論 文 の 内 容 の 要 旨

Molecular Design of Novel End-functionalized Thermo-sensitive Poly(2-isopropyl-2-oxazolines) (P*i*PrOx) and Their Application as Functional Materials
(末端官能基を有する新規温度応答性ポリ(2-イソプロピル-2-オキサゾリン)の分子設計とその機能性材料としての応用)

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A great deal of study has been done over the past years towards the development of drug delivery systems for therapeutic purpose based on polymeric micelles featuring longevity in blood circulation. In most studies, these drug carriers are composed of a biocompatible hydrophilic poly(ethylene glycol) (PEG) outer shell, because this polymer can prevent non-specific adsorption of the polymeric micelle to proteins and cells, so that allow the micelles to evade recognition by the reticuloendothelial system (RES). However, there has been less study on the introduction of other hydrophilic polymers on the outer corona other besides PEG to develop micellar drug delivery systems. Charged hydrophilic polymers have been used for delivery to mucosal surfaces, such as the respiratory, gastrointestinal, and urogenital tracts. Polymeric micelles with a corona made up of natural or semi-synthetic polysaccharides are investigated as well as vehicles in the oral administration of poorly-water soluble drugs. Recently, polymeric micelles based on block copolymers of PEtOx and poly(ε-caprolactone), were also evaluated as a candidate of novel drug carriers and shown to have low cytotoxicity and hemolytic activity.

In the meanwhile, of great interest is also the design of “intelligent drug carriers” able to achieve site-specific delivery of drugs. There have been developed two kinds of active targeting so far. The one is chemical affinity targeting using molecules such as sugar residues or antibodies as homing devices and the other is physical affinity targeting using pH, thermally, or magnetically responsive carriers. In particular, the physically targeted polymeric micelles utilizing temperature change could be designed to have a small size and thermo-sensitive polymer chains on their outer hydrated shell. Thus, these types of micelles are expected to present a double targeting character: passive targeting resulting from both their small size and highly hydrated shell structure, and active physical affinity targeting resulting from their thermo-sensitive outer shell.

There have been prepared the thermo-sensitive polymeric micelles from amphiphilic block copolymers composed of a thermo-sensitive outer shell (PNIPAAm) and hydrophobic inner core.**[1]** These micelles exhibited a small diameter with a low critical micelle concentration, providing a carrier that may have long blood circulation times and a low RES uptake. The concept of physical affinity targeting is based on the hyperthermia strategy. In short, when the temperature is increased above the transition temperature of the thermo-sensitive block chains (32 ^{o}C), the outer shell chains dehydrate and collapse, allowing aggregation between micelles and favoring binding interactions with cell

membrane surfaces. Hydrophobic molecules are shown to be incorporated into the inner hydrophobic core of the thermo-sensitive micelles. Consequently, these micelles were considered valuable for site-specific delivery of drugs using changes in temperature as a trigger. However, PNIPAAm is a non-biodegradable polymer, and its biocompatibility is still in question. Therefore, a novel thermo-sensitive polymeric material with good biocompatibility is required to develop even maintaining or overcoming the clear thermo-sensitivity of the conventional PNIPAAm.

From this point of view, a careful interest could be taken in poly(2-oxazoline) (POx). POx becomes hydrophilic when the 2-sustituent is a shorter alkyl group like methyl or ethyl, but hydrophobic when it is a longer or bulky alkyl and aryl groups. In particular, it should be noted that poly(2-isopropyl-2-oxazoline) (P*i*PrOx) in water also presents a lower critical solution temperature (LCST) under physiological conditions even around the human body temperature, as revealed by turbidity studies.**[2]** The repeat unit of P*i*PrOx is isomeric to that of PNIPAAm. However, the unique phase separation property of P*i*PrOx has not been studied in detail though it was found that P*i*PrOx exhibits sharp thermo-sensitivity comparable to that of PNIPAAm. Furthermore, while the synthetic methodology and polymerization mechanism of versatile POx derivatives including derived copolymers have been extensively investigated, there have been little studies on the solution properties of POx oligomers. The main reason of the deficient study on this issue is considered deriving from the failure in controlled synthesis of primary structures of POx polymers. The polymerization of 2-oxazolines proceeds usually in living nature, but at the same time often undergoes the remarkable side reactions such as chain transfer reaction occurring spontaneously among the reactive sites and 2-oxazoline monomers. These types of side reactions inevitably result in the defective polymer backbone structures involving wide molecular weight distributions, so that limit the further precise architecture of nanostructures such as polymeric micelles and demotivate the detailed study on their solution properties.

Based on these backgrounds, it was highly inspired to develop a novel thermo-sensitive polymeric micelle through the well-defined synthesis of narrow-disperse P*i*PrOx. Most of all, it should be elucidated where the side reactions are derived from and which is the best way to solve these undesirable synthetic problems, through the fundamental investigation on the aspect of polymerization mechanism of P*i*PrOx. This work is worth a lot to progress the study on their LCST phenomenon as well as the future application with them. Furthermore, the design of thermo-sensitive polyion complex (PIC) micelles, able to carry charged compounds including enzyme and DNA become even more attractive as an intelligent vehicle utilizing temperature changes as a physical affinity control.

