Natural and bio-inspired underwater adhesives: Current progress and new perspectives

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I. INTRODUCTION

Many marine organisms harness diverse protein molecules as underwater adhesives to achieve strong and robust interfacial adhesion under dynamic and turbulent environments. Natural underwater adhesion phenomena thus provide inspiration for engineering adhesive materials that can perform in water or high-moisture settings for biomedical and industrial applications. Here we review examples of biological adhesives to show the molecular features of natural adhesives and discuss how such knowledge serves as a heuristic guideline for the rational design of bio-inspired underwater adhesives. In view of future bio-inspired research, we propose several potential opportunities, either in improving upon current L-3, 4-dihydroxyphenylalanine-based and coacervates-enabled adhesives with new features or engineering conceptually new types of adhesives that recapitulate important characteristics of biological adhesives. We underline the importance of viewing natural adhesives as dynamic materials, which owe their outstanding performance to the cellular coordination of protein expression, delivery, deposition, assembly, and curing of corresponding components with spatiotemporal control. We envision that the emerging synthetic biology techniques will provide great opportunities for advancing both fundamental and application aspects of underwater adhesives. © 2017 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). https://doi.org/10.1063/1.4985756

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to species and possess their own unique characteristics, but sometimes they do share some common features.

In this review, we briefly summarize recent progress in the molecular mechanisms of underwater adhesion associated with four different organisms: mussels, sandcastle worms, caddisfly larvae, and barnacles. We then discuss how the underlying molecular features of natural adhesives have served as blueprints for the rational design of underwater adhesive materials based on biologically inspired or biomimetic strategies. Current bio-inspired designs are mainly based upon L-3, 4-dihydroxyphenylalanine (Dopa)-based and coacervates-enabled adhesives, inspired by the widespread presence of Dopa residues and the increasingly appreciated coacervate structures in the adhesive components of different marine species. These advances have greatly promoted the development of advanced adhesive techniques and expanded the application range of conventional adhesives. In addition, these bio-inspired designs have also served as testbeds to assess the hypothesized mechanisms of underwater adhesion in biological organisms and have enhanced our understanding of the design principles in biological adhesion.

In view of possible pathways towards constructing optimized or improved underwater adhesives, we propose that several important but ignored aspects should be strengthened in future bio-inspired research. These new opportunities would include but not limited to improving upon current Dopa-based and coacervates-enabled adhesives with new features or engineering conceptually new types of adhesives that recapitulate important characteristics of biological adhesives.

II. NATURAL UNDERWATER ADHESIVES

A. The underwater adhesives in mussels

Mussels are well known for its remarkable ability to attach their byssus to diverse substrates even in humid, alkaline, and high ionic strength environment. The adhesive plaque of mussels contains at least 20 different proteins, referred to as mussel foot proteins (Mfps) in the field (Fig. 1). Regarding how these adhesive proteins of different regions in the byssal plaque contribute to underwater adhesion, readers are encouraged to refer to several excellent review papers. Here, we mainly focus on the molecular features of adhesive proteins that are believed to be directly associated with interfacial underwater adhesion of mussels.

Among all these proteins, Mfp-3/5 located at the plaque-substrate interface are key proteins that contribute to the interfacial adhesion to various substrates (Fig. 1). These two proteins, random coil structures in solution, are both rich in Dopa residues, post-translationally hydroxylated tyrosine (Table I). Dopa has been considered as the key residue that contributes to byssus adhesion by...
TABLE I. Major adhesive proteins in the adhesion plaque of *Mytilus* byssus.

