Development of Toroidal Nanostructures by Self-Assembly: Rational Designs and Applications

YONGJU KIM,† WEN LI,† SUYONG SHIN,‡ AND MYONGSOO LEE*†

†State Key Lab of Supramolecular Structure and Materials, College of Chemistry, Jilin University, Changchun 130012, China, and ‡Department of Chemistry, Seoul National University, Seoul 151-747, Korea

CONSPECTUS

Toroidal nanostructures are symmetrical ring-shaped structures with a central internal pore. Interestingly, in nature, many transmembrane proteins such as β-barrels and α-helical bundles have toroidal shapes. Because of this similarity, toroidal nanostructures can provide a template for the development of transmembrane channels. However, because of the lack of guiding principles for the construction of toroids, researchers have not widely studied the self-assembly of toroidal nanostructures as compared with the work on other supramolecular architectures.

In this Account, we describe our recent efforts to construct toroidal nanostructures through the self-assembly of rationally designed building blocks. In one strategy for building these structures, we induce interfacial curvatures within the building blocks. When we laterally graft a bulky hydrophilic segment onto a oligophenyl rod or β-sheet peptides, the backbones of the self-assembled structures can bend in response to the steric effect of these large side groups, driving the oligophenyl rod or β-sheet peptides to form nanosized toroids. In another strategy, we can build toroids from bent-shaped building blocks by stacking the macrocycles. Aromatic segments with an internal angle of 120° can associate with each other in aqueous solution to form a hexameric macrocycle. Then these macrocycles can stack on top of each other via hydrophobic and π–π interactions and form highly uniform toroidal nanostructures. We provide many examples that illustrate these guiding principles for constructing toroidal nanostructures in aqueous solution.

Efforts to create toroidal nanostructures through the self-assembly of elaborately designed molecular modules provide a fundamental approach toward the development of artificial transmembrane channels. Among the various toroids that we developed, a few nanostructures can insert into lipid membranes and allow limited transport in vesicles.

Introduction

The construction of well-defined nanostructures by molecular self-assembly through rational design is a major challenge in supramolecular chemistry.1,2 A variety of supramolecular architectures has been created by thoroughly investigating the self-assembly behavior based on various self-assembling building block amphiphiles.3–7 The supramolecular architectures have a well-defined size and shape including fibers, ribbons, tubes, helices, cylindrical micelles, vesicles, spherical micelles, bilayers, and toroids.8–14 Among diverse nanostructures, toroids have a unique annular shape with an internal pore in the central region.15,16 It shows a short nanotube-like shape with a length of a few nanometers. Interestingly, a structural motif of toroidal nanostructures is
found commonly in many transmembrane proteins. For example, the \( \beta \)-barrel, which is encountered in the outer membranes of bacteria, mitochondria, and chloroplasts, exhibits a closed \( \beta \)-sheet structure where the first and last \( \beta \)-strands are connected by hydrogen-bonding (Figure 1a). The \( \alpha \)-helical transmembrane region is also another example. It contains a bundle of several protein helices that span the membrane and enables specific molecules to be transported across the lipid bilayer (Figure 1b).18

On the structural basis of the toroidal nanostructures, several research groups have designed and constructed self-assembled toroids through amphiphilic block copolymers, DNAs, rod–coil amphiphiles, peptides, and proteins.19–25 However, because of the lack of a guiding principle for the preparation of toroids, self-assembly into the toroidal nanostructure has not been widely studied compared with the other supramolecular architectures such as fibers, micelles, sheets, and vesicles. In recent research, we have studied the construction of toroidal nanostructures through the self-assembly of rigid–flexible amphiphilic molecules and synthetic peptide block molecules. From our work, we can draw following two general principles: the induction of interfacial curvature or the stacking of the macrocycles. In the interfacial curvature principle, a bulky and hydrophilic flexible segment is placed in the middle of the hydrophobic rigid segments such as \( p \)-oligophenyl rods or \( \beta \)-sheet peptides. As a result, curvature at the interface of the building blocks can be induced to decrease steric repulsion between the bulky hydrophilic segments. Finally, the amphiphilic building blocks can self-assemble into highly curved toroidal nanostructures. In another principle, the toroids can be constructed by the stacking of the macrocycles. Bent-shaped aromatic segments with an internal angle of 120° can form hexameric macrocycles at the initial stage. The resulting noncovalent hexameric macrocycles can further stack on top of each other to form highly uniform toroidal nanostructures through hydrophobic and \( \pi \)-\( \pi \) interactions. Interestingly, slight molecular modifications in the bent-shaped block molecules can lead to the formation of interesting expandable toroids.

