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Review

An effective treatment for Alzheimer's disease must consider both amyloid and tau

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Alzheimer's disease (AD) is a devastating neurodegenerative disorder resulting in cognitive impairment, loss of executive functions and progressive dementia. AD is the most common cause of dementia and incidence is increasing, probably due to a rapidly ageing population. Despite research efforts and a substantial unmet medical need, no effective cure has been identified and treatment remains symptomatic. In this review, I assess the current status of AD research and examine future approaches for the development of a potential disease-modifying treatment. Research has focused primarily on amyloid pathology, after a correlation was discovered between mutations in several genes associated with amyloid processing and AD. The Amyloid Cascade Hypothesis suggests that increased amyloid beta (Aβ) aggregation is the major cause of AD, triggering the toxic events that lead to progressive neurodegeneration. However, no drug candidate targeting the cascade has yet produced a successful treatment. It is now speculated that treatment requires early targeting of Aβ, when pathology remains reversible, and clinical trials are focusing on assessing Aβ compounds in pro-dromal AD. Lack of an effective Aβ-focused treatment has resulted in the consideration of hyperphosphorylated neurofibrillary tangles of tau (NFT), another major pathological hallmark of AD. Studies have repeatedly demonstrated a strong correlation between NFT build up and cognitive decline, and recent studies have identified a number of tau genetic markers associated with AD. Compounds preventing the hyperphosphorylation of tau may therefore halt disease progression; however, the failure of previous tauopathy trials in progressive supranuclear palsy (PSP) has highlighted potential set-backs. The importance of tau as an independent cause of AD, and therefore a target for treatment, may be clarified by ongoing tau-focused clinical studies. Although Aβ and tau are both highly relevant, their relationship in causing AD remains unknown. Amyloid- and tau-targeting treatments may individually prove effective, however the convergent progression of Aβ and tau pathology suggests combination therapy may eventually be required, particularly in late stages of disease when both are abundant. While ongoing work focuses on single target therapies, a dual Aβ and tau targeting approach may be more likely to produce a breakthrough.

Key words: Alzheimer's disease (AD), amyloid beta (Aβ), tau, neurodegeneration, tauopathy, dementia

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Introduction

Alzheimer's disease (AD) is an age-related, neurodegenerative disorder characterized by progressive neuronal loss in areas of the brain associated with cognitive learning and memory. AD occurs due to a combination of pathological changes in the brain which result in severe neuronal and synaptic loss, causing the brains of patients to weigh up to one-third less than that of an age-matched non-demented individual (Laferla, Green and Oddo, 2007). AD is the most common cause of dementia, accounting for approximately 60–80% of all cases (AD Facts and Figures, 2010). It is estimated that 35.6 million people worldwide suffer from dementia, with numbers expected to double every 20 years (Prince *et al.*,

2013; WHO, 2012). As well as the substantial personal cost, the total estimated worldwide financial burden of dementia was $604 billion in 2010 (Wimo *et al.*, 2013).

Extracellular amyloid beta (Aβ) aggregates, and intracellular hyperphosphorylated neurofibrillary tangles (NFT) of tau, constitute the two major pathological hallmarks of AD (reviewed by Finder, 2010). These characteristic pathologies have resulted in the proposal of two theories regarding the cause of AD. The Amyloid Cascade Hypothesis identifies increased Aβ aggregation or decreased Aβ clearance as the primary cause of disease, developing years prior to clinical onset (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). Accumulation of pathogenic Aβ peptide species and insoluble plaque formation is believed to trigger a number of detrimental processes, including hyperphosphorylation of tau, which lead to neuronal death (reviewed by Pimplikar, 2009). The Tau Hypothesis is based on evidence that tau tangle pathology occurs prior to Aβ plaque formation and more closely correlates with disease progression and severity than Aβ plaque load (Braak and Braak, 1991). Although the mechanism by which Aβ and tau interact remains uncertain (Ittner and Gotz, 2011), evidence has implicated both to be causative of AD.

AD results in a spectrum of symptoms including mild cognitive impairment, deficits in short-term and spatial memory, emotional imbalances, loss of executive functions and progressive dementia (reviewed by Pimplikar, 2009; Singh *et al.*, 2012). The disease can be divided into two main categories, sporadic late-onset AD (LOAD) and early-onset familial AD (FAD) (Finder, 2010). FAD accounts for less than 1% of all cases (AD Facts and Figures, 2010), with onset occurring between the ages of 55 and 65 due to genetic predisposition (Bird, 1999). Although uncommon, mutations identified to cause FAD have provided important insights into the potential causes of sporadic AD, for which the greatest risk factor is ageing (Finder, 2010). FAD mutations implicated Aβ as a primary cause of disease, resulting in the Amyloid Cascade Hypothesis becoming the dominant focus of research. However, failure to develop an Aβ targeting compound into a successful treatment for AD has cast doubt upon its relevance, resulting in the Tau Hypothesis re-surfacing. There are currently a number of ongoing clinical trials assessing the ability of tau inhibitors to reduce AD progression (ClinicalTrials.gov Identifiers: NCT01689233 and NCT01689246). Definitive conclusions regarding the relevance of these tau-based drug candidates lie with the completion and publication of clinical trial results.