| Protein species | Mass (kDa) | Dopa (mol. %) | Amino acid sequence\(^a\) | Major Functions |
|-----------------|------------|---------------|--------------------------|----------------|
| Mfp-3 \((M.\ edulis)\) | 6          | 20            | ADYYGPNYGPpR8YGGN      | Interfacial adhesion |
|                 |            |               | YNRYNFyGRRYGGYKGW      |                 |
|                 |            |               | NNGWNRRGRRGYW          |                 |
|                 |            |               | SSEEYKGGYYPGNAYHYs     |                 |
|                 |            |               | GGSYHGSGYHGGYKGY      |                 |
|                 |            |               | YGKAKKYYKYKNsGY       | Interfacial adhesion |
|                 |            |               | KYLKKARKYHRKGYYY       |                 |
|                 |            |               | GGSS                    |                 |
| Mfp-5 \((M.\ edulis)\) | 9          | 28            | GGNYRGYCSNKCRSG        | Interfacial adhesion |
|                 |            |               | YIFYDRGFCKYGGSSYK      |                 |
|                 |            |               | YDCGNYACLPRNPYGRV      |                 |
|                 |            |               | KYCTKKS3CPDFYYYN       |                 |
|                 |            |               | NKGYYYYNDKDYGCFNC      |                 |
|                 |            |               | GSYNGCGLRSGY           |                 |
| Mfp-6 \((M.\ Californianus)\) | 11         | 3             | GGNYRGYCSNKCRSG        | Cross-linking, anti-oxidation |
|                 |            |               | YIFYDRGFCKYGGSSYK      |                 |
|                 |            |               | YDCGNYACLPRNPYGRV      |                 |
|                 |            |               | KYCTKKS3CPDFYYYN       |                 |
|                 |            |               | NKGYYYYNDKDYGCFNC      |                 |
|                 |            |               | GSYNGCGLRSGY           |                 |

\(^a\)Symbols for standard amino acids follow convention. Post-translational modifications: Dopa (Y) and 4-hydroxyarginine (R) in Mfp-3, Dopa (Y) and O-phosphoserine (S) in Mfp-5, and [S-S] in Mfp-6 denoting crosslinked Cysteine (C) are highlighted. Regenerated with permission from Lee *et al.*, *Annu. Rev. Mater. Res.* \textbf{41}, 99 (2011). Copyright 2011 Annual Reviews.

forming bidentate hydrogen bonds with surfaces.\(^12\) In addition, Dopa residues may undergo cross-linking either through auto-oxidation of Dopa to dopaquinone or in the presence of catechol oxidase.\(^8\) High Dopa content in Mfp-3 (20 mol. %) and Mfp-5 (28 mol. %) therefore ensures protein adhesion on the surface and provides cohesion in the plaque. In addition, protein-protein interactions among adhesive proteins may lead to improved cohesion.\(^13\)

Dopa residues are susceptible to be oxidized to dopaquinone in alkaline seawater, leading to decreased interfacial adhesion.\(^14\) Facing such challenge, mussel secretes another important protein, Mfp-6, in the byssal plaque. Mfp-6 contains a couple of cysteine residues and can rescue adhesion of Mfp-3/5 by reducing dopaquinone back to Dopa coupling the oxidation of thiols.\(^15,16\) In addition, the high proportion of hydrophobic residues in Mfp-3/5 provides a microenvironment to shield Dopa from oxidation and results in hydrophobic interactions that may enhance Dopa wet-adhesion on the substrate.\(^17\)

Besides the conversion of tyrosine to Dopa in Mfp-3/5, a significant number of serine residues in Mfp-5 are also phosphorylated (Table I).\(^18\) Phosphoserine occurs in sequences strikingly reminiscent of acidic mineral-binding motifs that appear in statherin, osteopontin, and others. Given the binding affinity phosphoproteins have for calcareous materials, it may provide an ideal adhesive adaptation to enhance the byssal adhesive repertory for calcareous surfaces.

Mussel foot proteins can adaptively bind to different substrates through synergistic roles of diverse protein residues. Forces that possibly participate in the adhesion between Mfps and substrates of different surface chemistries include electrostatic interactions, hydrogen bonds, hydrophobic interactions, cation–π interactions, π–π stacking, and metal-coordination.\(^6\) For example, hydrophobic residues in Mfps can help clear up the hydration layers on a substrate\(^11\) and directly form strong hydrophobic interactions with the surface.\(^9,19\) The hydrophobic force, along with Dopa hydrogen bonds, also enhances the adhesion of Mfps. In addition, positively charged residues, such as lysine and arginine, can help remove the layer of salt on the surfaces and significantly facilitate the binding of Dopa to the surfaces.\(^20,21\) Last but not least, the “one-two punch” synergy between adjacent Dopa and cationic residues would also promote adhesion in aqueous solution through the formation of hydrogen bond and coordination bond.\(^22\)

