

Nanotechnology for the Treatment of NeuroAIDS

Keywords: HIV; ARV; NeuroAIDS; Neurocognitive disorders; Blood-brain-barrier; Latency reactivating agents; HIV reservoir; Latency

Abbreviations: HIV: Human Immunodeficiency Virus; ARV: Antiretroviral Drugs; BBB: Blood-Brain-Barrier; MNP: Magnetic Nanoparticle; LRAs: Latency Reactivating Agents; HAART: Highly Active Antiretroviral Therapy; HAND: HIV Associated Neurocognitive Disorders; MENPs: Magneto-Electric Nanoparticle

Introduction

Highly Active Antiretroviral Therapy (HAART) has significantly declined mortality rates of people living with HIV/AIDS (PLWH/A); however, HIV virus still remains dormant in brain compartments while more than 50-60% of the infected patients exhibit HIV associated neurocognitive disorders (HAND), ultimately progressing to neuroAIDS [1-3]. This is mainly attributed to the integration of the HIV-1 genome into the host genome causing viral latency. The cells that harbor latent HIV typically stay in specific anatomic sites e.g. secondary lymphoid tissue, testes, liver, gut and the CNS [4,5]. The situation is more complicated because in addition to the latent reservoir, other cryptic viral sources exist during HAART, including a very small amount of active virus replication that occurs even during therapy [6]. It is not clear whether this is due to poor HAART penetration into the sites of virus replication or to residual replication that occurs even at ideal drug concentrations. Moreover, neurotoxicity and drug resistance makes the treatment of HIV infection more challenging. Thus, complete eradication of HIV-1 reservoirs from CNS remains a clinically formidable task to cure or treat NeuroAIDS [7].

One of the major reasons for the failure of neuroAIDS treatment is poor patient compliance with HAART. Due to lifelong therapy, patients fail to adhere to the treatment schedule which leads to ineffective drug levels in the body causing the rebound of viral replication [8-10]. Despite the best intentions and efforts on the part of the healthcare professionals, non-adherence of patients with HAART remains very high. Clinical trial data on HIV drugs shows that missed doses of antiretroviral agents were most likely to occur due to neurocognitive defects and other personal issues (e.g. forgetfulness, sleeping through a dose, being too busy to take the dose, feeling sick and depression) [8]. Furthermore, diseases in PLWH/A can be greatly exacerbated by drugs of abuse, such as cocaine, methamphetamine etc., which decreases likelihood of adherence to HAART regimens [2]. No single intervention strategy will likely improve the adherence of all PLWH/A; attempts to improve patient adherence will likely depend upon a set of key factors. Among all strategies, decreasing the frequency of medication administration may have the greatest potential to improve compliance and achieve better treatment outcomes.

To achieve the effective treatment for an HIV-infected individual, all sources of replication-competent HIV must be eliminated. Achieving this objective may require an amalgamation

Opinion

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of diverse approaches reflecting the variety of reservoirs that exist in infected patients along with the active infection. So, to overcome the limitations of CNS delivery, a number of strategies [nanoparticles, lipid carrier, tagging drugs to ligands that cross the BBB through a carrier mediated transport, macrophage mediated transport (Trojan horse) or receptor mediated transport (e.g. insulin, transferrin)] have been used to improve the permeability of ARVs drugs across BBB [11-13]. Each of these strategies presents strengths and limitations. To address the issue of adherence and patient compliance, our group has worked on these aspects and developed a novel layer-by-layer (LbL)-magnetic nanoformulation that can release the ARV and LRA for longer duration in sequential while sustaining manner (up to 5 days) [14]. Additionally, our group discovered a novel magneto-electric nanoparticle (MENPs) to overcome the constraint of uncontrolled release of drugs from the magnetic nanocarriers [15]. We have explored the novel dual property (Magnetic and electrical property) of the nanomaterial for the on demand delivery of ARV drug across in-vitro BBB for the potential application of neuroAIDS treatment [16]. We have also explored more biocompatible and novelmagneto-liposomes used to pack monocytes/macrophage that deliver ARV drugs across BBB [17]. All the aforementioned studies are in preclinical stages and needs great amount of both experimental and clinical validation before this HIV nanotherapeutics can be used in clinical setting.

Outlook

Application of nanotechnology in the nanomedicine field has shown exciting prospects for development of a novel drug delivery system to administer the desired therapeutic levels of ARVs/LRAs across the BBB. Nevertheless, all existing nanocarrier based drug delivery systems have many limitations that affect the target specificity, delivery efficacy, release kinetics and bioavailability of desired amount of drugs at the target site. So, from a drug delivery point of view, a targeted brain specific delivery and drug release (sustained or on demand release) from the nanocarrier is very much needed to eradicate HIV reservoirs. Most importantly, poorly-

understood mechanistic details behind the delivery of existing nanocarriers across the BBB and ambiguous release strategies of nanocarrier bound drugs/agents to the target are prohibiting the advancement of nanodelivery system. In conclusion, state-of-the-art of HIV eradication using nanotechnology suggests that developing a nanomedicine for site-specific drug delivery to CNS and smart assaying to monitor HIV progression will be needed for better neuroAIDS management and its treatment.

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Conflict of Interest

The authors state no conflict of interest and have not received any financial support for the preparation of this manuscript.

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