Design, Synthesis and Biological Assessment of Redox Chemical Delivery Systems for Targeting brain: Application in Neuroimaging and Alzheimer's Disease Treatments.

The delivery of drugs to the brain remains a major challenge in the treatment of central nervous system (CNS) disorders. The blood-brain barrier (BBB), a physiological barrier that protects the brain from various pathogens thanks to its excellent barrier properties, constitutes a serious bottleneck in new drug development for CNS diseases. Over the past decade, our team contributed to address this issue by exploring various strategies based on Bodor's redox Chemical Delivery Systems (CDSs).

After a proof of concept phase that validated 1,4-dihydroquinoline/quinolinium salt (DHQ2) as a new generation of CDSs to deliver neuroactive drugs into the brain [**1**], we highlighted the potential of radiolabeded [^{11}C]DHQ2 to deliver meta-iodobenzylguanidine (MIBG) in rat brain [**2**]. This finding paves the way towards exploiting [^{123}I/^{18}F]MIBG as radiotracers for neuroimaging the norepinephrine transporter (NET) involved in various neuropsychiatric disorders.

Although 3'-deoxy-3'-^{18}F-fluorothymidine ([^{18}F]FLT) has been developed as a proliferation tracer for oncological PET studies, low-grade brain tumors are poorly visualized due to the low uptake of [18F]FLT in brain tissue, preventing its use in PET imaging to detect brain tumors at an early stage. To address this issue, FLT was linked to various [^{11}C]DHQ2 and injected in rats, suggesting that this CDS is a promising approach to target low-grade brain tumors for PET imaging [**3**].

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases within the elderly population affecting more than 20 million people worldwide. Despite huge research efforts made in developing curative pharmacological treatments, only symptomatic treatments mainly based on the cholinergic strategy are currently available. Thus, rivastigmine, donepezil and galantamine are the only three marketed acetylcholinesterase inhibitors (AChEIs) prescribed to patients with mild-to-moderate AD. However, more pronounced cholinergic dysfunction in advanced stages of AD requires higher doses of AChE inhibitors resulting in serious adverse peripheral cholinergic effects. Therefore, the design of new approaches aiming at developing highly central selective AChEIs free from adverse peripheral effects is highly desirable. To address this issue, a "bio-oxidisable" prodrug of AchEIs has been developed to improve drugs distribution to the brain while reducing peripheral side effects **[4]**.

References.

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