The important roles of Dopa in mussel adhesion have been greatly appreciated, but little has been known about the roles of other residues, particularly those post-translationally modified residues such as phosphoserine and 4-hydroxyarginine other than Dopa. Beyond their specific contribution to adhesion, such molecular residues may coordinate with Dopa to enhance catechol-mediated adhesion.
This important but easily neglected aspect should be taken into account in evaluating the specific roles of other residues in underwater adhesion in the future. Undoubtedly, understanding the roles of post-translationally modified amino acids necessarily requires knowledge about the protein sequences and enzymatic activities of their corresponding enzymes. Unfortunately, such enzymatic information remains poorly understood.

Perhaps another important but less well-studied aspect would be related to how mussel foot proteins interact and how those specific interactions synergistically contribute to underwater adhesion. The diverse protein interactions include the intramolecular and intermolecular interactions of specific adhesive proteins, the intermolecular interactions among different interfacial proteins, and those between interfacial adhesive proteins and proteins with special roles such as Mfp-6 and Mfp-2. Certain molecular interactions, for example, those between Mfp-6 and Mfp-3, had been initially studied, and corresponding molecular mechanism and their potential roles in adhesion were proposed. However, information about most of those diverse interactions still remains unclear and requires further investigation in future research. Importantly, the assessment of diverse protein interactions should be closely correlated with their specific microenvironment conditions (such as pH) and their temporal sequence in which different adhesive proteins are deposited on substrates. Knowledge about the diverse molecular interactions among adhesive molecules would be useful for advancing a more comprehensive and deeper view of the molecular mechanism of mussel underwater adhesion.

B. Coacervate-enabled adhesives in marine organisms

Sandcastle worms are another type of sessile creature in the ocean that can harness underwater adhesive proteins for their own benefits (Fig. 2). They build tubular shells by gluing together sand grains and mineral particles, with a multipart, rapid-set, self-initiating adhesive. The adhesive is composed of oppositely charged polyelectrolytic components. Among all the proteins identified, they can be classified into two types of proteins: the positively and negatively charged proteins. For example, Pc-3B is a representative of the negatively charged proteins that usually contains a significant amount of phosphoserine residues. The positively charged proteins such as Pc-2 and Pc-5 are often rich in both lysine and histidine residues. Both types of proteins contain a significant amount of Dopa residues resembling that of adhesive proteins in mussels. The oppositely charged macromolecules are always distributed in unique pairs between two types of secretory granules. Pc-2 and Pc-5 are located in the homogeneous granules along with sulfated polysaccharide. Polycations including Pc-1 and Pc-4 are located only in the heterogeneous granules along with polyanionic Pc-3A, Pc-3B, and Mg$^{2+}$ ions.

FIG. 2. (a) Sandcastle worms (Phragmatopoma californica), living along the west coast of North America, are well known for their ability of building tubular shells by gluing grains of sand and other mineral particles together using the adhesive glues that they produce. (b) The secreted sandcastle glue binds glass beads together. Adapted with permission from R. J. Stewart, C. S. Wang, and H. Shao, Adv. Colloid Interface Sci. 167(1), 85 (2011). Copyright 2011 Elsevier.
The adhesive’s high charge density, segregation of the opposite charges into separate molecules, and balanced charge ratio at physiological pH highly suggest a role of coacervation in underwater adhesion by sandcastle worms, even though the complex coacervates might be a transient state during the formation of the sandcastle glue. Coacervation is defined as a liquid-liquid phase separation driven by electrostatic force, arising from the association of oppositely charged macro-ions. The coacervates often exist as spherical aggregates of colloidal droplets embraced by hydrophobic forces or ionic strength. The coacervates, divalent cations (such as Mg$^{2+}$ and Ca$^{2+}$), and Dopa residues, along with the universal adhesion promoter phosphates, are believed to synergistically contribute to the strong underwater adhesion of sandcastle worms.

Coacervate structures may play a more widespread role in the underwater adhesion of marine organisms. For example, coacervates are likely associated with the underwater adhesion of the silk-like fibers secreted by caddisfly larvae (Fig. 3). Using energy dispersive X-ray spectroscopy and the tandem mass spectrometry, Stewart et al. discovered that around 60% of the 15 mol. % of serine in the adhesive silk was phosphorylated. The caddisfly larvae glue has a balanced ratio of positive to negative charges, similar to that of sandcastle worms. But the oppositely charged residues in the caddisfly larvae glue are distributed in alternating patches on one macromolecule rather segregated into different proteins.

