

Towards Effective Treatment Strategies for Alzheimer's disease (AD)

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Alzheimer's disease (AD) is an insidious and tragic neurological disorder, and the most common type of progressive cognitive impairment and memory loss of the aged. An estimated 5.4 million people in the United States have AD. Healthcare treatment for AD in this country currently involves a staggering 15 million unpaid caregivers and 183 billion dollars in annual costs, and the projected yearly expense of AD healthcare is estimated to soar to 1.1 trillion dollars by the year 2050 [1,2]. Currently, this places a tremendous socioeconomic burden on both AD caregivers and an already strained healthcare system, and in the near future the prognosis for AD incidence and soaring healthcare costs is even more stark and overwhelming. Globally, 5 million new cases of AD are diagnosed annually, with one new AD case being reported every 7 seconds [1,2]. Importantly, our increasing life expectancy and the demographics of our aging population cast significant healthcare concerns over our medical and socioeconomic capability to manage this rapidly expanding healthcare concern. Currently, there are no adequate preventive or curative treatments for this leading cause of senile dementia in our aging population, and pharmacological strategies and treatments directed at AD symptoms, and specifically targeted to neurotransmitter deficits and the progressively amyloidogenic and inflammatory nature of this brain degeneration, have met with extremely disappointing results [1-7].

This year, at the 106th anniversary of Alois Alzheimer's (1864-1915) description of his first patient with AD in 1906 [3], a tremendous amount of scientific insight and understanding into the contributory mechanisms of this devastating neurological affliction has been systematically acquired. However, there still remain many gaps in our knowledge on the AD process, on the genetic and epigenetic risk factors for AD, and how AD initiates and progresses. Indeed, the neurobiological factors associated with aging, the single most important risk factor for this common brain disease, remain incompletely defined [4-6]. For example, according to the 'amyloid cascade hypothesis' of AD, abnormal and pathogenic processing of beta-amyloid precursor protein (β APP) by secretases into neurotoxic amyloid beta ($A\beta$)-peptides has been proposed to be central to the etiopathology of this uniquely human brain disorder [5-7]. A considerable amount of research effort has focused on secretase-mediated mechanisms of β APP processing, and the latest pharmacological approaches have used $A\beta$ -peptide-lowering strategies to provide therapeutic benefit against $A\beta$ -initiated neurodegenerative pathology. However, dedicated anticholinesterase, glutamatergic agonist and $A\beta$ -peptide immunization strategies have had limited impact in the clinical management of AD [4-7]. One unexpected benefit of the widely prescribed class of cardiovascular drugs called statins (3-hydroxy-3-methyl-glutaryl-coenzyme A inhibitors), besides their cholesterol lowering abilities, has been their ancillary effects in potentiating the enzymatic mechanisms that generate neurotoxic $A\beta$ -peptides [5-7].

Novel research approaches, strategies, methodologies and clear outcome-defined clinical treatments based on the rapidly evolving AD research area are urgently required to more effectively address the current AD situation [2,3,5-7]. The recent discoveries of docosahexaenoic acid (DHA) derivatives such as the brain's endogenous neuroprotection system involving neuroprotectin D1 (NPD1), and the novel manipulation of anti-micro RNA (antagomir) and antagomir-based strategies

directed against degenerating human brain cells [8-10] have provided highly novel therapeutic applications and AD treatment strategies that have not previously been considered. Indeed such novel alternatives, and perhaps combinatorial treatment strategies, are currently receiving a considerable amount of research attention as they are scrutinized by both academia and the pharmacology industry. These emerging AD treatment strategies include:

- A daily exercise routine in both adults and the aged including a heart-and brain-healthy lifestyle;
- Multiple gamma and beta-secretase inhibitors designed to reduce $A\beta$ -peptide generation, and minimize both off-target effects and hepatotoxicity;
- $A\beta$ -peptide immunization strategies;
- Omega-3 fatty acid dietary (fish oil) supplementation such as DHA and DHA derivatives, such as neuroprotectin D1 (NPD1); most recently in combination with antioxidants such as vitamin E;
- Various cholesterol-reducing 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-coA) reductase inhibitors (statins);
- Recently characterized lipid and water-soluble antioxidants including chelators for neurotoxic metals such as aluminum and mercury;
- Natural plant extracts and nutraceuticals from the extensive African, Asian, native American and South American pharmacopeia including ginkgo biloba, huperzine, acai, curcumin and tumeric;
- Recent gene expression inhibition and activation strategies using small non-coding RNA, micro RNA (miRNA) and anti-miRNA (antagomirs) to interfere with the expression of disease causing genes.

Indeed, the need for more highly efficacious treatments for AD is way past due. Currently, ClinicalTrials.gov, a website maintained by the US National Institutes of Health, describes 1013 AD studies and human clinical trials at the planned, recruiting and completed stage to more effectively address the expanding AD healthcare problem [11].

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