Chemical Engineering Doctoral Defense

Antibody Based Diagnostic and Therapeutic Approach for Alzheimer's Disease

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abstract

Alzheimer's disease (AD) is the most common form of dementia leading to cognitive dysfunction and memory loss as well as emotional and behavioral disorders. It is the 6th leading cause of death in United States, and the only one among top 10 death causes that cannot be prevented, cured or slowed. An estimated 5.4 million Americans live with AD, and this number is expected to triple by year 2050 as the baby boomers age. The cost of care for AD in the US about \$200 billion each year. Unfortunately, in addition to the lack of an effective treatment or AD, there is also a lack of an effective diagnosis, particularly an early diagnosis which would enable treatment to begin before significant neuronal damage has occurred.

Increasing evidence implicates soluble oligomeric forms of beta-amyloid and tau in the onset and progression of AD. While many studies have focused on beta-amyloid, soluble oligomeric tau species may also play an important role in AD pathogenesis. Antibodies that selectively identify and target specific oligomeric tau variants would be valuable tools for both diagnostic and therapeutic applications and also to study the etiology of AD and other neurodegenerative diseases.

We synthesized and purified recombinant human tau (rhTau) in monomeric, dimeric, trimeric and fibrillar forms and demonstrated that trimeric but not monomeric or dimeric rhTau is extracellularly neurotoxic to neuronal cells. We designed a novel biopanning protocol based on phage display technique and atomic force microscopy (AFM), and used it to isolate single chain antibody variable domain fragments (scFvs) that selectively recognize the toxic tau oligomers. These scFvs selectively bind tau variants in brain tissue of human AD patients and AD-related tau transgenic rodent models and have potential value as early diagnostic biomarkers for AD and as potential therapeutics to selectively target toxic tau aggregates.

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