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Tau Immunotherapies for Alzheimer's Disease and Related Tauopathies: Progress and Potential Pitfalls.

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Abstract

Tau immunotherapies have now advanced from proof-of-concept studies to Phase 2 clinical trials. This review briefly outlines developments in the field and discusses how these therapies may work, which involves multiple variables that are connected in complex ways. These various factors are likely to define therapeutic success in humans and have not been thoroughly investigated, at least based on published reports.

Keywords

Alzheimer's disease; antibodies; clinical trials; immunotherapies; mechanisms; tau; tauopathy

Introduction

There are currently eight clinical trials ongoing on tau immunotherapies with several additional ones in late-stage preclinical development. However the field is still in its infancy. Several therapeutic mechanisms may be involved and the importance of each one is not very clear. In addition, it is entirely unclear if the same pathway(s) of tau clearance will apply in human tauopathies. It is also quite possible that these promising therapies may work differently in different tauopathies, such as Alzheimer's disease versus Progressive Supranuclear Palsy. The purpose of this review is to provide an up-to-date status of the field and to point out the various uncertainties and barriers to success, and how these may possibly be overcome.

We published the first report showing the success of active tau immunization targeting the phospho-serine 396,404 region of the tau protein [1,2]. This study was undertaken based on the success of targeting the amyloid-β peptide by similar means [3], and was originally laid out in an R01 application that was funded in 2001 and contained one aim to test this approach (Immune Therapy for AD Plaques and Tangles, NIH, 1R01AG020197, Principal Investigator: Einar M. Sigurdsson). A 30 amino acid peptide surrounding this region, Tau379–408[P-Ser396,404], was selected based on various computer algorithms that

Conflict of Interest:

EMS is an inventor on various patents on immunotherapies and related diagnostics that are assigned to New York University. Some of those focusing on the tau protein are licensed to and are being co-developed with H. Lundbeck A/S.

suggested that it was highly immunogenic, which we confirmed to be the case, and because of its prominent appearance in Alzheimer's disease based on numerous prior publications. In the initial report, we showed that prophylactic immunizations in a mild alum adjuvant attenuated the development of brain tauopathy in JNPL3 mice, which have a familial tau mutation, P301L, and develop motor impairments as tau pathology advances in brain and spinal cord regions that influence movement. Less tau pathology in the immunized mice was associated with functional improvements in motor tests, which further supported this approach. In this study, we also showed that antibodies isolated from a high titer mouse entered the brains of tauopathy mice but not wild-type mice following peripheral injection, and could be found within neurons bound to pathological tau within 1 hour after administration. We subsequently showed that this immunogen worked as well in a different tauopathy mouse model, htau/PS1, that does not have a tau mutation, and in which cognitive improvements were detected following the immunization regimen [4]. In later studies, we showed that tau antibodies could have the same effect [5,6], and provided various insights into the possible mechanisms of clearance [7–19]. These studies have been confirmed and extended by various groups showing benefits of immune-targeting the pS396/404 tau epitope [2,4,6–9,12,20–27], and other tau epitopes [20,23–25,27–49], which as mentioned above has resulted in eight clinical trials (for a recent review of these trials see [50]), with several more likely to be initiated in the near future. We have highlighted many of these studies in some details in various reviews over the years as they have been reported so it is not necessary to elaborate further on those particular aspects (see for example [51–53]). Instead, I will go over some key points to consider as the field of tau immunotherapy matures.

How does it work?

At the time of the R01 submission detailing this approach, very little was known about how various amyloids spread within or between organs. For tau in particular, there was no particular evidence for extracellular spread of tau between neurons. Hence, specifically targeting extracellular tau with antibodies could not be well justified, although we mentioned it as a target in more general terms [2,54]. However, as detailed previously [2,54], several papers had been reported over the years showing that antibodies could enter neurons, in particular under pathological conditions, for example to neutralize viruses. Various low affinity receptors that bind Fc portions of antibodies exist on neurons and are likely an important part of the immune system when need arises. Antibodies have to be able to travel to any site within the body to combat infections. Since tau is mostly found intracellularly, it could be reasoned that as long as the antibodies could get into the brain, as had been shown in the Aβ immunization studies, they would likely be able to enter neurons to neutralize and/or promote clearance of pathological tau, as we subsequently showed in our first report. We have previously elaborated on the intracellular mechanisms involved [54]. With regard to the extracellular component, it should be mentioned that in the prior decades, several studies by multiple investigators on different amyloids, other than tau, suggested that a spread through anatomically connected regions of the same organ or by various means between organs, was an inherent feature of these proteins and peptides that acquire the β-sheet conformation that defines amyloids. We have previously put forward this possibility in a brief review of these studies [55]. When extracellular spread of tau pathology was then