Despite substantial efforts in drug development and an increased understanding of the underlying pathology of AD, no effective treatment has yet been identified. All currently approved drugs target symptoms and improve quality of life rather than modify disease progression. These treatments have relatively short-term, limited benefits (Takeda *et al.*, 2006; Raina *et al.*, 2008) and emphasize the urgent need to continue the research efforts. Repeated failures to develop an effective, disease-modifying therapeutic, suggests the need to re-think the current approach to AD treatment. This review considers the hypothesis that the Amyloid Cascade is an insufficient target for the treatment of AD, and development of a potential cure must consider both amyloid and tau pathology together.

The Amyloid Cascade Hypothesis

The Amyloid Cascade Hypothesis identifies Aβ aggregation or decreased Aβ clearance as a trigger of the toxic events leading to substantial neurodegeneration (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). Aβ is generated through the proteolytic processing of the type 1 integral membrane glycoprotein, amyloid precursor protein (APP) (Finder, 2010). APP was identified in 1987 (Kang *et al.*, 1987) and duplication of the *APP* locus was subsequently reported to cause autosomal-dominant early-onset AD and cerebral amyloid angiopathy (CAA) (Rovelet-Lecrux *et al.*, 2006). Processing of APP to Aβ occurs via one of the two major pathways, the amyloidogenic pathway and the non-amyloidogenic pathway, through cleavage by a group of enzymes called alpha (α), beta (β) and gamma (γ) secretases. It is now widely accepted that Aβ occurs in two predominant forms, Aβ1-40 and Aβ1-42, sharing a common N-terminus but differing in their carboxy-termini (Younkin, 1998; Jankowsky *et al.*, 2004).

Under normal, non-pathological circumstances, the non-amyloidogenic pathway predominates, resulting in the cleavage of APP by α-γ-secretases. This pathway precludes deposition of intact Aβ peptide by producing a smaller, less amyloidogenic form of Aβ only 40 residues in length (Aβ1-40), which is less likely to aggregate and cause toxicity (Jarrett, Berger and Lansbury, 1993). Under pathogenic circumstances, APP is cleaved by β-γ-secretases to produce the more amyloidogenic Aβ1-42, the major species detected in the brains of AD patients (Iwatsubo, 1998; Finder and Glockshuber, 2007). Overproduction of Aβ1-42 has been reported to cause FAD and is speculated to be a cause of sporadic AD (Younkin, 1998). Aβ1-42 is considered pathogenic due to its greater hydrophobicity and longer length of 42 residues (Jarrett, Berger and Lansbury, 1993).

Processing of APP by γ-secretase activity constitutes the final step in the release of both Aβ1-40 and Aβ1-42 (Herreman *et al.*, 2000). Two genes, Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*), encode for the proteins presenilin 1 (PS1) and presenilin 2 (PS2), respectively, both of which contribute to the secretase complex. Mutations in these genes have been identified as being correlative of AD (Younkin, 1998).

The Tau Hypothesis

The Tau Hypothesis identifies tau hyperphosphorylation as an independent and primary cause of AD, due to observations that tau tangle pathology occurs prior to Aβ plaque formation and that NFT load more closely correlates with disease progression and severity than plaque load (Braak and Braak, 1991). Alois Alzheimer first reported his findings of NFT in 1907 (Alzheimer, 1907), and a correlation between tangle formation and

Alzheimer's dementia was identified in 1968 (Blessed, Tomlinson and Roth, 1968). The structure and composition of these characteristic tangles were not established until 1988 (Goedert *et al.*, 1988). In AD brains, hyperphosphorylated tau is the major component of both NFTs in pyramidal neurons, and neuropil threads in distal dendrites (Finder, 2010). NFTs are filamentous inclusions of tau which occur both in AD and in other tauopathies (Lee, Goedert and Trojanowski, 2001; Querfurth and LaFerla, 2010). Under normal conditions, tau is a soluble, abundant protein found in axons, which maintains assembly and stability of microtubules and vesicular transport (Finder, 2010; Querfurth and LaFerla, 2010). Microtubule-associated tau protein has been reported to be critical for normal neuronal activity in the mammalian brain (Iqbal *et al.*, 2005).

