

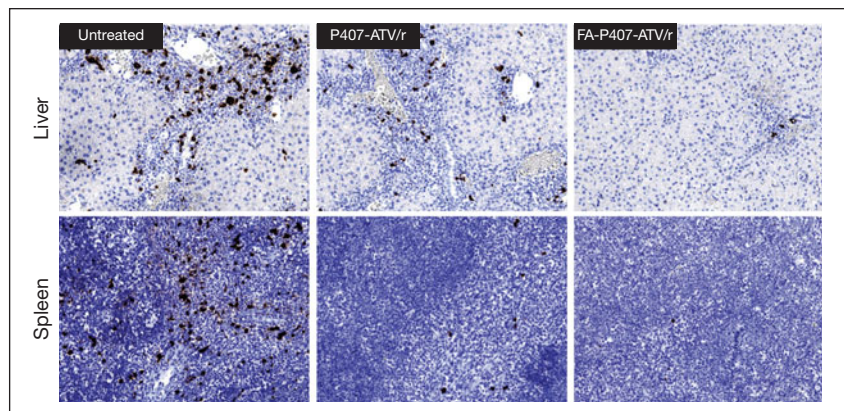
Bio Focus

Biomaterial NanoART combats HIV

Advances in biomaterials are ultimately expected to revolutionize approaches to disease treatment by enabling a host of improved drug delivery platforms. A development in this direction has recently been demonstrated by a collaborative team of medical researchers based at the University of Nebraska, together with collaborators at the University of Kansas, Fudan University, and the US National Institutes of Health. In their contribution to the February issue of *Biomaterials* (DOI: 10.1016/j.biomaterials.2014.11.012; p. 141), the researchers report that nanoformulations (i.e., nanoparticle composites comprised of small molecule drugs embedded in a polymer carrier matrix) can be harnessed to improve treatment of human immunodeficiency virus (HIV). Their studies were conducted on HIV-infected mouse models.

Highlighting the critical importance of drug delivery, H.E. Gendelman and colleagues examined drugs that have been widely used to treat HIV for more than a decade, and they show that they are endowed with enhanced efficacy when delivered through the new nanoparticle system. These delivery systems are referred to as “nanoART” for “nanoformulated antiretroviral therapy.” The unique nanoART advance implemented by the researchers involved decorating the drug-carrying polymer matrix (which is based on poloxamers, a class of nonionic triblock copolymers) with folic acid through covalent modification. Folic acid, in turn, acts as a sort of homing beacon, directing the particles, once injected into the body, to bind to macrophage immune cells. These cells exhibit a relatively large number of folic acid receptors at their surfaces.

Macrophages are clever cellular targets for the tethering of drug payloads



Antibody-stained liver and spleen tissues from HIV-infected mice. Tissues were collected on day 14, where drug nanoformulations (or buffer alone for the untreated condition) were administered at day 0. FA-P407-ATV/r indicates treatment with folic acid-modified polymer-antiretroviral drug nanoparticles, and P407-ATV/r represents treatment with a folate-free version of the nanoparticles. A general cell stain is shown in purple; dark-stained particles indicate the presence of HIV proteins. Reproduced with permission from *Biomaterials* 41 (2014), DOI: 10.1016/j.biomaterials.2014.11.012; p. 141. © 2014 Elsevier Ltd.

for two key reasons. First, macrophages naturally internalize foreign substances, such as nanoparticles, into intracellular compartments called endosomes. The cells can thereby be converted into a type of cellular drug depot upon uptake of nanoART. Second, as part of the immune system, macrophages naturally migrate to tissues that are susceptible to experiencing disease symptoms, including the brain, lungs, spleen, and lymph nodes. The cells can thus act as specialized vehicles for directed drug transport to key treatment sites. This feature is particularly relevant to HIV infection, as these same macrophage-frequented tissues have been previously shown to behave as HIV viral reservoirs. Selected drug delivery in this way can reduce drug concentrations required for effective treatment, thereby minimizing unwanted side effects.

The Nebraska team had previously confirmed that folate-coated nanoART indeed increases drug bioavailability site-specifically at lymphatic tissues. In this new report, they further demonstrate that the drug delivery system effectively

combats HIV in those tissues. Using amplified gene signatures of the virus to monitor infection levels in the spleen, animals that received a single treatment of folate-nanoART had at least a tenfold decrease in viral levels two weeks later, with half the mice exhibiting no detectable HIV. Other experiments showed that folate-based targeting of nanoART, versus folate-free particles, yielded a noticeable improvement in viral suppression (see Figure), and up to fivefold higher drug concentration in lymphatic plasma.

As a result of these improvements, the researchers suggest that improved drug administration schedules for HIV management are possible. NanoART could eventually permit biweekly (or even more infrequent) drug dosing. This would be a dramatic boon to achieving patient compliance when compared to the daily treatment regimens that are currently demanded.

NanoART, full of potential, may see human trials ahead as a major step toward clinical reality.

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