Dopa-containing Mfp-3S has recently been identified as the first known naturally occurring self-coacervating adhesive protein in the mussel. The Mfp-3S coacervate was reported to have an effective interfacial energy of $\leq 1$ mJ m$^{-2}$ and therefore could quickly spread on surfaces and penetrate into cracks because of their low surface tension with water. In addition, owing to their concentrated nature arising from liquid-liquid phase separation, coacervate structures could be easily delivered to a target place without dismissing, an intrinsic advantage of acting as underwater adhesives.

Although coacervate structures have been commonly found associated with underwater adhesion of several marine organisms, detailed information regarding how those coacervates undergo phase transitions and spontaneously solidify at the interfaces remains poorly understood. For example, previous observations suggested that the pre-organized adhesive modules stored in independent granules were secreted separately and intact in the case of sandcastle worms but rapidly fused with minimal mixing and expanded into a crack-penetrating complex fluid. Within 30 s of secretion into seawater, the fluid adhesive turned into a porous solid adhesive joint. There are many interesting yet unresolved questions about the phase transition of coacervates in sandcastle worms. For example, what are the driving forces that result in the fast rupture of the granules and what are the underlying chemistries during the rapid solidification of the coacervates? The latter is closely correlated to the enzyme activities of catechol oxidase, which is co-packaged with adhesive molecules inside the granules even before secretion of the granules. This would connect with another interesting and relevant question: what are the molecular mechanisms that biology has harnessed to inhibit the enzymatic activities before granule secretion and spontaneously activate the function of enzymes right

FIG. 3. (a) Caddisfly larva constructs their “home” by holding the glass beads together with their secreted glues in water. (b) SEM showing caddisfly silk adhered to glass case. Caddisfly silk can combine the glass case together through adhesion. Adapted with permission from R. J. Stewart, T. C. Ransom, and V. Hlady, J. Polym. Sci., Part B: Polym. Phys. 49(11), 757 (2011). Copyright 2011 Wiley Periodicals, Inc.
after secretion? Therefore, additional characterization of the environmentally triggered setting mechanisms and multiphasic structures of the sandcastle glue will be highly needed to reveal additional insights into the design and manufacture of novel underwater setting nano- and micro-structured adhesives.

In the case of caddisfly larvae, complex coacervation is believed to play a role for silk fiber formation as well as their wet adhesion properties owing to the striking similarities to the sandcastle glue with regard to the high density and the balanced ratio of positive to negative charges. The detailed knowledge of the underwater adhesion of caddisfly silk, particularly how the coacervate structures contribute to both interfacial adhesion and their strong mechanical properties, is still lacking. Another important and interesting aspect is relevant to potential cross-linking strategies in the caddisfly silk proteins: as silk proteins do not contain any Dopa or cysteine residues that typically involve cross-linking for enhanced cohesion, would any other cross-linking strategy be harnessed in caddisfly adhesion? If no cross-linking reactions occur, how do the silk proteins achieve sufficient cohesion? Answering these questions will provide new insights into coacervate-enabled underwater adhesion in marine organisms.

C. The unique underwater adhesives in barnacle

Barnacles are perhaps the only sessile crustacean that permanently attach to various foreign surfaces during most of their lifespan. Once they attach to an object that is kept still or floating on the ocean surface, they spend their rest lifetime on the substance. Essentially, they utilize adhesive functional complexes, referred to as the barnacle cement, to accomplish such permanent attachment.

The cement combines the adult body with the calcareous shell on the top and also attaches the shell and the body onto the substrate (Fig. 4). More than 90% of the cement is proteins. The cement comprises several proteins that can be classified into three types: hydrophobic proteins (cp100k and cp52k); charged proteins with hydrophilic feature (cp20k); hydrophilic proteins rich in Ser, Thr, Gly, Ala, Val, and Lys residues (cp19k and cp68k). cp100k, cp52k, and cp68k constitute the major components of barnacle cement. The cp100K and cp52k proteins are essential for the insoluble property of the cement. Bearing a low content of Cys residue, they are thought to tie up with other cement proteins to form the cross-linking framework and provide cohesion for the barnacle body. cp19k, cp20k, and cp68k serve as surface adhesive proteins, playing the role of interfacial adhesion in a way that Mfp-3 and Mfp-5 do in mussels. While cp20k is more related to the adherence with the calcareous shell, cp19k is mainly found to adhere onto a foreign substratum.

