Multifunctional Nanotherapeutics for the Treatment of NeuroAIDS in Drug Abusers

Jayant, R.D., Tiwari, S., Atluri, V., Tomitaka, A., Yndart, A. (FIU, Immunology), Colon-Perez, L.M. (UF, Psychiatry), Febo, M. (UF, Psychiatry), and Nair, M. (FIU, Immunology)

Introduction: HIV-1 infection remains incurable due to drug addiction and the presence of persistent viral brain reservoirs. Thus, neutralizing the drug of abuse effect on HIV-1 infectivity and elimination of latently infected cells is a priority. The development of a multi-component [antiretroviral drugs (ARV), latency reactivating agents (LRA) and drug abuse antagonist (AT)] sustained release nanoformulation targeting the CNS can overcome the issues of HIV-1 cure and will help in improving the drug adherence. The novel magneto-liposomal nanoformulation (NF) was developed to load different types of drugs (LRAs, ARVs, and Meth AT) and evaluated for *in-vitro and in-vivo* BBB transmigration and antiviral efficacy in primary CNS cells. We established the HIV-1 latency model using human astrocyte cells (HA) and optimized the dose of LRA for latency reversal, Meth AT. Further novel NF was developed, characterized for size, shape drug loading and BBB transport *in-vitro*.

Methods: For NF biodistribution and BBB transport Magnex Scientific 4.7 Tesla MR scanner was used for performing high-resolution imaging for all the MRI studies. The T2 and T1 relaxometry pulse sequences were run on a Varian VnmrJ 3.1 console. The T2 and T1 relaxation rates were assessed separately using MRI on a series of phantom tubes filled with a mixture of Agarose with varying concentrations of magnetic nanoparticle (0-100μM). More details about the image capturing is provided under supplemental method section.

Results and Discussion: We confirm relaxivity properties of the paramagnetic MNPs in our phantom studies using 4.7T. MNPs produced faster T2 relaxation and T1 recovery in a concentration dependent manner (Fig.5A-i-iv). Further, spin echo T2 image acquisitions revealed no morphological changes or any evidence of tissue damage after NP treatment (Fig.5B-i). We observed distinct regional and time dependent changes in NF-mediated T2 relaxation, which was dependent on magnetic field driven entry to the brain. At time= 0, T2 values for different tissues at 4.7 T were 40 ms for muscle, 60 ms for brain tissue and > 100 ms cerebral spinal fluid. Starting at 30 minutes we observe reduced T2 (from 120 ms to 65 ms) in CSF compartments (cerebral aqueduct and dorsal 3rd ventricle). This is indicative of NF entry in the brain. Changes in T2 were not observed to occur early in mice without magnetic field application prior to imaging. Latter in these mice, we observed stable and consistent T2 values across the different tissue compartments (Fig. 5B-ii-iv). Finally, to check the *in-vivo* toxicity of NF, H&E staining was performed to observe any morphological or pathological sign with respect to major organs (i.e. Brain, Liver, and Kidney). The postmortem analysis revealed that there was no evidence of morphological and cytotoxic damage to any of the major organs pertaining to the NF treatment.

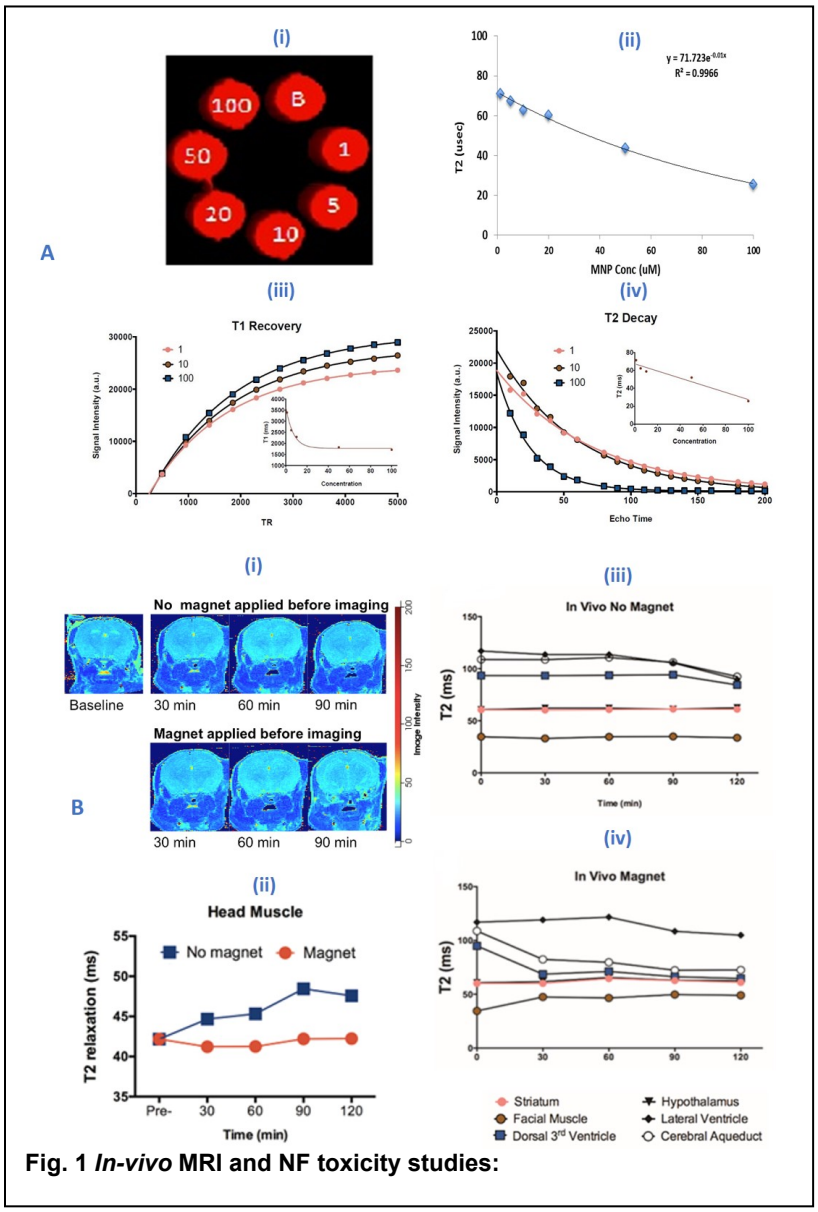

Fig. 1 *In-vivo* MRI and NF toxicity studies:

Acknowledgements: The National High Magnetic Field Laboratory is supported by the National Science Foundation through NSF/DMR-1157490/1644779 and the State of Florida. Supported also by NIH/NIDA grant R01DA037838 and R01DA034547 to Madhavan Nair.

Reference: Jayant, R. D., et al., Int J Nanomed, 10, 1077 (2015)