Nanocarrier’s Function Integration and Synchronization for Cancer Drug Delivery Cascade

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ABSTRACT SUMMARY
The cancer drug delivery process is a cascade of five steps consisting of circulation in blood, accumulation and penetration into the tumor, cellular internalization and intracellular drug release, or the CAPIR cascade. Thus, the most challenging aspect of cancer nanomedicine design is the integration and synchronization of all functions required to accomplish the CAPIR cascade into one system, particularly, many of which are in opposite in different CAPIR steps.

INTRODUCTION
Taking advantage of the enhanced permeability and retention effect† found in animal models, current nanomedicines deliver more anticancer agents to tumor tissues and reduce toxicity compared with conventional chemotherapy agents, but such enhanced drug delivery does not result in much improved overall survival of patients.‡ Further analysis shows that delivering active (free) drugs to the cytoplasm of cancer cells for actions can be divided into five cascade steps (Fig. 1). Thus, cancer drug delivery is a ‘CAPIR’ cascade. The key to maximizing efficacy is to design a nanosystem capable of fully accomplishing this CAPIR cascade — missing any step would make it unable to deliver active drug to all tumor cells, diminishing therapeutic efficacy.§ For example, DOXIL was found to effectively accumulate in the tumor tissues, but it could not penetrate the tumor, resulting in low therapeutic efficacy.¶ Thus, the utmost challenge of nanomedicine design is the integration and synchronization of all functions required to accomplish the CAPIR cascade into one nanomedicine, particularly, many of which are in opposite in the different CAPIR steps.¶

We thereby hypothesised a “cluster bomb”-like nanocarrier — the whole nanocarrier accomplishing the mission of blood circulation and tumor accumulation, while its contained small nanocarriers as “bomblets” accomplishing the missions of tumor penetration and cell internalization and drug release. This nanocarrier integrated and synchronized its functions and thus efficiently accomplished the CAPIR cascade, resulting in improved delivery and therapeutic efficacies (Fig. 2A).

RESULTS AND DISCUSSION
The self-assembly of the dendrimer (D) with DOPE lipid (L), cholesterol (C), and DSPE-PEG (PEG) formed a stable dendrimer/DOPE/cholesterol/PEG (DLC-PEG) nanoassembly at a molar ratio of 1/60/60/1.5. The DLC-PEG nanoassembly was estimated by TEM to roughly contain 20 dendrimers (5 nm in diameter) aggregating together and coated with a lipid monolayer (Fig. 2A). Anticancer drug doxorubicin (DOX) was loaded into DLC-PEG. The resulting DLC-PEG/DOX had a diameter, 45 ± 5 nm, and a DOX-content of 9 ± 2 wt%. DLC-PEG was found to fuse with cell membrane to release the dendrimers directly into the cytoplasm or the extracellular medium for tumor penetration.

Fig. 1 The CAPIR cascade of cancer drug delivery — A cascade of five steps: circulation in the blood compartments, accumulation in the tumor from the hyperpermeable tumor vessels, penetration into the deep tumor tissue to reach all tumor cells and subsequent internalization by them, and finally intracellular drug release.
**CONCLUSION**

We demonstrated that a nanoassembly simultaneously undergoes peg/depolymerization, size, and charge transitions, integrating and synchronizing the needed functions for the CAPIR cascade of cancer drug delivery. Consequently, the nanoassembly could significantly enhance the DOX antitumor efficacy and minimize its side effects. This nanoassembly behaving like a “cluster bomb” may be a very promising concept unifying the needed properties for high chemotherapeutic efficacy.

**REFERENCES**


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