Phosphorylation and dephosphorylation of tau is regulated by various kinases and phosphatases that add or remove phosphate residues, respectively (Iqbal *et al.*, 2005; Querfurth and LaFerla, 2010). Under pathological conditions, such as AD and other tauopathies (Lee, Goedert and Trojanowski, 2001), hyperphosphorylation of tau results from both an imbalance in tau kinase and phosphatase activity and changes in tau's conformation (Iqbal *et al.*, 2005). These changes render tau protein insoluble and reduce its affinity for microtubules, causing it to detach and spontaneously self-associate into paired helical filament structures (Querfurth and LaFerla, 2010). These filaments then aggregate into NFTs, disturbing and impairing axonal transport (Finder, 2010). Toxic forms of tau protein eventually 'choke' the neurone by preventing the possibility of normal neuronal metabolism and causing progressive neurodegeneration (Iqbal *et al.*, 2005; Wischik *et al.*, 2010). The resulting toxicity eventually leaves behind only a marker of a previously existing neurone, referred to as a 'ghost' tangle (Wischik *et al.*, 2010).

The amyloid hypothesis fails to explain all aspects of AD; evidence suggests tau may fill the gaps

Studies have provided a wealth of supporting evidence for the Amyloid Cascade Hypothesis, emphasizing Aβ to be a primary cause of AD. However, the pathogenic nature of Aβ has become increasingly questioned due to evidence reporting the presence of Aβ plaques in healthy individuals, the lack of a defined pathogenic Aβ species and the repeated clinical failures of Aβ targeting drug candidates (reviewed by Pimplikar, 2009). Recent research suggests that NFT formation occurs early and is a primary cause of toxicity (Wischik *et al.*, 2010), whilst Aβ plaque formation may be a late-stage, neuroprotective event (reviewed by Maccioni *et al.*, 2010). The theory that tau is an independent cause of AD is strengthened by observations that tau oligomers are directly toxic to neurons and tau pathology correlates with clinical cognitive decline in AD (Wischik *et al.*, 2010). Tau hyperphosphorylation may be a convergent point of toxicity in the AD brain (Maccioni *et al.*, 2010), highlighting the potential for tau-targeting therapeutics in clinical AD.

Genetics

Supporting evidence for the Amyloid Cascade Hypothesis was provided by the mapping of several Aβ-increasing FAD mutations to the *APP* gene (Owen *et al.*, 1990) and the predisposition of Down's syndrome patients to AD due to elevated lifetime APP production (Glenner and Wong, 1984; Rovelet-Lecrux *et al.*, 2006).

Studies have identified over-expression of APP, and subsequent generation of the Aβ1-42 peptide, to be central to neuronal degeneration observed in AD (Skaper, 2012). Down's syndrome patients present with elevated APP, due to triplication of chromosome 21 (the location of the *APP* gene), and develop increased Aβ accumulation in early life (Singh *et al.*, 2012). Such patients often develop AD in their 30s, suggesting that increasing Aβ production predisposes individuals to AD (Singh *et al.*, 2012).

FAD, which typically manifests with an early-onset pathogenesis (Laferla, Green and Oddo, 2007), is characterized by similar Aβ pathology to sporadic AD, providing insights into the possible causes of disease. A number of mutations, including 32 *APP* missense mutations, over 150 *PS1* mutations and 20 *PS2* mutations, have been identified as correlative of AD (Pimplikar, 2009; Finder, 2010). These mutations result in either elevated production of total Aβ or a specific increase in the levels of Aβ1-42, (Citron *et al.*, 1992; Cai, Golde and Younkin, 1993; Bekris *et al.*, 2010). Interestingly, protective mutations such as the A673T variant of APP, result in a 20% reduction in lifelong production of Aβ and prevent individuals from developing cognitive impairments and AD (Jonsson *et al.*, 2012). Therefore, mutations that increase Aβ production predispose individuals to AD, whereas those that decrease Aβ appear protective. However, some *PS1* mutations promote neurodegeneration and frontotemporal dementia (FTD) without causing an increase in Aβ plaque pathology or altering the Aβ40 to 42 ratio (Shioi *et al.*, 2007), suggesting that their ability to cause neuronal toxicity in AD may be distinct from their effects on Aβ production. Furthermore, no correlation between increased Aβ42, induced by FAD mutants and age of disease onset was reported (Scheuner *et al.*, 1996). Therefore, although some studies provide strong evidence for the involvement of *APP*, *PS1* and *PS2* in AD, they do not identify Aβ is the single primary cause of disease. Indeed, reports of neuronal dysfunction via pathways independent of APP and Aβ (Shioi *et al.* 2007; Baki *et al.*, 2008) have reduced the focus on Aβ as the causative agent of AD (Caughey and Lansbury, 2003, reviewed by Pimplikar, 2009).

