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Department of Materials Science U5 - Seminar room – 1st floor

Towards early diagnosis and treatment of Alzheimer's disease by targeting toxic soluble Aβ oligomers

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Abstract

Amyloid formation in various diseases is characterized by protein misfolding and aggregation in cross β-sheet secondary structures (1). Misfolding of amyloid β (Aβ) and tau proteins and their aggregation and accumulation are the main hallmark of Alzheimer's disease (AD). Recent clinical studies collectively suggest the necessity of diagnosing AD at an early stage for effective therapy. However, early diagnosis of AD remains a major challenge, which impedes successful treatment. Self-assembled cyclic D,L-α-peptides can mimic the cross β-sheet structure of the amyloids and inhibit their aggregation and toxicity by interacting with their early oligomers (1-3 mers), most probably due to their structural and functional similarities to those of the pathogenic amyloids. Recognized by the oligomer-specific antibody A11, cyclic D,L-α-peptide 1 and its analogs engage, disrupt, and clear amyloid oligomers through an "off-pathway" mechanism and reduced toxicity in cells [2-4]. In an AD mouse model, brain PET imaging using stable 64 Cu-labeled cyclic D,L-α-peptide 1 gave unprecedented early amyloid detection in 44-day pre-symptomatic 5xFAD mice better than clinically used 11 C-PIB. No tracer accumulation was detected in the cortex and hippocampus of imaged pre-symptomatic AD mice; instead, intense PET signal was observed in the thalamus, from where Aβ oligomers may spread to other brain parts with disease progression. Effectively crossing the blood brain barrier, the cyclic D,L-α-peptide analogs also reduced Aβ oligomer levels, prolonged lifespan of AD transgenic Caenorhabditis elegans, and abated memory and behavioral deficits in AD mice (5,6). These results illustrate the utility of self-assembled cyclic D,L-α-peptide analogs as novel tools for studying β-sheet assembly and disruption with promise for early detection and treatment of amyloid diseases.

References

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