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Preface

Human immunodeficiency virus type 1 (HIV-1) has become one of the deadliest modern day infectious diseases. After over three decades of intense research it continues to remain the killer disease of the 21st century, despite the discovery of highly potent antiretroviral drugs and drug delivery systems (DDSs). Such drugs and DDSs are limited by severe adverse effects, significant drug interactions, frequent dosing, limited bioavailability, adherence issues, and poor access to viral reservoir sites like macrophages. However, these limitations are currently being addressed through several innovative formulation systems such as nanotechnology-based systems. Among the numerous applications of nano-biotechnology approaches, one of the most promising uses that exploits the unique ability of nanoformulation to combine and improve on different pharmacological profiles is its employment to improve on the short-comings of conventional antiretroviral drugs.

This Theme Issue of *European Journal of Pharmaceutics and Biopharmaceutics* is devoted to emerging trends and challenges of nano-biotechnology in HIV/AIDS therapy. The combination of articles hopes to shed further light on the potential offered by nanotechnology to improve the modern day approaches taken to enhance HIV/AIDS treatment and prevention strategies. The Theme Issue highlights the challenges associated with the current treatment of the disease and discusses the potential of nanotechnology to provide more effective treatment and prevention for HIV/AIDS. Before highlighting the contributions, the Guest Editors take the opportunity to thank Dr. Achim Goepferich, Editor-in-Chief of *European Journal of Pharmaceutics and Biopharmaceutics*, for giving us the privilege to work on this Theme issue and for his tremendous support throughout.

The opening paper by ***Cautela et al.***, considers the prevention of male-to-female HIV transmission by studying composite films for vaginal delivery of tenofovir disoproxil fumarate and emtricitabine. The authors describe their work on different types of films containing the antiretroviral drugs tenofovir disoproxil fumarate and emtricitabine. The results support that films may be a suitable dosage form for the vaginal delivery of these drugs in the context of topical pre-exposure prophylaxis (PrEP) that could be acceptable to users and provide prolonged protection from viral infection.

In the second paper of this issue ***Lee et al.,*** consider the design and evaluation of a CXCR4 targeting peptide 4DV3 as an HIV entry inhibitor and a ligand for targeted drug delivery. In their paper they examine the feasibility of utilizing the cell surface chemokine receptor CXCR4 for HIV entry inhibition and as an intracellular portal for targeted drug delivery. Molecular modeling suggests simultaneous binding of a single 4DV3 molecule to four CXCR4 molecules and differences in CXCR4-binding sites could explain the discrete inhibitory effects observed for 4DV3, the 44,708 antibody and AMD3100. The results suggest that 4DV3 might serve as a prototype for a new type of dual function ligand, one that acts as a HIV-1 entry inhibitor and one that acts as a CXCR4 drug delivery targeting ligand.

The next paper of this Theme Issue is HIV PrEP strategies and ***Hoang et al.,*** examine the development of rectal enema as a microbicide to overcome non-adherence issues arising from the behavioral changes and daily discipline current treatment regimens require. The authors describe their preclinical efforts toward optimizing a tenofovir based enema formulation for rectal PrEP. They observed that the composition of the enema vehicle played a more important role than the tenofovir prodrug properties in achieving rapid and therapeutically relevant tenofovir diphosphate concentrations in mouse colorectal tissue. Their results suggest that further work is warrented to examine the preclinical (non-human primates) and clinical development of a hypo-osmolar tenofovir enema products for rectal PrEP.

Oral drug administration remains the preferred approach for treatment of HIV in most patients and ***Savage et al.,*** investigate improving the oral bioavailability of Maraviroc (a first in class co-receptor antagonist) through the formation of solid drug nanoparticles in order to improve the drugs oral bioavailability which is limited by poor permeability as well as its affinity for CYP3A and several drug transporters. To overcome Maraviroc's low bioavailability and modify its pharmacokinetic profile, a series of 70 wt% MVC solid drug nanoparticle formulations (containing 30 wt% of various polymer/surfactant excipients) were generated using emulsion templated freeze-drying. Their lead formulation demonstrates to be fully water-dispersible to release drug nanoparticles and in vivo studies showed a 2.5-fold increase in AUC and increased apparent permeability compared to a conventional Maraviroc preparation. Their data support the potential development and use of oral formulations with the advantages of dose reduction and a once-daily dosing.