The complicated intermolecular interactions among the same or different types of proteins that contribute to the surface adhesion and bulk cohesion of barnacle cement remain largely undetermined. However, one distinct feature of these adhesive cement proteins is that, compared

![Fig. 4. Schematic showing the cross sections of the barnacle cement and various possible factors that involved in barnacle adhesion. (a) The spatial arrangement of functional proteins involved in the cement adhesion. (b) The adhesive capacity of the cement is affected by several factors including surface morphology, surface roughness, surface free energy, and the surrounding environment. Adapted with permission from K. Kamino, Biofouling 29(6), 735 (2013). Copyright 2013 Taylor & Francis Group.](image)
with the adhesive proteins in mussels and tube worms, they involve no post-translational modifications (apart from the N-terminal-glycosylation of cp52k) and do not contain any Dopa residues. These observations suggest an apparently different mechanism in underwater adhesion by barnacles.

When observed under atomic force microscopy (AFM), the nanoscale structures of the barnacle (*Balanus amphitrite*) cement exhibited rod-shaped, globular and irregularly shaped morphologies. The rod-shaped structures could be stained with amyloid protein-selective dyes (Congo red and thioflavin-T). About 5% of the bulk cement was amyloid or amyloid-like proteins. Kamino et al. recently revealed that cp100k indeed possessed an amyloid \(\beta\)-sheet structure. In addition, certain peptide segments of the cp52k protein were found to be able to self-assemble into amyloid nanofibers in aqueous solutions. These observations thus suggested that amyloid structures were part of the components that might play key roles in the formation of the barnacle cement. Interestingly, some researchers even considered the solidification of barnacle glues as a specialized form of wound healing, in which protein aggregation and cross-linking into fibrils was similar to the processes of blood clotting.

Barnacle cement is a multi-protein complex with multifunctionalities. Although information about the gene and protein sequences has been decoded, the physicochemical properties, self-assembly, and the structure-functionality relationship of individual proteins have not been fully assessed. In addition, further analysis of the multi-protein complex in terms of the complicated intra- and intermolecular interactions as well as the underlying molecular mechanisms leading to the self-assembled structures has been lacking. Future studies to unlock the information would provide new insights into the specific roles of individual components in adhesion as well as how different components synergistically contribute to underwater adhesion.

In addition to barnacles, many other organisms including algal cells, marine flatworms, and bacterial biofilms seem to utilize amyloid structures to achieve interfacial adhesion in water settings. It is likely that amyloid structures might serve as more common building blocks for underwater adhesives in nature than currently appreciated. Nanofibers have high aspect ratios and large surface areas, features that are likely to enable stronger adhesive strengths. In addition, the outstanding mechanical properties as well as their ultra-stability even under extreme conditions make them ideal building blocks of robust adhesives that can tolerate various harsh environmental conditions. The molecular features and self-assembly of those amyloid-like proteins relevant to adhesion phenomena are therefore worthy of further investigation.

### D. Spatiotemporally controlled processing of adhesive molecules for efficient underwater adhesion

One important but ignored aspect about underwater adhesion is the dynamic government of the expression, delivery, deposition, assembly as well as curing of the different adhesive components in a spatiotemporally controlled manner. Such dynamic processes necessarily involve complex mechanisms that are coordinated or regulated by special cells. Although little has been known about the mechanisms, information regarding how marine organisms govern such processing details would provide inspiration for advancing new underwater adhesives.