With these principles, this Account describes recent research in the development of toroidal nanostructures via rigid–flexible amphiphiles and synthetic peptides. In the later part of the Account, a few toroids are subjected to function as artificial channels because of their unique annular shape with an internal pore in the central region, which is similar to the shape of the transmembrane protein.

**Toroidal Nanostructures from Self-Assembly of Rigid–Flexible Amphiphiles**

The rigid–flexible amphiphilic small molecules are composed of rigid aromatic segments and flexible coil segments. They can form supramolecular structures with dimensions as small as a few nanometers, which are not common in microphase separated flexible block molecules. Therefore, the rigid–flexible amphiphiles can be excellent candidates for creating well-defined supramolecular architectures such as nanometer-sized toroids.26 These amphiphilic combinations lead to the formation of a nanostructure with a rigid hydrophobic core surrounded by flexible hydrophilic chains in an aqueous solution.27

Molecules 1 and 2 have a bis(ethylene glycol) chain and a longer tris(ethylene glycol) chain, respectively, as a flexible hydrophilic segment with the same hydrophobic segment, hepta-\( p \)-phenyl group and hydrophobic chain (Figure 2a).28 In an aqueous solution, molecule 1 self-assembles into planar sheets, whereas molecule 2 forms a ribbon-like nanostructure due to a different volume of hydrophilic chain. For the formation of the toroid, curvature at the interfaces of the amphiphiles was introduced through molecule 3, which...
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Self-assembled toroids can also be constructed through the stacking of the macrocycles from bent-shaped aromatic segments. Amphiphiles 4 and 5 have an internal angle of 120° from a meta-linked aromatic segment and an oligoether dendron side group (Figure 3). 29,30 The self-assembly of amphiphile 4 leads to the toroidal nanostructure through the formation of hexameric macrocycles. The negatively stained TEM images revealed a light exterior and a dark interior, indicating that the assembled objects are toroid-shaped nanostructures with internal cavities. The toroidal nanostructures were further confirmed by the cryogenic-TEM image as shown in the inset of Figure 3a. The internal and exterior diameters of the toroids are approximately 3 and 8 nm, respectively, showing a highly uniform toroid size that is consistent with the size distribution of DLS result. Finally, the toroids are composed of stacks of several hexameric macrocycles, resulting in a height of approximately 3 nm.

On the basis of the stacking of the macrocycles, we were able to create larger toroids through a slipped packing arrangement, J-type stacking. Amphiphile 5 is basically composed of a meta-linked aromatic segment and an oligoether dendron side group and showed a similar structure to that of 4 (Figure 3b). 30 The differences between 4 and 5 are the formyl group, the volume of hydrophilic dendron, the pyridine-linked aromatic segment, and the length of the aromatic segment. The formyl group of 5 led to a weaker intermolecular dipole interaction than that from the cyano group of 4, and the introduction of the pyridine group induced the formation of water clusters at the nitrogen atom. Because of the weak dipole interaction of the formyl group and the steric repulsion of the water cluster, slipping motion between adjacent aromatic segments could be induced. The spectroscopic results showed that the absorption maximum of 5 in aqueous solution is red-shifted and the fluorescence intensity is apparently enhanced with respect to those observed in chloroform solutions in great contrast to the case of 4 (Figure 3c). These results are indicative of J-type stacking of the aromatic segment, suggesting that 5 self-assembled with a slipped packing arrangement in the hexameric macrocycles. Finally, by the self-assembly of 5, we can construct the larger toroids than those of 4 in aqueous solution. The TEM and AFM experiments clearly showed toroidal objects with a uniform diameter of 11 nm and an internal cavity diameter of 4 nm, which is consistent with the DLS experiment result, 12 nm (Figure 3b, d). In short, we could introduce the J-type stacking via the rational design of building blocks and expand both external and internal diameters of the toroids.

FIGURE 2. (a) Chemical structures of 1, 2, and 3. (b) Schematic illustration of the formation of toroids via the coassembly of 1 or 2 with 3. (c) TEM image of toroidal nanostructures of 1 containing 3 (90 mol % relative to 1) in aqueous solution; the inset is a cryo-TEM image of the toroids. (d) Size distribution graphs of 1 and 1 containing 3. Reprinted with permission from ref 28. Copyright 2009 American Chemical Society.