shown to likely be an important part of tau pathogenesis (for review see [56,57]), pharmaceutical companies became particularly interested in targeting tau with antibodies as potential therapy for AD. Indeed, it seemed simpler and possibly safer than targeting tau intracellularly. The extracellular approach was more in line with targeting Aβ plaques, which had been shown to be successful, although those trials were starting to fail for other reasons. Those failures, and the well-known fact that the extent of tau pathology correlates better with the degree of dementia than Aβ burden, further shifted the early stage therapy studies to tau from Aβ. We have over the years in various venues suggested that both extra- and intracellular pathways are involved in antibody-mediated clearance of tau, and that the importance of each one may depend on several factors such as: 1) the tauopathy being targeted; 2) the stage of the disease, and; 3) the tau antibody (charge, epitope, isotype, affinity, whole vs. fragment), which we discuss below.

1) The tauopathy being targeted:

It has been shown by many groups that cerebrospinal fluid (CSF) levels of tau and pTyr181 tau increase in AD but not in various other tauopathies, compared to normal controls [58–60]. This consistent finding suggests that extracellular tau is unlikely to be an important component of tau pathogenesis in non-AD tauopathies. Hence, in those less common conditions, tau antibodies may need to work intracellularly to be effective. In this context, it is also important to note that recent mass spectroscopy studies show that most of CSF tau consists of tau fragments with ragged N- and C-termini that approximately consist of Tau150–250 [61,62]. Although there should be less tau degradation in interstitial fluid, a gradient of such cleavage likely exists in biological fluids that should influence antibody target engagement and clearance of pathological tau. Therefore, an antibody that targets tau outside the 150–250 region and only works extracellularly is likely to be less effective than: 1) such antibody that binds to tau intracellularly, where tau is less likely to have ragged termini, or; 2) an extracellular antibody that targets the 150–250 region. Likewise, recent mass spectroscopy studies of total brain tau indicate the presence of a protease resistant core of varying lengths within residues 243–406 of the tau protein in AD and other taupathies [63], suggesting at least a larger intracellular target pool for antibodies against this core.

2) The stage of the disease:

It is likely that at least certain antibodies may work better or worse than others, depending on the stage of the tauopathy, with sub-variables including the brain region and the particular tauopathy. Analysis of brains from different stages of the disease has shown that particular tau epitopes appear at different stages of the disease. The presumed epitope profile of each individual may have to be considered when deciding whom to enroll in a clinical trial and eventually which tau antibody to describe for therapy. It is also likely that the accessible pool of intra- and extracellular tau changes during the course of the disease, which may then also influence the choice of antibody.

3) The tau antibody (charge, epitope, isotype, affinity, whole vs. fragment):

With more publications on tau antibody therapies, it has become evident that various features of the antibody can greatly influence its mode of action and efficacy. The influence of some of these features was widely expected such as the epitope and isotype based on

related studies targeting Aβ and to some extent other amyloids/protein aggregates. However, other features have been less studied and have sometimes led to surprising results. For example, we have shown that a low affinity antibody is more effective than a high affinity antibody against the same region [12]. However, this is a complex issue as these antibodies are likely conformational to some extent and recognize different tau species [12], which may have different degree of importance for tau pathogenesis. The potential influence of antibody size has not been well studied but we have shown that it greatly affects antibody uptake into neurons and not necessarily as you would expect [9,11]. Finally, the importance of antibody charge for intracellular access has been well studied for potential cancer antibody therapies but not for tau antibodies or similar approaches targeting other amyloids. We have recently shown that antibody charge can robustly affect antibody uptake into neurons [19,64], which may explain why some labs detect tau antibodies inside neurons [2,7–9,11,12,14,39,40,65], whereas others do not for different antibodies [34,41,43]. This issue has particular importance for clinical trials because the humanized antibodies are likely to have a different charge than the mouse antibodies that they are based on. Therefore, the efficacy of the clinical candidate may be very different from its mouse counterpart, even though the binding site is the same. Other subtle structural changes associated with the humanization may also change the affinity profile of the antibody against different tau species. As mentioned above, higher affinity does not necessarily enhance efficacy and may actually have the opposite effect. It is also particularly difficult to anticipate how changes in affinity profile may influence efficacy because we do not really know which specific tau species are most pathogenic and/or most closely linked to functional deficits. It is also important to note that tau seeding or spreading may not necessarily be directly linked to tau toxicity. Both features of the disease are likely important for disease manifestation but may need to be tackled by different sets of antibodies, each of which may be more efficacious in certain tauopathies or at different stages of the disease.