The recent work by the Miserez group may provide new clues in the context of how marine organisms ensure efficient underwater adhesion by sequential secretion of adhesive molecules of different features in a temporally controlled manner. Using Asian green mussel as a model system, the Miserez group assessed the temporal sequence of different adhesive proteins that were deposited on substrates (Fig. 5). The groove located at the Asian green mussel secreted adhesive proteins including Pvfp-3, -5, and -6. During the course of the plaque deposition, Pvfp-5 was the first protein to be placed. Pvfp-3 was subsequently secreted in addition to Pvfp-5, followed by the deposition of Pvfp-6 in the final step. Underwater adhesion typically involves the displacement of surrounding surface water on the surfaces before attachment. The sequential secretion of adhesive proteins thus may help divide this complicated process into several simple steps. Pvfp-5 might serve to displace surface bound water from the substrate. Such hypothesis was supported by the modeled structures, showing that all Dopa/Tyr residues in Pvfp-5 were strategically distributed on the periphery of the elongated protein. In addition, displacement of surface water might
FIG. 5. Time-regulated secretion of adhesive proteins of different features contributes to Asian green mussel underwater adhesion. Sequential secretion of the three adhesive proteins (Pvfp-3, -5, and -6) in the plaque is temporally controlled by the organism. During the course of the plaque deposition, Pvfp-5 is the first protein to be placed. Pvfp-3 is subsequently secreted in addition to Pvfp-5, followed by the deposition of Pvfp-6 in the last step. Adapted with permission from Petrone et al., Nat. Commun. 6, 8737 (2015). Copyright 2015 Nature Publishing Group.

even be enhanced by the close proximity of multiple Dopa-Lys pairs within Pvfp-5. The Cys-rich protein Pvfp-3 might play important roles in protecting Dopa residues of Pvfp-5 from oxidation through the formation of cysteinyl–Dopa bonds and disulphide bridges within the adhesive plaque. In addition, Pvfp-3 might serve as the first functional layer for the attachment of Pvfp-6 and other proteins.

In another study, Harrington and co-authors investigated mussel byssus dynamic assembly using a synergistic combination of histological staining and confocal Raman microspectroscopy. Using this combined approach, they could carry out in situ tracking of specific proteins during induced thread formation from soluble precursors to solid fibers in Mytilus edulis. They found that byssus assembly involved both biologically non-regulated and regulated steps. While spontaneous self-assembly of complex micro- and nano-scale biomolecular architectures from specific protein building proteins was not directly controlled by the organisms, the subsequent thread maturation including cross-linking and macroscale molecular alignment was strictly governed by biologically regulated steps. The complementary roles and interactions of physically driven versus biologically controlled processing steps might be critical in such natural material fabrication. Applying Raman mapping of the plaque, the authors further revealed that the core and plaque vesicles did not mix as they coalesce, suggesting that they were stored in densely packed phases of different features (for example, liquid crystal and coacervate, respectively). In addition, the vesicle-bound proteins comprising the plaque
could self-assemble into a complex foamy architecture without metal coordination, implying that metals might participate in a later finishing step. As the authors pointed out, these findings would provide new guidance towards the development of advanced materials with biomedical and industrial relevance, for example, injectable, self-assembling soft matter scaffolds for tissue repair or drug delivery.

In addition to the cell-regulated mechanisms in governing various molecular processing details, other intriguing and important aspects about marine underwater adhesion are how organisms store the adhesive precursors of different features and how they prevent those molecules from premature hardening before they are eventually extruded and cured. For the sandcastle worm, pH may play a critical role in the glue setting. When the glue is still in its granules, the granule’s low pH keeps the coacervated solution with low viscosity and low interfacial tension. These features enable the glue to easily spread on the target surface in the sea. When this mixture is exposed to a higher sea water pH, the solution can be spontaneously hardened to adhesion.\(^42\) It would be interesting to probe the molecular features of these adhesive molecules and assess how such features allow the molecules to adapt or respond to different environmental pHs to fulfill the bonding as desired.

In the case of the barnacle glue, multiple proteins are produced by a single cell type and packed in cytoplasmic secretory granules.\(^43,44\) During the secretion process, there was no obvious physical separation of glue components besides the granule formation. After they are released from the gland cell cytoplasm, the adhesive complexes seem to have no interaction with the granular membranes.\(^45\) The glue is secreted as a liquid with low viscosity before it solidifies to form a rubbery mass and then hardens to become “cement.” Transport of the adhesive components begins at the intracellular canals, followed by transportation through the extracellular canals before finally reaching the substratum. In stark contrast to the diverse glue components produced by one single cell type in barnacle, the adhesive glands of tubeworms consist of multiple secretory cell types and morphologically distinct secretory granules, which remain physically separated until extruded from the body.\(^46\) Although much remains unknown, knowledge in these aspects will certainly provide new clues for engineering underwater adhesives with better performance towards practical applications, for example, adhesives with easiness for storage and quickness for hardening.

