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Targeting HIV-1 reservoir by combination antiretroviral drug loaded nanoformulation: Towards functional HIV cure

Presently, HIV patients ingest combination antiretroviral therapy (cART), has proven to significantly reduce plasma viremia below detection limits. Patients are able to live fairly normal lives on cART. However, some serious long-term side effects due to high cARV drug levels are produced. Additionally, another concern is low-level replication of HIV-1 primarily in tissue reservoirs of suppressed individuals. Subsequently, even a brief interruption in treatment may allow HIV-1 rebound from the reservoirs into the plasma. Hence, a highly motivated, adherent patient taking cARV daily is needed to achieve a nondetectable plasma viral load (pVL). Therefore, cARV therapy faces major challenges including adherence, a daily large oral dose, with associated drug side effects, and costs. Here, cARV nanomedicine could be a potential alternative. Currently, HIV-1 research is focused on formulation ARV drugs that prolong bioavailability of drugs to improve drug-adherence and improves therapeutic or prophylactic opportunities of HIV-1 patient populations. The other major issue is to suppress HIV-1 replication in the reservoirs. To achieve these goals, our research is focused to formulate anti-CCR5 antibody loaded cARV nanoparticles (NPs), with the aim to prolong cARV bioavailability and to block HIV replication within the HIV reservoir to improve drug efficacy to prevent/treat HIV-1 infection. We formulated, cARV drugs (i.e. dolutegravir (DTG) + emtricitabine (FTC)) loaded Poly (lactic-co-glycolic acid) (PLGA) NPs (DTG+FTC NPs) and to target HIV-1 infected cells (a HIV-1 reservoir model), these NPs were surface labelling with anti-CCR5 antibody. For bio distribution study of cARV NPs, IRDye 800CW loaded NPs were formulated and administration subcutaneously (SubQ) in humanized mice model, Hu-CD34-NSG mice (n=3) with functional human immune reconstitution. The mice were imaged for 14 days under IVIS Lumina XR *In Vivo* Imaging System. After 14th day, animals were sacrificed and organ of interest (female reproductive track (FRT), colon, lymph nodes, spleen and brain) were imaged. Bio distribution of IRD NPs demonstrated whole body distribution within 1 h of SubQ administration. Overtime accumulation of IR NPs reveals high accumulation at the HIV-1 virus infection site (FRT and colon), and reservoirs (lymph nodes, spleen, and brain), even after 14 days of study. Positively, the injection site shows high NPs presence even at day 14 of study, conferring the depo and slow release properties of NPs. To target the HIV-1 infected cells (a HIV-1 reservoir model), DTG+FTC loaded NPs were surface labeled with anti-CCR5 antibody and their binding efficacy was evaluated by flow cytometry. Further, CCR5 targeting analysis after treatment with anti-CCR5-DTG+FTC NPs shows enhance binding efficacy with the CCR5 receptor expressing cells (i.e. HIV-1 reservoir cell type). At the tissue level, NPs accelerates prolonged penetration. Whereas *in-vivo* study demonstrates NPs results in enhanced and prolonged accumulation at the site of infection and within latent reservoirs in this animal model of HIV-1 for entire study period. Moreover, targeted cARV NPs enhances latent cells at the HIV-1 reservoirs. Present focus of our study is to evaluate potency of the HIV-1 protective/treatment efficacy of the target specific cARV NPs. Our cARV encapsulated polymeric nanoparticle (NPs) as nanodrug delivery system shows slow drug release and protects drugs from systemic clearance as well as HIV-1 reservoir organ accumulation. Therefore, we predict use of targeted cARV NPs will lead to monthly dosing in humans that potentially could overcome the adherence burden of the HIV patient and potentially could achieve functional HIV-1 cure.

Speaker Biography

Subhra Mandal has graduated from International School of Advanced Studies-SISSA, Trieste, Italy with her Doctorate degree. Soon after completion, she joined Prof. Carl Figdor, a world-class immunologist in Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, as Post-Doctoral researcher for European Research Council (ERC) Advanced grant project. Since 2015, she is working as co-investigator with Dr. Chris Destache as a NIAID (R01) grant, she has more than 10 years of research experience in design, characterization and application of various types of nanocarriers for effective drug delivery system and nano-drugs for cancer, neurodegenerative diseases and HIV/AIDS theranostics. She is active editorial board member of various journals and participates in peer-reviewing manuscripts for various journals. She is an active member in various scientific societies such as RSB, ASM and AAPS.

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