Consists of only a hydrophilic bulky dendron with a lack of hydrophobic chains. When 1 or 2 was coassembled with 3 in aqueous solution, the average hydrodynamic radius \( R_o \) of both mixed solutions decreased with increasing content of 3 in dynamic light scattering (DLS) experiments (Figure 2d). This indicates a decrease in the size of the aggregates upon the addition of 3.

The transmission electron microscopy (TEM) image in Figure 2c exhibited the formation of highly curved toroids as a result of the coassembly of 1 and 3. The diameter of the toroid exterior and the internal pore were measured to be \( \sim 10 \) and \( 1.5 \)–2 nm, respectively. The cryogenic-TEM image in the inset of Figure 2c also showed dark toroidal objects against the vitrified solution background. These sizes indicate that the highly curved toroids are composed of a single layer of the molecules in which the hepta-p-phenyl rod segments are oriented perpendicularly to the plane of the rings (Figure 2b). Water-soluble toroids with a hydrophobic cavity were formed successfully by the induction of the curvature based on the coassembly of laterally grafted rod amphiphiles.

Self-assembled toroids can also be constructed through the stacking of the macrocycles from bent-shaped aromatic segments. Amphiphiles 4 and 5 have an internal angle of 120° from a meta-linked aromatic segment and an oligoether dendron side group (Figure 3). 29,30 The self-assembly of amphiphile 4 leads to the toroidal nanostructure through the formation of hexameric macrocycles. The negatively stained TEM images revealed a light exterior and a dark interior, indicating that the assembled objects are toroid-shaped nanostructures with internal cavities. The toroidal nanostructures were further confirmed by the cryogenic-TEM image as shown in the inset of Figure 3a. The internal and exterior diameters of the toroids are approximately 3 and 8 nm, respectively, showing a highly uniform toroid size that is consistent with the size distribution of DLS result. Finally, the toroids are composed of stacks of several hexameric macrocycles, resulting in a height of approximately 3 nm.
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Toroidal Nanostructures from Self-Assembly of Synthetic Peptide Building Blocks

Peptides are the major molecular scaffolds of the biological world and are made of the same building blocks as proteins. Because the constituents of peptides and amino acids are biocompatible, nanostructures self-assembled from peptide building blocks have received considerable attention as potential sources of engineered bioactive material. Furthermore, the synthetic peptides can have advantages in terms of diverse primary structures, since the basic 20 natural amino acids and endless non-natural amino acids are available as building blocks. There are excellent papers for channel formation based on the synthetic peptide building blocks.34,35

Self-assembled β-sheet peptides have attracted a great deal of attention in various research areas. The β-sheet fibrils are organized in such a way that each β-strand is arrayed perpendicularly to the fibril axis. Although the β-sheet structure has mostly formed one-dimensional (1D) nanostructures, some toroidal structures can be generated as discrete intermediates during the fibrillization of β-amyloid and α-synuclein.36 Based on these findings, we designed artificial β-sheet peptides that could self-assemble into toroidal nanostructures. The block copolymer 6 has a β-sheet forming peptide-based block as a rigid hydrophobic segment and a sugar and a highly charged poly(L-arginine) block as a hydrophilic segment (Figure 4a).15

The β-sheet forming peptide block is composed of alternatively placed hydrophobic (tryptophan), positively charged (lysine), and negatively charged (glutamic acid) amino acids. It has been demonstrated that many peptides with a potential to form β-sheet nanofibers often transform into higher order aggregates through lateral hydrophobic interactions. Therefore, we conjugated the hydrophilic poly(ethylene glycol) (PEG) with a peptide segment to inhibit further aggregation by increasing the

