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## A New Research Paradigm Is Needed in Alzheimer's

By [Mike Williams](#)[BioWorld Perspectives Contributing Writer](#)

*Editor's note: The following is Part I of a two-part series on Alzheimer's disease. To make sure you receive Part II, [opt in](#) to BioWorld Perspectives for free.*

To those concerned about health care costs and who worry about the impact of population growth and an aging population on the financial viability of health care providers, and who also remain unconvinced by the U.S. administration's math as it applies to health care [1], the continued lack of drugs to effectively treat stroke and Alzheimer's disease (AD) is a major concern.

### Alzheimer's Is Growing at an Alarming Rate

According to 2007 data from the World Health Organization, approximately 15 million individuals suffered strokes worldwide annually, of whom one-third died and 5 million were permanently disabled. By 2050, the annual incidence of stroke is estimated to increase by 70 percent, adding further to the growing numbers of permanently disabled requiring care.

With AD, 36 million individuals are estimated to be affected in 2010 growing to 115 million by 2050 [2]. And AD caregivers in a 2 to 1 ratio add an additional 200 million or so individuals indirectly affected by the disease. These are staggering numbers by any measure — but especially for two diseases with few, if any, effective treatments despite major investments by biopharma over the past two-and-a-half decades.

The search for drugs to treat stroke proved to be a singular failure [3] as it became apparent that the dosing regimens and various animal models used preclinically bore little relationship to the clinical situation [4]. The search for drugs to treat AD has unfortunately become increasingly reminiscent to that of stroke — well-funded research around dogmatic hypotheses, in this instance amyloid deposition [5] and tau hyperphosphorylation [6], animal models engineered to mechanistically reflect these hypotheses rather than AD itself, and a deluge of publications, but little to no progress in identifying effective treatments.

### Lilly and Myriad: 'Right Target, Wrong Compound'

The latter came to a head in August with Lilly's announcement that it was discontinuing Phase III trials of its g-secretase inhibitor, semagacestat [7,8]. This compound, which blocks the formation of toxic amyloid, worsened cognitive function in a cohort of 2,600 AD patients, decreased their ability to function on a daily basis and was associated with an increased incidence of skin cancer [7,8]. To Lilly clinicians, this was a "completely unexpected finding" [7] despite the fact that a compound purporting to have a similar mechanism of action — Myriad's Flurizan (tarenflurbil) — had also failed in Phase III trials in 2008 due to a lack of efficacy [9]. (See *BioWorld Today*, [Aug. 18, 2010](#), and [July 1, 2008](#).)

When the data on tarenflurbil were announced, there was considerable concern that the compound: 1) was assessed in patients in too advanced a stage of AD to be effective having shown no efficacy in Phase II; 2) was too weak to effectively inhibit its target; 3) failed to reach the brain in sufficient amounts; and 4) had been advanced to Phase III with questionable efficacy in Phase II — a casebook example of a "right target, wrong compound" scenario.

A similar debate is now ongoing for Lilly's semagacestat, to which has been added rumors that dosing in Phase III was suboptimal due to toxicity concerns [10]. Despite the failures of tarenflurbil and semagacestat in Phase III, other g-secretase inhibitors are in clinical trials and it remains to be seen whether a "better" g-secretase inhibitor exists and will actually work or, conversely, generate data similar to that for tarenflurbil and semagacestat and thus provide the nail in the coffin for a causal effect of amyloid in AD [11].

### Amyloid: Nothing to do with Alzheimer's?

Russell Katz, director of the FDA division of neuropharmacological drug products, said [12] that "the great fear is that maybe amyloid has nothing to do with the disease" — a not unreasonable conclusion given clinical data to date. John Hardy, a key proponent of the amyloid hypothesis, has argued that a better understanding of the normal function of amyloid would aid in understanding its role in AD pathophysiology [5]. The latter, however, may be confounded by the recent finding that amyloid peptides can function as antibiotics with a possible role in the innate immune system [14].

The present data and previous failures with amyloid vaccines [5] have led to a growing skepticism regarding the amyloid hypothesis [10,11], which, to a good many working in the AD area, has been their exclusive research focus for the past 25 years. As one insider noted, the field has been skewed by "years of amyloid tail chasing, and an NIH funding system that rewards those that stay the course."

