**ABSTRACT SUMMARY**
Various pH and/or reduction-responsive degradable polymeric nanocarriers have been designed and developed for active intracellular anti-cancer drug release. Notably, these novel bioresponsive nanocarriers have exhibited significantly improved anti-cancer efficacy as compared to the non-responsive controls.

**INTRODUCTION**
Biodegradable polymeric nanocarriers are one of the most promising platforms for targeted and controlled anticancer drug delivery. These nanoscale polymeric drug formulations have demonstrated clear advantages of decreased side effects, better pharmacological profiles, and improved drug tolerance over the current clinical approaches. It should be noted, however, that current drug formulations suffer slow and deficient intracellular drug release, which has resulted in compromised treatment benefits.

In recent years, significant effort has been directed to the development of bioresponsive nanosystems that are sufficiently stable under extracellular conditions while rapidly release drugs following uptake by target cancer cells. In particular, pH and reduction-sensitive nanocarriers have received most attention due to existence of a slightly lower pH in the endo/lysosomal compartments and a high redox potential in the cytosol and cell nucleus. We have recently developed varying types of bioresponsive degradable polymeric micelles and vesicles for active intracellular anti-cancer drug release.

**RESULTS AND DISCUSSION**
To develop acid-responsive biodegradable drug carriers, we have designed a novel acetal-containing cyclic carbonate monomer, TMBPEC, which can readily undergo ring-opening (co)polymerization to provide amphiphilic PEG-PTMBPEC block copolymers. The acetics in PEG-PTMBPEC micelles, though sufficiently stable at pH 7.4, were prone to fast hydrolysis at mildly acidic pH of 4.0 and 5.0. The *in vitro* release studies showed clearly a pH dependent release of paclitaxel (PTX) and doxorubicin (DOX). The intracellular drug release rate could further be improved by incorporating a disulfide bond between PEG and PTMBPEC blocks. We recently found that core-crosslinked pH-sensitive degradable micelles based on PEG-b-P(TMBPEC-co-AC) diblock copolymer containing photo-crosslinkable AC groups in the hydrophobic polycarbonate block while highly stable with minimal PTX release under physiological conditions quickly released drug at endosomal pH, elegantly resolving extracellular stability and intracellular drug release dilemma. By decreasing the weight fraction of the hydrophilic block in PEG-PTMBPEC copolymer, we could also obtain pH-sensitive degradable polymersomes. These polymersomes were able to load both hydrophilic DOX-HCl and hydrophobic PTX, and more importantly both drugs were released in a controlled and pH-dependent manner. We have also prepared pH-sensitive degradable chimaeric polymersomes based on designed asymmetric PEG-b-poly(trimethoxybenzylidene tris(hydroxymethyl)ethane methacrylate)-b-poly(acrylic acid) (PEG-PTTMA-PAA) triblock copolymers. Notably, these chimaeric polymersomes exhibited efficient loading and triggered release of DOX-HCl. Endosomal pH-activable PEO-g-DOX prodrug as well as DOX prodrug nanogels have also been developed.
Taking advantage of high reducing potential in the cytosol and cell nucleus of cancer cells, we have designed different types of reduction-sensitive degradable micelles.\(^{10}\) For example, we found that shell-sheddable biodegradable micelles based on PEG-SS-PCL efficiently released DOX into the cytoplasm of RAW 264.7 cells, resulting in markedly enhanced antitumor activities as compared to the “traditional” reduction-insensitive PEG-PCL controls.\(^{11}\) Improved intracellular drug release and antitumor effect were also demonstrated for DOX-loaded reduction-sensitive dextran-SS-PCL micelles.\(^{12}\) The following systematic studies on shell-sheddable micelles showed that the intracellular DOX level and cytotoxicity of DOX-loaded PEG-SS-PCL micelles were intimately dependent on extent of shell-shedding.\(^{13}\) Employing lipoic acid, we have developed reversibly crosslinked dextran nanoparticles,\(^{14}\) interfacially crosslinked PEG-PCL micelles,\(^{15}\) and core-crosslinked degradable micelles.\(^{16}\) These disulfide-crosslinked micelles displayed excellent stability against dilution while were prone to rapid de-crosslinking and/or dissociation to quickly release loaded DOX under the intracellular reducing environment.

**CONCLUSION**

We have demonstrated that bioresponsive degradable polymeric nanocarriers efficiently deliver and release anticancer drugs into cancer cells, resulting in markedly enhanced antitumor activity.

**REFERENCES**


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