Review

'Too much good news' – are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease?

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Scores of compounds ameliorate cognitive deficits or neuropathology in transgenic mouse models of Alzheimer's disease (AD), yet these triumphs in mice have not translated into successful therapies for people. Why have studies in mice failed to predict results of human trials? We argue that most transgenic mouse 'models of AD' actually simulate the asymptomatic phase of the disease, and the results of interventional studies in these mice should be considered in the context of disease prevention. In addition, recent advances in imaging technology and biomarker discovery should aid in comparisons of mouse and human neurological status and, importantly, might allow us to predict better the response of people to drugs tested in mice.

Introduction

Since the first transgenic mouse 'model of Alzheimer's disease' was introduced in 1995 [1], there have been ~300 reports of interventions that ameliorate neuropathology or cognitive deficits in these mice. These successful interventions include caloric restriction, environmental enrichment, antioxidants such as α-lipoic acid, omega-3 fatty acids and vitamin E, non-steroidal anti-inflammatory drugs (NSAIDs), hormones such as melatonin, estradiol, and dihydrotestosterone, Aβ immunotherapy, agents that alter Aβ production or aggregation such as *r*-flurbiprofen, muscarinic acetylcholine receptor agonists and inositol derivatives, and nutrients such as blueberries, pomegranate juice, curcumin, green tea, ginkgo biloba, garlic and even Cabernet Sauvignon. This embarrassment of riches prompted the pioneering neurogeneticist John Hardy to lament that there has been 'Too much good news' [2]. Why has the tremendous success in transgenic mice not translated into effective therapies for human disease? We will argue that most transgenic mouse 'models of AD' actually model the latent or asymptomatic phase of the disease, and preclinical interventional studies in these mice should be considered in the context of disease prevention. We will also ask what more can be learned from existing mice that would increase the predictive validity of preclinical studies in these models. Inherent differences between rodent and human physiology that impede the translation of rodent results to humans, but that are not specific to AD models, have been reviewed recently [3] and will not be discussed further here.

Alzheimer's disease has a long asymptomatic phase

Past and current criteria for a diagnosis of AD rely upon the presence at autopsy of characteristic neuropathological lesions, amyloid plaques formed from aggregated beta-amyloid protein (Aβ) and neurofibrillary tangles (NFTs) comprised of abnormally processed forms of microtubule-associated protein tau (MAPT). Since 1975, excluding definitions provided in the *Diagnostic and Statistical Manual of Mental Disorders*, the formal definition of AD has changed four times [4–7] as neurologists and neuropathologists struggled with how to reconcile observations of individuals with substantial neuropathology but apparently normal cognition [8–11]. Imaging studies [11–18] have bolstered inferences drawn from neuropathology studies [10] that there is a long asymptomatic or latent phase of AD, during which cognitive function is largely sustained in the presence of amyloid pathology and abnormal neurophysiology. Intervention during this asymptomatic phase, before the massive loss of synapses and neurons during the dementing phase of the disease, is much more likely to be effective than intervention once symptoms are clinically apparent (Figure 1).

Transgenic mice are incomplete disease models

There are still no mice harboring a single Alzheimer's-linked gene variant that develop the progressive cognitive deficits, plaques, tangles and neuronal loss characteristic of the human disease. Aβ is generated from the proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases. Mutations in APP and the presenilins, which form part of the γ-secretase complex, are sufficient to cause the complete AD phenotype in the human brain (reviewed in Ref. [19]). However, when expressed in mouse brain, human transgenes with these same mutations replicate some, but not all, aspects of AD. APP transgenic mice develop memory loss and plaques, but no NFTs and little or no neuron loss. Although APP transgenic mice fail to replicate the full human disease, they appear to simulate the pre-dementia phase of AD: these mice develop

