Biometals and Their Therapeutic Implications in Alzheimer's Disease

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Abstract No disease modifying therapy exists for Alzheimer's disease (AD). The growing burden of this disease to our society necessitates continued investment in drug development. Over the last decade, multiple phase 3 clinical trials testing drugs that were designed to target established disease mechanisms of AD have all failed to benefit patients. There is, therefore, a need for new treatment strategies. Changes to the transition metals, zinc, copper, and iron, in AD impact on the molecular mechanisms of disease, and targeting these metals might be an alternative approach to treat the disease. Here we review how metals feature in molecular mechanisms of AD, and we describe preclinical and clinical data that demonstrate the potential for metal-based drug therapy.

Keywords Alzheimer's disease · Iron · Copper · Zinc · Chelation therapy

Introduction

Alzheimer's disease (AD) is characterized by profound dementia, commonly presenting as impairment to memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving, and functional abilities. At an anatomic level, AD manifests with neuronal and synaptic loss, particularly in the hippocampus, frontal cortex, temporal lobe, parietal lobe, and cingulate gyros. The aging population

demographic of our society will inevitably lead to increased AD incidence in the future, adding to an already substantial financial and social burden. Despite an extensive effort by the scientific community, there remains no disease modifying therapy to halt or slow the decline of patients with AD.

The current dominant therapeutic approaches for AD have emerged from the amyloid cascade hypothesis. This hypothesis was raised in 1992 [1], and encapsulates the dominant thinking in AD research. This hypothesis emphasizes the importance of β -amyloid ($A\beta$), the major component of senile plaques [2], as an upstream factor in AD pathogenesis, and posits that $A\beta$ initiates a cascade of toxicity, which recruits tau, the major component of tangles in AD pathology [3], and consequently causes neuronal dysfunction, neurotransmitter deficits, and, ultimately, neuron death. $A\beta$ is generated by cleavage of amyloid precursor protein (APP) [4], which can occur via 2 sequential pathways: the nonamyloidogenic and amyloidogenic pathways. The first cleavage event, by α -secretase or β -secretase, determines whether $A\beta$ is generated; the proceeding cleavage by γ -secretase determines the species of $A\beta$ to be generated. β -secretase activity is contributed mostly by an integral membrane aspartic protease named β -site APP-cleaving enzyme 1 [5], and γ -secretase is a protease complex consisting nicastrin, presenilin enhancer 2, anterior pharynx-defective 1 and presenilin, which harbors the active site [6].

The implication of the amyloid cascade hypothesis is that targeting $A\beta$ should prevent molecular pathology of AD and alter the course of the disease. Accordingly, $A\beta$ -based therapeutics have been extensively investigated in preclinical models and clinical trials. Most prominently, phase 3 trials have been performed on drugs that lower $A\beta$ by inhibiting its production [7, 8] and lowering its levels by immunotherapy [9, 10], all of which failed to reach their respective clinical endpoints. There is an urgent need, therefore, for fresh approaches to treat AD.

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We have for several years been investigating the role of transition metals (e.g., iron, copper, and zinc) in the pathogenesis of AD, and whether targeting metals could impact on the course of disease. There is dysregulation of the homeostatic mechanisms of iron, copper, and zinc in AD, and these metals can bind pathologically to A β and tau proteins [11]. We, and others, have integrated the metal hypothesis of AD with the amyloid cascade hypothesis, and preclinical and clinical data demonstrate that metals might be a more tractable drug target to address underlying disease mechanisms of AD. In this review, we will describe the setbacks with A β -targeted drug discovery and discuss current and future opportunities for metal-based drug therapy.

Clinical Trial Setbacks for Drugs That Target A β

Despite extensive empirical data demonstrating the upstream role for A β in AD toxicity, targeting this peptide by multiple avenues has not been effective in clinical trials [12]. AN-1792 was the first active immunotherapy strategy for AD. In PDAPP mice (overexpressing a disease-related mutant APP), immunization prevented and rescued the AD behavioral and pathological phenotypes [13]. The multinational phase 2a trial in people with mild-to-moderate AD was suspended when 6 % of patients had a side effect, including 4 with aseptic meningoencephalitis [14]. In a follow-up analysis of the phase 1 clinical trial, the treatment group had less plaque burden at autopsy (some even had complete plaque removal) but dementia presentation was not different between the treatment and placebo group [15]. In the phase 2 trial, those who responded to the immunization (anti-AN1792 titers >1 : 2200) had improved cognition and attenuated brain volume loss compared with placebo patients [16].

