success of tau therapies and their development into new treatment options for patients.

COMBINATION THERAPIES

With the commercial availability of anti-Aβ immunotherapies, therapies combining anti-tau and anti-Aβ strategies can now be explored in clinical trials. AD therapies targeting both initiation and execution mechanisms combined might provide more effective therapies. Currently, E2814 is being tested in combination with lecanemab in the presymptomatic DIAN-TU cohort, with a readout expected in 2028. Another combination trial with E2814 and lecanemab in early symptomatic MCI patients was launched in 2024, with readout expected in 2027. As different stages of pathology are present in various brain regions, combination of Aβ and tau therapies could target distinct stages of the disease process concomitantly. Combination therapies present an attractive perspective, although they raise additional inherent questions or challenges: are synergistic or complementary effects achieved? What is the impact of combination trials on adverse effects (ARIA, neuroinflammation)? How should these trials be designed and evaluated? What is the ideal timing for each treatment? Will efficacy of the respective targets be evaluated first based on biomarker efficacy, and how will their respective contribution on functional/clinical outcome be assessed? While this is not the aim of this perspective, combination trial designs and evaluation represent highly interesting prospects that will require in-depth and critically constructive consideration and optimization.

Furthermore, beyond Aβ (A) and tau (T), and their combination therapies, alternative targets are intensively pursued for AD therapies,[70,83,84,132] as crucial components of the biological framework. Neuroinflammation (involving TREM2, APOE, and others), as an essential component of the pathogenic process,[152–156] is now incorporated within the biological definition of AD, represented by the A(I)TN framework.[11,19,152–156] Within this framework "I" represents inflammation and is intensively pursued as target for AD and primary tauopathies, for developing increasingly effective disease-halting therapies. Finally, also other hallmark processes that drive the neurodegenerative process[19]—represented by N in the ATN framework—are intensively investigated for therapy development, including synaptic and neuronal network dysfunction, aberrant proteostasis (autophagy/lysosomal dysfunction), cytoskeletal abnormalities (e.g., neurofilaments), altered energy homeostasis, DNA/RNA defects, and neuronal cell death.[70,83,84,132,157]

LEARNINGS, CHALLENGES, AND FUTURE DIRECTIONS

We highlighted recent clinical advances that marked a turning point in AD therapeutics. Anti-Aβ therapies, lecanemab and donanemab, showed the first proof of disease modification based on Aβ clearance (PET based) associated with significant, moderate clinical benefit, and are regulatory agency approved. Trials with the second-generation tau antibody bepranemab and the tau-directed ASO BIIB080 followed up, delivering the first clinical evidence that slowing tau pathology is feasible, as shown by PET imaging, with early signs of cognitive benefit (bepranemab). These latter results represent proof of principle that tau-directed interventions have disease-modifying potential in humans. While corroboration of disease-modifying outcomes in multiple, large future tau trials will be critical and many challenges remain, these studies provide a basis for tau trial optimization, toward increasingly effective trials.

Such progress was built on decades of iterative Aβ trials, which pioneered the regulatory and biological framework for disease-modifying trials. This framework is built on the biological definition of AD, combined with imaging and biomarkers innovations, enabling validated biomarker endpoints, target engagement as a prerequisite for efficacy, as well as acceptable clinical outcomes (CDR-SB and iADRS). The Aβ experience also clarified key parameters for successful biologics: appropriate epitope targeting, antibody isotype and affinity, and pharmacokinetics. Furthermore, the concept of threshold of biological change required to achieve clinical benefit was set and critical for success. These insights catalyzed more rational trial designs, including biomarker-based patient selection/exclusion and disease staging.

The tau field has now capitalized on these foundations. Learnings from first-generation tau antibodies guided the refinement of second-generation candidates toward epitopes closer to the MTBR—a node for tau aggregation and propagation. Understanding of affinity, isotype, and pharmacokinetic properties ensures sufficient target engagement in the brain (or its closely related measurable compartment—the CSF), resulting in measurable biological effects on tau pathology (tau PET). Importantly, the absence of ARIA with tau-targeted therapies contrasts favorably with Aβ immunotherapy, supporting broader safety margins. Various tau-targeting trials are ongoing and will be critical to yield increasing insights and efficacy.

Clinically, these findings enable valuable back-translation to human tau biology. The effects of bepranemab/E2814 on tau pathology (tau PET/MTBR tau) and cognition (bepranemab) suggest that trans-synaptic propagation of extracellular free tau—outside nanotubes or vesicles—occurs in humans, contributes to tau pathology progression and is therapeutically tractable. Current outcomes support the involvement of the MTBR-region--encompassing forms, and efficacy of an IgG4 antibody supports the concept shown preclinically that strong effector function may not be necessary for tau immunotherapy. Together, the present data validate preclinical screening cascades in preclinical models as used for bepranemab and BIIB080 as more predictive of clinical translatability. Noteworthy, the recent outcomes indicate safety and early efficacy of recent trials, despite incompletely understood mechanisms. Future trials will be critical for confirmation as well as optimization toward increasingly effective tau therapies. While mechanistic understanding is not essential for effective therapies, it can guide innovative, more effective therapies.