Understanding the genetic basis of tau pathology in AD is advancing rapidly. Initial evidence linking tau tangle formation to neurodegeneration was provided by other tauopathies, displaying characteristics similar to AD. Tauopathies encompass a number of disorders, all of which result from the accumulation of abnormally hyperphosphorylated tau and are associated with NFT formation and dementia (Iqbal

et al., 2005). Over 30 mutations found on chromosome 17 (the location of the gene which encodes for tau, *MAPT*) are associated with FTD and parkinsonism, supporting dysfunctional tau protein as a primary cause of neurodegenerative disease (Goedert and Jakes, 2005). Identified mutations in *MAPT* reduce the ability of tau protein to interact with microtubules and increase its tendency to assemble into abnormal filaments (Goedert and Jakes, 2005), consistent with tau pathology in sporadic AD. A recent genome-wide association study found genetic markers associated with elevated levels of tau and phosphorylated tau in the cerebrospinal fluid of AD patients (Cruchaga *et al.*, 2013). Research led by Dr. Alison Goate yielded particular genetic signals linked to enhanced tau pathology in the brain and a faster rate of cognitive decline (Cruchaga *et al.*, 2013). Although additional research is required to identify where these candidate genes are expressed and whether more may be associated with tau-related pathology, the results highlight the possibility of novel therapeutic targets or alternative models of AD. In addition, the findings demonstrate the ability of tau pathology to cause AD independently of Aβ pathology.

Pathophysiology

The Amyloid Cascade Hypothesis fails to explain the poor correlation between plaque load and the degree of dementia in humans (Terry *et al.*, 1991). Although one study identified a correlation between cognitive dysfunction and Aβ plaque formation in the entorhinal cortex (ERC) (Cummings *et al.*, 1996), many have reported a weak and inconsistent, if any, relationship between Aβ pathology and cognitive decline (Crystal *et al.*, 1988; Arriagada *et al.*, 1992). It was reported by Crystal *et al.* (1988) that cortical senile plaque count did not distinguish between demented and non-demented individuals. This was supported by reports of non-demented individuals presenting with significant plaque load upon autopsy (Wischik *et al.*, 2010). Live molecular imaging techniques have since confirmed the presence of plaques in the brains' of cognitively normal individuals *in vivo* (Nordberg, 2008; Villemagne *et al.*, 2008). These findings suggest that plaques are not necessarily causative of memory deficits, indicating flaws in the Amyloid Cascade Hypothesis. Importantly, the lack of correlation between plaque load and cognition has likely influenced the clinical failure of many Aβ-targeting therapeutics. However, recent data have suggested that the species of Aβ is important for toxicity, and that Aβ plaques may constitute a less toxic aggregate (reviewed by Pimplikar, 2009). The exact role of Aβ in AD therefore remains unknown.

Conversely, tau aggregation and the resultant brain lesions observed in AD have been repeatedly reported to correlate with clinical dementia and cell death (Iqbal *et al.*, 2005; Wischik *et al.*, 2010). Hyperphosphorylated tau is reported to spread in a clearly defined sequence, mapping clinically to measurable stages of cognitive decline and physically to stages of loss of brain function seen in AD patients (Braak and Braak, 1991; Braak *et al.*, 2011). Transgenic mice expressing human mutant *MAPT* predominantly in layer 2 of the ERC, demonstrated a subsequent spreading of pathology with ageing to regions of the brain innervated by ERC neurons, particularly the hippocampus which is greatly affected in the later stages of AD (Liu *et al.*, 2012). The spreading of tau pathology was found to be consistent with that seen upon post-mortem examination of human AD brains (Liu *et al.*, 2012). These findings suggest that tau-targeting treatments designed to inhibit the spreading of pathology in the early stages may have the potential to halt disease progression.

Animal models and clinical trials

Identifying FAD mutations allowed AD to be modelled in animals, although their usefulness remains controversial due to the repeated failure of drugs effective in animal models to treat AD in humans. Currently used animal models have been developed using mutated *APP*, *PS1* and *MAPT* genes, commonly APP_{Swe}, $PS1_{M146V}$ and $MAPT_{P301L}$ (Oddo *et al.*, 2003). These models develop plaques and tangles in an age-dependent manner and closely represent human AD (Oddo *et al.*, 2003; 2006; Filali *et al.*, 2012). Importantly, mice expressing a combination of mutant *APP*, *PS1* and *MAPT* genes display plaques and tangles, and a reduction of both Aβ and tau is required to ameliorate cognitive decline (Oddo *et al.*, 2006). Aβ reduction alone failed to demonstrate improvement in the cognitive phenotype in both spatial and contextual learning and memory paradigms, highlighting the potential role of tau in cognitive decline in the presence of concomitant Aβ pathology (Oddo *et al.*, 2006).