FIGURE 3. (a) Molecular structure of bent-shaped rod amphiphile 4 and schematic representation of helical stacking of hexameric toroidal macrocycles and negatively stained TEM image. The inset is a cryo-TEM image. Reprinted with permission from ref 29. Copyright 2010 John Wiley and Sons. (b) Molecular structure of bent-shaped rod amphiphile 5 and negatively stained TEM image of 5 from 0.002 wt % in an aqueous solution. The inset is an AFM image on mica. Reprinted with permission from ref 30. Copyright 2012 American Association for the Advancement of Science. (c) Absorption and emission spectra of 4 and 5 in CHCl₃ (solid line) and an aqueous solution (dashed line). (d) The DLS data. 0.002 wt % of 5 in an aqueous solution.
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solubility of the 1D β-sheet structures. Finally, the rationally designed peptide 6 self-assembled into toroidal nanostructures in aqueous solution. As shown in Figure 4b, discrete toroidal nanostructures were found to coexist with β-ribbon nanostructures. The coexistence of toroids and β-ribbons with the uniform sizes 9.8 ± 0.8 nm in width suggests that toroids are likely to form via end-to-end connections of β-ribbons. The FT-IR spectrum showed two bands at 1684 and 1628 cm⁻¹, the characteristics of antiparallel β-sheet conformation (Figure 4c,d). The DLS analysis revealed that the aggregated objects have a 5.8 nm hydrodynamic radius, and this DLS result was consistent with cryo-TEM data (Figure 4e).

Cyclization of diblock peptides can self-assemble into well-defined nanostructures in aqueous solution by decreasing the conformational entropy. An example is provided by the peptide macrocycle 7, which consist of an α-helical peptide segment and a β-sheet forming segment (Figure 5).37 The α-helix-forming segment is based on many alanines and two lysine groups. The lysines are introduced to increase water solubility and to prevent aggregation between α-helix segments. The β-sheet forming segment is a repeat of hydrophobic (tryptophan) and positively (lysine) or negatively (glutamate) charged amino acids as previously mentioned. Oligo(ethylene glycol)-based linker segments are placed between the α-helix- and β-sheet-forming sequences to decouple both segments. The macrocyclization of synthetic peptides as a key feature was designed under the following hypotheses: (1) a macrocyclization of peptide will partially stabilize the α-helical structure by decreasing the conformational entropy of the unfolded state, and (2) coil-to-rod transition in the β-sheet segment induced by self-assembly will further constrain and stabilize the helical structure. As a result of macrocyclization, we could construct both α-helical structure and β-sheet structure on each building block in the aggregates. Interestingly, because the α-helical peptide segment is bulkier than the β-strand segment, we could induce curvature at the interfaces and the macrocyclic peptide finally self-assembled into toroids. As shown in the negatively stained TEM image of Figure 5, the self-assembly of 7 in aqueous solution could form the toroidal nanostructure successfully. Therefore, the macrocyclic design principle can provide a promising starting point for developing the toroidal nanostructure based on artificial synthetic peptide assembly.

Potential of Toroidal Nanostructures for Artificial Transmembrane Channels

Many artificial transmembrane channels have been investigated,38–42 and notable examples are described in
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The synthetic toroids described above are formed in aqueous solution with a hydrophilic exterior. Therefore, one may speculate whether the toroids can function as channels across the hydrophobic lipid membrane environment. However, there are generally two different models, the so-called barrel-stave and toroidal models, for the formation of transmembrane channels based on antimicrobial peptides. Many antimicrobial peptides, which contain an abundant and diverse group of molecules that are produced by many tissues and cell types, induce the formation of an aqueous pore across the membrane bilayer by the barrel-stave pore or toroidal pore models. In the barrel-stave model (Figure 6a), peptide helices form a bundle in the bilayer membrane and their hydrophobic portions are placed in contact with the hydrophobic segment of the lipid bilayer. This type of transmembrane channel is induced by alamethicin. Contrastingly, in the toroidal pore model, the hydrophilic part of peptide channels associate with the hydrophilic head groups of the lipids and cause the lipid monolayers at both sides of the membrane to be connected continuously through the pore (Figure 6b). The pore inducing peptides are amphipathic because the peptides are located at the water–lipid interface in the polar head-groups throughout the channel. Peptides such as magainins, protegrins, melittin, LL-37, and MSI-78 generate this type of transmembrane channel. Based on these models, we predicted that our well-designed toroids with a hydrophilic exterior would be able to function as artificial transmembrane channels by adopting the toroidal model. Indeed, the toroid with hydrophilic exterior functions as proton channels across a lipid bilayer.

