Layer-by-Layer Assembly of Liposomal Nanoparticles with PEGylated Polyelectrolytes Enhances Systemic Delivery of Multiple Anticancer Drugs
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Purpose
Layer-by-layer (LbL)-engineered nanoparticles (NPs) are a promising group of therapeutic carriers with an increasing number of biomedical applications. The present study uses a controlled LbL process to create a multidrug-loaded nanoplatform capable of promoting blood circulation time, biodistribution profile, and controlling drug release in the dynamic systemic environment.

Methods
LbL assembly is achieved by sequential deposition of poly-L-lysine (PLL) and poly(ethylene glycol)-block-poly(L-aspartic acid) (PEG-b-PLD) on liposomal nanoparticles (LbL-LNPs). Using a modular design, doxorubicin (DOX) was incorporated into the core and mitoxantrone (MTX) was loaded onto the surrounding shell layers, creating a novel dual-drug delivery system. The present study describes the detailed mechanistic basis for assembly of LbL-LNPs, and their physicochemical characterization.

Results
This generates spherical and stable multilayered NPs ~240 nm in size, enabling effective systemic administration. The numerous functional groups and compartments in the polyelectrolyte shell and core facilitate loading with doxorubicin and mitoxantrone. The nanoarchitecture effectively controls burst release, providing different release kinetics for each drug. LbL-LNPs are pH-sensitive, indicating that intracellular drug release can be increased by the acidic milieu of cancer cells. LbL-LNPs were highly cytocompatible with MCF-7 cells at all the concentrations tested and also effectively prevented drug-induced hemolysis. We further demonstrate that the LbL nanoarchitecture significantly reduces the elimination rates of both drugs tested, and markedly extends their systemic circulation times, paving the way for efficacious tumor drug delivery.

Conclusion
Because this delivery system accommodates multiple drugs, improves drug half-life, and diminishes burst release, it provides an exciting platform with remarkable potential for combination therapeutics in cancer therapy.