

## Editorial

# Drug Discovery for Alzheimer's Disease: Filling the Pipeline

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### INTRODUCTION

This issue highlights advances in the field of drug discovery for Alzheimer's disease (AD) that were discussed at the 7<sup>th</sup> International Conference on Alzheimer's Disease Drug Discovery (held on October 12-13 2006 in New York) following previous conferences on similar theme [1-2]. The conference involved around 150 attendees from academia, the pharmaceutical and biotechnology industries and focused solely on the development of new drugs for AD and related dementias. This meeting was co-sponsored by the Alzheimer's Drug Discovery Foundation (ADDF) and the following generous partners: Accera, Inc., Acumen Pharmaceuticals, Inc., Eisai Inc., Elan Pharmaceuticals, Inc., Forest Laboratories, Inc., Marteck Biosciences Corporation, Neurochem Inc., Ortho-McNeil Neurologics Inc., Pfizer Inc., sanofi-aventis U.S. Inc., Wyeth Research, and Targacept, Inc.

### Anti-Amyloid Based Therapeutics

Several classes of drugs are now in development that can both prevent the build-up or promote the removal of what is thought to be the principle causative agent in AD;  $\beta$ -amyloid peptide. Presentations by Jordan Tang (Oklahoma Medical Research Foundation (Oklahoma City, OK), and Founding Scientist, Zapaq Inc. (now Athenagen, South San Francisco, CA) and Michael Wolfe (Brigham & Women's Hospital, Harvard Medical School, Boston, MA) focused on strategies targeting  $\beta$ - and  $\gamma$ - secretases that could eventually lead to therapeutics to prevent production of  $\beta$ -amyloid. In contrast talks by Berislav Zlokovic (Rochester University, Rochester, NY) and Dale Schenk (Elan Pharmaceuticals, Inc., South San Francisco, CA) focused on new therapeutics and immunization strategies that facilitate the removal of  $A\beta$ . Anti- $A\beta$  aggregation strategies were also discussed by David Summa of Acumen pharmaceuticals, Inc. (South San Francisco, CA) who gave a talk on small molecule inhibitors of  $A\beta$ -derived oligomers (ADDLs).

### ApoE as a Therapeutic Target

The apolipoprotein E4 (apoE4) isoform is the principle known genetic risk factor for AD and is consequently a promising therapeutic target. ApoE4 likely contributes to AD pathology by interacting with multiple factors through various pathways. Potential therapeutic strategies include changing the structure of apoE4 to be more apoE3-like, inhibiting the protease that cleaves apoE4 into toxic fragments, and protecting mitochondria from apoE4 toxicity. A talk by Robert Mahley (University of California, San Francisco) dis-

cussed how the structural features that distinguish apoE4 and apoE3 determine their functional differences, suggesting that these structural features hold the key to understanding how apoE4 is involved in AD.

### Neuroprotective Strategies

Several talks in the conference focused on novel neuroprotective strategies to prevent the damage caused by AD. Two ADDF funded investigators, Drs. Frank Longo (Stanford University, Palo Alto, CA) and Nicholas Webster (University of California, San Diego), discussed new therapeutic strategies centered on the neurotrophin family of growth factor proteins. These variously target  $A\beta$ -neuro-trophin receptor interactions or alternatively neurotrophin induced cell survival pathways. Talks were given by other ADDF funded investigators including Drs. Illana Gozes (Allon Therapeutics Inc., Vancouver, BC) and Roberta Diaz-Brinton (University of Southern California, Los Angeles) who have developed strategies based on a neuroprotective peptide and a steroid hormone respectively. Other neuroprotective strategies discussed included anti-oxidants such as epigallocatechin gallate (EGCG) - the main active component of green tea. Jun Tan (University of South Florida, Tampa, FL) discussed how this potent phyto-chemical reverses Alzheimer-like pathology in a transgenic mouse model. A presentation by D. Martin Watterson (Northwestern University, Chicago, IL) discussed targeting glial activation for the prevention of neuronal death using anti-inflammatory lead molecules. Other neuroprotective strategies were discussed by Dale E. Bredesen (Buck Institute for Age Research, Novato, CA) and Daniel Alkon (Blanchette Rockefeller Neuroscience Institute, Morgan-town, WV) who gave talks on targeting the neurotoxic C-terminal fragment of amyloid precursor protein (APP) and activation of brain-specific PKC isozymes respectively.

### Targeting the Synapse

While the amyloid targeting approach may prove to be effective as a disease modifying strategy, there is still some concern that this could have undesirable or unwanted side effects. Work by the group of Ottavio Arancio and colleagues (Columbia University, New York, NY) raised the possibility that  $\beta$ -amyloid may have a role to play in the consolidation of memory.  $A\beta$  oligomers are likely to be involved in synaptic dysfunction and cognitive impairment observed in mouse models of AD and thus contribute to the synaptic and memory deficits at early stages of AD. In this case, it may be necessary to strike a careful balance between physio-

logical and pathological levels of the peptide. Since the molecular mechanisms for neurite sprouting after trauma and in AD may overlap, Stephen Strittmatter (Yale University, New Haven, CT) discussed the role of Nogo Receptor signaling in AD. The Nogo receptor functions as a surface neuronal molecule that modulates APP/A $\beta$  metabolism, and therefore may play a role in the pathogenesis of AD.

