論 文 の 内 容 の 要 旨

論文題目　Well-defined Reactive Block-type Phospholipid Polymers for Advanced Soft Polymeric Materials
（新しいソフトマターとしての精密に構造制御された反応性ブロック型リン脂質ポリマー）

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The principal of this doctoral dissertation is to fabricate versatile, reactive, well-defined phospholipid copolymers that i) have predetemined molecular weight with low polydispersity, ii) have desired polymer chain architecture, and iii) can be functionalized or applied for various application. Not only focusing on polymer products, but the studies of polymerization processes are also emphasized. The processes to synthesize desired engineered polymers are studied to clarify i) the concept of reversible degeneration radical polymerization (RDRP) to provide well-defined polymers, ii) polymerization conditions that suitable for preparation of phospholipid polymers, and iii) improve the processes for better environmentally-friendly polymerization.

After the well-defined, reactive ABA triblock-type phospholipid polymers were successfully obtained. The functionalization of the polymers allows utilization of the engineered polymers in many fields of application. In this thesis, the soft polymeric materials, *i.e.* hydrogels, were formed by well-defined polymers. The specific functionalization of polymers leads to tunable hydrogels with stimuli-sensitiveness. The homogeneity of well-defined polymers also improve the hydrogel properties such as diffusivity in hydrogel network. The overall of the doctoral dissertation is shown in Figure 1.

Motivation and design of the thesis

The well-defined polymers can play important roles in smart materials, their properties cannot be obtained from conventional preparation methods. The well-defined polymers also show many roles in wide range applications from polymer sciences to electrical application, and biomedical applications. To obtain well-defined polymers, the polymerization techniques have to be employed. The reversible deactivation radical polymerization (RDRP) is the term for controlled/living polymerization, which chain termination is limited and the propagation is allowed in well-controlled manners. The applications of well-defined polymers are significant and expanding, especially in biomedical application, thus, the well-defined polymers were subsequently functionalized by crosslinkable moieties and used to fabricate hydrogels.

