Why age (and timing) really matters in developing drugs for neurodegenerative disease

"*Yes, it costs more to do things right. But is our present model of bringing forward medications that might not work and testing them at a disease stage when they are unlikely to succeed cost effective?*"

KEYWORDS: Alzheimer's ■ animal model ■ clinical trial ■ drug development

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Diseases of the aging nervous system are continuing to afflict a larger and larger portion of the population. Diseases such as stroke, Alzheimer's and Parkinson's impact nearly 10 million Americans [1–3]. These sizeable markets have attracted significant interest from the pharmaceutical industry and a tremendous amount of effort and money have been expended seeking medications to relieve the suffering. However, the track record in moving drugs from successful preclinical testing to effectiveness in human trials has been poor. In stroke and traumatic brain injury, a wide range of NMDA receptor antagonists have been remarkably successful in minimizing secondary damage in rodent models, yet had no impact in a series of human clinical studies [4]. In Alzheimer's, anti-inflammatory drugs and anti-amyloid approaches have found considerable success in mouse models of select aspects of the disease, yet, to date, none have slowed progression of disease in mild-to-moderate patient populations [5–7]. These consistent failures have led one of us (DM) to facetiously argue that the most efficacious treatment for human neurodegenerative disorders would be conversion to mice!

However, there are a couple of important considerations that have not been accounted for in most of the drug development literature. One is the impact of age on these studies. For all of the neurodegenerative conditions, the afflicted are those of advanced years with typically one or more comorbidities. These patients also experience varying degrees of polypharmacy to treat both existing and potential conditions (e.g., statins for heart disease risk) leading to unpredictable interactions with the tested agent. Yet, rodent studies of human conditions are almost always performed on very young animals. These younger animals are known to have remarkable reserve capacity in most organ systems compared with their aged counterparts [8]. As a result, removing the pathologic insult often leads to spontaneous restoration of functional capacity due to capacious residual plasticity. However, an aged human with neurodegenerative disease typically accumulates considerable damage before symptoms emerge and the minimal residual reserve capacity is insufficient to effect a functional restoration. Thus, even when the agent is on target and impacts the pathology, the trials may fail as there is no detectable clinical improvement.

A second consideration is the timing of the drug administration relative to the stage of the disease. In rodent models, agents are administered very early in the disease process. For stroke, some drugs can be applied before stroke is induced or very shortly thereafter. In mouse models of amyloid deposition for Alzheimer's, animals are often treated when the first deposits begin to appear in the brain (usually 3–6 months of age in an animal with a 24-month mean lifespan). There are now over 100 agents reported to 'cure' amyloid-depositing mice (partially reviewed elsewhere [9]). Most of these agents can arrest amyloid deposition at an early stage, but rarely has removal of pre-existing pathology been demonstrated. However, in Alzheimer's disease, we now understand that most of the amyloid and much of the tau pathology is present before the initial symptoms begin [10]. Even patients in the mild cognitive impairment phase, from which more than half the patients progress to Alzheimer's, there is large-scale synaptic loss and shrinkage of vital brain structures such as the hippocampus [11,12]. Like many disorders, the functional reserve becomes exhausted before the symptoms are manifest (Type 1 diabetics lose 90% of β-cells before showing hyperglycemia; striatal dopamine depletion reaches 80% before parkinsonian tremors emerge). Thus, clinical trial failure may result from starting too late in the pathological process. Mouse studies catch the disorder early by design

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owing to the desire for a positive outcome. It is not surprising that the rodent studies fail to predict human responses under these circumstances.

These considerations led us to propose two modifications in the present drug-development models to overcome these failures and make the rodent models more predictive. The first is to conduct the rodent trials under more challenging conditions. Specifically use mice at a fractional lifespan equivalent to the human age of typical onset of the disease. Given the roughly 24 month average lifespan of the inbred C57 mouse line that many models are based upon, this would mean a 20-month-old mouse is comparable to a 65-year-old human. Our research group at the Byrd Alzheimer Institute (FL, USA) is one of the few studying amyloid-depositing mice at this age. Importantly, when we treated these old mice with immunotherapy against the Aβ peptide (the precursor of amyloid), we found that while effective, it led to adverse events (microhemorrhage) not seen in younger mice treated in the same manner [13]. Subsequently, results from the first patients to come to autopsy in a Phase I human immunotherapy trial, found microhemorrhage in patients dying 1–3 years into the trial [14]. Thus, at least in these studies, a potential adverse event could be modeled in the appropriate aged mouse model. Further studies in humans have used lower doses of the immunotherapy agents (or modified agents) to diminish this risk. Importantly, in the mouse studies, there still was a cognitive benefit despite the fact that 28-month-old mice had possessed amyloid in their brains for 75% of their lifespans. Although only Phase II data are available, there was a modest cognitive benefit in patients that completed all doses in an immunotherapy trial with bapineuzimab [15].

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A second modification deals with the conduct of human clinical trials. Recent advances in the development of amyloid imaging PET ligands and measurements of amyloid (and tau) in spinal fluid have led to the possibility of detecting individuals at risk of developing Alzheimer's disease prior to the onset of symptoms [16]. Recently, the diagnosis of Alzheimer's was redefined to include a presymptomatic phase during which pathology is accumulating, yet symptoms are not reliably detected with neuropsychological evaluation [17]. What emerges now is the option of treating those destined to develop Alzheimer's at an early disease stage, comparable to that when successful treatments are started in mouse models. The goal will not be to cure, but to delay or prevent the disease, a considerably more manageable task. Together, these modifications will increase the validity of the mouse studies and their translation to the human prevention trials.

> *"Mouse studies catch the disorder early by design owing to the desire for a positive outcome. It is not surprising that the rodent studies fail to predict human responses under these circumstances."*

Why is this not done now? One answer may be that only recently has Alzheimer's disease been redefined to include a presymptomatic phase for US FDA studies. However, a major consideration has been money. Old mice cost much more than juveniles due to housing costs and attrition through their lifespan. Prevention trials require considerably more cases to obtain statistical power and longer time frames in which to observe sufficient conversion to disease to find significant drug effects. Yes, it costs more to do things right. But is our present model of bringing forward medications that might not work and testing them at a disease stage when they are unlikely to succeed cost effective? We need to bite the pecuniary bullet and change both the preclinical and clinical drug-testing paradigms in order to save the world from the impending economic devastation that is Alzheimer's disease.

Financial & competing interests disclosure

D Morgan is supported by the following grants; AG04418, AG 18478, AG 15470 and NS 76308 from NIH. AG Smith is part of the ADCS and the ADNI-2 consortia. D Morgan has consulted with the following pharmaceutical companies: Eisai, Forest, Merck, Pfizer (and Wyeth), Lundbeck, Baxter, Bristol-Myers-Squibb, NeurImmune, Bioarctic and Elan. AG Smith is on the speakers bureau for Forest and Novartis, has served on advisory boards for Pfizer and Accera and has received institutional research support from Baxter, Pfizer, Wyeth, Elan, Janssen, Bristol-Myers-Squibb, AstraZeneca, Pico-Tesla and Myriad as a principal investigator. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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