### III. BIO-INSPIRED DESIGN OF UNDERWATER ADHESIVES

The widespread observations that natural underwater adhesives are rich in diverse protein molecules has opened up many great opportunities in the design of bio-inspired or biomimetic adhesives using natural adhesives as design blueprints. The ultimate goal of bio-inspired design along this line is to address the significant limitations of traditional adhesives that usually compromise their adhesion performance under water or moisture settings. Although most of the synthetic adhesives developed thus far have not gained immediate translational applications in biomedical and industrial fields, they indeed have significantly enhanced our understanding of the underlying mechanisms of marine adhesion. Current research in this area can be summarized into two types of design: Dopa-based and coacervate-enabled adhesives, inspired by the widespread presence of Dopa residues and the increasingly appreciated coacervate structures in the diverse adhesive components of different marine species. The research activities directly reflect our current level in understanding natural underwater adhesion and applying existing knowledge about biological molecular adhesion. For example, as the “key” molecular features that contribute to barnacle adhesion remain illusive, it is not surprising that very few initiatives have been focused on creating self-assembling complex adhesives inspired by the barnacle cement. This is in sharp contrast with a large number of research devoted to developing Dopa-based adhesives inspired by mussel foot adhesion.

Future bio-inspired research not only relies on deeper knowledge of marine underwater adhesion but also requires more comprehensive learning of nature building upon existing knowledge. We propose several potential aspects that should be strengthened in future bio-inspired research. These research opportunities include but not limited to improving upon current Dopa-based and coacervate-enabled adhesives or engineering conceptually new types of adhesives that recapitulate important characteristics of biological adhesives.
A. Dopa-inspired design

The versatility of Dopa in natural underwater interfacial adhesion phenomena has promoted a wide range of biomimetic research efforts focused on Dopa-containing or Dopa analogue-containing peptides, polymer constructs, and recombinant Mfp variants. For example, the Messersmith research group had developed adhesive hydrogels based on the cross-linking of catechol with tetra-functional branched and linear poly (ethylene glycol) (PEG) upon the addition of an oxidation agent. The mussel-mimetic PEG hydrogel, exhibiting efficient tissue adhesion and provoking minimal inflammatory response, was promising for extended surgical and biomedical applications. These hydrogel materials could be implemented as surface coatings for antifouling, anti-bacteria purposes or for tissue engineering. Similarly, the Wilker group had designed a series of catechol-containing copolymers, with tunable catechol content and molecular weight. Among those, the adhesive polymer poly [(3,4-dihydroxystyrene)-co-styrene] achieved optimal adhesion performance, using commercial glues as well as natural proteins secreted by mussels as a benchmark. After cross-linking either in the presence of metal ions or upon oxidation, the adhesive polymer exhibited stronger adhesion. With good cytocompatibility, the polymer had been applied for biomedical applications. Other copolymers such as poly [(3,4-dihydroxymandelic acid)-co-(lactic acid)] containing catechol residues had been used as degradable adhesives to replace traditional permanent adhesives in certain circumstances.

Informed by the richness of both catechol and lysine residues in the mussel adhesive proteins, the Messersmith research group developed a simple analogue, polydopamine (pDA). In basic environment, dopamine could rapidly polymerize to form pDA coatings that adhere to a wide range of inorganics, organics, and even “non-sticky” substrates such as polytetrafluoroethylene (PTFE) (Fig. 6). pDA could act as a “primer” to trigger metal or organic deposition for surface modification and