As evident from this overview, the most variables rest within the antibody itself and these can be interdependent. Therefore, it is appropriate to discuss these in more detail, specifically for tau antibodies.

3a) Charge: We have published our preliminary findings within this important topic, with a more comprehensive manuscript under review [19,64]. Specifically, we showed that tau antibodies against different tau epitopes (1B9: P-Thr212/P-Ser 214; 2C11: P-Ser262; Tau-5: 210–244; and 4E6: P-Ser396/404) are taken up to a varying degree in primary neuronal cultures from tauopathy mice. This difference in uptake influences their efficacy and may be explained by charge differences as defined by their isoelectric point (IEP). Compared to the 4E6 antibody (IEP=6.5), the other antibodies are taken up to a much lesser degree (1B9 IEP=8.0; 2C11 IEP=7.8; Tau-5 IEP=5.1), indicating that a slightly acidic pH may be ideal for uptake, which decreases for more acidic or basic antibodies. To better compare how uptake affects efficacy, we then demonstrated that partial humanization of the 4E6 antibody, in which the Fc region and a part of the non-binding Fab region were replaced with a human scaffold, robustly shifted the IEP from 6.5 to 9.6. This charge difference greatly reduced its neuronal uptake and efficacy. This latter experiment highlighted as well that humanization can dramatically alter the efficacy of the antibody, and that such

antibodies should therefore be carefully studied before clinical trials to make sure that they will act as intended. We are not aware of other studies examining this for therapeutic tau antibodies but a report on single domain llama anti-tau antibody fragment as an imaging probe revealed a basic IEP (pI 9.5–10) for their diagnostic candidate [67]. It is likely that the potential effects of charge on neuronal uptake depends on the size of the molecule (antibody vs. fragment).

3b) Epitope: The epitope that was a part of the immunogen in our original report has been most studied and repeatedly shown to be a good target [2,4,6–9,12,15,20–27].

As mentioned above, an active vaccine, ACI-35, encompassing this epitope is now in clinical trials [68]. Targeting numerous other epitopes has been shown to be effective in several studies. These include non-phosphorylated- [27,30,32,41,42,46–48,69,70], phosphorylated- [20,24,25,27,29,35,39,43,49], conformational-/oligomeric [20,31,33,34,40,44,45], and a truncated epitope [66,71]. Since these studies have various designs, they cannot be easily compared to identify the best epitopes to target. However, a few studies have examined side by side antibodies that bind to different tau epitopes but those antibodies differ in other ways such as in their affinity, isotype and possibly charge as well [9,12,20,23–25,27,31,32].

3c) Isotype: This potentially important aspect has not been well studied, at least not publically. If the antibody is acting extracellularly, one question that is being asked is if it should have an effector function or not, to facilitate microglial phagocytosis of the antibody-tau complex. Only one report has explored this issue on antibodies with an identical Fab binding portion, indicating that an effector function is not necessary for efficacy in clearing pathological tau [72]. A prior study comparing two antibodies that recognize a similar epitope (pSer404) with comparable affinity suggested that effector function is beneficial, with an IgG2aκ isotype being effective whereas an IgG1aκ was ineffective [23]. For tau antibodies acting intracellularly, isotype may influence receptor-mediated uptake which relies on the Fc portion [8,40]. Antibodies of different isotypes may also differ in their charge which affects uptake. More studies are needed to clarify this variable but it is likely to be less important than for Aβ because the pool of extracellular tau is much smaller than for Aβ. Also, unlike Aβ, tau does not deposit in the vasculature, although it can be associated with it, which limits vascular side effects of the tau immunotherapy, which otherwise might be enhanced by microglial phagocytosis.

