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（要　旨）
(Summary)

Toward the success in the clinic, targeting the diseased site represents one of the greatest merits of nanomedicine. One of the earliest hopes for nanomedicine is to combat severe diseases such as cancer. To this end, the delivery system should fulfill the following properties:

1) Biodegradability: for long-term safety,

2) Antifouling (in the bloodstream): for prolonged circulation time and reduced immunotoxicity,

3) Interactivity (within the targeted tissue): for higher accumulation in the target.

In this thesis, I have designed PGlu(DET-Car) based on ethylene diamine-based carboxybetaine (i.e., a polyzwitterion) for tumor-targeted delivery of the coated nanomaterials. The molecular design of PGlu(DET-Car) fulfills the aforementioned three properties, and provides a simple structure of drug delivery carriers for efficient tumor theranostics. In contrast with polyzwitterions (and other stealth agents) that are limited to one function (i.e., antifouling), PGlu(DET-Car) can maintain the neutral net charge for the antifouling property at physiological pH 7.4 for prolonged blood circulation, but would switch its property to become interactive with the tissue components in response to tumorous weakly acidic pH leading to the enhanced tumor accumulation of the coated nanoparticles.

First, I have synthesized the polymers in order to investigate the tumorous pH-responsive performance of PGlu(DET-Car); three control polymers that do not switch the property at tumorous pH were prepared. One is PGlu(DPT-Car) and another is PGlu(EDA-Car), as the cationic control and the neutral control, respectively, as confirmed by potentiometric titration. The third control is poly(ethylene glycol) (PEG_{20k}), as the conventional polymer of antifouling. The prepared polymers had similar hydrodynamic volume to PGlu(DET-Car), and thus their performance can be comparable regardless of the effect of the polymer size.

Then, quantum dots (QDs) were chosen as the model nanoparticle because of the narrow distribution in size, reactive moieties on the surface, and Cd element for the detection *in vitro* and *in vivo* by inductively coupled plasma mass spectrometry. The number of polymers coated onto the QDs was optimized to reach ~35 polymers per QD, in association with a hydrodynamic size of ~30 nm. Therefore, the comparison of the performance of QDs can be solely based on the coating polymer.

After fluorescent labeling of the polymers (and polymer coating of QDs), tumorous

pH-dependent interaction of PGlu(DET-Car) system with anionic extracellular matrix analog (heparin) was confirmed by an increase in the size, as observed through fluorescence correlation spectroscopy. In comparison, both of the antifouling polymers (PGlu(EDA-Car) and PEG_{20k}) systems did not show a significant change in the presence of heparin, while the cationic polymer PGlu(DPT-Car) system showed interactions with heparin as suggested by the increase in the hydrodynamic size.

Cellular uptake of the polymers was studied through flow cytometric analysis and confocal laser scanning microscopic observation. The cellular uptake of the antifouling polymers PGlu(EDA-Car) and PEG_{20k} systems was negligible, in contrast to the cationic polymers PGlu(DPT-Car) system which showed significant cellular uptake at both pH 7.4 and tumorous pH 6.5. Meanwhile, PGlu(DET-Car) system enabled enhanced cellular uptake at tumorous pH compared to the treatment of cultured cells at pH 7.4. It should be noted that these polymers did not show cell toxicity as indicated by the high cell viability and the low cellular membrane disruption after incubation with the polymers (even PGlu(DET-Car) and PGlu(DPT-Car) at tumorous pH).

Finally, upon intravenous administration into mice having a subcutaneous tumor, PGlu(DET-Car)-QDs exhibited blood circulation time comparable (or even higher) to the antifouling PGlu(EDA-Car)-QDs and PEG_{20k}-QDs, as well as a similar biodistribution in healthy organs. Most importantly, the tumor accumulation of the PGlu(DET-Car)-QDs was significantly higher than that of PGlu(EDA-Car)-QDs and PEG_{20k}-QDs. These data sets strongly indicate that PGlu(DET-Car) underwent an increased protonation at the tumor site. The increased protonation of PGlu(DET-Car) should facilitate interaction of the coated QDs with the surrounding negatively charged components at the tumor tissue leading to increased cellular uptake, and ultimately enhanced tumor accumulation.

In other words, I have designed PGlu(DET-Car) to achieve three favorable properties, while the currently used coating polymers are usually limited to only one property. PGlu(DET-Car) is a poly(glutamide) (i.e., poly(amino acid)) for biodegradability, a polycarboxybetaine with a neutral net charge at pH 7.4 (i.e., polyzwitterion) for antifouling property in the bloodstream, and responsiveness to tumorous weakly acidic pH for interaction with tumor tissue components and enhanced tumor accumulation. To the best of my knowledge, PGlu(DET-Car) is the first coating polymer to have all of the aforementioned properties. This polymer will become a cornerstone in the field of nanomedicine for a new class of functional nanomaterials toward enhanced tumor delivery.

The rationale of this thesis is based on transcending the limitations of the monofunctionality of the coating polymers into the realm of multifunctionality. The findings herein will be the basis of future smart design of antifouling polymers with a built-in targeting property for nanomedicine, that would attract the interests of the pharmaceutical and biotech industries.