Novel treatments and current clinical trials for Alzheimer's disease therapies show promise

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The past 25 years have seen an explosion of scientific investigations into the basic neurobiology of Alzheimer's disease (AD). Unfortunately, the gap between bench and bedside remains as vast as ever. Recent progress, however, has resulted in the development of novel, and in some cases, unconventional approaches for effective treatment. New therapies are currently undergoing preclinical investigation or are in clinical trial phase. A special issue of the *Journal of Alzheimer's Disease* (October 2008), guided by guest editor Muhammad Omar Chohan, MD, explores these exciting developments.

"The scientific community in general and the pharmaceutical industry in particular have invested heavily in just a few areas of AD therapeutics. The result is quite clear: symptomatic drugs are the best that can be offered to patients with this devastating disease," commented Dr. Chohan, Neuroimmunology Lab, Department of Neurochemistry, New York State Institute for Basic Research in Developmental Disabilities. "Despite the seemingly desperate state of affairs, we now see a steady influx of novel, unconventional therapeutic approaches. This special issue of the Journal of Alzheimer's Disease presents perspectives written by leaders in the field who believe that it is high time for innovation in AD therapeutics."

Bringing together 14 contributions from worldwide experts, Dr. Chohan has assembled a two-part Special Issue. The first part concentrates

mainly on preclinical studies and novel agents that are still in the experimental phase, while the second describes current clinical studies and some of the major issues involved.

The issue opens with a focus on immunotherapy. Einar Sigurdsson proposes active immunization against tau, while Michal Novak and his group elaborate on passive tau immunization. This is followed by an update on glycogen synthase kinase-3 (GSK-3) inhibitors by Daniel Perez and Anna Martinez, who lead a major AD clinical trial with a GSK-3 inhibitor. Although amyloid immunotherapy has been a particular focus of almost all large pharmaceutical efforts, there has been limited progress in that area. Beka Solomon proposes a completely novel approach based on phage-display technology which holds promise in amyloid-based vaccine development.

While there is growing literature on the involvement of oxidative stress in AD pathogenesis, clinical data have not shown substantial benefit from antioxidant agents. Xiongwei Zhu and colleagues discuss some of these issues and propose development of advanced clinical therapies around this theme. Two papers by Silvia Mandel and colleagues and Ashley Bush focus on a yet another novel approach: the role of metals and drugs based on the Metal Hypothesis. Kiminobu Sugaya and colleagues then discuss the promises and realities of cell replacement in the future of AD therapeutics. Finally, Antonio Cattaneo and colleagues discuss the potential of Nerve Growth Factor as a therapy for AD.

The development of AD therapeutics has been plagued with many failed and equivocal clinical trial outcomes. The second part of the special issue begins with a perspective from Saad Shafqat discussing the plight of dementia care in a developing country. This is followed by a series of stimulating analyses of current AD clinical trials both in the US and in Europe. First, Bruno Vellas and colleagues share their experience in the development of disease-modifying agents. Next, Robert Becker and

colleagues and Cynthia Carlsson present an autopsy-style evaluation of failed AD clinical trials and make several important recommendations. Khalid Iqbal and colleagues wrap up the issue by discussing the multifactorial and heterogeneous nature of AD and the importance of patient stratification in the design of future clinical studies.

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