Synthesis of hybrid drugs resulting from structure-based analysis of protein aggregation

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In this propject, novel hybrid multifunctional compounds for preventing protein aggregation will be synthesized. Using Alzheimer diseases (AD) as the primary model, three existing A! binders which differ significantly, both in size and mode of action, will be used: monoclonal antibodies or recombinant fragements thereof (scFv) raised against various conformations of A!, D-peptides selected from phage display libraries, and aminopyrazoles specifically designed as beta-sheet ligands will be fused covalently to furnish hybrid compounds. By optimizing the length of flexible spacers, two different epitopes on A! will be targeted simultaneously leading to drastically improved affinities and specificities. Highly stable scFv-A! complexes will provide a means for docking D-peptides or aminopyrazoles to monomeric Alzheimer's peptide and thereby facilitate the structural elucidation of their adducts. NMR analysis of the ligands themselves or A!-ligand complexes will complement molecular dynamics calculations, reveal key noncovalent contacts responsible for tight binding, and will also provide guidelines for improved molecular design. These novel hybrid compounds will be tested in cell and animal models. Apart from offering remedies to deadly AD, they will help to elucidate pathogenic mechanisms of protein aggregation.

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