As of May 2014, all Aβ-targeting treatments have failed to generate significant improvements when trialled in the clinic, according to the ClinicalTrials.gov database (Table 1). Anti-amyloid immunotherapy became the focus of Aβ-targeting research, following the finding that anti-amyloid monoclonal antibodies dissolved Aβ aggregates and prevented their formation *in vitro* (Solomon *et al.*, 1996). However, Aβ immunotherapy has been faced with a number of safety and efficacy drawbacks, including encephalitis, a lack of clinical improvement and an absence of effect on NFTs (Rosenmann, 2013). As a central role of NFTs in dementia is becoming more apparent, it is likely that clearance of amyloid pathology is insufficient to improve dementia symptoms in AD patients. Indeed, although amyloid pathology has often been found to be upstream of tau pathology, amyloid-toxicity has been reported to be tau-dependent, highlighting the potential for tau-targeting therapies to prevent both pathologies (Rosenmann, 2013).

The failure of anti-amyloid trials has triggered discussions assessing the cause of drug candidate failure. Importantly, recent Phase III trials of bapineuzumab and solanezumab reported that approximately 25% of study patients diagnosed with mild AD had negative positron emission tomography (PET) Aβ imaging (Karran & Hardy, 2014). As these patients lack Aβ pathology, they are unlikely to benefit from anti-amyloid treatments, therefore impacting the overall efficacy outcome of the study. In addition, many argue that the

targeted patient population often presented with abundant and irreversible Aβ pathology at the time of the trials (Karran, Mercken and De Strooper, 2011). Karran, Mercken and De Strooper (2011) proposed an Aβ trigger scenario explaining AD progression. They suggested that during disease progression an Aβ deposition threshold is eventually reached, whereby there is sufficient 'aggregate stress' to initiate or accelerate tau pathology, which then becomes self-sustaining and Aβ-independent. At this point, therapeutic intervention cannot be effective. Interest in this theory has initiated clinical trials testing individuals with early signs of dementia, termed prodromal AD, who are considered at risk of developing AD (Karran, Mercken and De Strooper, 2011). These trials present a huge clinical challenge, particularly regarding the selection of the clinical trial population and ethical considerations. F. Hoffmann-La Roche Ltd. is currently assessing a monoclonal antibody that recognizes Aβ, gantenerumab, in patients within the prodromal phase (Ostrowitzki *et al.*, 2012). The mechanism by which anti-amyloid antibodies remove Aβ from the brain is speculated to be via effector cell-mediated phagocytosis or direct dissolution of amyloid (Weiner and Frenkel, 2006). Gantenerumab is reported to cause Fc receptor/microglia-mediated phagocytosis of amyloid, followed by lysosomal degradation (Bohrmann *et al.*, 2012). If unsuccessful in Phase III, this trial will suggest past failures are not due to administration of Aβ-therapeutics too late in disease progression, confirming flaws in the Aβ-focused approach to AD treatment. Importantly, previous anti-amyloid trials (Table 1) have tested several compounds, each with distinct mechanisms of action. It is therefore probable that different stages of the disease process and various forms of Aβ have already been targeted, further emphasizing the failure of this approach. Targeting Aβ alone at clinically relevant stages of AD, when Aβ and tau pathology are abundant, has so far appeared insufficient to successfully treat the disease, probably due to its highly complex, multi-factorial pathology. Ongoing preventative anti-amyloid investigations, including the Dominantly Inherited Alzheimer's Network (DIAN), Alzheimer's Prevention Initiative (API) and Anti-Amyloid treatment in Asymptomatic Alzheimer's Disease (A4) trials (Carrillo *et al.*, 2013), will provide further insights into early AD development and progression, and may answer the long-standing questions regarding the Amyloid Hypothesis.

Tau-based drug discovery is advancing rapidly, although limited focus on tau in previous years has hindered the progression of such therapeutics to Phase III trials. A number of inhibitors of tau aggregation have already been identified, with three distinct mechanisms of action (reviewed by Brunden, Trojanowski and Lee, 2009). Tau-based research has focused primarily on compounds that either inhibit the kinases responsible for phosphorylation of tau or inhibit the aggregation of tau. Compounds preventing the disassociation of tau from microtubules have also been investigated,

Table 1. Progress of late-phase clinical trials targeting the Amyloid Cascade Hypothesis

