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Title:

Blood–Brain Barrier Peptide Shuttles as a Platform for Systemic CNS Drug Delivery

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Abstract

Antisense oligonucleotides (ASOs) are an emerging class of gene-specific therapy for various diseases, with more than 10 ASOs currently approved by the FDA. Amongst them, only two ASOs (Spinraza and Tofersen) are for CNS related diseases, spinal muscular atrophy (SMA) and Amyotrophic lateral sclerosis (ALS) respectively. The slow progress in translation of ASOs targeting neurological diseases is not due to the lack of ASOs potency but rather their inability to reach their CNS target due to the presence of a formidable blood-brain barrier (BBB) that impedes the CNS entry of most neurotherapeutics. To bypass the BBB, Spinraza and Tofersen are directly delivered into the CNS through intrathecal (IT) injections. The IT route of CNS drug delivery is invasive and adverse effects related to lumbar puncture has been reported in nearly all patients. Therefore, to address this limitation, we have developed a safe and highly efficient CNS drug delivery platform based on BBB-penetrating peptides (BPP). We have demonstrated the ability of the BPPs to systemically (*i.v.* route) deliver Spinraza (in PMO chemistry) into the CNS and significantly upregulate the level of target gene (*SMN2*) in the brain (20%) and spinal cord (55%) in *SMN2* transgenic adult mice. We have also assessed the brain distribution of fluorescently (Cy7)-labelled BPP-ASO conjugate. We have shown that 79% of *i.v.* injected Cy7-BPP-ASO reaches brain parenchyma. We have further demonstrated that BPPs efficiently deliver a broad spectrum of therapeutics with diverse sizes and physicochemical properties, including small molecules, peptides, and bispecific modalities. This non-invasive CNS delivery platform harnesses BPPs to achieve efficient brain penetration, thereby unlocking the full therapeutic potential of neurotherapeutics.

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