A few passive immunotherapy approaches have undergone phase 3 clinical assessment, including bapineuzumab, gantenerumab, and solanezumab. Bapineuzumab appeared, in a 12-month phase 1 study, to be safe in patients with mild-to-moderate AD. Two phase 2 studies were conducted, showing no significant benefits in cognitive measurements [17], but reduced cortical amyloid burden [18]. Some cognitive and functional improvements were observed in a subset of apolipoprotein E ϵ 4 noncarriers [17], which prompted 4 additional phase 3 trials. Two completed trials failed to show effect on either cognitive or functional outcomes, and the other trials were discontinued [10]. Gantenerumab was shown to bind to cerebral A β in APP/presenilin 1 (PS1) transgenic mouse model, to reduce amyloid burden in mouse brain, and to prevent the formation of new plaque [19]. Roche started a phase 2 trial (clinical trial number: NCT01224106) and the Dominantly Inherited Alzheimer Network initiated a phase 2/3 trial (clinical trial number: NCT01760005) to test for efficacy. These trials are ongoing. Solanezumab was

developed by Lilly, and in phase 2 clinical trials there was a significant dose-dependent increase in A β 42 in cerebrospinal fluid but no indication of clinical benefit [20]. In phase 3, 2 trials were performed and no benefits in cognitive functions of patients with AD were found [9]. However, a secondary analysis of patients with mild AD pooled from both trials showed a significant effect on cognition, promoting the Dominantly Inherited Alzheimer Network's 5-year phase 2/3 trial (clinical trial number: NCT01760005), which is currently ongoing.

Small molecules that could modulate γ -secretase, and thus production of A β , have been tested in phase 3 clinical trials. A γ -secretase inhibitor, semagacestat, was tested in a phase 2 trial and a significant reduction in plasma A β 40 was found [21]. However, the phase 3 trial was halted after interim analysis showed worsening of cognition and increased incidence of skin cancer [8], which was predicted previously [22]. Later, a γ -secretase modulator, tarenflurbil, was tested in a 12-month phase 2 study in people with mild-to-moderate AD. This trial found no effect on cognition, although with higher dose and patients with mild AD there were small benefits [23]. This encouraged a phase 3 clinical trial in 1600 patients with AD but found no beneficial effects in cognitive function and quality of life [7], which resulted in termination of 2 additional phase 3 trials and further development of this compound. Currently, there are still a few phase 3 clinical trials ongoing for AD targeting A β , including the abovementioned gantenerumab and solanezumab, and a β -secretase inhibitor, MK-8931.

Challenges in Targeting Amyloid

Despite the setbacks in drug discovery, the amyloid cascade hypothesis still represents the best explanation of the pathological phenomenon in AD. However, direct targeting of A β is difficult owing to the unidentified toxic species of A β and its complex interaction with tau.

Various A β species exist within the brain, including A β 1-39, A β 1-40, A β 1-42, A β 1-43, and A β 3-42. The toxic species of A β is still unknown and therefore we do not have a clear target for pharmacotherapy; this is one possible explanation of why A β -based drugs have not been effective so far. Traditionally, it was believed that A β 1-42 is predominately responsible for toxicity observed in AD. Two key observations support this theory: 1) familial AD mutations in APP elevate the expression of A β 1-42 [24, 25]; and 2) A β 1-42 is more prone to aggregation and is more toxic than A β 1-40 [26, 27]. However, it was reported that pyroglutamate-A β , which is also presented in AD plaques, could also be the toxic isoform of A β [28–31]. Pyroglutamate-A β is more prone to aggregation compared with A β 1-42 [29]. Mice overexpressing this peptide showed a selective hippocampal

neurodegeneration [31], and passive immunization against this peptide reduces the amyloid burden in an APP/PS1 double-transgenic mouse model [30]. In addition, A β 1-43, generated by a disease-related PS1 mutant, was recently profiled as an overlooked neurotoxic isoform as this species was shown to have a higher propensity to aggregate and was more toxic than A β 1-42 [32].

