

Editorial

Advances in Alzheimer Therapy and Development of Innovative New Strategies

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The 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, held in Geneva on April 19-22, 2006, brought together more than 750 basic and clinical research scientists/physicians to provide an update on the latest progress in understanding the origin, pathogenesis, diagnosis and treatment of Alzheimer's disease (AD). This thriving symposium series, occurring every alternate year, has proven to be a valuable conduit to disseminate the most current knowledge on recent advances in the therapy of AD – the most common cause of dementia, infamous for its devastation of intellectual and social abilities and wreckage of daily functioning capacity. This disease curses the elderly without bias for ethnicity, sex or social class. Now, beyond a hundred years from the first description of this peculiarly human disease, we still yearn to understand and better treat it before many of us will have to personally face it in the years to come.

In line with specific highlights of the prior 8th International Montreal/Springfield Symposium that were published in *Current Alzheimer Research* 2(3): 275-385, 2005, we are proud to extend this in the present issue. Our selection of topics covers a broad and representative array of the basic and clinical research presentations from the 9th International Geneva/Springfield Symposium. Herein, authors have attempted to develop thought-provoking and forward-looking contributions that are stimulating to read. Each of the 19 articles within the current issue readily achieves this, and we are personally indebted to the authors for the quality of their contributions and their patience in awaiting publication.

DECREASED NEUROTROPHIN RESPONSIVENESS – A PREQUEL TO AD?

It was hypothesized some 20 years ago that degeneration of cholinergic basal forebrain neurons in AD, that are fundamental in memory and attention, results from a loss of neurotrophic support from target regions that provide nerve growth factor (NGF). To gain a greater understanding of the molecular mechanisms that underlie the onset of cholinergic deficits during the progression of AD, Mufson and colleagues examine (page 340-350) postmortem human brain tissue harvested from the Religious Orders Study (ROS). This is a longitudinal clinical pathologic study of aging and dementia in retired Catholic clergy. Each ROS participant

received a detailed annual clinical evaluation, which included a battery of tests to quantitatively monitor orientation, attention, memory, language, and perception, and all agreed to brain autopsy and neuropathological evaluation. Subjects were categorized clinically as having no cognitive impairment (NCI), mild cognitive impairment (MCI; considered a latent stage before AD), or AD. Their article provides a critical review of their studies to define the role that two members of the NGF family, specifically, NGF and brain derived neurotrophic factor (BDNF) together with their receptors, play in cholinergic basal forebrain cell degeneration and AD. Particular attention is focused with regard to their time dependence in relation to the clinical onset of AD.

NGF-MIMETICS MOLECULES AND proNGF

Extending the theme of 'NGF-cholinergic dependency in brain aging, MCI and AD', Cuellar and collaborators provide (page 351-358) an in depth review of not only why the cortical cholinergic system is vulnerable in MCI and AD, but also a strategy to counteract this. Of particular interest is a thought-provoking analysis of recent studies directed toward elucidating the role of proNGF and its maturation to mature NGF – the form that provides cholinergic trophic support.

MARKERS AND RISK FACTORS TO DEFINE AND FOLLOW AD – ARE WE GETTING CLOSER?

To date, a diagnosis of AD is generally made by clinical evaluation and exclusion of other potential causes of dementia. Without ultimate histopathologic confirmation of the presence or absence of the hallmark features of AD following autopsy, however, a diagnosis cannot be made with certainty. Studies of histopathologic correlation have shown an accuracy of greater than 85%, utilizing NINCDS-ADRDA criteria. At this time, however, there is no specific laboratory test to support the diagnosis of probable AD, let alone of MCI. Mehta provides (page 359-363) a thoughtful review that focuses on amyloid- β protein (A β) and its various fragments in the plasma and/or CSF of patients with AD and age-matched nondemented controls. His article provides a synopsis of the core requirements for a differential marker as well as a clear overview of the problems and limitations that have hampered the search for an 'ideal' marker of AD – consequent to the heterogeneity and complex nature of the disease.

