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Retro-inverso peptide inhibitors of β-amyloid oligomer formation as a novel treatment for the progression of Alzheimer's disease

David Allsop
Lancaster University, UK

Inhibition of Aβ oligomer formation could have a major impact on clinical progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD). We are working on retro-inverso (RI) peptides and RI-peptides attached to the surface of nanoparticles as therapeutically useful inhibitors of early-stage Aβ aggregation. The inhibitor RI-OR2-TAT consists of the Aβ binding peptide RI OR2 (rGffvlkGr) attached to a retro-inverso version of the transit peptide 'TAT' to target the inhibitor into the brain. Fluorescein-RI OR2-TAT has been shown to cross the blood brain barrier (BBB) of APPswe/PS1ΔE9 transgenic mice and bind to β amyloid plaques. Moreover, daily peripheral injection of RI-OR2-TAT into these mice for 21 days resulted in a 25% reduction ($p<0.01$) of Aβ oligomer levels, a 32% reduction ($p<0.0001$) of amyloid plaque count, a 44% reduction ($p<0.0001$) in the numbers of activated microglial cells, and a 25% reduction ($p<0.0001$) in oxidative damage. Covalent attachment of RI OR2 TAT toliposomes, to produce peptide-inhibitor nanoparticles (PINPS), has resulted in a remarkably potent multivalent inhibitor that has several advantages over the free peptide for further development as a potential drug. These include biocompatibility, stealth properties (to avoid detection by the immune system) and the possibility of designing multi-ligand systems directed at more than one target. Various drug candidates aimed at inhibiting the formation of Aβ, or inducing the clearance of senile plaques from the brain, have failed in recent years. Our RI peptide and nanoparticle-based therapies are an alternative approach to more conventional drugs and could offer some hope for success in future human clinical trials.

Biography

David Allsop is a Professor of Neuroscience at Lancaster University. He has been working on Alzheimer's disease for around 30 years, and has published more than 120 papers on this and other neurodegenerative diseases. He is a member of the Research Executive Committee of The Alzheimer's Society, UK.

d.allsop@lancaster.ac.uk

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