The various isoforms alter the aggregation propensity and therefore its solubility. In AD, A β exists in both soluble and insoluble forms, with the later associated with plaques. Plaques (containing insoluble amyloid fibrils) were initially thought to be the toxic A β source in the earlier version of amyloid cascade hypothesis [1]; however, subsequent findings suggest that soluble A β oligomers are more likely to be the source of A β toxicity, while insoluble fibres are inert (for a review see [33]). Numerous studies have postulated specific toxic forms of A β ; however, the field is without a clear conclusion. A higher molecular weight A β oligomer (about 56 kDa) was purified from Tg2576 mice (an APP mutant mouse model of AD) and demonstrated to be toxic [34]. It was then found that naturally secreted oligomers (a mixture of trimers and dimers) can inhibit LTP in vivo [35] and disturb cognitive function in mice [35, 36]. The toxic species of these “naturally secreted oligomers” was narrowed down to the “A β dimer” (based on its 8-kDa molecular weight), as that “A β dimer” isolated from AD brains is capable of impairing memory in mice [37]. However this so-called dimer was identified to be an APP fragment containing A β [38].

Therefore, the toxic species of A β in AD is still under debate. It is unknown if any of the drugs tested in clinical trial, which target alternative cleavage of APP, or target A β species immunologically, have been effective in isolating the toxic A β isoform. Moreover, it was recently shown that not all the therapeutic antibodies bind to A β species in plasma or post-mortem brain samples, which potentially explains why they were not effective in clinical trial [39].

It is also still unknown how A β induces toxicity to neurons, which has slowed the development of drugs that target intracellular consequences of A β toxicity. It is generally accepted that tau protein is an intracellular mediator of A β toxicity. A β induces tau hyperphosphorylation, aggregation, and enhances tau toxicity. Treating cell cultures with multiple forms of A β , including soluble A β 1-42 [40], A β oligomer [41], and A β fibril [42] induces tau hyperphosphorylation. A β -induced tau hyperphosphorylation consequently caused microtubule disassembly [41, 43], reduction of total soluble tau and an increase in tau fragments [44], missorting of tau into dendritic areas [41], activation of the nuclear transcription factor of activated T cells' apoptotic pathways [45, 46], and cell toxicity [41, 44]. 2xTg (tau and APP mutant) or 3xTg (tau, APP and PS mutant) mice exhibit enhanced neurofibrillary tangle formation [47–50], which was attributed to activation of glycogen synthase kinase (GSK)-3 β and Cdk5 [49, 51],

and inhibited proteasome activity [50]. Additional overexpression of tau does not enhance A β pathology in vivo [51], supporting the notion that tau pathology is downstream of A β . The effects on tau seen in the 2xTg mouse can be recapitulated by direct A β fibril injection, implying that A β is the minimal fragment of APP required to transform tau [52]. Similarly, A β vaccination reduces both A β and tau pathology and protects against neuron loss [53–55].

Interestingly, A β -induced cytotoxicity was shown to be tau-dependent in primary neuronal culture with either genetic depletion of tau, or using an undifferentiated neuronal culture (which has a lower tau level than differentiated neurons) [56, 57]. Tau knockout studies revealed that the A β -induced axonal transport deficits and impairment of hippocampal LTP were mediated by tau [58, 59]. Reduction of endogenous tau was also shown to ameliorate cognitive behavioral deficits and the death rate of APP overexpressing mice [60–62]. However, while young APP^{+/+}tau^{-/-} mice (4–7 months old) exhibit better cognitive function [60, 61], aged APP^{+/+}tau^{-/-} mice (12 months old or older) showed enhanced degeneration [63], indicating that loss of tau function alone may be toxic. Further investigations found that loss of tau induces parkinsonism and dementia phenotypes [64–66], suggesting that excessive lowering of tau should be avoided in therapeutic strategies for AD.

While substantial laboratory data show a role of tau in mediating A β -induced cytotoxicity, tau-based therapies have yet to be explored in phase 3 clinical trials. Targeting tau, or other downstream mediators of A β toxicity, might be a more effective approach to treating the disease. It has been shown that AD plaque burden begins 20 years before the onset of disease [67], so targeting A β when the disease is clinically manifest might be too late in the temporal sequence of the disease.

While the amyloid cascade hypothesis of AD still maintains broad support, the failure of drugs that target A β has led to growing skepticism of this explanation of AD. Indeed, positron emission tomographic (PET) imaging data have shown that amyloid can be removed from the brain by immunotherapy, and this does not translate into improved clinical outcomes [68]. This supports the hypothesis that the presence of amyloid plaque in the brain reflects the presence of the disease but is not directly involved in neurodegeneration. It has been suggested that amyloid plaque is a protective response to underlying disease processes, as the presence of plaque inversely correlates with oxidative burden and synaptic loss [69, 70]. Copper enhances A β cytotoxicity to cultured cells, which is ameliorated by co-incubation with zinc [69], which rapidly precipitates the protein [71]. Plaque may therefore be a protective response in AD by performing metal sequestration [72]. Targeting plaque “tombstones”, therefore, would not affect disease progression, but correcting the underlying disturbance in metal homeostasis could be a more tractable therapeutic avenue.