3d) Affinity: As mentioned above, we have recently reported that a low affinity antibody against the P-Ser396,404 region is effective in various culture and in vivo models, whereas a high affinity antibody against the same region is ineffective in the same models but more promising as a diagnostic imaging probe [12]. The antibodies are of the same isotype (IgG1k) but it should be emphasized that they differ not merely in affinity but also in their binding profile against various tau peptides and tau species from mice and humans. Although the profile differences are to some extent affinity related, they are also likely due to subtle differences in the exact epitope recognized although it is within the same region. A prior study showed that a low affinity antibody against a conformational epitope (MC1, aa7–9 and 312–342 [73]) was effective in a mouse tauopathy model, whereas a high affinity antibody, DA31, recognizing total tau (aa 150–190) was ineffective [31]. However, since the

epitopes are very different, other factors may influence these findings. Most recently, our preliminary findings showed that partial humanization of a consistently effective mouse tau antibody, 4E6, strongly enhanced its affinity for various aggregated and insoluble tau species but rendered it ineffective in tauopathy culture models [19]. This lack of efficacy may be because it no longer bound to pathological tau in solution and likely in part because its neuronal uptake was very limited after the humanization. As mentioned above, such reduced uptake can be explained by its shift to a strongly positive charge from a slightly negative charge (see Antibody charge above).

3e) Size: Most of the antibodies that have been tested for efficacy are whole antibodies (150 kDa). When antibody fragments have been examined, they have been scFvs (25 Da) which differ in affinity as well, and have not been compared to otherwise comparable whole antibodies containing the same CDR regions [74,75]. Also, these two studies used ultrasound [74] or vectored expression [75] of the anti-tau scFvs, which further complicates direct comparison with standard whole antibody therapy design. Hence, it is difficult to say anything about how size influences efficacy. When we examined antibody uptake in some detail, we compared whole antibodies, 4E6 and 6B2 against the P-Ser396/404 region, to their single Fab fragments (50 kDa) [9]. We expected it to be less because we had seen that about 80% of whole antibody uptake was Fc-mediated [8]. To our surprise, the percentage of neurons with antibody vs. Fab signal increased from about 25% to about 70% in tauopathy brain slices and from less than 10% to about 60% in wild-type slices. The Fab fragment is taken up by bulk endocytosis, which is a much less prominent uptake pathway by whole antibodies (about 20% with 80% being receptor-mediated [8]). It is also a less specific pathway than receptor-mediated endocytosis that may explain the wild-type uptake. We have since reported in preliminary findings that tau antibodies in wild-type neurons are cleared much faster than in tauopathy neurons as detected by multi-photon imaging, presumably because the wild-type neurons do not have tau aggregates for the antibodies to bind to [18]. It has yet to be reported if there are efficacy differences between whole antibodies and their Fab fragments. Although the affinity should be the same, avidity of whole antibodies will be greater. Because of their smaller size, more of the fragment may enter the brain but its half-life is shorter and more of it may be lost via non-specific uptake and subsequent degradation. Even smaller antibody fragments, such as single domain antibodies (sdAbs; 13 kDa) that contain only a heavy chain variable region, should be explored for efficacy and diagnostic imaging potential.

Toxicity concerns.

Most of the initial work on this important topic was conducted by the Rosenmann lab, which examined the feasibility of an active induction of an autoimmune disorder in mice by immunizing them with full length recombinant tau protein [76]. To promote this scenario, the mice received two very strong adjuvants, neither of which is approved for human use. The overall approach was indeed detrimental with the mice developing tauopathy and neurological deficits. Subsequently, her group showed that similar toxicity could be observed with repeated immunizations with phospho-peptide immunogens using the same strong adjuvants [77], but according to their prior work, not if fewer immunizations were

used [28]. Others later reported no obvious side effect of mouse immunizations with full-length recombinant tau using a milder adjuvant [37]. We have previously mentioned in reviews our then unpublished observations of enhanced mortality in 3xTg mice and in wild-type mice of the same mixed strain background [51,78], which has now been detailed in a publication [15]. Briefly, this particular mixed strain background led to a strong antibody response to Tau379–408[P-Ser396, 404], and substantial mortality after the fifth immunization. Surviving mice had sustained strong antibody titers until they were killed for analysis at an old age. Likewise, in a follow up study, mice of this strain background that received 4 immunization, from 2–6 months of age, maintained strong antibody titers until the end of the study at 22 months of age, which resulted in not only less tau pathology but also near complete clearance of Aβ deposits [15]. Together, these findings suggest that patients receiving active tau immunizations should be carefully monitored to minimize unnecessary vaccine boosts that may have detrimental side effects. Immune response is haplotype-dependent and varies between individuals. Apparently, this has not been an issue in at least one of the two active tau immunization clinical trials, which administers a KLH-linked tau294–405 in alum adjuvant [79]. Information about the second trial has been limited [68].

