Nanomedicine for neuroHIV/AIDS management

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“The outcomes of our NIH-funded projects proposed that nanomedicine, developed using nanobioengineering/technology, can cross the BBB to eradicate brain HIV infection. Tunable efficacy features of nanomedicine allow their functional manipulation in personalized manner according to the patient disease profile requirement to achieve maximum therapeutics without causing side effects.”

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The neurological complications of AIDS comprise neurocognitive impairment and HIV-associated dementia (HAD; or AIDS dementia) [1]. Regardless of current advances in our understanding of the pathogenesis, availability of highly active antiretroviral therapy and neuro-virological aspects of HAD, it remains a daunting scientific and therapeutic challenge. Also, presence of HIV latent reservoir and inability to cross the blood–brain barrier (BBB) makes it difficult for highly active antiretroviral therapy to completely eradicate the HIV from the CNS of infected patients [1]. To target active and latent virus, shock-and-kill approaches have been suggested for the complete eradication of HIV infection [1–4]. Beside viral infection, the neurocognitive disorders caused by disease progression and its synergism in drug abusers is a major obstacle for deciding the effective therapy for neuroHIV/AIDS treatment and its management [5]. Serious efforts are being made to develop target-specific nanomedicine consisting of more effective anti-HIV drugs that has the capability to cross the BBB without inducing any side effects at target site [1,2,6,7]. Moreover, the investigation of noninvasive methods to deliver nanoformulation (NF) to the brain and successful release of therapeutic agent (on-demand remote-controlled manner) remain as unresolved issues for formulation scientist [1,2]. The outcomes of our NIH-funded projects proposed that nanomedicine, developed using nanobioengineering/technology, can cross the BBB to eradicate brain HIV infection. Tunable efficacy features of nanomedicine allow their functional manipulation in personalized manner according to the patient disease profile requirement to achieve maximum therapeutics without causing side effects. The state-of-the-art nanomedicine technology to treat neuroHIV/AIDS is discussed below.

Nanomedicine approach: a possible solution

In order to investigate therapy for neuroHIV/AIDS, multidisciplinary research-oriented efforts involve materials science (to explore novel smart drug-nanocarriers [NCs]), surface chemistry (for loading of selected drugs), system biology (to explore machine learning for process optimization) and pharmacology (to introduce best appropriate combination of therapeutic agents) suggested that least component-based pharmacological therapeutic cargo of better efficacy and its successful delivery to the brain are in demand urgently. Up to some extent, these challenges have addressed via developing nano-enabled formulation, in other words, ‘nanomedicine’ exhibited better efficacy and least side effects. Thus, the practice of nanomedicine has significantly improved recently in order to develop elite therapies to manage CNS diseases [2,7–9]. The properties of a developed selective nanomedicine, mainly delivery and release of a selected drug in sustained or on-demand manner, are completely tunable and an effective dose can be designed according to patient profile. Because of these salient features of a therapeutic cargo, the

nanomedicines are also presented as ‘personalized nanomedicine’. The performance of a nanomedicine depends on selected drug NCs (around 100 nm), targeted drug (CRISPR/Cas9) and delivery methods (noninvasive method is always preferred) [2,7–9]. As of now, developed NFs and related adopted delivery methods for treatment of neuroHIV are discussed in next section.

State-of-art nanomedicine for neuroHIV treatment

Surface receptor-based therapeutics delivery to the brain has been demonstrated but the limited amount of delivery due to larger size of cargo is a remaining challenge. Stimuli such as ultrasound/focused ultrasound and magnetic field-based BBB opening demonstrated good amount of drug delivery to the brain [1]. However, transient opening of the BBB is not well-recommended because this may allow the delivery of unwanted elements to the brain which may accelerate the secretion of inflammatory agents [1]. Recently, we demonstrated magnetically guided delivery of magnetic drug-NCs to the brain [6]. This method is completely noninvasive and has been demonstrated in animals without causing toxicity and altering neuronal behavior.

Our group has adopted magnetically guided delivery of a selected therapeutic agent across the BBB for neuroHIV/AIDS and neuroprotection management. The 3'-Azido-2',3'-dideoxythymidine-5'-triphosphate (AZTTP) drug-loaded magnetic nanoparticles successfully crossed the BBB under the influence of static magnetic field and sustained released drug-reduced p24 antigen level (0.8T) [10]. Jayant *et al.* utilized a layer-by-layer approach to develop an NF consisting of tenofovir and vorinostat to explore shock-and-kills method for HIV-virus eradication [11]. This NF also crossed the BBB under the influence of static magnetic field and the systematic release of drugs first activated the virus followed by virus killing to eradicate virus level. In another approach, on-demand release of AZTTP (100% at 64 Oe) was demonstrated using magneto–electric nanoparticles (MENPs), drug-NCs and ac-magnetic field through electromagnetic coils as external stimulation [3]. Magnetically guided approach allow MENPs-AZTTP NF across the BBB and further ac-magnetic field was applied to release the drug for virus eradication in an on-demand manner. The ac-magnetic field stimulation caused polarization change on MENPs surface resulting in the release of AZTTP without compromising efficacy. In a recent report, ac-magnetic field stimulation on MENPs also produced localized electric field and ultrasound enough to open the cell membrane pore called ‘nanoelectroporation’. In this process, MENPs acted as a nanoporation generator and delivered inside the cell. It has been also investigated that neither MENPs (50 µg) nor ac-magnetic field (60 Oe) affect cell viability [12]. A similar magnetic-guided delivery method has also been utilized for the delivery of brain-derived neurotrophic factor (BDNF) [13] and TIMP-1 [14] for neuroprotection of HIV-infected brain. Further, magnetically guided delivery of Beclin1siRNA across the BBB was examined to control the inflammatory effect of HIV infection [15]. In this research, Beclin1siRNA was bound with MENPs and further released via ac-magnetic stimulation [15].