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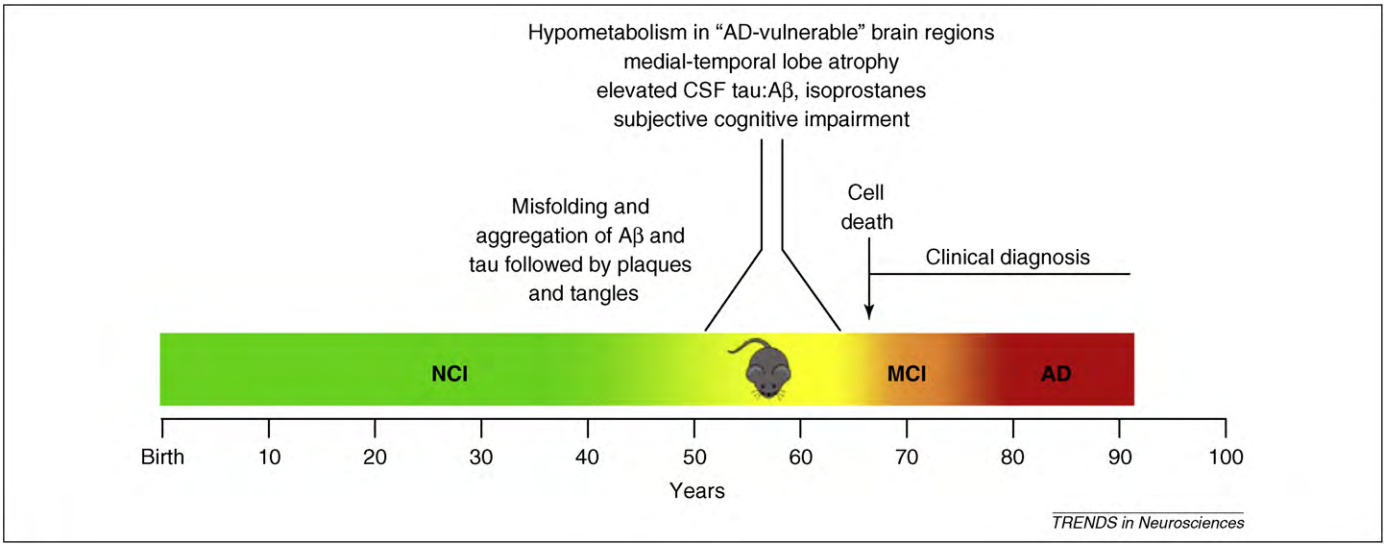

Figure 1. APP transgenic mice model asymptomatic Alzheimer's disease (AD). APP transgenic mice exhibit functional abnormalities similar to those observed in people at risk for AD (such as cognitive impairment and hypometabolism in brain regions particularly vulnerable to AD), but do not display the neuronal cell death seen in people clinically diagnosed with mild cognitive impairment (MCI) or AD. NCI, not cognitively impaired; CSF, cerebrospinal fluid.

an age-dependent assortment of Aβ assemblies [20,21], including amyloid plaques [22], age-dependent cognitive deficits [22,23], and hypometabolism in brain regions that are vulnerable in AD [24,25]. Not all APP transgenic mice become cognitively impaired; a small number of very old APP transgenic mice will possess abundant plaques but minimal cognitive deficits [23], reminiscent of cognitively intact humans with abundant plaques at death [26]. Transgenic mice expressing human presenilin variants display no neuropathology, but plaque deposition in APP transgenic mice is potentiated when these mouse lines are crossed [22].

Despite the absence of linkage to AD, transgenic mice expressing human tau variants linked to another neurodegenerative disorder, frontotemporal dementia (FTD), have been used to study neurofibrillary pathology, because, unlike in humans, the expression of APP and presenilin variants in mice is insufficient to induce neurofibrillary changes. In support of this approach, AD-related post-translational modifications in tau, revealed by phosphorylation- and conformation-specific monoclonal antibodies, are promoted by FTD-linked tau mutations [27,28]. Pronounced cerebral atrophy is seen in some mouse lines expressing these human tau variants [28–31]. Unlike APP transgenic mice, all tau mice that exhibit neuropathology eventually develop neurological deficits. This observation suggests that, whereas Aβ initiates a disease process that might progress to a stage of cognitive impairment, cognitive dysfunction is actually mediated by tau. Consistent with this hypothesis, Aβ can induce neurodegeneration in cultured hippocampal neurons from wild-type, but not from tau-knockout, mice [32], and memory function in an APP transgenic line was rescued when endogenous mouse tau levels were reduced through crosses with tau-knockout mice [33].

Studies in mice from at least four independent laboratories have shown that Aβ potentiates tau pathology in transgenic mice expressing mutant human tau [34–37], consistent with the hypothesis that tau abnormalities develop downstream of Aβ in AD [38]. The ability of Aβ to induce NFTs comprised of wild-type human tau has never been demonstrated in transgenic mice. Because tau mutations are not required for NFT formation in AD, this failure of current mouse models seriously compromises our ability to study the nexus of interactions between Aβ and tau in AD and the mechanisms through which asymptomatic AD worsens to a state of clinically significant cognitive impairment.

Have preclinical studies in APP transgenic mice predicted the results of clinical trials?