COMPUTER-BASED METHODS FOR PREDICTING AND ASSESSING PREDICTION OF DEMENTIA

In contrast to finding and following an endogenous marker of the disease process, Korczyn and Aharonson overview (page 364-369) the advantages and limitations of neuropsychological tests that have proved an important aid to diagnose dementia. In particular, they focus on the use of computerized neuropsychological tests, which have several advantages over traditional 'pen and paper' cognitive tests – detailing technical possibilities as well as current limitations. They describe a specific test battery: NexAde. This represents a new approach to computerized neuropsychological testing, whereby a sensitive test battery can be administered on a regular computer, without requiring the time and expense of a skilled administrator.

THE CURRENT STATUS OF SPECIFIC THERAPEUTIC APPROACHES TO AD AND RELATED NEURODEGENERATIVE CONDITIONS

A wide number of inspiring approaches are currently being followed to potentially offset or halt the progression of AD. Whereas there is a common goal uniting the approaches – efficacy with a well-tolerated side-effect profile – numerous strategies are being followed to achieve this based on manipulating different targets. We are delighted that leading scientists within many of these fields have provided authoritative reviews describing their current status

1. Stem Cells – An Exciting Way Ahead

The discovery of multipotent neural stem cells (NSCs) that can differentiate into specific types of neurons and glial cells in the adult brain has radically transformed our understanding of neurogenesis, and indicates that neurons may potentially regenerate throughout life. Sugaya and colleagues present (page 370-377) an elegant review of the potential of NSCs in neurodegeneration and specifically in AD. A realistic analysis of the limitations and obstacles is presented in the translation of this promising therapeutic approach to utility to insure that NSCs differentiate into the specific cell type required and, importantly, survive *in vivo*. Of particular interest are the innovative ways that the investigators have found to circumvent these complications to move NSCs closer to use as an intervention strategy in AD.

2. An Inflammatory Component of Neurodegeneration – TNF- α

The neuroinflammatory hypothesis asserts that inflammatory processes play a critical role in promoting the degenerative course in AD, Parkinson's disease (PD), amyotrophic lateral sclerosis and multiple sclerosis (MS). Although inflammation represents a first line of defense against injury and infection, a disproportionate response can instigate additional injury to neural cells and, thereby, drive the disease process. Tweedie and colleagues have focused (page 378-385) their research to characterize the role of TNF- α in neurodegenerative disorders, by inhibiting its synthesis - to test the hypothesis that it is a critical factor in neuroinflammation. They review the role of TNF- α in a wide array of dis-

eases and describe interesting new inhibitors that act post-transcriptionally at the level of TNF- α synthesis.

3. Anticholinesterases – Moving Beyond the Classical Approach

Thus far, the only clinically approved drugs that are effective in AD are neurotransmitter orientated in their mode of action, and focus on the functional significance of acetylcholine and glutamate in brain. Current AD drugs can reduce the severity of cognitive symptoms, improve the quality of life and may stabilize the symptoms of a mild to moderate AD patient for between 1 and 3 years, but do so without significantly modifying the course of the disease. Clearly, greater efficacy would be valuable. In this context, the review by Li and collaborators (page 386-396) of their design and development of a series of interesting and highly active novel dimeric inhibitors assumes significance. These drug candidates link the active moieties of known active anticholinesterases in ingenious ways to provide yet more potent compounds with actions beyond the cholinergic system.

4. Tau Aggregation Inhibitors

Alois Alzheimer's initial description of the disease that bears his name detailed the presence of two very different proteins, now known as tau and A β , in the brain of the same demented subject. Tau is a key microtubule-associated protein in efficient axonal transport that is impaired in AD and tauopathies consequent to abnormal excessive tau phosphorylation and aggregation. Pickhardt and colleagues provide (page 397-402) an interesting review of an inducible cellular model for tau-induced pathology. Emphasis is focused on tau aggregation and toxicity, which appear to be closely correlated, to provide a model to assess the efficacy of aggregation inhibitors – an intriguing series of low molecular weight compounds with a N-phenylamine core.

