

## Editorial

# Progress of 'Current Alzheimer Research' and Update on Roles of Lipids, Estrogen, Neurotrophins and Cytokines in Alzheimer's Disease

*Current Alzheimer Research* has successfully completed four years of publication-reporting novel findings and reviewing major accomplishments in the field of Alzheimer's disease (AD). With this confidence, *Current Alzheimer Research* is presenting its fifth volume to pursue, without interruption, the journal's core mission of disseminating new knowledge about AD. During the last year, the journal has published five issues in its fourth volume in a timely manner, as promised [1]. The fourth volume alone (including five issues) has featured a total of 78 articles and 4 editorials. These articles, comprising 'research' and 'review' studies have succeeded in capturing the most recent advances in AD research. Briefly, various leading experts from different sub disciplines of AD have articulated on a wide range of topics such as potential disease-specific molecular markers, cholinesterase inhibitors, vaccination, oxidative stress, tauopathy and obesity and dementia as related to AD. Several unique and controversial topics have been presented in order to encourage ground breaking research in novel directions. These articles discuss basic science questions reported from neuronal cell culture and animal studies as well as human-based clinical studies. Moreover, the fourth volume published three 'hot topics' issues, which have comprehensively updated some interesting themes related to AD. The fourth volume of *Current Alzheimer Research* is enriched by international contributors hailing from at least 16 countries: Australia, Austria, Brazil, Canada, France, Germany, India, Iran, Ireland, Israel, Italy, Spain, Sweden, UAE, UK and the USA. The articles, beginning from the first volume (and the first issue) of the journal, have been listed in PubMed/MEDLINE. In addition, the journal is indexed in the 'Alzheimer Research Forum', 'Current Contents' and PsycINFO databases. *Current Alzheimer Research* has also been selected for coverage in the Thomson Scientific products and services, such as 'Science Citation Index Expanded' (also known as SciSearch®), 'Neuroscience Citation Index®', 'Journal Citation Reports/Science Edition®', 'BIOSIS Previews' and 'BIOSIS Reviews Reports and Meetings'. The Bentham Science publisher is providing free online Abstracts of each article and the complete Editorial on the journal's website (<http://www.bentham.org/car/>).

The main thrust in this year's, the fifth, volume of *Current Alzheimer Research* remains reporting both mechanism-oriented and translational-based research in the field of AD and other dementias. Drug target developments, brain imaging, morphometric studies and pharmacological research will be other areas of discussion in the journal. Furthermore, *Current Alzheimer Research* will continue to report results from clinical drug trials that will also consist of properly-justified, evidence-based negative data. AD is an active and fast emerging field of research, as exemplified by the fact that an 'Alzheimer's disease' search captures over 4,100 citations on PubMed/MEDLINE during the last year, alone. Therefore, in addition to timely dissemination of this knowl-

edge, it is a great necessity to collate the vast literature and extract its essence in thorough review articles. By discussing research studies from both primary research and presenting review articles, *Current Alzheimer Research* will continue to make an important contribution and provide a valuable resource to the AD field.

In the fifth volume, *Current Alzheimer Research* plans to present six different issues describing different areas of AD research as critical review and original research articles. This work should address the mechanism of neurodegeneration and neurobiological aspects of AD, investigate potential new drug targets and analyze novel therapeutic approaches. *Current Alzheimer Research* will cover research topics that employ behavioral, cellular, genetic and *in vivo* models. The fifth volume will continue to publish the widely popular 'Hot Topic' issues, which are based on a particular theme of AD research and are written by a group of renowned experts in the field. Indeed, the next issue of the journal will be a special 'Hot Topic' issue entitled "Production and fate of amyloid peptides: Recent advances and perspectives" (Guest Editor: Dr. Frédéric Checler). Another 'Hot Topic' issue lined up for future publication is related to "Structure-function implications in Alzheimer's disease pathology" (Guest Editors: Drs. Hermona Soreq and Ehud Gazit). Such important contributions are the key to success and progress for *Current Alzheimer Research*.