More than 200 interventions have been reported to ameliorate cognitive deficits or AD-related pathology in APP transgenic mice (Table S1 in supplementary material online). This success in mice has not translated into therapies for human disease (Tables S2A–C in supplementary material online). Only two classes of drugs are currently approved for symptomatic treatment of AD: cholinesterase inhibitors such as donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) and the uncompetitive NMDA receptor antagonist memantine (Namenda®). Why have studies in mice apparently failed to predict results of human trials? As discussed above, we believe that APP transgenic mice are models of asymptomatic AD, and the results of interventional studies in these mice should be considered in the context of disease prevention. To regard these mice as models of full-blown disease risks misinterpreting results of preclinical testing of AD therapies. With this in mind, it is useful to reconsider the predictive validity of interventional studies in APP transgenic mice. There have been few large prevention trials for AD (Table S2A in supplementary material online). However, three large randomized, placebo-controlled trials have tested the effects on incident dementia and cognition of hormone replacement therapy, Ginkgo biloba and two different NSAIDs.

The Women's Health Initiative Memory Study (WHIMS) is the largest randomized, controlled trial to

date of the effects of hormone replacement therapy on incident dementia and cognition in post-menopausal women. Evidence that hormone replacement therapy protected against AD had come from epidemiological studies [39–41], including one that showed an 87% reduction in risk for AD among women who had taken estrogen preparations for longer than one year [42]. WHIMS enrolled more than 7000 post-menopausal women, 65 years and older who were free of probable dementia, in two parallel studies, one comparing orally administered conjugated equine estrogens plus progestin to placebo, and the other comparing estrogens only to placebo. Intended as an 8.5-year trial, the estrogen plus progestin component of WHIMS was prematurely discontinued after this combination therapy was associated with increased risk for cardiovascular disease, stroke, and breast cancer in women in the larger Women's Health Initiative study. Analysis of data from women exposed to hormones for an average of ~5 years showed that combined estrogen plus progestin treatment increased the risk of all-cause dementia (~50% in both the hormone-treated and placebo groups were classified as probable AD) [43,44]. Some cases of dementia appeared within the first year of treatment, suggesting that these participants already had subclinical cognitive dysfunction at study onset. One interpretation of this result is that hormone therapy accelerated progression to dementia in these subjects, perhaps through the promotion of undetected cerebrovascular events [43]. Among women who remained clinically normal during the study, hormones had minimal effects on cognition [45,46].

Although the largest randomized controlled trial of hormone replacement therapy and dementia, WHIMS was not the only study to examine the connection between estrogen and cognitive aging. Other randomized, placebo-controlled trials are listed in Tables S2A,C (supplementary material online) and additional observational and longitudinal studies are reviewed in Ref. [47]. No consistent story has emerged from these studies, either as regards the effects of estrogen on cognition or protection against AD. The effects of estrogen replacement in ovariectomized transgenic mice (APP, APP/PS1, and 3XTg-AD mice) are similarly variable, with some reports of beneficial effects of treatment on behavior or neuropathology and other reports that treatment is ineffective (Table S1 in supplementary material online). However, in comparing the effects of hormone replacement in mice and humans, one might question the degree to which ovariectomized young adult mice model post-menopausal women, in whom hormone loss interacts with an aged brain. In addition, the conjugated equine estrogens used in WHIMS do not appear to exert the same effects on cognition as 17β-estradiol, most commonly used in mouse studies [48].

Extracts of Ginkgo biloba have been used for millennia in traditional Chinese medicine and are currently licensed in Germany for the treatment of memory dysfunction [49]. The Ginkgo Evaluation of Memory (GEM) study enrolled more than 3000 subjects, 75 years or older with normal cognition or mild cognitive impairment (MCI). Subjects were administered Ginkgo biloba extract or placebo and followed for an average of ~6 years. Ginkgo did not reduce the incidence of all-cause dementia or AD, either among those who were cognitively normal at enrollment or those who had been diagnosed with MCI [50], frequently the prodrome of AD [51]. Ginkgo also had no effect on measures of cognition, which declined slightly in both the cognitively normal and MCI groups over the course of the study [52]. However, during the early years of the study (3–4 years after randomization) a comprehensive neuropsychological test battery was administered only to those participants suspected of having converted to dementia; thus it is possible that early subtle effects of Ginkgo on memory could have been missed.

Two studies have reported beneficial effects of Ginkgo on cognitive function in APP transgenic mice [53,54]. To our knowledge, there have been no longitudinal studies in mice that have addressed whether the effects of Ginkgo decline or remain stable over time.