5. Lowering Amyloid- β Peptide: Single Target, Multiple Approaches

The other hallmark protein relating to Alois Alzheimer's initial description of the disease is A β . Various soluble and insoluble forms of A β products, deriving from the enzymatic cleavage of amyloid β precursor protein (APP) that is normally found in nerve cells, accumulate within both the intra- and extracellular compartments of normal and, in particular, AD brain. Although the specific neurotoxic species of A β , and mechanisms via which they damage neurons remain to be fully elucidated, it is clear that A β generation and disposition can be modified at many levels.

A β is generated from APP following its sequential cleavage by β - and γ -secretase activities. Mechanisms that increase or lower APP levels may modulate the products of its cleavage – including A β . Avramovich-Tirosh and colleagues review (page 403-411) the pharmacological action of an exciting series of multi-functional compounds deriving from the Youdim laboratory. These appear to lower APP and A β levels, post-transcriptionally *via* the 5'-untranslated region of APP mRNA, and specific agents offer iron metal chelating, radical scavenging and neuroprotective properties that are of potential utility in not only AD but also PD and other neurodegenerative diseases.

In a non-amyloidogenic pathway, APP can be cleaved by α -secretase within the A β sequence to preclude formation of any A β form, but provide an APP N-terminal extracellular domain that possesses neurotrophic properties. Fahrenholz describes (page 412-417) the identification of the disintegrin and metalloproteinase protein, ADAM 10, as possessing α -secretase activity *in vivo*, and reviews mechanisms controlling its regulation – particularly upregulation by agents such as retinoic acid. Furthermore, the activation of α -secretase via G protein-coupled receptor stimulation is critically over-viewed as elevation of its activity is clearly of potential value in AD.

The biogenesis of A β is mediated from the proteolytic cleavages of APP by two membrane associated protease activities: β -secretase, also known as Memapsin 2 and BACE1, initially cuts APP in the ectodomain to produce a membrane anchored 99-residue fragment. Thereafter, this is further cut within the transmembrane domain by γ -secretase to produce A β . It has long been accepted that inhibitors of either β -secretase or γ -secretase would lower the generation of A β and may thus be effective in treating AD. Achieving this goal, however, through the design and development of effective, selective, well-tolerated and centrally active inhibitors has been an uphill battle. Two articles reviewing these secretases are provided by leading groups in each of these highly competitive fields. Ghosh and colleagues review (page 418-422) the medicinal chemistry and biological activity of Memapsin 2 inhibitors deriving from their collaborative studies with Tang and colleagues. By contrast, Checler and colleagues describe (page 423-426) the components that, together, form the multi-catalytic protease, γ -secretase. In particular, a critical part of the γ -secretase complex, presenilins 1 and 2, are pleiotropic proteins that affect apoptosis by modulating p53. Their interesting article details p53 regulation by presenilin 1 and 2 at a transcriptional level, via generated C-terminal intracellular fragments of APP – and thereby defines an additional level of complexity in the design of γ -secretase inhibitors.

Foundations to develop immune therapy in humans afflicted by AD derive from extensive basic and clinical research during the last decade. Indeed, both active and passive A β immunotherapy protocols have reached clinical trials, and the basis of these is comprehensively reviewed in two separate and synergistic articles. As described by Lemere and colleagues (page 427-436), the toxicity associated with the well-known AN1792 active immunotherapy phase IIa study in mild to moderately affected patients likely developed consequent to an autoimmune response to the immunogen, A β ₁₋₄₂. Would the targeting of a different epitope have provided an effective treatment that avoided this toxicity? – This is the focus of each of the stimulating articles by Arbel and Solomon (page 437-445), and by Lemere and colleagues. Each details powerful rationales for different approaches that open numerous avenues for future clinical and basic research.

