AIDS

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New perspectives on nanotechnology and antiretroviral drugs: a small solution for a big promise in HIV treatment?

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In this issue Li W et al [1] present a well-designed multidisciplinary study, aimed to demonstrate the potential benefit of a multifunctional polymeric nanodevice for delivering HIV treatment. The study offers a new perspective on the use of nanotechnology for combination HIV management, since the proposed system is a smart biodegradable PLA-based nanoparticle with a double therapeutic function, encapsulates the non-nucleoside reverse transcriptase inhibitor 14f with the surface conjugated to the third-generation HIV-1 fusion inhibitor T1144.

Among antiretroviral drugs, nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are considered valid therapeutic tools, even if their clinical application has been limited by some well-known factors such as the short half-life after administration and the rapid induction of drug resistance [2]. The less commonly used fusion inhibitors also are strongly limited by the unfavorable pharmacological profile of these peptides, but also by their high production costs, the difficult administration schedule and the induction of adverse effects [3]. Beyond the limitations of the single drugs, a combination of different antiviral activities is necessary for effective HIV therapy, which requires addressing multiple phases of HIV replication. For this reason, “cocktail” therapies are largely used in current clinical practice. Yet, the different pharmacological profiles, half-lives and bioavailability of the cocktail components may result in decrease global antiretroviral activity [3].

In this scenario, nanotechnology may play a relevant role. The potential advantages in using
nanoparticles for treatment of HIV infection include their capability to incorporate, encapsulate, or conjugate a variety of known antiretrovirals, in order to optimize the pharmacological profiles of these drugs, their specific homing in infected cells, and their anti-HIV activity [2, 4]. In fact, the preclinical study with nanoformulated antiretroviral therapy has suggested that intracellular translocation of nanoparticles could significantly improve the anti-HIV activity of the drugs due to their compartmentalization in endosomes where HIV active replication occurs [5]. Moreover, nanoformulation has been demonstrated to allow drug penetration into HIV sanctuaries (e.g. central nervous system, genital tract, lymph nodes, latently infected CD4+ T cells, etc), for effective eradication of the virus, with a potentially substantial impact on HIV treatment and prevention [6]. Interestingly, it has been recently reported that even complex anti-HIV molecules can successfully penetrate into the blood brain barrier if conjugated to iron oxide nanoparticles coated with an amphiphilic polymer [7].

Concerning the optimization of reverse transcriptase inhibitor activity upon nanoformulation, recent studies have demonstrated the role of cationic nanogels-NRTIs targeted for the brain specific apolipoprotein E receptor in protection from neurotoxicity together with excellent antiviral activity in brain macrophages [8]. Also, regarding the issue of HIV sanctuaries, a recent review discussed the use of different types of nanoparticles to shuttle NRTIs and NNRTIs into HIV reservoirs, since the ability to deliver combination antiviral therapy into HIV sanctuaries will be probably the next major clinical challenge [9]. Moreover, the authors of the current article have already demonstrated that encapsulation of DAAN15h in PEG-polymeric nanoparticles increased its antiviral activities on CD4, CCR5 or CXCR4–positive cells, enhancing its pharmacokinetic profile [10]. Now they suggest for the first time the nanoformulation of the NNRTI 14f and the fusion inhibitor T1144. This association in one single nanodevice of anti-transcriptase activity and HIV fusion inhibition represents a real novelty. The multifunctional anti-HIV nano-cocktail will be able to inhibit HIV-1 fusion with cells through the activity of its surface T1144 peptide, which will enhance cellular uptake of 14f and thus provide sustained controlled release of the drug into the target cell. The beauty of this new concept of HIV therapy is evident and resides in the possibility of enhanced combination therapy which targets multiple key points of viral replication with greatly increased antiviral activity. From a clinical point of view, the strongly improved intracellular antiviral activity without cellular toxicity, the increased f14 blood concentration and circulation time upon in vivo administration, with promised efficacy on a wide spectrum of HIV-1 strains, including resistant ones is appealing.
Together, these nano-strategies could lead to the formulation of a completely new class of “intelligent” anti-HIV drugs, with the possibility of a combined antiretroviral approach for both extra- and intracellular reservoirs of HIV. Thus, nanotechnology offers a unique opportunity to combine and improve different pharmacological profiles of antiretroviral drugs, with more convenient drug administration and potentially better patient adherence to HIV therapy. For these reasons, we believe that this multivalent nano-platform, able to optimize drug delivery and pharmacokinetic properties while providing a combinatorial therapeutic effect on resistant HIV strains, represents a promising approach in the landscape of new strategies for HIV cure.

References