Beginning in March 2001, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) enrolled 2520 non-demented elderly subjects (>70 years) at high risk of AD. Subjects were given a cognitive assessment battery and randomly assigned to receive standard over-the-counter analgesic doses of the non-selective cyclooxygenase (COX) inhibitor naproxen, prescription anti-inflammatory doses of the selective COX-2 inhibitor celecoxib, or placebo. The original intent of the study was to follow the subjects for up to ten years of treatment, but the study was terminated prematurely in December 2004 due to safety concerns. At that time the average treatment assignment was 24 months. Not only was there no beneficial effect of NSAID treatment at the point the trial was terminated, but the occurrence of AD appeared to be slightly increased in the naproxen group compared to placebo [55]. These results astonished researchers and disappointed patients, given the numerous epidemiological studies that had drawn attention to the apparent protective effects of NSAIDs [56–59], including one study that showed an 80% reduction in the risk of developing AD among individuals who had taken NSAIDs for more than two years [58]. However, the end of the ADAPT story has not yet been written. At the 2009 International Conference on Alzheimer's Disease, ADAPT Principal Investigator John Breitner reported that naproxen conferred a delayed protective effect: 2.5 years after cessation of the treatment phase of the study, the incidence of AD among naproxen-assigned subjects was ~1/3 that of those given placebo [60]. To assess the magnitude and duration of the apparent protective effects of naproxen, the ADAPT study was reactivated in March, 2009 and will follow study participants for an additional three years. One interpretation of the ADAPT results is that naproxen accelerated progression to AD among those with clinically unrecognizable cognitive impairment at trial onset, similar to what has been proposed for estrogen + progestin treatment in WHIMS. Unfortunately, transgenic mice do not yet exist that would allow us to test this hypothesis. Among the subjects who did not progress to dementia, NSAIDs had no significant effects on cognitive measures [61].

There have been several reports of beneficial effects of NSAIDs on neuropathology or memory function in APP transgenic mice (Table S1 in supplementary material online).

In summary, estrogens, Ginkgo biloba extract, and naproxen have all been reported to ameliorate cognitive deficits in APP transgenic mice, yet none of these agents significantly affected cognition in elderly human subjects (those not on the cusp of the transition to clinical cognitive impairment) nor reduced the incidence of AD, although naproxen might yet show a delayed benefit. Although it might be tempting to conclude that APP transgenic mice are poor disease models, this conclusion is premature. It is also possible that cognitive measures, which do not faithfully reflect underlying disease processes, are the wrong surrogate outcomes for evaluating disease progression. In the face of similar neuropathology, individuals with greater 'cognitive reserve' (e.g. having higher levels of education) are better able to maintain cognitive function than are individuals with less reserve [62] (Figure 2). Interestingly, people who volunteer for clinical trials might have higher than average levels of cognitive reserve [63] (~1/3 of WHIMS participants had 4 or more years of college education [45], GEM participants had an average of 14.4 years education [52], and ~1/2 of ADAPT participants had at least a college degree [61]). The difficulties in relating cognitive function to disease progression within a single species are only magnified when comparing species. However, it is probably not surprising that agents that improve cognition in transgenic mice, which presumably have little cognitive reserve, have no measurable effects on people without obvious cognitive deficits.

An underlying assumption of preclinical studies in APP transgenic mice has been that interventions that ameliorate cognitive dysfunction in mice interrupt the pathological pathway that, in humans, culminates in AD. If true, agents that improve cognition in mice should reduce incident AD. The GEM result challenges this assumption, and suggests that whereas correcting acute Aβ-mediated synaptic dysfunction might temporarily improve cognition, this will not necessarily prevent or delay the decline towards AD. Such a scenario could occur, for example, if the cognitive deficits displayed by APP transgenic mice (or unrecognized in 'asymptomatic' people) are due to acute effects of extracellular Aβ at synapses, whereas dementia results from a slowly-developing tau-mediated neurotoxicity, which, once initiated, can proceed independently of Aβ (Figure 3). If this scenario is correct, tests of cognition in APP transgenic mice cannot be used to predict the outcomes of AD prevention trials.

It should be noted that studies in transgenic mice arguably predicted the failure of immunotherapies directed against Aβ in trials in individuals with symptomatic AD. These observations in mice suggest that therapeutic efficacy will depend upon the stage of disease progression and highlight the importance of understanding which molecules are toxic at different stages of AD. Passive immunization of APP transgenic mice rapidly reverses spatial memory deficits [64,65]. However, similar immunization protocols failed to restore memory function in aged 3XTg-AD mice [66], which express transgenes for disease-linked variants of APP, presenilin-1, and tau [67]. Restoration of memory function in 3XTg-AD mice required chronic immunization against Aβ, a protocol that resulted in reductions in soluble tau as well as Aβ [66]. These results suggest that pathologically altered tau is a major factor in late-stage cognitive deficits and predict that Aβ immunotherapy will be ineffective if tau pathology becomes self-sustaining. In humans, the elimination of plaques from large regions of the brain following Aβ immunotherapy failed to halt the progression of AD [68], actually confirming the findings in 3XTg-AD mice that reduction of Aβ is insufficient to rescue memory function once downstream processes are underway. Conversely, studies in mice predict that immunization against Aβ might prevent cognitive decline if administered early enough. Immunization trials in asymptomatic individuals with amyloid pathology have not yet been conducted.