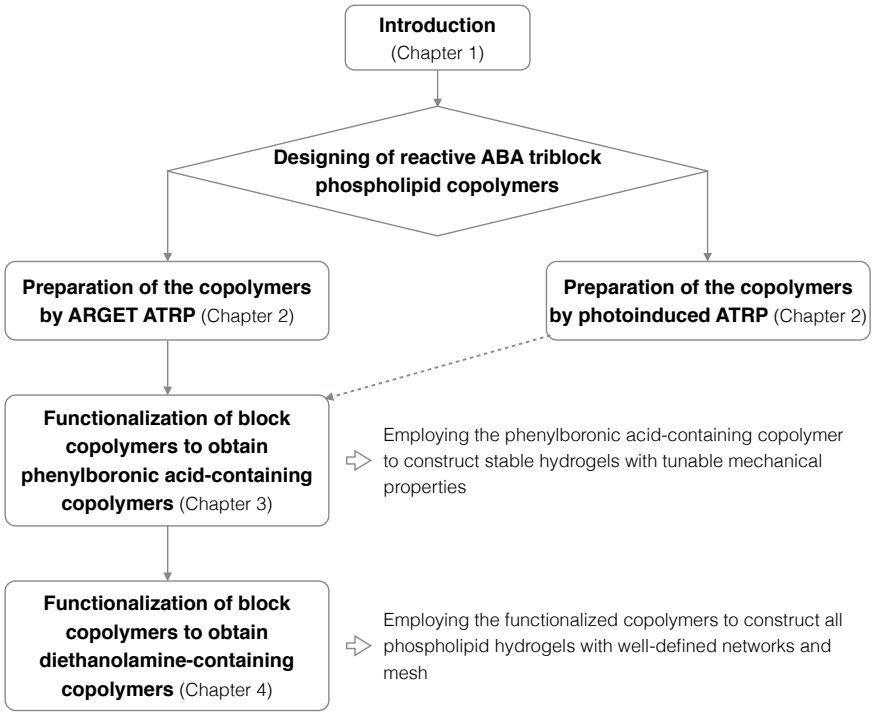

Figure 1 Overview of this thesis

Advances in engineered hydrogel, particularly the use of well-defined synthetic hydrogels, have led to the design of precisly controlled platforms for study of stem cell fate, tissue morphogenesis and disease pathogenesis. Thanks to three-dimensional environment of hydrogels, the hydrogel models can replicate some features of the *in vivo* architecture and allow control of the cellular signaling, cell–cell interactions, and specific physiological environment for living cells. However, the limitations of hydrogels from conventional polymers are 1) slow response to external stimuli, 2) unable to control hydrogel mesh sizes from random copolymers, 3) heterogeneity of polymer network. The utilizations of well-defined polymers can overcome those limitations.

The scientific contributions of the thesis

To achieve the objective of preparation of well-defined, reactive block-type phospholipid polymers. Many studies were conducted and reported in this doctoral dissertation, they can be listed as follows:

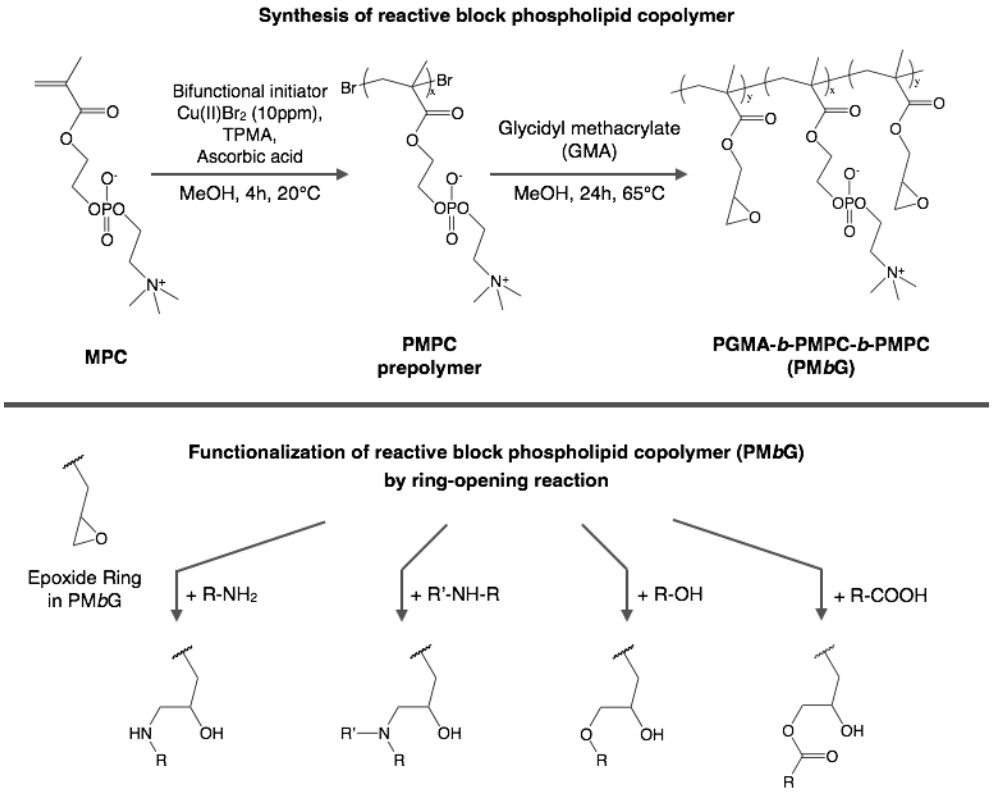

Figure 2 Preparations and functionalizetions of block-type phospholipid polymers

The first and formost contribution is the seccess of fabrication of well-defined ABA triblock-type phospholipid copolymers composed of poly(2-methacrylotloxyethyl phosphorylcholine) (PMPC) as middle B segment and poly(glycidyl methacrylate) (PGMA) as A segments in both ends of polymer chain, named PM*b*Gs. The PM*b*G properties can be controlled, especially the targered degree of polymerizatio of PMPC middle chain (monomer units-per-chain) at fixed amount of GMA units. The PMPC is hydrophilic polymer with good cytocompatibility and bio-friendly characteristics. While the PGMA contain versatile epoxide active group, that can easily react with nucleophiles, which allows the PM*b*Gs to be functionalized by various active groups, depends on the anticipated properties of the polymers. The preparation and functionalization of PM*b*Gs is illustrated in Figure 2.

The second contribution of this thesis is throughly studies of two atom transfer radical polymerization (ATRP) processes for preparation of block-type phospholipid polymers. As phospholipid polymers have high potentials for biomedical applications, the preparation processes should not be engaged with biotoxic or impurities. The activator-regenerated by electron transfer (ARGET) ATRP and photoinduced ATRP were used in this research. These two techniques required extremely low amount of metallic catalyst, so-called, greener ATRP methods. For ARGET ATRP, the biocompatible reducing agent, *i.e.* ascorbic acid, was used, whereas the photoinduced ATRP used external UV light source as reducing agent. The polymerization can also be precisely controlled and polymer chain growth were in

good fashions.

The third contribution is the functionalization of PM*b*Gs to fabricate responsive block-type copolymers by modification of epoxide group in PGMA segment. The stimuli-responsive moiety in this research is phenylboronic acid (PBA). The PBA unit has been widely employed for preparation of reversible phospholipid hydrogels that can be used as cell container. The phenylboronic acid-functionalized triblock-type phospholipid copolymers (PM*b*Bs) can form stable hydrogle when mixed with poly(vinyl alcohol) (PVA) as the PBA can act as crosslinking with PVA chain. The properties of PM*b*B/PVA hydrogles are both polymer architecture-dependent and pH-dependent. The morphology of dried hydrogels were obviously examined to be polymer architecture-dependent, as hydrogel with longer PMPC tends to br more flexible. The pH-sensitive, reversible, tunable PM*b*B/PVA hydrogels were successfully achieved. With only difference in pH, soft gel to hard gel (storage moduli can be tuned for 5-times) can be obtained as the merits of PBA. The hydrogels also reversible by simply addition of sugar molecules, which proves the usefulness of PM*b*B/PVA hydrogels in biology researches.

The fourth contribution is the ability to control hydrogel properties in miniscales, especially to control the mesh size of hydrogels. The hydrogel mesh size is an important factors for biological applications, as the diffusion of nutritions, gases, biomolecules, and wastes can be free or restricted depends on mesh of hydrogel network. Predetermined polymer chains allows the formation of hydrogels with desirable size of polymer network, as the length of PMPC segment can be well-controlled, the mesh size of the hydrogels from a common triblock-type phospholipid polymers should also have homogeneous mesh size. To achieve this engineered hydrogels, the amine-modified block copolymers (PM*b*Ds) were prepared. As PM*b*Bs and PM*b*Ds share the same PMPC properties, the formation of PM*b*B/PM*b*D hydrogels should permits the control of mesh size by referred to PMPC chain length. The diffusivity test also confirmed this theory, and it emphasizes the importance of well-defined block-type polymers for the new, next engineered materials.

The scientific contributions of the thesis

Finally, all accomplishments stated in this doctoral dissertation widen both polymization sciences (from studies of RDRP, *i.e.* ARGET ATRP and photoinduced ATRP) to the application of versatile, reactive, well-defined phospholipid polymers for biomedical application. Indeed, the hydrogels from well-defined phospholipid polymers is only a simple example of utilizations of the versatile PM*b*Gs. I strongly believe that the PM*b*Gs and the functionalized of it will provide families of reactive, well-defined phospholipid copolymers that will play important roles in the future engineered smart materials.