The first issue of the 5th volume of *Current Alzheimer Research* presents eleven selected articles that describe some of the most exciting and emerging topics in the field of neurodegeneration and their potential utility to develop drug targets for the treatment of AD. The first six articles of this issue can be grouped to address two major aspects of AD research. While the effects of cytokines, lipoprotein and amyloid are discussed in the context of neurodegeneration, the roles of neurotrophins, estrogen and A $\beta$  detoxification model present the preventive approach. In addition, the remaining articles of the present issue discuss different types of dementia, epidemiological studies and clinical analysis and their relevance in AD therapy.

This issue starts with a timely presentation by Sagin and Sozmen (pp. 4-14) on the role of cholesterol metabolism and genetics in AD. They also update studies of cholesterol reducing agents, such as statins, as a protective operator in AD. Recent work suggests that central nervous system (CNS) lipids play a key role in the pathogenesis of AD. This role is largely due to the rich lipid content of CNS structures and the presence of the blood brain barrier. Among these lipids, the cholesterol remains a unique molecule mainly by its *de novo* synthesis in the CNS and special apolipoproteins used for its efficient recycling within the CNS. Moreover, the presence of cholesterol in the membrane enables it to function as a regulator of a number of protein related processes such as the beta amyloid precursor protein (APP),

which is cleaved proteolytically to generate toxic amyloid  $\beta$ -peptides ( $A\beta$ ) in the brain, leading to memory loss and other associated neurodegenerative symptoms. The role of lipids has previously been featured in this journal [2].

Moving from lipids to lipoprotein, Jaeger and Pietrzik review (pp. 15-25) the functional role of lipoprotein receptors (LRP) in AD. In addition to the effect of lipoprotein receptors on APP processing and  $A\beta$  production, LRP1 has been shown to bind  $A\beta$  directly or indirectly. The authors discuss two LRP1 mediated clearance mechanisms of  $A\beta$ , which may play a crucial role in the prevention of AD. Further on the topic of 'clearance' mechanism, recent studies suggest that clearance of the amyloid plaques from the brain and the blood could be effective in stopping and/or delaying the progression of the disease. Small peptides derived from the  $A\beta$ -42 sequence, in particular KLVFF, have shown to be effective binders of  $A\beta$  peptides. Taking advantage of this property, Sundaram and colleagues (pp. 26-32) have generated the retro-inverso (RI) version of this peptide, fflvk, in different formats. A detox gel that incorporates RI peptides is believed to act like a 'sink' to capture  $A\beta$  peptides from the surrounding environment. By testing these detox gels for their ability to capture biotinylated  $A\beta$ -42 peptides *in vitro*, they showed that the detox gel could be a potential candidate for treatment strategies to deplete the brain of toxic amyloid peptides.

In addition to the presence of  $A\beta$ -loaded plaques, AD is characterized by an elevated immune response. Indeed, increased expression of interleukin-1 and tumor necrosis factor- $\alpha$ , has been observed in AD cerebrospinal fluid and temporal brain tissue. Aleong and Poirier provide (pp. 33-37) evidence that pro-inflammatory cytokines modulate glial expression of apolipoprotein E protein. These results are consistent with the notion that elevated cytokine expression directly modulates immunosuppression and indirectly ApoE-mediated neuronal remodeling.

From the molecular 'culprits', we proceed to two following articles that address the preventive side of the disease. Schulte-Herbrüggen and colleagues critically review (pp. 38-44) advances on neurotrophins from pathophysiology to treatment in AD. This is important, as neurotrophic factors are not only responsible for neuronal development but also critical for the maintenance of neurons. NGF has been identified as a dynamic pattern during neurodegeneration in AD. The authors mention that while NGF lacks action in early stages of AD, NGF level is elevated in brains with severe AD, partly due to a pathologically altered axonal transport of NGF in the neurons. Thus, pharmacological interventions strategies should be further tested on a neurotrophin substitution in mild to moderate cases of AD [*ibid*, 3,4]. In addition to NGF, studies demonstrate that estrogen is neuroprotective and that reduced brain estrogen activity may influence the clinical course of AD. Kelly and colleagues highlight (pp. 45-51) the role of estrogen in AD, which exerts beneficial effects on the brain throughout life. Changes in levels of estrogen receptors have been detected in postmortem brain tissue of AD patients. The authors propose a relationship between wild-type ER- $\alpha$  and level of cognitive impairment in AD, and also suggest the possibility that variant isoforms

of ER- $\alpha$  may be present in the frontal cortex of various subjects.