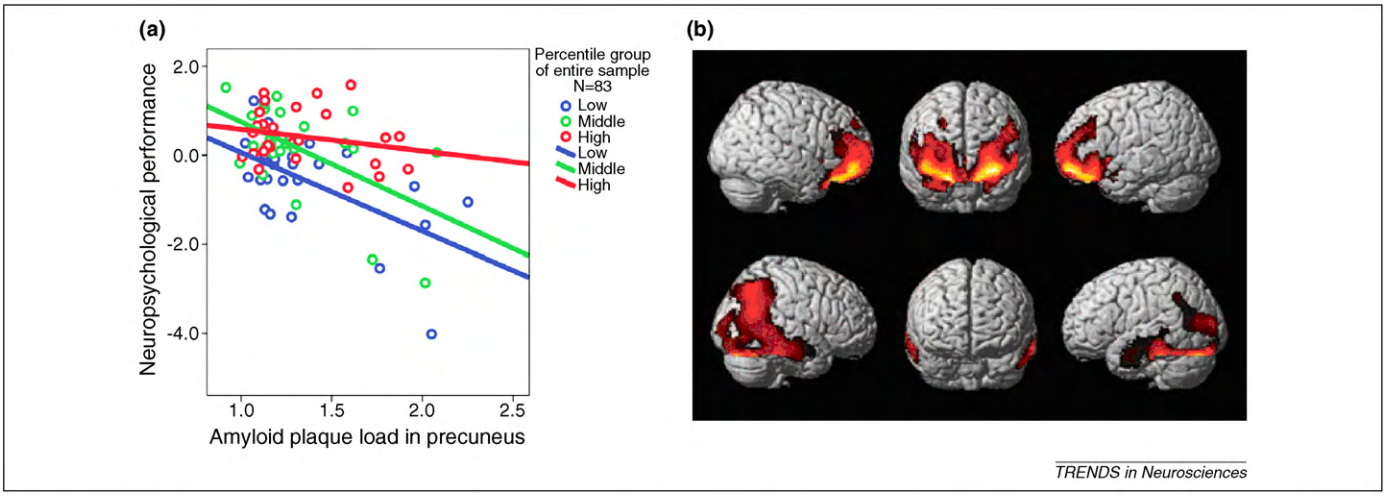

Figure 2. Cognitive reserve protects against neuropathology. **(a)** In the presence of similar neuropathology [in this case amyloid plaques in the precuneus region of the cortex, imaged with Pittsburgh Compound B (PIB) and positron emission tomography (PET)], subjects with higher cognitive reserve (color-coded by tertile strata of residual American National Adult Reading Test intelligence quotient) have better neuropsychological performance. Solid lines represent the ordinary least squares regression lines for each stratum. Adapted, with permission, from Ref. [89]. **(b)** Conversely, among subjects with similar levels of neuropsychological performance, those with higher cognitive reserve function in the presence of greater neuropathology and more pronounced neurophysiological abnormalities. Statistical parametric mapping (SPM) shows regions, *upper row*, with statistically significant increases in amyloid pathology (PIB-PET) and, *lower row*, with decreases in metabolic rate (fluorodeoxyglucose-PET), in high-educated compared with low-educated subjects with mild AD. The red–yellow scale indicates the level of statistical significance of the differences (yellow indicates most significant difference). Adapted, with permission, from Ref. [90].