The functional toroids can be constructed by self-assembly of rigid–flexible diblock macrocycles. An amphiphilic macrocycle (8), consisting of a hexa-p-phenyl rod and a PEG flexible coil, self-assembles into toroidal nanostructures with a hydrophilic exterior and interior in bulk and aqueous solution (Figure 7). In the aqueous solution, the hexa-p-phenyl rods are aligned axially with their preferred direction, and the interior and exterior are filled by the hydrophilic flexible coil segments. This generates barrel-like supramolecular toroids illustrated in Figure 7c. The average diameter of the toroids was measured to be approximately 7 nm uniformly on the basis of the DLS study and TEM study. The TEM images showed an obvious contrast between the periphery and center of the toroids, which is characteristic of projection images of toroidal nanostructures, and indicated that the diameter of the internal pore was approximately 2 nm (Figure 7b).

The primarily membrane transport activity experiment on 8 was performed with uniformly sized vesicles composed
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of fresh egg-yolk phosphatidylcholine (EYPC) and cholesterol. The vesicles entrapped a pH-sensitive dye, 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS), and the emission of the intravesicular HPTS was monitored after adding the toroidal structures of 8 (Figure 7d). As opposed to the vesicles without 8, those with 8 showed that the increase in pH resulted in a significant increase of fluorescence intensity, thereby indicating that 8 is membrane-active. Therefore, we could suggest that this self-assembled toroid functions as an artificial transmembrane proton channel primarily, and this may be based on the association of hydrophilic PEG coil with the hydrophilic head groups of the lipids by the toroidal pore model.

As previously described, we hypothesized that the induction of curvature between the adjacent building blocks would form toroidal aggregates with a highly curved structure. On the basis of this hypothesis, we designed an organic/peptide hybrid T-shape building block 9 that consists of a β-sheet forming peptide and an oligo(ethylene oxide) dendron (Figure 8a).52 Because the steric repulsion of the bulky and hydrophilic dendron in the middle of the peptides induces curvature at the interface between each building blocks, the T-shape molecules can self-assemble into highly curved toroidal nanostructures (Figure 8b). The toroids showed highly uniform diameters (11 nm exterior and 3 nm interior) as shown in negatively stained TEM images and DLS results. The cryo-TEM image also showed dark toroidal objects against the vitrified solution background, confirming that the toroids have been formed in aqueous solution (Figure 8c). The FT-IR spectrum peaks at 1631 and 1691 cm\(^{-1}\) revealed that the β-sheet structure had an antiparallel conformation (Figure 8d). Finally, all of these data indicated that the toroids have a single layer of T-shapes building blocks, which consists of an antiparallel β-sheet interior and a hydrophilic oligo(ethylene oxide) dendron exterior, and the β-strands in the toroids are oriented perpendicularly to the plane of the toroids.

An additional T-shaped building block, 10, was also prepared for application as a transmembrane channel in the lipid bilayer membranes. Molecule 10 had a hydrophobic flexible chain instead of the hydrophilic oligoether dendron to interact with the hydrophobic space of lipid bilayer membranes, as in barrel-stave model. The relative volume fraction of the flexible hydrophobic dendron of 10 was similar to that of 9 to form the optimal curvature. A circular dichroism (CD) spectrum of peptide 10 in only methanol solution did not show the well-defined secondary structures of peptide (Figure 9a, open circle). However, peptide 10 adopted β-sheet conformation within dioleoylphosphatidylcholine (DOPC) liposomes, showing characteristic peaks of β-sheet such as an intense negative minimum of ellipticity at 216 nm, a strong positive maximum at 197 nm,
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and a crossover point at 203 nm (Figure 9a, closed circle). To investigate the potential as transmembrane channels in the lipid bilayer, we performed a black lipid membrane experiment. A step-change behavior was obtained at an applied voltage of $+40$ mV across the membrane separating 1 M KCl, suggesting strong evidence of a single-ion channel (Figure 9b). The current ($I$)/voltage ($V$) plot in Figure 9c revealed that the ion channel formed by the peptide 10 showed an ohmic behavior, and a single-channel conductance of 263 pS was calculated from the slope for symmetrical 1 M KCl. The Hille equation for the single-channel conductance estimated the inner-channel diameter, $d_{\text{Hille}} \approx 0.5$ nm, which showed contraction compared with inner diameter of toroids from 10. Furthermore, an ion-transport assay with a small unilamellar vesicle (SUV) and pH-sensitive HPTS could suggest that 10 can form the pore in the membrane. When 10 was added at the indicated time point (300 s), the gradual signal of ion transport across the membrane was detected by the increase in relative fluorescence that accompanied the rise in intravesicular pH (Figure 9d). From all of these observations, we could speculate carefully that the toroidal nanostructure is formed from 10 and is incorporated into the lipid membrane, showing the transport activity of ions through its pore. However, because another model such as membrane leakage caused by 10 can be possible to explain its membrane activity, we will confirm the existence of the toroidal nanostructures on the membrane surface in further study.