An additional concern from these findings is that recently announced diagnostic initiatives using brain imaging and CSF biomarkers [12,14] are, to a major extent, based on the amyloid hypothesis.

In the absence of convincing evidence that amyloid is causal, rather than a result of the disease process [15], proof positive of the predictive value of any diagnostic will be dependent on a therapeutic that alters disease progression in the clinic and for which changes in the diagnostic analytes track with disease outcomes [16]. Since selection of the right compound is dependent on validated biomarkers this becomes a *bona fide* catch-22 situation.

#### AD Concerns Indicate the Need for a New Research Paradigm

While diagnostic tests — like that recently published by the AD Neuroimaging Initiative [17] — are essential in the clinical trial setting for appropriate patient enrollment and for tracking disease status during experimental drug treatment, concern has been expressed at the value of such diagnostics in the general population [18]. Part of this relates to the fact that 11 clinical trials using therapies targeted at reducing plaque burden in AD showed no improvement in cognitive function [19]. Additional concerns relate to the invasive nature of the spinal tap procedure; the potential for over- and mis-diagnosis; cost; and, most importantly, the increased emotional burden resulting from an AD diagnosis in the absence of any effective therapeutics.

With the evolving controversy that amyloid may, as many suspected, be the result, rather than the cause of AD [11,15], there is considerable need for a new research paradigm. This should be, in part, a more open-minded approach to the evaluation of targets distinct from those adhered to by the quaintly named "BAPTists" (b-amyloid) and TAUists (tau) who have dominated the field [20] and, perhaps, following from the unprecedented sharing of data from the 11 failed AD trials [19], a sea change in the way that AD trials are recruited and conducted.

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## Alzheimer's Needs Attention: AD Is a Complex Disease with Few Treatment Options

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The [increasing skepticism](#) regarding amyloid as being causal in Alzheimer's disease (AD) is based on a string of clinical failures. Meanwhile, attention increasingly has turned to the prevention of tau hyperphosphorylation [1] as an alternative, although this approach has not been as exhaustively studied in the clinic as amyloid.

### Aluminum Cookware on the List of Potential AD Causes

The major target of the tau approach is to find drug-like inhibitors of "tau kinase," the combined activity of two multifunctional kinases, GSK3 and CDK5. Efforts have been confounded by compounds with poor solubility and potential side effects associated with the inhibition of the normal physiological function(s) of GSK3 and CDK5. More recently, however, two other kinases, DYRK1A and AKAP-13, [were identified](#) as being involved in tau phosphorylation and offering the possibility of alternate, more selective targets.

To date, the only compound thought to act by altering tau function that has reached advanced clinical status is TauRx Therapeutics Ltd.'s Rember (methylthionium chloride), which was reported in the popular press in 2008 to slow AD progression for 19 months [2]. LMTX, a follow-on compound with improved bioavailability and tolerability, [is scheduled](#) to begin Phase III trials this year. Merck & Co. Inc. also appears to be hedging its bets on amyloid via a recent collaboration with Alectos Therapeutics Inc. on the enzyme, O-linked N-acetyl-glucosaminidase, a novel, non-kinase approach to tau hyperphosphorylation. (See *BioWorld Today*, [Aug. 10, 2010](#).)

Various other putative causes/risks for AD have been espoused, often with minimal or questionable data and usually devoid of any discrete mechanistic basis. Among these are aluminum cookware, automobile exhaust fumes, surgical anesthesia, stress, lack of exercise, high blood pressure, hypercholesterolemia, diabetes, obesity and a lack of intellectual stimulus. However, as [recently noted](#) by Lon Schneider, a leading AD researcher, "We don't know what the drug targets for Alzheimer's disease are . . . because we don't know the causes of Alzheimer's." It's a sad commentary on 25 years of intensive research on amyloid.

### A 'Depressing and Distressing' Decision for AD

In the spring of 2010, the National Institutes of Health (NIH) convened what was described as a "court" comprised of scientists without a vested interest in AD research. In reviewing data on AD risk and potential causality, this group commented on the "primitive state of research" in AD (perhaps [echoing](#) Schneider's comments) and came to a "verdict" [that was](#) "depressing and distressing."

Many of the studies were anecdotal and suffered the bias that has plagued research in the area – the inability to accurately diagnose the disease before it is at a late stage. Vitamin E, the "Mediterranean diet" and the individual level of education had no effect in reducing risk, while the cholinesterases, the only drugs actually approved for the treatment of AD, "had no effect." The thoughts of this AD-agnostic NIH court on the evidence for the amyloid and tau hypotheses, if any, were not reported.

