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A NOVEL APPROACH TO THE THERAPY OF ALZHEIMER'S DISEASE BASED ON PEPTIDE NANOLIPOSOME INHIBITORS OF AMYLOID AND TAU AGGREGATION

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Considerable advances have been made over the last 30 years in understanding the neuropathology of Alzheimer's disease (AD) but this knowledge has not led to the successful development of new drugs. Currently available drugs only treat the symptoms of AD and many potential disease-modifying drugs have failed in clinical trials. Many of these drugs aim to reduce accumulation of β-amyloid (Aβ) in senile plaques and consist of inhibitors of β secretase or γ-secretase, which block Aβ production, or Aβ immunotherapy, which results in clearance of amyloid from the brain. These drugs have run into various problems and were probably given too late during the course of AD. Our proposed therapeutic candidates consist of modified peptides that inhibit the aggregation of Aβ or tau attached covalently to the surface of nanoliposomes. The latter contain a PEGylated lipid which has a maleimide group for covalent linkage to a thiol group (cysteine residue) on the peptide. The peptide developed against Aβ is retro-inverted (D-amino acids, with sequence reversal) and is stable against proteolysis. This is linked to a TAT sequence for targeting to the brain. Similar types of peptide-liposomes are under development for inhibition of tau aggregation (neurofibrillary tangle formation).Our approach is novel and specifically targets the early stages of aggregation of Aβ and tau. Multiple inhibitory peptides attached to the liposome surface create a potent, multivalent inhibitor that can cross the BBB and enter cells. Moreover, our peptide-liposomes hide from the immune system, and should not invoke an undesirable immune response. There is increasing recognition that combination therapies may be warranted to address the complex biology of AD and our development allows for Aβ or tau peptide inhibitors alone or in combination to be attached to the surface of the liposomes, resulting in a therapeutic with dual action against plaques and tangles.

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