Drug type	Drug name	Phase	Reason for failure
Aβ aggregation inhibitor	Alzhemed™ (Tramiprosate)	III	Results obtained could not support a claim for clinical efficacy (ClinicalTrials.gov Identifier: NCT00088673)
γ-Secretase Inhibitor	Semagacestat	III	Evaluated in two Phase III trials, the Interrupting Alzheimer's dementia by evaluating treatment of amyloid pathology (IDENTITY) trial and the IDENTITY-2 trial (ClinicalTrials.gov identifier: NCT00594568 and NTC00762411). Patients receiving Semagacestat displayed an increased deterioration in cognition and activities of daily living compared to placebo-treated controls. Semagacestat was also found to be associated with an increased risk of skin cancer compared to placebo (Karran, Mercken and De Strooper, 2011)
γ-Secretase modulators	Flurizan™ (tarenflurbil)	III	No statistically significant effect in co-primary outcome measures of cognition and activities of daily living was observed (ClinicalTrials.gov Identifier: NCT00105547)
Aβ active immunotherapy	AN1792	III	Safety findings were reported, including the development of aseptic meningoencephalitis and leukoencephalopathy in 6% of vaccinated patients (ClinicalTrials.gov Identifier: NCT00021723)
Aβ passive immunotherapy	Bapineuzumab	III	No significant efficacy found. Furthermore, vasogenic oedema was reported during the study, particularly in ApoE4 carriers. Due to these safety findings, the highest dose was discontinued (ClinicalTrials.gov Identifier: NCT00575055 and NCT00574132; Salloway *et al.*, 2014)
	Solanezumab	III	Failed to reach its cognitive or functional endpoints in either of two double-blind, placebo-controlled trials in patients with mild to moderate Alzheimer's disease EXPEDITION and EXPEDITION-2 (ClinicalTrials.gov Identifier: NCT00905372 and NCT00904683, Siemers *et al.*, 2010), despite acute and sub-chronic treatment attenuating or reversing memory deficits in transgenic mice (Imbimbo *et al.*, 2012)
	Gantenerumab	II/III	Ongoing (Clinical Trials.gov identified NCT01224106, NCT02051608 and NCT01760005)

Numerous failures and discontinuations have highlighted possible inconsistencies in the Amyloid Hypothesis. (Information from ClinicalTrials.gov, Alzforum.org, Rosenmann, 2013).

although to a lesser extent (reviewed by Boutajangout *et al.*, 2011; Zhang *et al.*, 2012). Glycogen synthase kinase 3β (GSK3β), cyclin dependant kinase 5 (CdK5) and microtubule-affinity-regulating kinase (MARK) have been reported to collectively represent the three major tau kinases responsible for phosphorylation of tau (reviewed by Geschwind, 2003; Chung, 2009). Substantial pre-clinical work has demonstrated that GSK3 and CdK5 inhibitors can prevent tau hyperphosphorylation (reviewed by Bhat *et al.*, 2008; Boutajangout, Sigurdsson and Krishnamurthy, 2011). Tau-based immunotherapy has also emerged as a potential approach for reducing both Aβ and tau pathology and has been explored in animal studies (reviewed by Rosenmann, 2013). Some of the most advanced tau-based therapeutics being evaluated in the clinic are the tau aggregation inhibitors. Rember® recently became the first tau-aggregation inhibitor to be clinically investigated by TauRx®, a company dedicated to tau-based therapeutics (taurx.com). TauRx® reported success in completed Phase II trials assessing Rember® (ClinicalTrials.gov Identifier: NCT00515333) and subsequently initiated two ongoing Phase III trials assessing the second-generation drug LMTX™ (ClinicalTrials.gov Identifier: NCT01689233 and NCT01689246). However, lack of published data regarding the completed Phase II trials, along with the current absence of any additional conclusive Phase III trials, highlights the need to be cautious when considering the potential of tau-based therapeutics. Furthermore, the Allon small peptide davunetide, developed to target tau pathology, failed to meet its primary and secondary endpoints when evaluated in a Phase II/III study in PSP (ClinicalTrials.gov Identifier: NCT01110720). Similarly, tideglusib, a GSK-3 inhibitor developed by Noscira, failed to meet its co-primary endpoints in two separate Phase II studies in PSP and AD (del Ser *et al.*, 2013; Tolosa *et al.*, 2014; ClinicalTrials.gov Identifier: NCT01049399 and NCT01350362). However, tideglusib was reported to reduce global brain atrophy compared with placebo in the PSP study, with the largest effect seen in the parietal and occipital lobes, indicating a possible neuroprotective effect (Höglinger *et al.*, 2014). Importantly, these brain areas are only minimally impacted in PSP, providing an explanation for the lack of clinical outcome in this population (Höglinger *et al.*, 2014). The pilot study of tideglusib in AD reported trends towards cognitive improvement, although these failed to reach statistical significance due to the small sample size (del Ser *et al.*, 2013). As tideglusib has been reported to target the frontal lobe and hippocampus, the potential of GSK-3 inhibitors in AD should be further explored (Höglinger *et al.*, 2014).

Tau-based therapeutics may still represent the first major breakthrough in disease-modifying treatment for AD; however, such claims have yet to be supported by successful Phase III trials. Unlike Aβ-targeting therapeutics, targeting tau pathology may hold the potential to delay cognitive decline at later stages in disease progression, when Aβ and tau pathology are present. This has been particularly supported by accumulating evidence from anti-tau immunotherapy, demonstrated to effectively reduce tau-pathology and improve the symptoms of dementia in animal models, including motor function and cognitive decline (reviewed by Rosenmann, 2013). As tau-based drug development is some 20 years behind Aβ, the advancement of current pre-clinical tau-targeting compounds to the clinic is highly anticipated and may prove extremely informative.