None of the numerous passive tau antibody studies in tauopathy mice have reported any side effects. However, one study that administered a total tau antibody to Aβ plaque mice reported treatment induced mortality that should be examined further for that antibody in various tauopathy and wild-type mice [80]. In the clinical trials, there have not been any major side effects reported and those that started first have now advanced to Phase 2. Human Phase 1 studies with one tau antibody were discontinued but apparently there were no safety or efficacy concerns, assuming that perhaps its half-life was too short.

A question that is often asked is if it is more likely that toxicity may be seen if a normal tau epitope is being targeted versus an epitope that is pathological or at least seen more prominently in the tauopathy than in healthy individuals. An advantage of targeting a normal tau epitope is that it is likely to be found as well in different forms of pathological tau, which then provides a greater pool to target. However, it should be kept in mind that these normal epitopes are often in the N-terminus, which appears to be cleaved away in many forms of tau (see Epitope section above). A short answer for antibodies is that targeting a normal tau epitope is unlikely to be very toxic, as supported by several reports on such antibodies, because it is unlikely that the antibody will see much of normal tau, which is primarily located in the cytosol. Intracellularly, findings from us and others indicate that tau antibodies mostly interact with tau in the endosomal-lysosomal system and may facilitate their lysosomal degradation [2,7–9,11,39,40]. Presumably, within these vesicles, antibody binding to tau may loosen up tau assemblies and thereby allow better access of lysosomal enzymes. Some antibodies may leak into the cytosol from the endosomes or lysosomes via unknown mechanism, such as tau antibody 6B2 as we have reported [9]. Such leakage may potentially interfere with normal functions of tau, although we have not detected any side effects of that antibody. It was also recently reported that an interaction of a tau antibody with cytosolic Fc receptor, TRIM21, inhibits seeded tau aggregation [65]. This finding suggests that tau antibodies may also have a cytosolic target to facilitate proteosomal clearance of misfolded tau. Extracellularly, tau is detected under normal and pathological conditions but it is not

clear if normal tau has any physiological extracellular function. If it does, clearing it extracellularly may be deleterious. It should also be kept in mind that other microtubule-associated proteins have similar functions as tau as reflected in the relatively normal phenotype of tau knockout mice [81]. Therefore, some antibody-mediated decrease in normal tau is unlikely to be detrimental per se, although there are always some concerns about possible development of an autoimmune disorder, in particular with active immunizations that are more irreversible than passive immunizations. Reduced tau levels have shown benefits in culture and mouse Aβ models [82,83], further alleviating concerns, and the feasibility of interfering with tau expression is being pursued as a potential therapy for AD.

Ongoing clinical trials.

There are currently eight clinical tau immunotherapy trials underway (Table 1). Two are on active- and six are on passive approaches.

The first trial uses a tau peptide encompassing amino acids 294–305 linked to KLH and administered in alum adjuvant in Alzheimer's patients [36,79]. This vaccine named AADvac-1, developed by Axon Neuroscience SE, is currently in Phase 2 [84].

The other active trial utilizes a phospho-serine 396,404 epitope that is administered in a liposome adjuvant in AD patients [22,68]. That vaccine termed ACI-35, originally developed by AC Immune SA and then licensed to Janssen, is presently in Phase 1 [68].

The six passive trials consist of antibodies targeting:

1. tau8–19 in healthy subjects and PSP patients, that was developed by iPerian and subsequently by Bristol-Meyers Squibb, and has now been licensed to Biogen [38,85,86] . Currently named BIIB092 (previously BMS-986168 and IPN007), it is in Phase 1–2 for PSP;
2. tau25–30 in AD (Phase 2, [87]) and PSP (Phase 2; [88]). It was developed by C2N Diagnostics, LLC (C2N-8E12; [32,89]) and has been licensed to AbbVie (ABBV-8E12);
3. an unidentified epitope that may be phospho-serine 409 (RO7105705) in healthy subjects and AD patients [72,90], and;
4. an unidentified epitope (LY3303560) in subjects that are healthy, or with mild cognitive impairments or AD (Phase 1, [91,92]) that is likely a humanized form of the conformational antibody MC1 [73,93], which as mentioned above has been effective in different mouse studies [20,31].
5. the middle region of tau in healthy subjects and AD patients (JNJ-63733657) [94,95].
6. Tau235–246 in healthy subjects (UCB0107) [95,96].