Metals in AD

While the amyloid cascade hypothesis may yet still prove to be valid, as described above, there are many challenges to targeting A β , and no approach so far has been effective in patients. Here, we present a hypothesis that targeting metals in AD might be an alternative, more tractable, therapeutic strategy. We outline the studies describing the manifest changes to metals (zinc, copper, iron) in the AD brain, and how changes to metals might impact on the established disease mechanisms of AD. Finally, we describe the outcomes of various preclinical and clinical attempts of targeting metals in AD.

Zinc

Bulk tissue analysis of the postmortem AD brain has generated inconsistent changes between AD and controls [73–77], which might reflect different anatomic areas examined and different sample preparations (e.g., tissue fixation affects zinc measurement [78]). But analysis of bulk tissue zinc content is likely to miss the most interesting changes to zinc in the AD brain. In AD, there is a redistribution of zinc into extracellular plaques and surrounding neuropil [71, 79–82]. Zinc binds A β residues 6–28 causing rapid aggregation and precipitation of the peptide [71, 83]; thus, co-deposition of zinc with A β could initiate plaque formation in the disease.

Zinc-induced plaque formation in disease is also supported by the anatomic distribution of plaque and zinc in the brain. Plaque formation only occurs in neocortical regions of AD-affected brains, but A β is expressed in all brain regions. The distribution of plaque closely aligns with the expression of a key zinc-transporting protein of glutamatergic neurons, ZnT3. ZnT3 traffics zinc into synaptic vesicles and zinc is released into the synapse upon exocytosis. APP transgenic mice crossed with mice lacking ZnT3 were shown to have reduced plaque burden compared with single transgenic mice [84], which demonstrates the contribution of endogenous zinc to amyloid burden in AD. Zinc “trapping” in amyloid plaque is also likely to be deleterious to synaptic function as loss of synaptic zinc in ZnT3 KO mice causes impaired cognition, recapitulating AD [85]. Synaptic zinc deficiency is further exacerbated in AD by lower expression of ZnT3 [82].

Zinc also interferes with A β processing. A disintegrin and metalloproteinase domain-containing protein 10, the α -secretase involved in the physiological processing of APP, is a zinc-dependent enzyme and zinc increases APP proteolysis [86], while zinc inhibits γ -secretase activity [87]. Zinc also increases PS1 expression, and presenilin protein also facilitates cellular zinc uptake [88]. Finally, A β bound to zinc is resistant to proteolysis by zinc-dependent matrix metalloproteases [89, 90].

Zinc might also impact on tau-related neurotoxicity in AD. Zinc can bind to tau and cause its aggregation [91–93]. Zinc is

elevated in neurons with neurofibrillary tangle pathology [79], which could alter tau translation and phosphorylation by GSK-3 β , protein kinase B, extracellular regulated kinase 1/2 and c-Jun N-terminal kinase [94–96].

Iron

Iron elevation in affected areas of brain is a feature of a number of neurodegenerative disorders, including Parkinson's disease and AD [97, 98]. Iron elevation in AD brains, first demonstrated in 1953 [99], is a consistently reported finding [99–108]. Neuronal iron deposition causes oxidative stress via the Fenton reaction, which might contribute to elevated oxidative stress observed in the AD brain [109]. Iron-induced oxidative stress has been shown to initiate several apoptotic signaling pathways in neurons [110], and damage proteins such as Ca²⁺-ATPase [111–114], glutamate transporter [115–117], apolipoprotein E [118, 119], and Na⁺/K⁺-ATPase [111, 114, 120, 121], as well as *N*-methyl-D-aspartate (NMDA) receptor [122–124], and lipids such as cholesterol [125–127], ceramides [128, 129], and unsaturated fatty acids [130–133], as well as sphingomyelin [134, 135]. Oxidative damage to proteins and lipids by iron can cause synaptic dysfunction and neuronal cell death [136].

Elevated iron can also cause cell death independently of free radical toxicity by causing ferroptosis, a type of Ras-related (apoptosis independent) cell death pathway [137]. This cell death pathway is only beginning to be explored in neurodegenerative diseases, but could have therapeutic implications as ferroptosis can be prevented by iron chelation or iron uptake inhibition [138, 139].