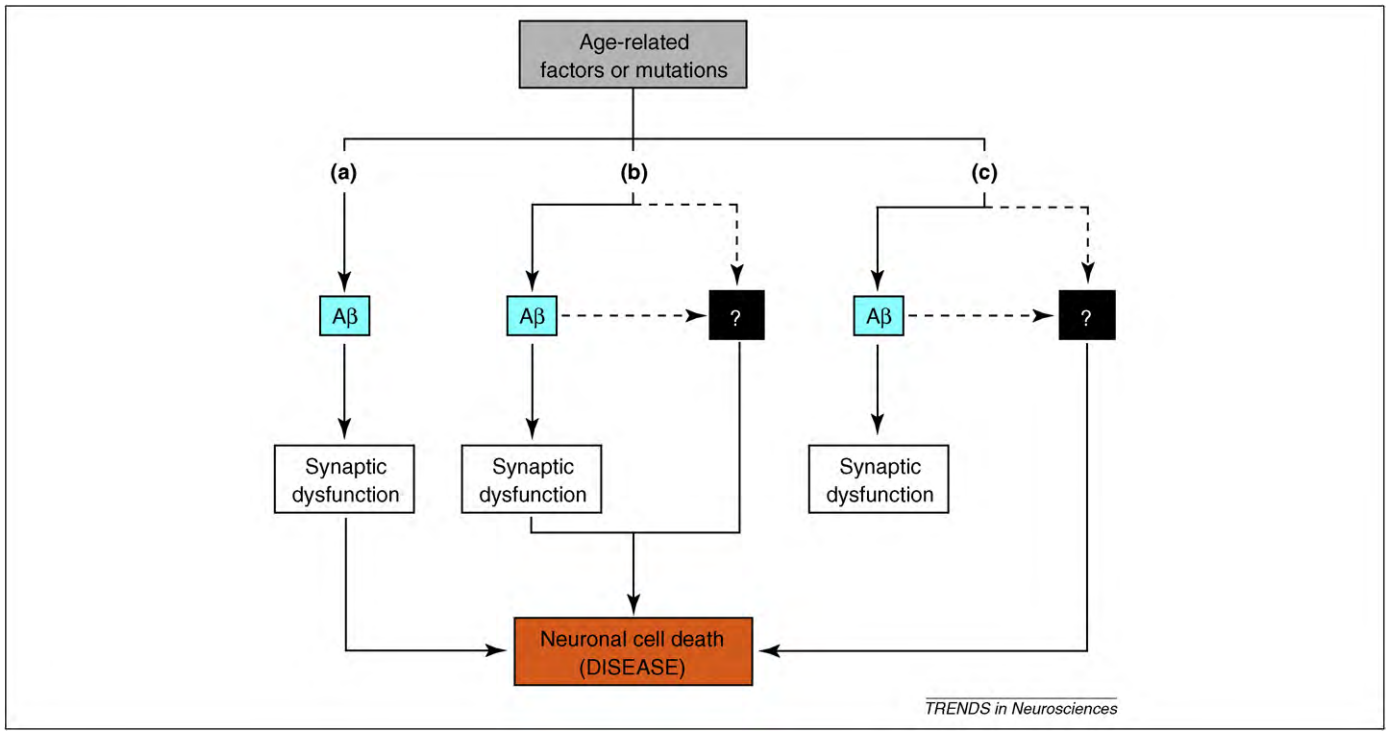

Figure 3. Will interventions that ameliorate cognitive dysfunction in mice interrupt a pathological process that in humans culminates in AD? Three models, with distinct pathways leading from age-related factors/mutations to AD, are presented. **(a)** Synaptic dysfunction (which manifests as behavioral deficits in mice and perhaps as subjective cognitive impairment in humans) is a necessary precursor for the expression of clinical disease. **(b)** Synaptic dysfunction sensitizes cells/systems to other factors that are necessary for the expression of clinical disease. This sensitization is necessary for the disease process to progress. The other factors might or might not be induced by Aβ. **(c)** Synaptic dysfunction is on a pathway parallel to the pathway leading to disease, but might be a surrogate marker for early stages of the disease process (i.e. an indication that abnormal species of Aβ are present). If **(a)** or **(b)** represent the course of AD, drugs that ameliorate behavioral deficits in mice should be beneficial in the prevention of AD in humans. If **(c)** is correct, drugs that ameliorate behavioral deficits in mice would not necessarily be beneficial for AD prevention.

Increasing the predictive value of preclinical studies in transgenic mice

How can we best increase the predictive value of preclinical studies in transgenic mice? The above discussion underscores the need for a better understanding of the neurological status of both the mice and the people in whom drugs are tested. In terms of neurological function, are these animals more similar to middle-aged humans at the very beginning stages of age-associated memory decline [69,70] than to elderly people (>65 years) most often enrolled in AD prevention trials? The 'cognitively normal' subjects enrolled in AD prevention trials almost certainly represent a mixture of those who are truly disease-free, those with amyloid pathology in the early, asymptomatic phase of the disease, and, as hinted by the ADAPT study, those on the verge of clinical cognitive impairment. If cognitive measures are inadequate for distinguishing between these subpopulations, other markers of neurological function are needed.

It is therefore worth asking whether there are biomarkers, in addition to cognitive performance, that (i) can be used as measures of efficacy to evaluate potential preventive agents for AD, and that (ii) would increase the predictive validity of preclinical studies in mice. Following an extensive review of neuropathological, biochemical, and imaging studies conducted over the past 25 years, a recent analysis [71] proposed a model for staging AD progression using specific biomarkers that can be measured *in vivo*. In this model, amyloid deposition, reflected either in a drop in the level of cerebrospinal fluid (CSF) Aβ42, the 42 amino-acid isoform of the amyloid-beta protein, or increased retention of the amyloid-binding agent Pittsburgh Compound B (PiB), is the earliest event in the progression of AD that can be detected *in vivo*. As the disease progresses, synaptic dysfunction is thought to manifest as regional hypometabolism revealed by fluorodeoxyglucose positron emission tomography (FDG-PET). Finally, as neurodegeneration accelerates, as revealed by structural MRI, cognitive dysfunction becomes clinically significant. Regional hypometabolism has also been observed in APP transgenic mice [24,25,72], using 2-deoxyglucose autoradiography, a terminal procedure (Figure 4). Recent advances in micro-PET imaging technology [73] now make it possible to envision longitudinal studies in mice of the response to treatment of metabolic activity and its correlation with cognitive performance. Proton magnetic resonance spectroscopy is also being used to describe metabolic changes during the progression of AD in humans [74,75] and in transgenic mice during aging [76–78] and treatment [79,80].

