Submitter Name: Venkata Atluri
Submitted email: vatluri@fiu.edu
PI Name: Madhavan Nair
PI email: nairm@fiu.edu

Magneto electric nanoparticle based CRISPR-Cas9/gRNA delivery to eradicate latent HIV infection and neuropathology in the brain

Venkata Atluri[1], Ajeet Kaushik[1], Adriana Yndart[1], Sneham Tiwari[1], Asahi Tomitaka[1], Purnima Gupta[1], David AlvarezCarbonell[2], Kamel Khalili[3], Madhavan Nair[1]

[1]Department of Immunology and Nano-Medicine, Center for Personalized Nanomedicine, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University; [2]Department of Molecular Biology and Microbiology, Case Western Reserve University; [3]Department of Neuroscience, Lewis Katz School of Medicine, Temple University

Combination antiretroviral therapy (cART) could not eliminate the HIV infection from the body due to the persistent latent HIV infection in long-lived cells including microglial cells in the brain in the form of proviruses. Elimination of HIV-1 reservoirs from the peripheral and central nervous systems (CNS) remains a formidable task due to the integration of HIV-1 DNA into the host genome and residing as latent form. To combat against HIV-1 integrated within the host genome, we have used a powerful type of genome editing technology: clustered regulatory interspaced short palindromic repeat (CRISPR)-associated 9 (Cas9). In addition, the presence of blood-brain barrier (BBB) restricts the delivery of therapeutic molecules into the brain. To overcome this, we have used a magnetically guided non-invasive delivery and on-demand controlled release of Cas9/gRNA across the BBB using magneto-electric nanoparticles (MENPs) as a drug nanocarrier. We have observed that our developed nanoformulation reduced HIV-1 LTR expression levels in latently infected microglial cells significantly when compared with free Cas9/gRNA. Furthermore, HIV associated dementia is mainly due to the neuroinflammation in the brain in response to the viral proteins rather than the infection itself. In this study, we have analyzed the NF-kB, NLRP3 mediated neuroinflammatory response in latently infected microglial cells treated with Cas9/gRNA nanoformulations and found significantly reduced NF-kB, and NLRP3 mediated inflammatory genes expression. Our results suggests that CNS delivery of our nanoformulation (CRISPR/Cas9-gRNA-MENPs) across the BBB certainly will have clinical significance as a future personalized nanomedicine to manage neuroHIV/AIDS and associated cognitive disorders.