In addition, one trial examining an antibody against phospho-serine 422 (RG7345, RO6926496) was discontinued in its early Phase 1 stage in healthy subjects that are unlikely to have that epitope, presumably because of a poor pharmacokinetic profile.

Several other active and passive immunotherapies are in preclinical studies as detailed above and at least some of these are in clinical development and will enter clinical trials in the near future. As the ongoing trials are in their early stages, not much has been published about their progress. However, the fact that many have advanced to Phase 2 indicates that the therapies are not toxic and most likely some degree of target engagement has been observed.

Future directions.

It will likely be several years before we know if tau immunotherapies will be efficacious to slow the progression of tauopathies. Assuming that at least some of them will work, it is then likely that more resources will be put into developing active tau immunizations. Those are inherently riskier than passive immunotherapies because of the potential for immune response related side effects, in particular unwanted T-cell activation that may be difficult to control. One way to minimize such adverse reactions would be to tailor the vaccine to individual recipients. For example, by considering the haplotype of the patient, a tau immunogen can be selected that is likely to provide the desired antibody response while minimizing T-cell epitopes that could be detrimental to that particular person. An appropriate antibody response could be further modulated with different adjuvants to ensure sufficient but not too strong immune response to the vaccine. Once sufficient antibody titer is achieved, period boosts could be provided to maintain it. Overall, that approach would be much less expensive than monthly antibody injections and therefore larger populations could be treated. Eventually, after establishing sufficient safety profile, active immunization could possibly be used prophylactically. That will likely first be tested in individuals with familial mutations that will cause AD or other tauopathies, and subsequently in persons that, for known or unknown reasons, have an increased risk of developing a tauopathy.

Advances in tau brain imaging have now resulted in several promising β-sheet dye compounds that appear to be selective for tau aggregates, although non-specific binding has now been reported for some of them and their use discontinued [97,98]. Also, these probes are not good at detecting non-AD tauopathies, suggesting some structural differences in the tau lesions [97,98]. Antibody fragments should be more specific and, if they can be delivered to the brain in sufficient amounts for PET detection, may allow documenting the epitope profile of the individual that could result in a more personalized immunotherapy, targeting those specific epitopes. Promising findings have been reported on this approach by us and others, supporting its further development [11,67].

Conclusions

Following our report in 2007 showing the feasibility of tau immunotherapies, findings from multiple groups have confirmed and extended this approach, which has resulted in several clinical trials that have now advanced into Phase 2. It will be several years until we know if any of these will be effective. Some may fail for various reasons, some of which are outlined

above. Hopefully many others will show disease modifying benefits, which should then spark the initiation of additional trials that may include combination therapies at the earliest stages of the disease that could be guided by improvements in tau imaging probes.

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Table 1:

Clinical trials on tau immunotherapy

	Tau Epitope	Subjects	Current Stage	Company
Active immunization				
AADvac-1	Tau294–305	AD	Phase II	Axon Neuroscience SE
ACI-35	P-Ser396,404	AD	Phase I	AC Immune SA - Janssen
Passive immunization				
BIIB092 (BMS-986168, IPN007	Tau8–19	Healthy, PSP	Phase I-II	Biogen (Bristol-Meyers Squibb; iPerian)
ABBV-8E12 (CN2–8E12)	Tau25–30	AD, PSP	Phase II	AbbVie (C2N Diagnostics)
RO7105705	P-Ser409?	Healthy, AD	Phase II	AC Immune SA – Genentech - F. Hoffman La Roche AG
LY3303560	Conformational (7–9, 312–342)	Healthy, MCI, AD	Phase I	Eli Lilly
RG7345, RO6926496	P-Ser422	Healthy	Phase I - discontinued	F. Hoffman La Roche AG
JNJ-63733657	Middle region	Healthy, AD	Phase I	Janssen
UCB0107	235–246	Healthy	Phase I	UCB Biopharma

Abbreviations: AD - Alzheimer’s disease; PSP - Progressive supranuclear palsy; MCI - Mild cognitive impairment