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Emerging Nanomedicine Approaches to Targeting HIV-1 and Antiretroviral Therapy

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After 30 years of the HIV-1/AIDS epidemic, no vaccine or cure has been developed. HIV-1 is ranked globally as the most deadly infectious agent accounting for over 1.2 million deaths worldwide in 2014. Approximately 37 million people worldwide are living with HIV-1, with 2 million new infections occurring in 2014 [1–3]. While HIV infection is now considered a chronic, manageable disease, there remains uncertainty concerning the extent of global access to diagnostics and long-term antiretroviral (ARV) treatment specifically in resource-limited settings. In fact, only half of the 14 million people eligible for combination antiretroviral therapy (cART) are currently receiving it [4]. While development of a vaccine remains under investigation, cART remains the primary treatment option. Currently there are >30 ARVs that have been approved for use in the treatment of HIV-1 [5]. cART has significantly improved AIDS-related morbidity and mortality, extending the expected lifespan of patients with HIV-1. However, there are several limitations, which include: HIV-1 eradication has not been achieved with ARVs, possibly secondary to inadequate drug penetrance into viral reservoirs; the need for lifelong, daily regimen of medications leading to pill fatigue and suboptimal adherence; chronic ARV toxicity; and the development of HIV-1 resistance to ARVs. Overall, failure to respond to recommended treatment regimens for HIV-1 results in prolonged illness, increased direct and indirect health costs associated with the need to start more costly second-line treatment, spread of resistant strains, and an increase in mortality.

Nanomedicine is the application of nanotechnology as a drug delivery system for the sustained release of drug at the site of action [6]. Nanomedicines physically encapsulate or chemically conjugate therapeutics, usually to a biodegradable polymer. With the existing limitations associated with current ARV regimens, it is necessary to develop new therapeutics or adjuvant therapies, such as nanomedicines. Key issues associated with HIV-1 pharmacology failure are viral resistance, drug toxicity, drug–drug interactions and intracellular pharmacokinetics. Viral resistance is caused by subtherapeutic intracellular

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drug concentrations resulting in viral mutation caused by selective pressure. Nanomedicines reduce viral resistance by increasing intracellular drug concentrations for prolonged cell exposure; maintaining effective intracellular drug concentrations while reducing the need for multiple doses; and prolonging systemic exposure through sustained release, which lowers the risk of missed doses and/or variation in a dosing regimen schedule and prevents the development of viral resistance. Drug toxicity occurs when plasma drug concentrations are directly linked to unwanted side effects and/or cellular toxicity, especially if the drug is not cell targeted. Drug–drug interactions occur when therapeutics induce or inhibit enzymes and/or cellular transport pathways of concomitantly administered therapeutics leading to a change in metabolite or parent plasma concentrations and/or changes to intracellular concentrations of a cell. Nanomedicines reduce drug toxicity and drug–drug interactions by reducing systemic exposure; targeting drugs to their site of action, that is, cells infected with HIV-1 and limiting the delivery of ARVs to sites of metabolism, such as the liver; and limiting off-target pharmacologic effects in cells that would not be infected by HIV-1.

The development of nanomedicines relies on understanding of chemistry, pharmacology and pharmacokinetics. Development of the nanomedicine's drug delivery system in conjunction with the therapeutic can result in optimization for efficacy and safety rather than focusing on solubility and permeability. Moreover, the nanomedicine, which will dictate the cellular exposure and pharmacokinetics of the therapeutic, can be tailored to provide sustained release of drug or rapidly degraded in the presence of an enzyme at site of action. These design considerations can occur somewhat independently from the therapeutic that is incorporated into the nanomedicine [6]. Additionally, using a cellular 'targeting' approach, which includes a nanomedicine's size, surface charge or surface ligand to increase intracellular drug concentrations [7], provides two different dosing strategies. First, maintaining current intracellular drug concentrations will decrease the total therapeutic dose required, limit systemic exposure and reduce side effects. Second, maintaining current plasma drug concentrations, which have acceptable systemic side effects, will increase intracellular drug concentrations with the aim of shortening the duration of treatment.

