ACS Chemical Neuroscience

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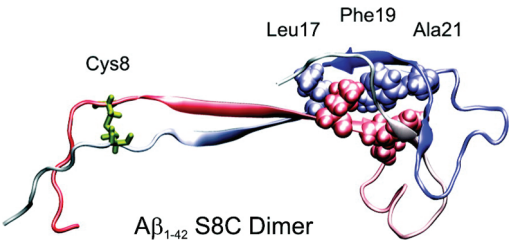
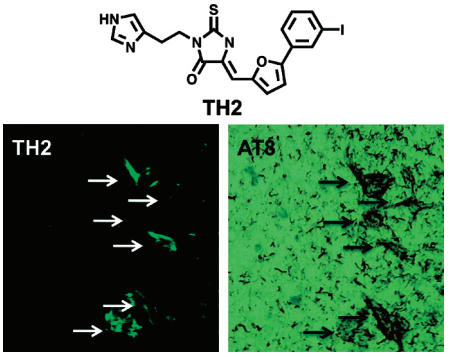
Engineering a Toxic Dimer



Alzheimer's disease (AD) is a serious neurodegenerative disease. A crucial step in the molecular pathogenesis of this disease is the uncontrolled proteolytic cleavage of the Aβ peptide fragment from the APP protein. Disparate soluble multiples of the Aβ peptide, known as Aβ oligomers, have been shown to be associated with early cognitive deficits in patients through synaptic pathology. Research on the structure and function of Aβ oligomers has been hampered by the lack of appreciable quantities of homogeneous Aβ oligomers.

Based on computational analyses, Müller-Schiffmann et al. (DOI: 10.1021/cn200011h) designed three cysteine substitutions of the Aβ peptide. Each peptide was expressed in a mammalian system to enhance dimer formation under physiological conditions. Two of the peptides exhibited proper proteolytic processing, trafficking, and assembly to an exclusive, homogeneous Aβ dimer. The third was shown to be neurotoxic and to cause synaptic pathology. Molecular dynamics simulations indicated a unique elongation-incompetent conformation in the peptide.

Imaging for Alzheimer's Disease



Neurofibrillary tangles are associated with Alzheimer's disease (AD). Previous studies indicated that the accumulation of these tangles occurs before the manifestation of clinical symptoms in AD. Consequently, even in early stages of AD progression, patients display considerable numbers of neurofibrillary tangles in the entorhinal cortex and hippocampus. Therefore, it would be useful to be able to visualize neurofibrillary tangles in vivo in conjunction with the imaging of Aβ plaques to assist in the diagnosis of this disease.

Ono et al. (DOI: 10.1021/cn200002t) describe novel probes for detecting neurofibrillary tangles for in vivo imaging in AD. Imaging techniques such as these can also be used in association with treatment options to determine if they are effective in reducing disease-associated pathologies.

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