The overload of iron in AD may also lead to increased A β production by increasing the expression of APP, and altering its processing. APP has a 5' untranslated region iron-responsive element [140]; in conditions of high iron (e.g., AD) restricted translation of APP by iron-responsive proteins is disinhibited, leading to increased translation of the transcript. High iron conditions also lead to increased processing of APP [141], which leads to accelerated degeneration in a mouse model of AD [142]. Iron is particularly enriched in plaques [99], and iron causes the aggregation of A β in vitro [143, 144]. Iron-stimulated aggregates of A β are cytotoxic in vitro [145–149].

Tau also binds to iron [150, 151], which causes it to aggregate [152], possibly depositing in vivo as iron-rich tangles in AD brains [108]. Iron treatment to cultured neurons increases tau phosphorylation [153–156], so upstream iron elevation might increase pathological tau in AD. Total tau levels are also decreased in AD cortex [157–160], and we showed that loss of tau expression causes iron- and age-dependent cognitive loss and cortical atrophy in mice [64]. Tau is required for APP trafficking to the neuronal membrane [64]. APP binds to ferroportin in the neuronal membrane and

facilitates iron export of neurons [106, 161], which is neuro-protective [162], so reduced tau or APP levels could lead to iron retention in neurons that is observed in AD.

Copper

Copper is also a redox-active metal that can catalyse the formation of the hydroxyl radical via the Fenton reaction [163], and can cause free radical-mediated damage and cell death in the same way as iron [163]. In the presence of amyloid copper undergoes redox cycling, which enhances the potential for copper induced toxicity in AD [164–166]. This is important because copper is increased in amyloid; however, copper levels are decreased in AD neuronal tissue [77], which could deprive copper-binding proteins such as superoxide dismutase and ceruloplasmin of the metal, which can impair their function. Superoxide dismutase is a major copper binding protein and antioxidant in neurons, which utilizes copper to convert the superoxide free radical into hydrogen peroxide [167]. Ceruloplasmin is another major copper-binding protein, which functions as a ferroxidase to promote iron export [168, 169]. The protein requires copper binding to perform this function, and low copper levels could lead to iron accumulation by impairing ceruloplasmin-mediated iron export [170].

Copper can also accelerate A β aggregation but, unlike zinc, copper induces oligomer, rather than fibril, structures [171–175]. Toxicity of A β oligomers can be attenuated in cultures by copper chelation [176, 177]. The mechanism of copper-A β induced cytotoxicity might involve oxidative stress, as the complex catalytically generates hydrogen peroxide [178–180]. The binding of copper to A β is likely to be a factor in AD because copper, too, is enriched in amyloid plaque [82]. Copper and A β are both released into the glutamatergic synaptic cleft, where hypoactivity of the glutamate receptor, NMDA [181], is thought to contribute to cognitive decline in AD [182]. The co-release of copper and A β might make them available for pathological interactions. The concentration of copper in the glutamatergic synaptic cleft approximates 15 μ M [183, 184], and copper in the synapse can modulate glutamatergic signaling by causing s-nitrosylation-dependent inhibition of the NMDA signaling [185, 186], contributing to glutamatergic dysfunction in the disease [181].

Tau also binds copper in vitro causing it to aggregate and generate hydrogen peroxide [187–191]. This recapitulates what is observed in AD brains where copper-containing neurofibrillary tangles area a source of oxidative stress [192]. In transgenic mice overexpressing mutant APP, presenilin and tau, copper exposure accelerates tau hyperphosphorylation [193]. However, in mice that overexpress only APP and presenilin, copper delivery drugs have been shown to reduce GSK-3 β -dependent tau phosphorylation [194].

Targeting Metals to Treat AD

Clioquinol and PBT2

5-Chloro-7-iodo-quinolin-8-ol (Clioquinol) is an antiparasitic agent that was withdrawn from clinical use owing to a speculated severe side effect, subacute myelo-optico-neuropathy (SMON). This side effect was only observed in Japan [195], and the association between SMON and clioquinol has since been questioned [196]. Indeed, no subsequent clinical trials have observed SMON in participants treated with clioquinol. Clioquinol has a moderate affinity for iron, copper, and zinc ($K_{d_{Cu}}$ is 1.2×10^{-10} M, $K_{d_{Zn}}$ is 7×10^{-8} M) [197], and for this reason it was explored as a drug for AD. Although it was initially considered a chelator [198–201], it has more recently been characterized as a copper/zinc ionophore, which functions to redistribute these metals into cells [196, 202–206]. Clioquinol is still considered a moderate iron chelator as it has been shown to lower iron levels in animal models of iron overload [64, 148, 207–210], and has not been shown to redistribute iron into cells using ionophore assays.