Tau and amyloid interact to cause disease

The relationship between Aβ and tau in AD pathogenesis remains controversial. Although drug development has often focused on targeting Aβ and tau pathology in isolation, both may require targeting for effective disease-modifying treatment. Continued research into their interplay will provide alternative methods for intervention. Current evidence from *in vitro* and *in vivo* models suggests three possible mechanisms by which they interact (Fig. 1).

Aβ is causative of some tau pathology

Several studies have provided evidence that tau tangles can be induced by Aβ. Ferrari *et al.* (2003) reported that exposure to Aβ was sufficient to induce tau filament formation in a human tissue culture system, in the absence of mutations in tau (Ferrari *et al.*, 2003). Furthermore, mice with mutations in the genes encoding APP and tau displayed a sevenfold increase in NFTs, compared with mice with mutations only in the tau gene (Lewis *et al.*, 2001). In the same study, Aβ plaque formation was unaffected by the presence of tau lesions (Lewis *et al.*, 2001). Similarly, intracranial injection of Aβ42 fibrils into mutant tau transgenic mice caused a fivefold increase in

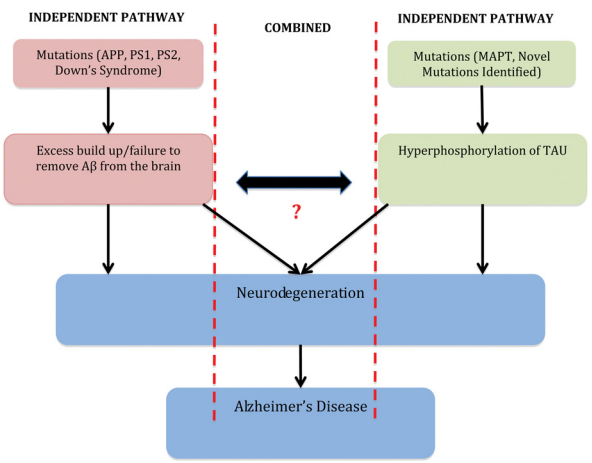

Figure 1. Progression of AD pathology. Flow chart to depict the toxic pathways reported to lead to development of AD. Whether Aβ is causative of tau pathology or vice versa is currently unknown. It appears likely that both eventually promote a pathway of neuronal degeneration, leading to progressive dementia and death.

NFT pathology as early as 18 days post injection (Gotz *et al.*, 2001). This increase in AD-like tau pathology suggests that Aβ may be toxic via acceleration of tau hyperphosphorylation, supporting the theory that compounds targeting Aβ may be sufficient to treat AD by preventing tau pathology. However, at later stages in disease progression, when hyperphosphorylated tau is self-sustaining, Aβ-targeting therapeutics have proven ineffective. Importantly, tau aggregates can form in the absence of Aβ pathology, for example in FTD, where mutations in tau-encoded *MAPT* genes result in the hyperphosphorylation of tau (Ballatore, Lee and Trojanowski, 2007). However, it is possible that while mutant tau may circumvent the need for Aβ-induction of hyperphosphorylation, wild-type tau may still require Aβ to trigger tangle formation. It may also be argued that although diseases such as FTD provide important insights into tau-based pathology in AD, they remain distinct from AD in their symptomatology and pathology. Regardless, the observation that tau pathology can occur in the absence of prior Aβ pathology has enhanced research into tau toxicity in isolation, building supportive evidence for the theory that tau develops early and acts as a primary and independent cause of AD.

Tau is required for neurodegeneration and Aβ pathology

With many Phase II and III clinical trials targeting Aβ failing to produce a marketed treatment for AD (ClinicalTrials.gov), the view that tau is a secondary effect of Aβ pathology is becoming less favourable. Rapoport *et al.* (2002) reported that tau-depleted neurons showed no signs of degeneration in the presence of Aβ, providing direct evidence to support an essential role for tau in the Aβ-mediated toxicity and neurodegeneration seen in AD (Rapoport *et al.*, 2002). Furthermore, Ittner *et al.* (2010) reported that tau reduction blocked Aβ and excitotoxin-induced neuronal dysfunction. Although tau is predominantly found in axons, it is thought to have an important dendritic role that confers Aβ toxicity at the post synapse through targeting of the Src Kinase FYN, a substrate of which is the NMDA receptor (Lee *et al.*, 1998). Tau therefore may be involved in the early-phases of AD, in contrast to the widely accepted theory that tau is secondary to Aβ toxicity. Transgenic mice expressing truncated tau (tTau) or deficient in tau ($Tau^{-/-}$) showed disruptions in postsynaptic targeting to FYN, arresting Aβ-mediated excitotoxicity by reducing interactions of NMDA receptors with postsynaptic density protein 95 (PSD95) (Ittner *et al.*, 2010). Excitotoxicity is increasingly accepted as the mechanism by which Aβ exerts toxicity and, by blocking this mechanism using mice deficient in tau or expressing truncated tau, memory deficits were prevented and survival was improved (Ittner *et al.*, 2010). Tau-initiated Aβ toxicity is further supported by the observation that NFT formation predates plaque formation (Braak *et al.*, 1996), suggesting tau pathology may be present prior to Aβ pathology. However, more recent research has suggested that only certain forms of Aβ are inducers of tau pathology and that Aβ plaques are a late-stage Aβ species, diminishing the significance of this claim (reviewed by Pimplikar, 2009). It is now accepted that Aβ oligomers may be a more toxic form of protein aggregation, with plaques being less relevant to disease progression, although research aimed at reducing Aβ plaques is still ongoing (ClinicalTrials.gov).

