**Designing New Chemical Entities to Inhibit Cytotoxic Protein Misfolding**

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Protein misfolding is a proteopathic process that is central to the pathogenesis of multiple diseases, both within the central nervous system (Alzheimer’s dementia, frontotemporal dementia, Parkinson’s disease, chronic traumatic encephalopathy) and external to the brain (type II diabetes). Of the multitude of protein misfolding disorders, Alzheimer’s disease (AD) is amongst the most socioeconomically devastating. Currently 47 million people worldwide have AD and there are no disease modifying therapies available. Two strategies for designing possible therapeutics to AD will be presented. Both are based on extensive molecular modelling approaches using both density functional theory and empirical force field calculations. The first approach endeavours to design therapies which target the HHQK tetrapeptidic motif within beta-amyloid, interacting with this target using electrostatic interactions, particularly aromatic-cationic interactions. The second approach is based on homology modelling of proteins to produce a model receptor, termed CCM, against which 11.8 million compounds were screened in silico using a high throughput computational strategy. The strengths and weakness of both approaches will be discussed.