6. Alpha-Synuclein, a Characteristic of PD, Provides an Approach to Affect AD

Alpha-synuclein pathology, although a hallmark of PD, is found together with amyloid plaques and neurofibrillary tan-

gles in AD and other neurodegenerative disorders. Although the biological function of this synaptic protein remains to be elucidated, increasing evidence reviewed by Windisch and colleagues (page 446-457) suggests an interaction with A β peptides and tau-hyperphosphorylation. Numerous hypotheses exist concerning the toxicity of alpha-synuclein aggregates. Due to their close association with neurodegenerative diseases, a variety of strategies are being developed to counteract alpha-synuclein aggregation. An interesting one, developed and reviewed by these investigators utilizes beta-synuclein-derived peptides, and the underpinning rationale and their actions in cellular and animals models are also described.

7. Clinical Approaches to AD Management – There is Much to Learn!

Many of the preceding articles have focused primarily on the ‘basic and mechanistic science’ of AD – critically reviewing numerous studies to define and characterize a target for intervention, as well as develop a intervention strategy (whether a small drug-like compound or biological) to both hit and regulate that target. Eventually, following significant studies defining efficacy vs. toxicity in large and small animals, such strategies may translate to human studies, where they are assessed in clinical trials to evaluate the benefits and risks of treatments. How do these studies emulate reality? Are their predictions concerning efficacy and tolerability accurate? What ethical considerations should be taken into account when treating an individual, and particularly one with cognitive impairment that has limited ability to comprehend the possible implications of participation in a clinical trial?

Two important articles focus both on these questions and others of equal importance that underscore the basis of all current clinic trials, whether in AD or other patient populations. Becker provides (page 458-467) a thought-provoking article on the role of clinical pharmacology in clinical trials, flaws in clinical trial design, and how such trials can be optimally designed to overcome numerous current limitations. Korczyn, in an equally stimulating article, reviews (page 468-472) the ethical problems associated with studies on demented individuals. This clearly vulnerable patient population has little ability to fully grasp the possible implications of participation in a clinical trial, and the consequent need for informed consent. The advantages and disadvantages of participation are detailed, as are the roles of the patient, caregiver, investigator, and institutional review board.

One of numerous interesting strategies to offset AD, not covered in the approaches reviewed in the preceding articles, focuses on the role of proteoglycans in the amyloid aggregation and fibrillogenesis process. The polyanionic glycosaminoglycan chains of tissue proteoglycans appear to bind to amyloid peptides and promote their aggregation in brain. Small sulfated or sulfonated compounds have been developed to interfere with this binding to potentially slow fibrillogenesis. One such agent, Alzhemed, has translated to clinical trials and phase 3, and its clinical development has been reviewed by Aisen and colleagues (page 473-478).

Finally, this special issue is completed with perhaps the most extensive review currently available on the pharmaco-

genetics of cholinesterase inhibitors, the most widely prescribed drug class used in AD treatment. Cacabelos and colleagues comprehensively detail (page 479-500) the genetic variation that gives rise to differing response to currently available anticholinesterases. The authors extensively review the genetic defects identified in AD during the last 25 years and, in particular, focus on drug metabolism.

In closure, this issue captures a snapshot, in the form of 19 thought-provoking review articles, of an enormously stimulating symposium. The articles cover a wide spectrum

of current and exciting AD basic and clinical research – focused towards AD diagnosis and treatment. We are appreciative of the numerous scientists that aided in the peer-review process and wish to thank the organizers of the meeting, sponsors and publisher and staff of *Current Alzheimer Research* for their cooperation and efforts in the genesis of this important issue (<http://www.bentham.org/car/>). Finally, we express our sincere gratitude to TorreyPines Therapeutics Inc. (La Jolla, CA 92037) for generously sponsoring this special issue.