Failure to eliminate HIV-1 at cellular and tissue reservoir sites contributes to the limitation of current ARVs [8–10]. Latent reservoirs of HIV-1 include brain, lymphoid tissue, bone marrow and the genital tract. The major cellular HIV-1 reservoirs are macrophage and $CD4^+$ T cells that are responsible for transporting and spreading HIV-1 to multiple sites [11,12]. Understanding viral latency and persistence is a key priority for ongoing cure research [8]. A major target and reservoir of HIV-1 is $CD4^+$ T cells; however, macrophages are also HIV-1 reservoirs that are responsible for carrying and spreading HIV-1 [13]. Macrophage drug delivery creates ARV depots, and these circulating macrophages provide intracellular concentrations that may have enhanced antiviral activity leading to eradication of virus in cellular and tissue reservoirs. This approach has been substantiated in recent studies that administer NanoART, a drug delivery system that is targeted to macrophage. The NanoART-'loaded' macrophage acts as a drug depot and distributes ARVs encapsulated in NanoART to cellular and tissue HIV-1 reservoirs including lymph nodes, gut and the CNS with subsequent viral load reduction [14–16]. Furthermore, a nanomedicine approach that used a β-glucan ligand to target macrophage found that the total dose of nevirapine delivered can be greatly reduced to amounts that are likely to be associated with less toxicity but provide

antiviral activity in a cellular reservoir [17]. Therefore, it may be possible to decrease the total ARV dosage for prevention or treatment required while maintaining current intracellular drug concentrations.

While multiple researchers have developed novel drug delivery systems for the treatment of a number of diseases, the development of nanomedicines that contain small molecule therapeutics and their large-scale manufacturing is still in early stages [18]. Clinically, the field of oncology has demonstrated considerable nanomedicine research. Both paclitaxel (Taxol®) and doxorubicin (Adriamycin®) have been successfully incorporated into nanomedicine formulations. Abraxane® is an albumin-based nanoparticle containing paclitaxel, approved by the US FDA in 2005 for the treatment of breast cancer. This formulation has greatly improved patient tolerance to the original vehicle (Cremephor® EL) that is responsible for the dose-limiting toxicity. Doxil® is a PEGylated lipid-based nanoparticle (‘stealth’ liposome) that contains doxorubicin, originally approved by the US FDA in 1995 for the treatment of chemotherapy refractory AIDS-related Kaposi’s sarcoma. Doxorubicin has a maximum-lifetime dose-limiting cardiotoxicity that is avoided by reducing the total administered dose. These two instances demonstrate that delivery of highly cytotoxic agents can be greatly enhanced utilizing nanomaterials. Currently, rilpivirine (TMC-278, Edurant®), a second-generation HIV-1 non-nucleoside reverse transcriptase inhibitor approved in 2011 as a once-daily tablet by the US FDA, is currently being tested as a once-monthly long-acting injectable nanoparticle in Phase II/III trials. Cabotegravir (GSK1265744), an integrase inhibitor, in Phase II/III trials for once-monthly injection, has shown great promise as a long-acting injectable nanoparticle for the treatment of HIV-1. The advantage of these injectable nanoparticle products is their monthly or even quarterly administration that maintains plasma concentrations significantly above the target plasma inhibitory concentration, and greatly improves patient compliance and reduces the chance for subtherapeutic plasma concentration and resulting viral resistance [18].

Antiviral activity of novel nanomedicine drug regimens needs to be proven *in vitro* prior to clinical investigation. New preclinical models that assess nanoparticle activity will need to focus on optimizing the dosing regimen. Due to the dynamic nature of drug exposure in the body, standard cell culture approaches need to be modified to utilize a more dynamic approach, such as a hollowfiber culture system. The hollowfiber system mimics cellular pharmacokinetic exposure providing an opportunity to study optimal dosing strategies using simulation of *in vivo* exposure. Additionally, more sensitive detection techniques and the ability to distinguish between drugs that are in nanoparticles from drugs that are external to nanoparticles may be necessary to bridge between *in vitro* and clinical models.

The advantages of nanomedicines to improve intracellular drug concentrations, and reduce systemic ARV exposure offer a potential that requires translational research. Clearly increasing intracellular drug concentrations while minimizing systemic exposure and toxicity in healthy tissue will improve drug therapy outcomes, and avoid unwanted side effects. Moreover, the development of nanomedicines with exceptionally long half-lives containing small-molecule therapeutics that were previously thought to have clinically limiting physicochemical and/or pharmacokinetic properties is now viable. Therapeutics with a long half-life will improve patient compliance through less complicated dosing

regimens, and minimize viral resistance by maintaining antiviral plasma concentrations for a prolonged time. Furthermore, therapeutics that are previously failed in clinical studies due to poor pharmacokinetics have the exciting potential to be developed as nanomedicines for successful clinical use. Recent advances in nanomedicine development have shown great promise to transform the prevention and treatment of HIV-1 with the ultimate goal of viral eradication.

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