### Still Looking for a Hypothesis, and Cure

One of the more consistent hypotheses of AD has been that it results from chronic brain inflammation [3]. Based on pharmacoepidemiological studies that found that patients with rheumatoid arthritis (RA) had a reduced incidence of AD, it was assumed that anti-inflammatory agents (e.g., NSAIDs like aspirin and indomethacin) used to treat RA also were effective in treating AD. Prospective clinical studies in AD patients with NSAIDs over the past decade have given equivocal results, however.

Nonetheless, there is considerable interest in delivering anti-TNF biologics like Enbrel (etanercept) to the brain to further

**assess the inflammation hypothesis.** More recently, GM-CSF, which is elevated in RA, was found in transgenic AD mice to reduce aspects of AD [4] having positive effects on learning and memory and reducing amyloid plaque load by 50%. While the latter study provides an alternative approach to the AD inflammation hypothesis, it also highlights a major confound in the preclinical assessment of compounds for potential utility in AD treatment – the almost exclusive use of transgenic mouse models that are engineered to reproduce the hallmarks of amyloid and/or tau pathophysiologies to assess novel hypotheses.

Like the stroke models that failed to recapitulate the human situation, [there is little evidence](#) that current AD transgenic models are predictive for the human disease. Thus, using these models to benchmark different mechanistic approaches to AD certainly brings into question the scientific logic.

Another hypothesis of considerable interest is that of mitochondrial dysfunction, a proposed target of the now failed AD therapeutic, Dimebon (latrepirdine, Medivation Inc.). After spectacular Phase II data [5], Dimebon [failed to demonstrate efficacy](#) in a Phase III trial. However, in the context of the "right target, wrong compound" [argument](#) being debated for semagacestat, the recent identification of P7C3 [6], a compound that is 300 times more potent than Dimebon in protecting neurons from apoptosis, may offer a better opportunity to validate this mechanism.

### The No. 1 Public Health Challenge of the 21st Century

At the close of the 2010 International Conference on Alzheimer's Disease (ICAD 2010) meeting in July, William Thies, the CMO/CSO of the Alzheimer's Association, [noted](#) that there was "too little happening in the field" of a disease that was "the No. 1 public health challenge of the 21st century." He further stated that "government must make an investment in Alzheimer research that proves they understand what's at stake – for individuals, families, the health care system and the nation as a whole."

Given such rhetoric, the recent and continuing disappointments in advanced stage drug candidates and the increasing health care burden of AD that has the potential to bankrupt Western health care systems (if mismanaged federal initiatives will not have not already [done the job](#)), one can only puzzle at ongoing NIH Roadmap priorities – notably those for rare diseases which led one *WSJ* blogger to comment, "We are fortunate that our government does not face deficits and is therefore able to spend tens of millions of dollars to find cures for diseases that affect only a few hundred Americans." Amen.

One bright light on the AD horizon is the Critical Path Institutes (C-Path) Initiative, the Coalition Against Major Diseases (CAMD), a consortium of pharmaceutical companies, research foundations and patient advocacy groups, with advisors from federal research and regulatory agencies that was the vehicle for the [unprecedented sharing](#) of industry data on failed AD clinical trials. Such sharing anticipates that review of the methodologies and outcomes can be used to retune future clinical trials, a longstanding goal of many drug hunters to whom the current Groundhog Day approach of using the same, or similar, trial design over and over again and expecting a different outcome is akin to throwing something on the wall hoping that it will stick.

To wait another decade to ascertain whether the dire epidemiological predictions for AD in 2050 are realistic will become a self-fulfilling prophecy unless research in the AD area becomes more objective, less exclusionary and can be elevated to the status of a WWII Manhattan Project-like approach. Effective leadership will be key to such an endeavor, but unfortunately, biopharma scientists of the stature of Roy Vagelos are long retired, leaving the field in search of seasoned individuals with a proven track record of thinking successfully outside the box.

While individuals akin to a Steve Jobs or a Craig Venter immediately spring to mind, with a clear mandate, C-Path probably can provide excellent candidates, a [renegade researcher](#) or two, who remain untainted by the group-think that has led AD drug research to its present precarious and unproductive state.

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