These significant advancements are limited to *in vitro* model only. Significant efforts are required urgently to optimize these NF and develop methods for testing in animal models to translate this neuroHIV/AIDS therapy at a clinical level. Intranasal delivery of Beclin1siRNA was demonstrated by our group in mice model using polyethylenimine and polymeric drug NCs [16]. Our findings presented MENPs as a suitable drug NC able to perform magnetically guided BBB crossing with uniform biodistribution inside the brain and act as a drug NC exhibits drug-release on applying ac-magnetic field. We have successfully demonstrated delivery of MENP to the brain of mice and evaluated MENPs biodistribution, biocompatibility and neuronal behavior in mice [6]. Our finding suggested that intranasal delivery of gene and magnetically guided delivery of therapeutic agent to the brain can be a possible future neuroHIV/AIDS therapy.

Chiappetta *et al.* developed an NF consisting of efavirenz (EFV)-loaded polymeric micelles for the treatment of HIV/AIDS in children [17]. This pharmacotherapy improved the utility and bioavailability of EFV (20 mg/ml), a first-line agent in the pediatric therapeutic cocktail, via encapsulating in poly(ethylene oxide)–poly(propylene oxide) block copolymer micelles. The efficacy of developed NF was tested in male Wistar rats (40 mg/kg). The results confirmed that advanced liquid aqueous EFV formulation is beneficial for pediatric HIV pharmacotherapy [17]. This research group also explored intranasal delivery for the administration of this advanced formulation to the brain [18]. It was observed that the loading of drug and bioavailability of the formulation was dependent on micellar size and composition. The high hydrophilic characteristics were recommended to improve drug payload (20–30 mg/ml) and intermediate hydrophobicity for intranasal brain delivery. The results suggested that bioavailability of drug was four-times higher than oral delivery and five-times in case of intravenous administration [18].

For neuroHIV/AIDS management and neuroprotection, various approaches were put in practice. For example, delivery of particularly designed nanoenabled antiretroviral therapy involving microphage-assisted delivery [19],

developing long-acting therapeutic agent [20,21], novel nano-NRTI formulations [22], new methods to cross the BBB to target CNS [23], NCs of desired characteristics [1,24–27] and *in vivo* demonstrations [28]. However, most of the approaches are multicomponent systems wherein whether an NF and applied external stimulation may cause side effects regarding toxicity and neurocognitive disorders. Thus, developing an effective system which is least component based is a favorable requirement to achieve the goal of complete treatment of neuroHIV/AIDS and other CNS diseases.

Challenges & future perspective

In spite of significant advancements in terms of neuroHIV eradication and neuroprotection, state-of-art nanomedicine demonstrated mainly *invitro* and up to some extent at the small animal model. The promotion of ‘nanomedicine’ or ‘personalized nanomedicine’ as future therapy required extensive preclinical studies performed in smaller and larger animal models. To make it possible, significant efforts required developing biocompatible novel surface functionalized smart-drug NCs, extensive studies to explore the biodistribution of drug NCs and NFs administrated in animals, developing pharmacology relevant nanotherapeutic cargos exhibit better efficacy, no drug–drug interaction and no adverse effects, evaluate acute and chronic nanotoxicity and neuronal behavior for longer duration, evaluation of homeostatic condition after NCs or NFs administration, developing combinational therapy able to monitor and eradicate neuroHIV/AIDS, development of NFs able to perform neuroprotection and virus eradication at the same time, introducing smart analytical tools for rapid assessment of neuroHIV infection variation, development of appropriate small and big animal models with respect to neuroHIV/AIDS, exploring novel methods able to deliver NFs to the brain noninvasively, studying the effects of adopted methods on motor coordination and the BBB integrity of animal, transforming developed technology toward human-compatible systems, introducing system biology involving numerical simulation and bioinformatics for better understanding needed to select/adopt any parameter, involvements of clinics, health agencies and stakeholder to improve awareness, data sharing, finance management and designing of nanomedicine-related regulatory system required to manage risk assessment and bioecosystems [8,29–31].

To implement the above-discussed points in the applied field requires serious efforts of scientists, health agencies and regulatory agencies. Keeping this in view, the NIH [32] has initiated huge funding for brain innovative programs involving academic–industrial partnership for the translation of personalized nanomedicine in order to manage and cure neurological diseases/disorders. Additionally, the US FDA [33] also supported the roadmap via public–private partnership for the development of personalized nanomedicine toward preclinical use and finally for the FDA approval.

In this editorial, we claim that the development a personalized nanomedicine and investigation of a suitable method to deliver developed therapeutic cargo to the brain is possible via exploring nanobioengineering. Synergistically, this combinational approach may be able to manage neuroHIV/AIDS involving viral infection eradication and neuronal protection without affecting neuronal behavior and other related side effects. We also express global request to promote nanobioengineering assisted multidisciplinary research approach to develop personalized nanomedicines for the complete cure of neuroHIV to have an AIDS-free society in future.

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