ION MOBILITY AS A PROBE FOR MOLECULAR STRUCTURE AND OLIGOMER STATES IN BIOLOGICAL ASSEMBLIES

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A brief description of the Ion Mobility Method will inaugurate the talk followed by several examples of current systems of interest to our group. Peptide and protein systems of interest will be drawn from those responsible for several important neurological diseases. Recent evidence indicates that Alzheimer's disease, Parkinson's disease and the prion diseases are caused by the early aggregation states of misfolded peptides and proteins that eventually go on to form amyloid plaques. The focus will be on the Alzheimer's peptide, ABeta. The dominant ABeta peptide is the 40 amino acid fragment AB40 (90% in healthy brains) which is only very mildly neurotoxic. Addition of isoleucine and alanine to the C-terminal end of AB40 yields the strongly neurotoxic AB42 (9% in healthy brains). We have examined the distribution and structure of the early oligomer states of these two systems and related alloforms. Major differences were found and a new paradigm for the etiology of Alzheimer's disease will be proposed. If time permits new data on the Parkinson's protein, Alpha synuclein will be presented including results of two important familial mutants of the wild type.

A second part of the talk will deal with the formation and stabilization of G-quadraplexes in DNA. These structures are composed of multiple G-quartets connected by single strand DNA loops and are predicted to be formed by self assembly in G-rich DNA regions in the genome. These G-rich strands are ubiquitous with over 500,00 candidate segments in the human genome, mostly in gene rich regions. In addition, several thousand TTAGGG repeats comprise the telomeric capping regions of all chromosomes whose reproduction is a critical element in cell mytosis. The ability to stabilize G-quadraplexes with differing loop regions may well contribute to possible cures for many types of cancers by selectively silencing gene expression. We will use Ion Mobility and high level molecular dynamics simulations to explore possible drug candidates for stabilizing the quadraplex structure.