We believe that, before preclinical data from mice are used to motivate clinical trials, positive results should be obtained in multiple lines of mice, preferably in multiple laboratories. Every effort should be made to ensure that negative results are also published and that studies are adequately powered to achieve statistical significance if differences do indeed exist between different treatment groups. Ethical and financial considerations dictate that investigators use the minimum number of animals required to power a study adequately, but effect sizes often

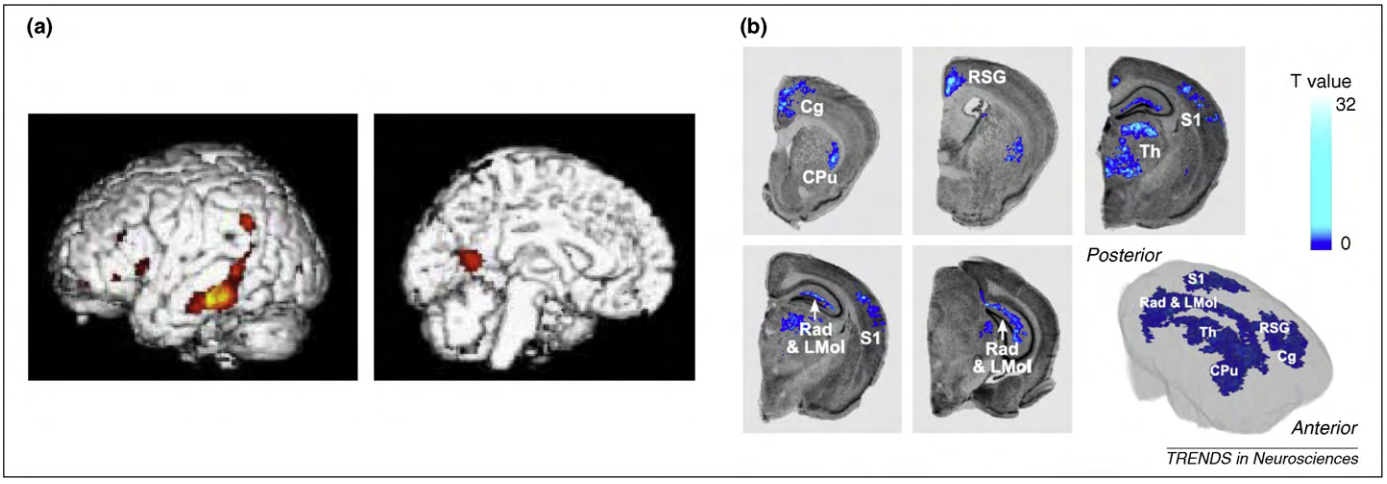

Figure 4. Individuals at risk for Alzheimer's disease (AD) and transgenic mice for human variants of APP and presenilins (PS) display hypometabolism in specific brain regions. **(a)** Fluorodeoxyglucose-PET and statistical parametric mapping reveal hypometabolism in the left lateral temporal, posterior cingulate, and inferior parietal cortices (red and yellow areas) of non-demented subjects at elevated risk for AD [carriers of the *ε4* allele of apolipoprotein E (*APOE*)]. Reproduced, with permission, from Ref. [17], copyright (2000) National Academy of Sciences, U.S.A. **(b)** Statistical parametric mapping applied to ^{14}C-2-deoxyglucose autoradiographic images reveals areas of hypometabolism (blue) in the brains of APP/PS1 transgenic mice relative to mice expressing only the PS1 transgene. Cg, cingulate cortex; CPu, striatum; RSG, retrosplenial granular cortex; Th, thalamus; S1, somatosensory cortex; Rad & LMol, radial layers and lacunosum moleculare of the CA1 and CA3 regions of the hippocampus. Other regions show increased glucose utilization in APP/PS1 mice compared to PS1 mice, including the nucleus accumbens, piriform cortex, amygdala, perirhinal cortex, dentate gyrus, and the stratum oriens and pyramidal cell layers of the CA1 and CA3 regions of the hippocampus (not shown here). Reproduced, with permission, from Ref. [72]. Significance is indicated with a *t* statistic (T value) color scale corresponding to the level of significance at the voxel level; bright blue represents areas where largest differences in hypometabolism are seen. Metabolic mapping of multiple transgenic lines is required to determine which mice show the metabolic pattern most similar to that seen in humans at risk for AD.