Conclusions

Nanostructures and nanomaterials have been an interesting research field due to their application potential that ranges from electronic and detection materials to biomaterials. Nanostructures exhibit significantly different properties that depend on their physicochemical parameters, such as size, morphology, and stability. Among the many kinds of nanostructures, toroidal nanostructures have a unique symmetrical and annular shape similar to transmembrane protein shapes such as $\beta$-barrel and $\alpha$-helical bundle. The work
described in this Account suggested that self-assembly of rigid–flexible amphiphiles and synthetic peptide-based amphiphiles can be attractive for generating highly defined toroidal nanostructures. The formation of curvature at the interface of building blocks or the stacking of the macrocycles can become the guiding principles for the construction of toroids. A few toroids showed activity as artificial transmembrane channels in a lipid bilayer through the toroidal model or the barrel–stave model, although the activity study was in the primary stage and should require more detailed research on the mechanism. Ultimately, this study has described a guiding approach to the development of toroidal nanostructures by self-assembly through rationally designed amphiphiles. We believe that the toroidal nanostructure can provide a fundamental understanding for the development of synthetic artificial transmembrane channels.

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ABBREVIATIONS
TEM, transmission electron microscopy; cryo-TEM, cryo-genic transmission electron microscopy; DLS, dynamic light scattering; AFM, atomic force microscopy; PEG, poly(ethylene glycol); EYPC, egg-yolk phosphatidylcholine; PBS, phosphate-buffered saline; HPTS, 8-hydroxypyrene-1,3,6-trisulfonic acid; FT-IR, Fourier transform infrared; CD, circular dichroism; DOPC, dioleoylphosphatidylcholine;

BIOGRAPHICAL INFORMATION
Yongju Kim graduated from Seoul National University, Korea, with B.S. and Ph.D. degrees in chemistry in 2005 and 2012, respectively. His thesis focused on the development and construction of a chemical library for biological functions. In 2012, he joined Prof. Myongssoo Lee’s National Creative Research Initiative Center for Supramolecular Nano-Assembly in a postdoctoral position. Then, he moved to Jilin University and joined Prof. Myongssoo Lee’s group in 2013. His research interests are the synthesis and development of self-assembling molecules based on the synthetic rigid–flexible amphiphiles and peptide molecules to apply to biological systems.

Wen Li was born in 1980 in Inner Mongolia, China. He received his Ph.D. degree (2006) in chemistry from Jilin University, under the supervision of Prof. Lixin Wu. He did postdoctoral research with Prof. Myongssoo Lee at Seoul National University. He is currently an associated professor in Jilin University. His current research interests are the development of self-assembly structures based on clusto-supramolecular complexes and peptide block molecules.

Suyong Shin received her B.S. degree in chemistry from Ewha Womans University, Korea, in 2012 and now is a third semester graduate student pursuing her Ph.D. degree at Seoul National University. Her current research focus lies in the development of stimuli-responsive self-assembling nanostructures by using coordination interaction and supramolecular assembly.

Myongssoo Lee received a bachelor degree in Chemistry from Chungnam National University, Korea, in 1982 and his Ph.D. degree in Macromolecular Science from Case Western Reserve University in 1993. After a short postdoctoral appointment at University of Illinois at Urbana–Champaign, he joined the Faculty of Chemistry at Yonsei University (1994) and Seoul National University (2009), and then moved to Jilin University in 2013, where he is presently "Tang Au-Chin" Distinguished Professor of Chemistry. In 2002, he became a director of National Creative Research Initiative Center for Supramolecular Nano-Assembly. He received the PSK–Willey Polymer Science Award for Young Scientist (2001), Yonsei Academy Award (2003), Scientist Award of This Month, Korea Ministry of Science & Technology (2006), Samsung Polymer Science Award (2008), and KCS Academy Award (2009). His main research interests include self-assembling molecules, controlled supramolecular structures, and peptide assembly.

FOOTNOTES
*Corresponding Author: E-mail: mslee@jlu.edu.cn.
The authors declare no competing financial interest.

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