James & Esther King Biomedical Research Program

Prabhakar, Rajeev

Department of Chemistry *2008 Program*
University of Miami *New Investigator (3-year project)*

Project Title: Effect of Nicotine on Amyloidosis and Oxidative Stress in Alzheimer's Disease (AD)

Project Summary: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of senile plaques and neurofibrillary tangles in the brain. The major component of these plaques is 42 amino acid residues containing amyloid beta (Ab) peptide. There is a direct association between cigarette smoking and AD, and recently it was demonstrated that current smokers are at roughly double the risk of developing AD as those who have never smoked. The potential therapeutic strategies for AD include blocking the generation and aggregation of Ab peptides, inhibiting the cytotoxic effects, and disruption of preformed fibrils. However, our efforts in this direction are hindered by the lack of atomic level understanding of biochemical processes occurring in AD. Due to inherent complexities, this understanding cannot be achieved by experiments alone. We have designed a radically different approach to realize this goal through the development and application of a comprehensive theoretical and computational strategy involving molecular dynamics (MD), quantum mechanics (QM), hybrid quantum mechanics/molecular mechanics (QM/MM), bioinformatics, and X-ray spectroscopic (X-ray photoelectron [XPS] and X-ray absorption [XAS]) techniques. In these studies, roles of Methionine35, nicotine, and metal ions (Cu, Zn, and Fe) will be elucidated. The outcome of these studies will advance our efforts to develop effective therapeutic strategies for treating AD.