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Opinion Article

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Design and Synthesis of Dual-Targeted Drug Delivery Systems for Alzheimer's Disease Treatment

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DESCRIPTION

Dual-targeted drug delivery systems are emerging as a transformative approach to addressing the complex and multifaceted nature of Alzheimer's Disease (AD), a neurodegenerative disorder marked by cognitive decline and progressive brain deterioration. AD is characterized by the presence of Amyloid-Beta (Aβ) plaques and neurofibrillary tangles of tau protein, which together drive neuronal death and dysfunction. Traditional drug delivery methods have often failed to adequately address the disease's complexity, as they typically target single aspects of the pathology. Dual-targeted drug delivery systems however are designed to tackle multiple mechanisms simultaneously, potentially enhancing therapeutic efficacy by addressing both the amyloid and tau pathologies or by targeting multiple brain regions involved in disease progression. These systems combine sophisticated delivery technologies with molecular targeting strategies, enabling the precise delivery of therapeutics to desired sites in the brain.

The design of dual-targeted systems for AD requires addressing two primary challenges: Overcoming the Blood–Brain Barrier (BBB) and ensuring targeted delivery to specific neural regions or cellular targets associated with Alzheimer's pathology. The BBB is a selectively permeable barrier that protects the brain but also restricts the entry of most therapeutic compounds. A range of strategies, including ligand modification, nanoparticle conjugation and receptor-mediated transport, have been developed to address this.

By using such receptor-mediated pathways, these dual-targeted systems increase the likelihood of drug molecules reaching the brain. Additionally, targeting ligands can be further engineered to recognize specific biomarkers associated with Aβ plaques or tau tangles, leading to a higher concentration of the therapeutic agent in affected areas. This dual-targeting strategy not only enhances drug penetration across the BBB but also ensures a higher degree of localization to disease-specific regions, potentially minimizing systemic side effects and enhancing treatment efficacy. Another critical aspect of designing dual-targeted systems is the selection of therapeutic agents with complementary mechanisms of action. Alzheimer's disease involves a complex interaction of processes, including oxidative stress, inflammation and neurodegeneration. Therefore, combining drugs that address multiple pathways could result in more comprehensive therapeutic effects. For instance, one part of the system could deliver an anti-inflammatory agent that reduces neuroinflammation, while another delivers a neuroprotective or anti-amyloid compound.

Peptide-based dual-targeted systems are also gaining attention, as peptides can be engineered to cross the BBB and bind specifically to AD-related targets. Additionally, peptides have the advantage of being biocompatible and less likely to elicit immune responses compared to synthetic compounds, which can make them suitable for chronic treatment regimens. Peptide-based systems can also be combined with nanoparticle carriers, allowing for enhanced stability and sustained release in the brain. Gene therapy and RNA-based therapies have also been explored as dual-targeted approaches, particularly in cases where gene expression modification is required to counteract the underlying disease mechanisms. For instance, RNA interference (RNAi) molecules can be used to silence genes that promote amyloid and tau production. Dual-targeted nanoparticles have been developed to deliver both small-molecule drugs and RNAi agents, enabling a multipronged attack on AD pathologies.

Despite the potential of dual-targeted systems, several challenges remain, including the complex regulatory landscape for combination therapies and the risk of unforeseen interactions between therapeutic agents. Furthermore, the pharmacokinetics and pharmacodynamics of dual-targeted systems can be difficult to predict, as interactions between drugs may alter their distribution and efficacy. Additionally, optimizing the stability and biocompatibility of these systems is essential to ensure safety in human applications.

In conclusion, combining multiple targeting and delivery strategies, these systems enhance drug specificity, reduce off-target effects and improve bioavailability in affected brain regions. Nanoparticles, peptides and gene-based therapies represent versatile tools that, when integrated into dual-targeted systems, offer a way to simultaneously combat amyloid and tau pathologies, neuroinflammation and other contributors to disease progression.