489b Breaking down Endolysosomal Barriers for Drug Delivery with Degradable Polymersomes

Fariyal Ahmed, Goundla Srinivas, Aaron Brannan, Michael L. Klein, Frank S. Bates, and Dennis E. Discher

Carrier-mediated entry of cytotoxic drugs into a cell's cytoplasm is often limited by release from the carrier as well as endosomal release after internalization. Here we demonstrate by molecular simulation and experiment that degradable, non-ionic polymersomes of PEG-(polyester) foster endosome rupture and release of cytotoxic drugs doxorubicin (DOX) and paclitaxel (TAX). These drugs are typical – soluble and insoluble – anticancer agents. We characterize the stability, delivery and intracellular toxicity of DOX- and TAX-loaded nano-polymersomes with breast and lung cancer cell lines that take up the vesicles. While degradable polymersome formulations retain their load for over a month at 4°C, they exhibit facilitated release at 37°C and low pH. Copolymer degradation fosters endosomal escape through copolymer-induced disruption of the lipid membrane, enhancing intracellular drug release and cytotoxicity up to 40-fold relative to free drug. More generally, the results show that macro-surfactants, which are increasingly being applied, will interact with cell membranes