The mucus in the vagina presents a barrier to the transport of active agents for the prevention and treatment of female reproductive tract infections. Nanoparticle-mediated drug delivery has been proposed to help facilitate the transport and release of active agents through the cervicovaginal mucus and underlying mucosa. ***Sims and his co-workers*** study modeling of nanoparticle transport through the female reproductive tract for the treatment of infectious diseases. They study "stealth" nanoparticles that have favorable mucus-penetrating properties with the goal of obtaining a better insight into what properties most impact prophylactic and therapeutic benefit. Their studies build upon existing work in the area to simulate nanoparticle transport through mucus gel, epithelial, and stromal compartments, with the goal of providing a platform that can systematically evaluate transport based on nanopraticle and tissue characteristics. Their modeling results showed that while unmodified and 2% PEG-modified nanoparticles were retained in mucus for about 1-4 hours, dependent upon decay constant values, and traverse to the epithelium, no nanoparticle penetration was observed in the stroma. In contrast, nanoparticles modified

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with 3% PEG, exhibited prolonged retention in each compartment, remaining for around 4-6 hours. The authors propose that in the future a combined mathematical/experimental approach may enable prediction and customization of patient tissue-specific approaches to attain effective nanoparticle-mediated drug delivery and release for the treatment of infectious disease.

In an excellent review that examines nanotechnology approaches taken to eradicate HIV reservoirs ***Woodrow and Cao*** describe HIV latency in cellular and anatomical reservoirs, and present an overview of current strategies for HIV cure with a focus on their challenges for clinical translation. The authors provide a summary of nanotechnology solutions that have been used to address challenges in HIV cure by delivering physicochemically diverse agents for combination therapy or targeting HIV reservoir sites. The review also considers nanocarrier-based gene delivery and immunotherapy used in cancer treatment that may have potential applications in HIV cure.

Current prevention strategies against the HIV utilize antiretrovirals that have demonstrated protection, but result in antiviral resistance and adverse toxicity. As a result, in the next paper of this issue, the delivery of Griffithsin from pH-responsive electrospun fibers was studied by ***Tyo et al.*** The work successfully fabricates pH-responsive fibers comprising of poly(lactic-co-glycolic acid) (PLGA) or methoxypolyethylene glycol-b-PLGA with varying ratios of poly(n-butyl acrylate-co-acrylic acid). They characterize the fibres and demonstrated selective release under pH-conditions found in the vagina following semen introduction, potent in vitro efficacy against HIV-1 and safety in vaginal epithelial cells, suggesting the future potential of this novel dosage form.

While a number of nanoparticle-based drug delivery systems have been investigated for delivery of HIV drugs and drug combinations, key challenges still persist which include the development and scaling of delivery systems that provide a drug combination targeted to HIV host cells and tissues where residual virus persists. In the next paper, ***Gao and colleagues*** review the progress in the development of nanoparticle-based drug delivery systems for HIV therapy. The authors examine the drawbacks of current dosage regimens including (1) challenges in patient adherence to oral dosage forms, (2) the requirement of life-long daily drug intake, and (3) limited penetration and retention in cells within lymph nodes. They examine the advances made to overcome these challenges through appropriately designed long-acting injectable nano-drug combinations. The authors conclude that with validation of the drug-insufficiency hypothesis in lymph nodes, progress has been made in the development of drug combination nanoparticles that are long-acting and targeted to lymph nodes and cells.

Tatham et al., develop and investigate a long-acting injectable nanoformulation of Maraviroc to mitigate against suboptimal adherence to antiretroviral therapy that leads to insufficient drug exposure and subsequent viral rebound and increased likelihood of resistance. A 70 wt.% MVC-loaded nanodispersion stabilized with polyvinyl alcohol and sodium 1,4-bis(2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate prepared using emulsion-templated freeze-drying gave promising results both in vitro and in pharmacokinetic studies in rats. The data support the development of a long-acting injectable nanoformulation of Maraviroc for potential application in HIV therapy or prevention.

The final paper of this Theme Issue uses microfluidic platforms to develop CNS-targeted polymeric nanoparticles for HIV therapy. ***Martins et al.,*** develop efavirenz-loaded PLGA nanoparticle through a conventional and microfluidic method which they targeted to the blood brain barrier in order to treat HIV neuropathology. Compared to the conventional method, nanoparticles produced through microfluidics presented reduced size (73 nm versus 133 nm), comparable polydispersity (around 0.090), less negative zeta-potential (-14.1 mV versus -28.0 mV), higher efavirenz association efficiency (80.7% versus 32.7%), higher drug loading (10.8% versus 3.2%) and an improved sustained in vitro efavirenz release (50% released within the first 24 hour). Their nanoparticles were demonstrated to be safe to blood brain barrier endothelial and neuron cells and functionalized nanosystems were able to interact more efficiently with blood brain barrier cells.

Taken together, this Theme Issue incorporates recent advances in formulation technologies for anti-HIV drug delivery approaches. These advances will bring great opportunities and we expect that scientific community engaged in the HIV prevention and therapeutic research areas may find this Theme Issue an interesting addition to the current literature. We extend our sincere appreciation to the contributors of this issue, who, through their willingness to put pen to paper, have contributed further to our ever improving knowledge on the trends and challenges of nano-biotechnology in HIV/AIDS therapy. We also would like to thank the reviewers and appreciate the assistance provided by the editorial office members in ensuring that the articles are published in a timely manner and at high standards.

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