# 審 査 の 結 果 の 要 旨

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In recent years, polymeric micelles are attracting much interest in the research field of drug delivery due to their easy preparation, based on the self-assembly in aqueous solution of amphiphilic block polymers, and the controllable modification of their properties. Taking advantage of the so-called enhanced permeability and retention (EPR) effect, which is due to leaky blood vasculature and impaired lymph drainage of solid tumors, micelles can specifically accumulate in tumor tissue. Moreover, the targeting of nanocarriers can be further improved by modifying their surface with specific ligands having high binding ability against receptors overexpressed on cancer cells. In addition, the specific stimuli in the microenvironment of tumor tissues can be used for tumor selective release of the loaded drugs. Thus, by increasing the specificity of drug delivery to tumor tissues, nanocarriers can minimize the off-targeting effects to and maximize the efficacy of the treatments. The review result of each thesis chapter is shown in the following.

In the First Chapter, the background and goal of this study was introduced. As one type of nanocarrier with many advantages over others, polymeric micelle is introduced. The targeting method of micelle and its functionalization with stimuli responsibility is also discussed. Challenging to existing antibody-drug conjugate (ADC), a new method of using micelle to deliver prodrugs used in ADCs is come up. Also, the significance of this research is pointed out.

In the Second Chapter, a micelle platform is designed to investigate the prodrug activation profile. In conventional research, the prodrug activation is measured by end-point methods and the information about microdistribution is hard to get due to the intrinsic properties of ADC prodrugs. However, when Hoechst is used as DNA-targeting probe, the prodrug activation process can be easily followed in real time with the information about microdistribution. With this Hoechst-loaded micelle, a consistent conclusion about the cleavability of peptide linkers used in ADC prodrugs, which is valine-citrulline has more selectivity over valine-alanine, is proved. Also, this Hoechst micelle supplies important information about prodrug activation and microdistribution in organs and tumor, which can be used for the following research.

In the Third Chapter, the installation technique of installing Fab on micelle surface is discussed. As the purpose of this research is to deliver ADC prodrugs in micelles, it is reasonable to modify micelle surface with antibody or its binding

fragment Fab. Here, it is proved that the length of cross-linker for Fab conjugation, which is the number of PEG units, affect installation efficiency. Also, it is pointed out that the cross-linker length does not affect micelle binding and cellular uptake, as long as the Fab density is kept consistent. However, when the Fab density increases from 30% to 60%, the cellular uptake decreases significantly.

In the Fourth Chapter, the results obtained from Chapter 2 and chapter 3 are used to design a therapeutic micelle, which is conjugated with MMAE prodrug in the core and modified with Fab on the surface. MMAE is a potent drug and its ADC product has been approved. Here, by delivering MMAE prodrug in micelle, the antibody utilization efficiency, which is indicated by Fab/MMAE ratio, has a 40 fold increment. In addition, the Fab modified MMAE micelle has comparable cytotoxicity with ADC, long retention in tumor tissue, good efficacy on tumor growth inhibition and excellent safety under multiple treatment.

In the Fifth Chapter, a functionalized micelle is introduced, which has responsiveness over the acidic pH environment in the cell endosome. As a general issue of enzymatically activated prodrug in micelle is the hindered access of enzyme exerted by PEG shell, a pH sensitive function is introduced for micelles by modifying polymer side chains with imidazole moieties. It is successfully proved that after introduction of pH sensitivity, micelle can undergo reversible dissociation under endosomal pH. Also, the prodrug activation is accelerated and the cytotoxicity is enhanced, both of which can be explained by the fact that enzyme has more access to cleavable linkers when the micelle dissociated into unimers.

In the Sixth Chapter, general conclusions are presented and the future application of this micelle platform in clinical therapy is discussed.

In the thesis mentioned above, a versatile polymeric micelle platform containing furans conjugating ADC prodrugs through Diels-Alder reaction was successfully developed. This platform provides a safe and effective strategy for developing carrier systems for highly potent anticancer agents, which have been delivered by antibodies so far, thereby, opening new opportunities for therapies capable of eradicating tumors while avoiding toxicities. We have applied a patent for developing these systems, and the venture company Nanocarrier is interested to take them to the clinic. I believe these findings will make a strong impact in the field of bioengineering, particularly in nanomedicine, promoting the rise of potent anticancer systems.

According to the reviews, this thesis is eligible for applying a diploma of Ph.D (engineering).