Pharmacokinetics, Biodistribution, and Toxicity of Folic Acid-Coated Nanoformulated Antiretroviral Therapy

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Purpose
Long-acting nanoformulated antiretroviral therapy (nanoART) of atazanavir (ATV) and ritonavir (RTV) were developed to patient compliance. Folic acid coated nanoART (FA-nanoART) facilitates drug targeting of viral tissue reservoirs. Encouraging preliminary efficacy studies prompted efforts to characterize the pharmacokinetics (PK), biodistribution, and toxicity of FA-nanoART in mice and monkeys.

Methods
The PK profiles were characterized in mice after single and multiple intramuscular (IM) administration of FA-nanoART and native drugs. IM single dose was administered at 10 and 20 mg/kg, and blood and tissues were collected for up to 42 days. Multiple doses were administered at 20 mg/kg on days 0, 3, 7, followed by weekly dosing for 4 weeks and then biweekly for 4 weeks, and blood and tissues (liver, kidneys, spleen, lung, brain, and site of injection) were collected up to ten weeks. The PK profile in monkeys was also characterized after multiple IM doses (days 0, 3, 7, 14, 21 and 28) of FA-nanoART (20 mg/kg ATV boosted with 7 mg/kg RTV, ATV/r). Blood samples were collected up to 112 days. Drug levels in plasma and tissues were determined using LC-MS/MS.

Results
After single dose administration, ATV/RTV levels were up to 20- and 25-fold higher following FA-nanoART treatment compared to native drug administration in plasma and tissues, respectively. After multiple dosing, plasma and tissue concentrations were up to 200-fold higher after FA-nanoART treatment compared to native drug throughout the 10-week study period. In monkeys treated with 6 doses of FA-nanoART, ATV/r levels were detectable for up to 112 days for ATV and 49 days for RTV. No local toxicities were observed at the site of injection, and serum chemistry profiles were normal in both mice and monkeys.

Conclusion
FA-nanoART clearly resulted in enhanced and sustained plasma and tissue levels of ATV and RTV compared to native (unformulated) drug and to previous generations nanoART formulations. Overall, tissue distribution of FA-nanoART correlated with tissue distribution of the folate receptor. These preclinical studies may further enable the development of nanoART for clinical intervention.