Now, moving from 'micro' to 'macro' levels, three articles discuss the types of dementia and clinical trial studies. Dementia is a common, chronic and progressive illness. Hickey and colleagues reflect on (pp. 52-60) different types of dementia, such as synucleinopathies and tauopathies including Alzheimer's dementia, dementia with Lewy bodies, Parkinson's disease, and Frontotemporal dementia. They also compare and contrast each dementia and the synucleinopathies and tauopathies alike. This knowledge should be useful to better diagnose patients with progressive cognitive decline and deterioration in functioning. Fernández-Martínez and collaborators describe (pp. 61-69) the prevalence and severity of neuropsychiatric symptoms in patients with AD and vascular dementia (VaD) by prospectively studying 65 patients with dementia and 28 for VaD. They report of no significant differences between AD and VaD patients, except for sleep disturbances, appetite changes and aberrant motor behavior that were more prevalent and severe in AD.

Elucidation of different risk factors for AD remains one of the major areas of research [5]. Several demographic, environmental and clinical risk factors have been determined as possible risk/protective factors of AD. Foroughan and collaborators point out (pp. 70-72) different risk factors of AD among the Iranian population. Their results confirm the previously reported relationship between AD and vascular factors. Prevention, early detection, and treatment of hypertension may have some implications in the primary and secondary prevention of AD.

In the clinical area, a recent clinical trial in patients with Mild Cognitive Impairment (MCI) found an increased rate of possible or probable AD diagnoses in patients assigned to rofecoxib compared to placebo. In this context, Aisen and colleagues describe (pp. 73-82) analyses of rofecoxib in patients with MCI of data from a randomized, double-blind trial. They performed additional post hoc analyses to explore explanations for the finding based on possible neuropathological, cardiovascular/cerebrovascular, or cognitive effects of rofecoxib. According to the authors, the present analyses are limited by their *post hoc* nature but provided little support for any of the possible explanations explored, and the significance of the observation that rofecoxib increased the rate of conversion from MCI to AD remains uncertain. In another studies, Porsteinsson and colleagues discuss (pp. 83-89) results of memantine treatment in patients with mild to moderate AD already receiving a cholinesterase inhibitor in a randomized, double-blind, placebo-controlled trial. As the authors rightly suggest, in this trial, memantine did not show an advantage over placebo based on protocol-specified primary or secondary analyses in patients with mild to moderate AD on stable ChEI regimens. There were no significant differences in tolerability and adverse events between the memantine- and placebo groups.

In conclusion, the major goal of the 5th volume is to continue to highlight the advances on AD from cellular, neurochemical and translational research [6]. Furthermore, *Current Alzheimer Research* will provide summary of important discoveries in AD field emphasizing the strategies on potential drug development. The journal remains open to novel

ideas, untested but unique hypotheses and 'out of the box' experimental paradigms. These will be peer-reviewed and discussed objectively in upcoming issues in order to promote research and construct the road to cure this devastating disease.

On behalf of Bentham Science Publishers and the Editorial Board, I greatly appreciate the invaluable support and patronage received from the readers, authors, sponsors and the neuroscience community. Particularly, I am grateful to the reviewers/ referees whose hard work and dedication behind the scenes with no compensation have made the 'peer-review' process possible and enriched the quality of the journal. I always look forward to your advice, comments and suggestions to improve this journal. I would also like to solicit review articles, and original reports in different areas of AD research. Our journey of seeking new knowledge about AD has indeed got some acceleration but is far from finished. For unraveling the mysteries of the etiology of this disease, at cellular and molecular levels, and devising appropriate preventive strategies, we need to work together and to share our responsibilities by extending continued support and making important contributions to this noble endeavor.

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