We hypothesized that clioquinol might correct metal miscompartmentalization in AD by redistributing zinc and copper from extracellular plaque (preventing A β aggregation) into zinc- and copper-deficient neurons (to restore normal function). Clioquinol might also remove iron from overload neurons. Indeed, clioquinol has shown efficacy in patients with AD and models in of disease. Clioquinol inhibits A β oligomer formation and protects against cell loss in an A β -injection model [211–213]. Nine weeks of oral clioquinol treatment in an AD mice lowered plaque burden and improved cognitive performance [196, 214]. In a phase 2 clinical trial of 32 patients, clioquinol prevented cognitive deterioration (Alzheimer's Disease Assessment Scale-cognitive) and lowered plasma A β 42 levels over 36 weeks [215]. While these data were promising, complications with the large-scale manufacturing of the compound made further development of this drug unviable.

PBT2 is a new 8-hydroxyquinoline based on the clioquinol chemical scaffold and has shown, by restoring cognitive function after 11 days of treatment, even greater efficacy in a mouse model of AD [203]. In a phase 2a clinical trial of 78 patients, 12 weeks of PBT2 treatment caused a dose-dependent lowering of cerebrospinal fluid A β and improved 2 measures of executive function at the highest dose in the study (250 mg) [216, 217]. In a recent phase 2b clinical trial of 1 year's duration, PBT2 did not show favorable clinical outcomes. While this was a longer study than then original phase 2a trial, the number of trial participants was less; indeed, there were only 15 patients allocated to the placebo group in the study. The primary endpoint to the phase 2b trial was improved Pittsburgh compound B–PET scan compared with placebo patients. While patients on PBT2 had a lowering

Pittsburgh compound B–PET signal, the result was also confounded by an inexplicable reduction in the placebo group. The trial also did not report improvement to any cognitive readout included in the study. The trial has been extended for a further 12 months to analyze cognitive and structural magnetic resonance measures, and is expected to conclude in late 2014.

PBT2 has also shown promise for Huntington's disease (HD). HD is a rare genetic disorder characterized by chorea motor dysfunction and dementia. In the R6/2 mouse model of HD, PBT2 increased lifespan and improved motor performance [218]. In a phase 2 clinical trial of 109 patients with HD across 20 sites in the USA and Australia, PBT2 treatment over 26 weeks improved measures of executive function, but without improving motor disability. PBT2 is scheduled to undergo a phase 3 study for HD.

Bis(thiosemicarbazone) Ligands

Agents that directly deliver copper have also been explored as therapeutics for AD given that both clioquinol and PBT2 function, in part, to deliver copper to neurons. The copper-containing bis(thiosemicarbazone) compound Cu^{II}GTSM, has been shown to lower A β levels, GSK3 β activity, and phosphorylated tau levels in cell culture and APP/PS1 transgenic mice [194, 219], which accompanied improved cognition in the Y-maze assay. A related compound, Cu^{II}ATSM, was not beneficial to the APP/PS1 transgenic model of AD, but conferred neuroprotection in 4 animal models of PD [220], which is also complicated by copper deficiency [168].

Iron Chelators

The first AD clinical trial investigating a metal-based drug was performed in 1991. Deferoxamine is a bacterial siderophore that has a strong affinity for iron, and also aluminium. Indeed, when the trial was performed it was hypothesized that deferoxamine would target aluminium toxicity in AD. In a single-blind trial of 48 AD patients, deferoxamine reduced the rate of cognitive decline over a 24-month period [221]. This encouraging trial data has not led to further AD clinical development of compounds that target iron. However, a recent Parkinson's disease clinical trial of the iron chelator, deferiprone, showed improvement in motor function over an 18-month period [222].

Conclusions

Despite extensive investment, the AD research community has been collectively frustrated by the lack of clinical outcomes and research breakthroughs that have been translatable into humans. The challenge before us, of developing new

treatments for AD, remains as extensive as it is urgent. Metal-based therapies for AD might be a therapeutic alternative that could confer benefits to patients. Extensive preclinical and clinical data underlie the rationale of metal based therapeutic approaches, and large-scale phase 3 trials are warranted.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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