### Targeting Tangles and Other Mechanisms

Several presentations were made that focused on targeting tangles and other mechanisms of neuronal injury that present tractable targets. Eckhard Mandelkow of the Max-Planck-Unit for Structural Molecular Biology (Hamburg, Germany) discussed the inhibition of tau aggregation and disaggregation of paired helical filaments by low molecular weight compounds. Cyclin-dependent protein kinase 5 (cdk5) enhances tau phosphorylation both *in vitro* and *in vivo*. A talk by Marcie Glicksman (Harvard University, Cambridge, MA) discussed academic based drug screening approaches to the discovery of novel cdk5 inhibitors targeting tau hyperphosphorylation. In addition to tau, other areas discussed focused on several different disease modifying strategies targeting AD. A promising new approach is to design drugs that focus on multiple targets identified for a particular disease. Moussa Youdim (Technion University, Haifa, Israel) described candidate therapeutics for AD based on the use of multi-functional drugs that are already in use to treat other neurologic disorders. Alpha synuclein presents an additional target for AD since polymorphisms in the alpha-synuclein gene are thought to be responsible for certain forms of familial Parkinson's disease, and are also found in Lewy Body Dementia as well as AD. Manfred Windisch (JSW Research, Graz, Austria) discussed the neuroprotective activity of beta-synuclein derived peptidomimetic compounds targeting alpha-synuclein. Kelvin Lee (Cornell University, Ithaca, NY) gave a talk on the use of proteomics, novel biomarkers in conjunction with intravenous immunoglobulin (IVIg) immunotherapy and in the clinical arena, Edward Tobinick (Institute for Neurological Research, Los Angeles, CA), discussed perispinal etanercept as a new treatment modality which can lead to clinical improvement in selected patients with AD.

### Cognitive Enhancement Strategies

Cognitive enhancement for AD is still a highly competitive area for drug discovery and development as numerous targets exist. Strategies for cognitive enhancement include targeting acetylcholine receptors such as M1 muscarinic receptor agonists and nicotinic receptor alpha-7 receptor agonists discussed by Abraham Fisher (Israel Institute for Biological Research, Ness-Ziona, Israel) and Gerhard Koenig (EnVivo Pharmaceuticals, Watertown, MA) respectively. Potent and selective nicotinic receptor agonists are now entering Phase II clinical trials for the treatment of age-associated memory impairment and mild cognitive impairment, a topic discussed by Geoffrey Dunbar (Targacept, Inc.,

Winston-Salem, NC). Michael De Vivo (Memory Pharmaceuticals Corp., Montvale, NJ) highlighted the targeting of different intracellular signaling pathways. Lead compounds such as MEM 1003, a calcium ion channel blocker, may reduce elevated Ca<sup>2+</sup> signaling in AD and have been shown to improve object location memory in aged rats. Nitric Oxide (NO) chimeras were discussed by Greg Thatcher (University of Illinois at Chicago, IL). NO plays a decisive role in signal transduction cascades that are compromised in AD and therefore drugs delivering NO bioactivity represent targets for AD therapy.

Drug molecules that target two or more synergistically interacting binding sites could prove more effective than a compound highly selective and highly potent at one binding site. Jerry Buccafusco (Medical College of Georgia, Augusta, GA) discussed the targeting of multiple neural systems using this approach. An underappreciated hallmark of AD is neurodegeneration of noradrenergic neurons within the locus ceruleus which may contribute to AD neuropathology and cognitive deficits. Treatment approaches focusing on the noradrenergic system were discussed by David Weinschenker (Emory University, Atlanta, GA). Clinical research in cognitive enhancement was discussed by Karin Yurko-Mauro (Martek Biosciences Corp., Columbia, MD), who gave a review of the Memory Improvement with Docosahexaenoic Acid Study (MIDAS). The MIDAS study is a randomized, double-blind, placebo-controlled study to examine the effects of DHA on cognitive functions in the elderly. The study tests the hypothesis that DHA is a potential nutritional neuroprotective agent for Age-Related Cognitive Decline.

### CONCLUSIONS

In the past 10 years there has been a steady increase in the overall number of different therapeutic strategies targeting AD [3]. The challenge that we now must address will be how to best support emerging early stage drug discovery efforts as they transition from academia to the private sector. It is clear that there is still a need for funding and a gap to bridge. Recognizing this, funding agencies such as ADDF and the NIH must be willing to take risks on early stage drug discovery for the benefit of AD patients, families and ultimately our whole economy. In the words of Mary Lasker "*If you think research is expensive, try disease*" [4]. Finally, we would like to thank the sponsors, Bentham Science Publishers and the Editor of the journal Professor Debomoy Lahiri.

### REFERENCES

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- [4] See: <http://www.laskerfoundation.org/>