In the present study, the molecular design of functional materials including controlled synthesis of novel thermo-sensitive poly(2-oxazolines) for the application to a smart drug delivery system with thermo-sensitivity in biomedical fields are described, mainly based on the strategy as shown in **Figure**. This thesis including general introduction (**Chapter 1**) and summary (**Chapter 5**) is composed of the five sections. **Chapter 2** describes versatile well-defined synthesis of end-functionalized thermo-sensitive poly(2-isopropyl-2-oxazolines), **Chapter 3** describes preparation and characterization of polyion complex micelles with novel thermo-sensitive

poly(2-isopropyl-2-oxazoline) (P*i*PrOx) shell via the complexation of oppositely-charged block ionomers, and **Chapter 4** describes precise control of lower critical solution temperature of thermo-sensitive poly(2-isopropyl-2-oxazoline) (P*i*PrOx) *via* gradient copolymerization with either 2-ethyl-2-oxazoline (EtOx) as a hydrophilic comonomer or 2-n-propyl-2-oxazoline (nPrOx) as a hydrophobic comonomer. Thus, the stability of thermo-sensitive PIC micelles was expected to increase with the introduction of more hydrophilic segments on outer corona, and what is more, their LCST variation attainable over a wide range of temperature as in the case of POx primary structures.

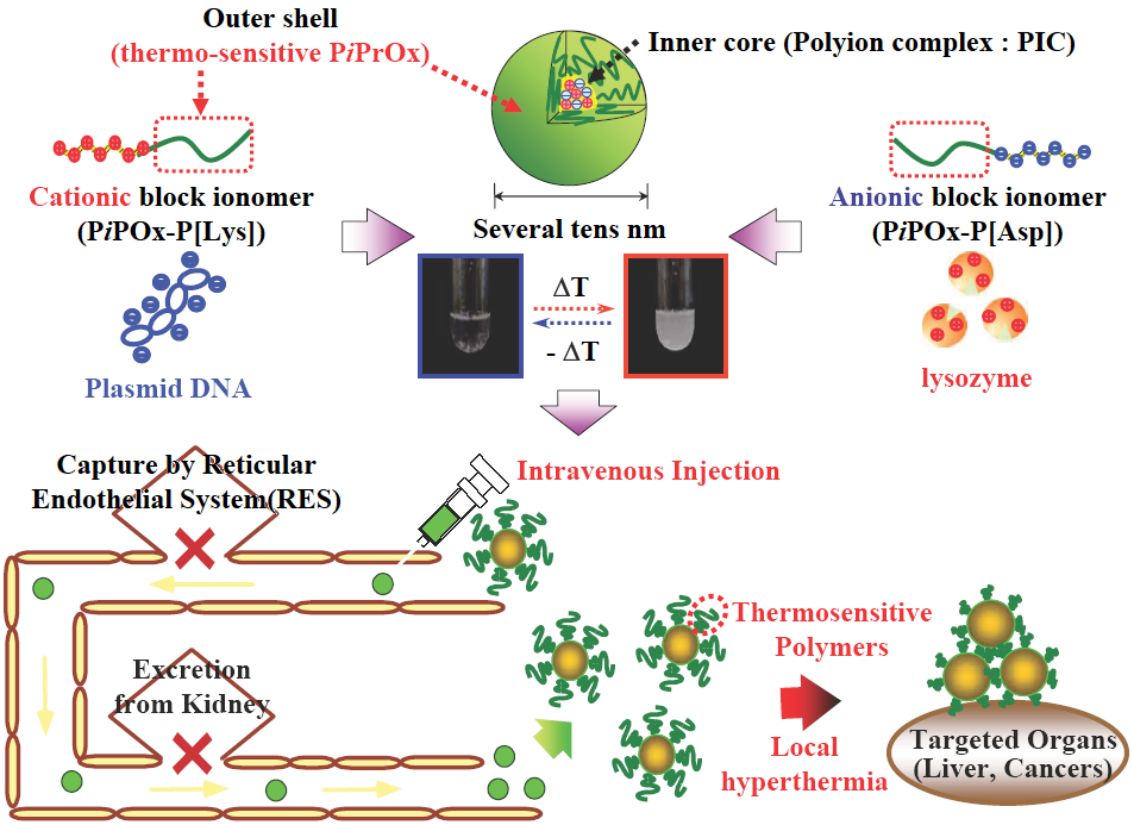

Figure. The schematic strategy of thermo-sensitive polyion complex (PIC) micelles for therapeutics.

Through this thesis, a novel way to prepare very precisely temperature-sensitive polymeric materials beyond the well-known conventional poly(*N*-isopropylacrylamide) (PNIPAAm) has been opened up and their possibility as a smart drug carrier in the biomedical fields was evaluated through the formation of thermo-sensitive PIC micelles among synthetic block ionomers.

References

[1] Chung, J. E.; Yokoyama, M.; Yamato, M.; Aoyagi, T.; Sakurai, Y.; Okano, T. *J. Controlled Release.* **1999**, *62*, 115.

[2] Uyama, H.; Kobayashi, S. *Chem. Letters* **1992**, 1643