are not known and there is a real risk that the necessary group sizes are underestimated. A recent analysis of drug-efficacy studies in a mouse model of amyotrophic lateral sclerosis (ALS) provides a cautionary tale [81]. Faced with the question of why so many treatments appeared to be effective in extending lifespan in transgenic mice, but ultimately failed in clinical trials for ALS patients, the authors of this study set out to identify confounding biological variables (e.g. litter and exclusion criteria) and then to determine a true 'noise floor' for survival times after controlling for these factors. This analysis revealed that the effects on survival reported as statistically significant in the majority of published studies actually fell within the noise of the studies as designed. A similar analysis of behavioral data from 'AD' transgenic mouse models might prove instructive – and alarming. Recent analyses of behavioral data pooled from different cohorts of Tg2576 studied over the course of more than 10 years in our laboratory show that ~35–160 mice/group, depending on age, are needed to reliably observe differences between transgenic and wild-type mice in the Morris water maze [82], a commonly used test of spatial reference memory. These numbers are well above those reported in the majority of behavioral studies of this line and point toward the necessity of defining alternative tests that require smaller, more practical numbers of mice.

It should also be recognized that 'efficacy' trials in mice and humans might actually be measuring very different things. Intention to treat (ITT) analyses, in which data from all randomized subjects are included in the final analysis, regardless of actual treatment received, are considered to be the gold standard for randomized controlled trials. Trials analyzed with ITT arguably assess treatment policy, not treatment efficacy [83,84]. This method is very different from that applied to animal studies, in which subjects are generally excluded from the analysis if treatment is for some reason suspended or the animals do not meet pre-established performance criteria. Interestingly, primary analysis of a study of Ginkgo extract in cognitively normal elderly showed that Ginkgo neither delayed progression to MCI nor reduced decline in memory function, but a positive treatment effect was observed when adherence to treatment was factored into the analysis [85]. Similarly, a trial of the humanized monoclonal antibody against Aβ, bapineuzumab, failed to show efficacy with an ITT analysis, but gave hints of a beneficial effect in an analysis confined to subjects who completed the trial [86]. The validity of conclusions based on analyses other than ITT is a subject for debate among clinical trialists, but the point here is that differences between designs and analyses of human and mouse studies might contribute to apparently different findings in the two species.

Finally, there are differences between APP transgenic mice and asymptomatic elderly that complicate interpretation of even the best-designed preclinical studies (Table 1), and every effort must be made to develop models that minimize these differences.

Table 1. Comparison of APP transgenic mice and asymptomatic elderly

	Asymptomatic elderly	APP transgenic mice
Amyloid plaques	Present in subset	Yes
Neurofibrillary tangles	Present in subset	No
Dendritic spine loss	Yes	Yes
Neuron loss	Minimal	Minimal
Regional hypometabolism	Present in subset	Probable
Cognitive reserve	Probable	No
Comorbidities	Probable	No
Autosomal dominant mutations	No	Yes
Risk-modifying genes	Yes	No

Conclusions

Despite being incomplete models, transgenic mice for human variants of APP, tau and presenilins have provided valuable insights into the molecular mechanisms underlying memory loss and cell death in AD [87]. Preclinical studies in these mice have not been as successful, at least in terms of their ability to predict the results of human clinical trials. This failure can at least in part be explained by the mistaken application of results in mice that model asymptomatic disease to trials in individuals with clinical disease. Researchers urgently need more complete mouse models of AD but, in the absence of such models, it is time to ask what can be done to increase the predictive validity of preclinical studies in existing transgenic mice. First and foremost, it must be recognized that interventional studies in APP transgenic mice should be considered as tests of prevention strategies. Translational research should involve an iterative process; just as results obtained in mice are used to guide studies in humans, data from human studies should be used to inform the design and interpretation of studies in mice. Unexpected results in humans can be used to generate hypotheses that might be tested in mice. For example, the dissociation between effects on cognition and risk of AD, as suggested by ADAPT, points to the need for functional outcomes in mice besides cognitive testing.

Alzheimer's disease is on the verge of becoming a worldwide public health crisis. As life expectancy increases, the number of AD cases is expected to increase from 35 million today to more than 115 million by 2050 [88]. It is to be hoped that more judicious use of existing transgenic mice in preclinical studies will accelerate the progress of research into the prevention of AD.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tins.2010.05.004.

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