Aβ and Tau demonstrate synergistic effects

It has been suggested that tau and Aβ interact by targeting different components of the same system to amplify each other's toxic effects downstream (reviewed by Ittner and Gotz, 2011). An example of such synergistic effects is the implication of both Aβ and tau in the impairment of mitochondrial proteins related to complexes I and IV of the oxidative phosphorylation system, in mice expressing $APP_{Swe}PS2_{N141I}MAPT_{P301L}$ which display both Aβ and tau pathology (Rhein *et al.*, 2009). It was found that deregulation of complex I was tau-dependent, whereas deregulation of complex IV was Aβ dependent, both at the protein and activity levels (Rhein *et al.*, 2009). Therefore, by acting on the same system, tau and Aβ may enhance the downstream toxic events related to AD. Although the mechanism of Aβ and tau interplay remains largely unknown, this provides evidence for a molecular link between the proteins and AD pathology. It appears almost certain that they interact to either cause or enhance the progression of AD. Therefore, although no proof of concept is currently available, a combined therapy targeting both pathologies may eventually constitute the most effective approach to treatment.

Conclusion

As proof of a single dominant underlying cause of AD remains inconclusive, it is logical to accept that both tau and Aβ pathologies are highly influential. Considering this statement, a disease-modifying therapeutic must target both pathological hallmarks. A range of drug candidates targeting Aβ alone have now been assessed, all of which have reported limited success in clinical trials. Of these, immunotherapy appears to most effectively target Aβ deposits in the brain, despite failing to reduce cognitive decline. Supporters of the Amyloid Cascade Hypothesis have therefore emphasized the potential of immunotherapy to treat early AD, before Aβ pathology becomes irreversible (Karran, Mercken and De Strooper, 2011). Indeed, observations of Aβ pathology in years prior to clinical onset of dementia warrant continued clinical trials assessing Aβ-targeting therapeutics in prodromal AD. Such ongoing trials will provide a definitive answer regarding the relevance of treatment approaches targeting the Amyloid Hypothesis. Previous research has implicated Aβ as one of the major contributing factors rather than the sole cause of disease. Substantial research now implicates hyperphosphorylated tau an independent cause of AD, and tau inhibitors are currently being investigated in clinical trials (ClinicalTrials.gov Identifier: NCT01689233 and NCT01689246). Due to the current lack of published data regarding these drug candidates, it remains premature to

suggest that tau-based treatments will provide a cure for AD. The outcome of the ongoing Phase III trials investigating tau inhibitors, along with continued research into tau genetic markers that predispose individuals to AD and alternative tau-targeting pre-clinical compounds, will begin to define the future of tau-based therapeutics (Cruchaga *et al.*, 2013). Success will have widespread implications for both AD and other tauopathies. In AD, it appears that tau pathology constitutes a final common pathway in disease progression and correlates closely with cognitive decline, highlighting the potential for tau inhibitors to prevent onset or worsening of cognitive impairment. Evidence strongly suggests that at clinically relevant stages of AD, where Aβ and tau pathology are abundant, Aβ targeting therapeutics are insufficient to effectively reverse dementia. Therefore, although targeting Aβ may be appropriate prior to dementia onset, numerous failures in Aβ therapeutics support the need to re-think the current approach to symptomatic AD, considering both Aβ and tau pathology together. Although amyloid- and tau-targeting therapeutics may still independently prove successful, the highly complex nature of AD pathology suggests that effective intervention will not consist of a 'one-drug wonder', and a combined therapy will almost certainly constitute the final step in the development of a cure.

Author biography

Claire Lansdall received a First Class BSc Medical Sciences Honours Degree at the University of Leeds, England in 2013. Throughout her studies, she developed an interest for Neuroscience Research, in particular for the neurodegenerative Alzheimer's disease. Her interests also include other neurological and psychological disorders. She is currently an Intern at F. Hoffmann-La Roche Ltd., working in the area of Neuroscience Clinical Development, and she will be commencing a PhD in Clinical Neurosciences at the University of Cambridge, England, in 2014. Her future aspirations include pursuing a career in academia and the Pharmaceutical Industry.

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