Future development will build upon these mechanistic and trial design insights. Third-generation tau therapies will benefit from refined patient stratification, selecting individuals with low-to-moderate tau burden, before irreversible neurodegeneration (high tau pathology), and considering APOE4 status (APOE4 homozygotes responded less to bepranemab). Trial optimization will rely on quantitative tau PET and fluid biomarkers to monitor target engagement, tau pathology progression, spreading, or clearance. Dosing strategies must balance efficacy with manufacturability and global accessibility, given the scale of the AD population (low doses are needed). Thus far, safety outcomes remain favorable, providing a solid basis for long-term treatment.

Several challenges remain. The impact of co-pathologies, timing of intervention, and threshold of biological effect required for clinical benefit are not yet fully defined. The interplay of tau and Aβ also raises critical questions regarding sequence and combination of therapies, particularly given ARIA risk with high-effector Aβ antibodies. Moreover, the exact toxic tau species and mechanisms of neuronal injury remain incompletely characterized, but their elucidation may open routes to small-molecule therapeutics, which are potentially more scalable and cost-effective. Corroboration of the current disease-modifying outcomes in future tau trials will be crucial. And optimization of Aβ and tau trials are under development. Additional pathways, including neuroinflammation, APOE/TREM2 signaling, and pathways driving the neurodegenerative process (i.e., its hallmarks), represent promising targets. Together these efforts contribute to development of increasingly effective disease halting therapies, as complete halting is not yet obtained.

The Alzheimer's field has thus moved beyond the binary view of "Aβ versus tau." Tau and Aβ are interacting drivers within a broader neurodegenerative cascade of events, demanding multi-modal and mechanism driven, disease-modifying therapies. Optimization of mono- and multitarget therapies targeting Aβ and tau as well as other targets will lead to increasingly effective AD therapies. Advances in biomarkers, adaptive trial design, and back-translation from clinical to molecular insights are accelerating the trajectory toward true disease modification.

Despite the cautious enthusiasm, we acknowledge that no current treatment can yet sufficiently halt disease progression for patients, and that many important challenges remain. However, the convergence of current developments may provide a hopeful path for AD and related tauopathies for transitioning from an inexorable disorder affecting millions of individuals daily to future treatable conditions.

ACKNOWLEDGMENTS

H.Z. is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the Swedish Research Council (#2023-00356, #2022-01018, and #2019-02397); the European Union's Horizon Europe Research and Innovation Program under grant agreement no. 101053962; Swedish State Support for Clinical Research (#ALFGBG-71320); the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862); the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C, and #ADSF-24-1284328-C); the European Partnership on Metrology, co-financed from the European Union's Horizon Europe Research and Innovation Program and the Participating States (NEuroBioStand, #22HLT07); the Bluefield Project; Cure Alzheimer's Fund; the Olav Thon Foundation; the Erling-Persson Family Foundation; Familjen Rönströms Stiftelse; Familjen Beiglers Stiftelse; Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270); the European Union's Horizon 2020 Research and Innovation Program under the Marie Skłodowska-Curie Grant Agreement no. 860197 (MIRIADE); the European Union Joint Program—Neurodegenerative Disease Research (JPND2021-00694); the National Institute for Health and Care Research University College; London Hospitals Biomedical Research Centre; the UK Dementia Research Institute at UCL (UKDRI-1003); and an anonymous donor. G.U.H. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198), JPND Consortium, SynOD, "alpha-synuclein OMICS to identify drug-targets" (funded by the Federal Ministry of Education and Research, BMBF, 01ED2405A). I.D. received funding from Stichting Alzheimer Onderzoek Belgium (standard grants, SAO-FRA20240028 and SAO-FRA20220006), Methusalem Fund UHasselt (BOF Methusalem Fase I – BOF22M02), and BOF25IU03–iBOF/25/028: 2025 iBOF: The Interuniversity BOF projects program. Many elegant studies have directed the field; however, selections needed to be made due to limitations in the number of references. We apologize for omitted references. The manuscript was accepted before the 18th Clinical Trials on Alzheimer's Disease Conference (CTAD, December 1–4, 2025), precluding inclusion of data presented at the conference. This article is dedicated to all that have been or are affected by AD and related tauopathies and to their caregivers, who are combating tauopathies daily and hourly. This article aims to join their fight against AD and tauopathies.

DECLARATION OF INTERESTS

G.U.H. participated in industry-sponsored research projects from AbbVie, Biogen, Biohaven, Novartis, Roche, Sanofi, and UCB; received research support from GE Health; has ongoing research collaborations with Roche, UCB, AbbVie, and Ferrer; served as a consultant for AbbVie, Alzprotect, Amylyx, Aprinoia, Asceneuron, Bayer, Bial, Biogen, Biohaven, Epidarex, Ferrer, Kyowa Kirin, Lundbeck, Novartis, Retrotope, Roche, Sanofi, Servier, Takeda, Teva, and UCB; and received honoraria for scientific presentations from AbbVie, Bayer, Bial, Biogen, Bristol Myers Squibb, Esteve, Kyowa Kirin, Pfizer, Roche, Teva, UCB, and Zambon. His institution received research support from AbbVie. H.Z. has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD; is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program; and is a shareholder of CERimmune Therapeutics (outside the submitted work). J.-P.C. is one of the inventors of bepranemab and a stock owner of Discoveric bio alpha.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (GPT-5) OpenAI, 2025, as a language assistant in order to improve written text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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