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Controlled-release macromolecular prodrug platform for targeting scavenger receptor A1

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Background: Despite advances in drug delivery systems, there are no targeted nanoscale drug delivery technologies on the market. Thus, there is still tremendous potential in improved therapeutic efficacy when targeted drug delivery is achieved. Herein, we describe an amino acid-based polymer platform that achieves active targeting of scavenger receptor A1 (SR-A1) and controlled drug release.

Methods: The polymer was fluorescently labelled and tested for SR-A interactions using competitive binding assays in RAW 264.7 cells against SR-A inhibitors. Selectivity of the polymer for SR-A1 was determined by performing cell uptake in macrophage cells and a derivative SR-A1-deficient cell line and analyzing with flow cytometry. As a proof-of-concept, paclitaxel was conjugated to the polymer through a hydrolysable ester bond using established chemistry. Drug release properties were assessed using *in vitro* and *in vivo* models, and the biodistribution of the polymer was measured in mice after IV and IP administrations.

Results: Polymer uptake by macrophages was inhibited by the SR-A inhibitor, which is consistent with SR-A interactions. The parent RAW 264.7 cells showed complete uptake of the polymer, but virtually no uptake by the SR-A1 deficient cell line after 24 hours, indicating remarkable selectivity of the polymer for SR-A1. Paclitaxel was successfully conjugated to the polymer, and this prodrug demonstrated controlled-release properties *in vitro* and in rats after IV injection with a half-life of 40-45 hours. Biodistribution studies show the polymer primarily distributes to liver and lymphatic organs after IV injection, as well as distribution to pancreas following IP administration.

Conclusion & Significance: Overall, this technology combines active targeting of SR-A1 with controlled drug release properties. Virtually any drug with a hydroxyl group can be conjugated to the polymer platform, and because of its distribution to myeloid cells, offers a unique delivery strategy for infectious disease agents (e.g., antivirals), chemotherapeutics, and CNS drugs.

Biography

David M Stevens has extensive experience in nanotechnology-based drug delivery systems for medical applications including cancer, diabetes, infectious diseases, and osteoarthritis. During his graduate work, he developed cross-linked polymeric nanoparticle and hydrogel formulations for sustained drug release applications which are currently undergoing commercialization. As a scientist at the Nanotechnology Characterization Lab, he develops novel drug delivery formulations including polymeric micelles, polyplexes, and prodrugs to overcome toxicities and/or improve pharmacokinetics of chemotherapeutics and anti-viral therapies.

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