![FIG. 6. (a) Molecular structure of dopamine. (b) Schematic showing deposition of pDA thin films on an object through a dip-coating process in dopamine solution. Polydopamine coatings applied for electrowless metallization: copper deposition on polydopamine-coated nitrocellulose film (c), coin (d), and three-dimensional plastic object (e). (f) Schematic showing the one-step assembly of coordination complexes on various substrates by mixing Fe$^{3+}$ and tannic acid (TA). Deposition of Fe$^{3+}$-TA coatings on polystyrene (PS) substrates of different shapes across multiple length scales: PS planar before (top) and after (bottom) coating deposition (g); differential interference contrast (DIC) microscopy image (h) and transmission electron microscopy (TEM) image (i) of the formed spherical Fe$^{3+}$-TA capsules in uniform size using PS spheres as templates; DIC microscopy image (j) and TEM image (k) of ellipsoidal Fe$^{3+}$-TA capsules. Reprinted with permission from Lee et al., Science 318(5849), 426 (2007). Copyright 2007 American Association for the Advancement of Science; Ejima et al., Science 341(6142), 154 (2013). Copyright 2013 American Association for the Advancement of Science.]
had been utilized for electroless metallization on various surfaces [Figs. 6(c)–6(e)]. In addition, it could conjugate with a wide range of biomacromolecules, such as bone morphogenetic protein 2 (BMP2) and enzymes. The functional pDA coatings had been applied in a wide range of areas, such as cell adhesion, tissue regeneration, silicification, anti-bacterial, encapsulation of yeast cells, and surface-initiated atom transfer radical polymerization (SI-ATRP). However, one of the limitations of the pDA coatings is their susceptibility to mechanical abrasion due to poor material robustness.

In addition to the pDA molecules, natural polyphenols had also been harnessed as building blocks for film and particle engineering. Using coordination complexes of natural polyphenols and Fe (III) ions, the Caruso group recently developed a facile and diverse strategy for the thin-film coating technique [Fig. 6(f)]. Metal-polyphenol films could conformally coat substrates of different composition, size, shape, and structure [Figs. 6(g)–6(k)]. The easy preparation of the metal-polyphenol films as well as their tunable physicochemical properties presented a new platform for engineering the assembly of advanced materials, biological interfaces, and superstructures for a wide range of applications.

Inspired by the “one-two punch” synergistic interplay between abundant catecholic Dopa and lysine residues in adhesive foot proteins, Maier et al. proposed a new platform to explore molecular synergies in bioadhesion, based on Cyclic Trichrysobactin (CTC), a natural bacterial catechol siderophore, and Tren-Lys-Cam (TLC) molecule, a synthetic analog of CTC (Fig. 7). These siderophores and synthetic analogs exhibited robust adhesion energies \( E_{\text{ad}} \geq 15 \text{ mJ/m}^2 \) to mica in saline pH 3.5–7.5. Moreover, 2,3-dihydroxy catechol (2,3-DHBA) in the molecules showed better oxidation resistance compared with Dopa. The discovery that 2,3-dihydroxy catechol and alkyl ammonium (e.g., Lys and Dab) functionalities resist oxidation and promote adhesion suggests a new design principle for future bio-inspired synthetic polymers.

In addition to the chemical approaches towards biomimetic underwater adhesives, recombinant protein techniques have also been used to develop underwater adhesives. The resultant recombinant adhesive proteins usually contain either the full length adhesive protein molecules or segmented adhesive protein domains that are directly associated with marine organisms. The modular genetic strategy allows for the incorporation of extra functional groups or domains into the protein molecules, aiming to reduce the cytotoxicity of the molecules to the host and/or introduce new functionalities into the adhesive proteins. For example, to increase the expression level in a heterologous host *Escherichia coli* (*E. coli*), the Cha group designed recombinant fp-131/151 proteins based on Mfp-1, Mfp-3, and Mfp-5 proteins. With the *in vitro* modification of tyrosine to Dopa catalyzed by tyrosinase, the designed proteins showed a considerable level of adhesive strength even compared with the original Mfp-3/5. In addition, the same group constructed artificial extracellular matrix (ECM) mimics based on recombinant adhesive protein fp-151 by rational fusion of biofunctional components originating from ECM materials, including fibronectin, laminin, and collagen. These ECM mimics showed superior cellular attachment, proliferation, and differentiation. In addition, those fp-151 proteins had been applied as a blending partner to prepare sticky nanofiber networks fabricated through electrospinning. The nanofibrous scaffolds incorporated with fp-151 could serve as a new multifunctional platform for surface decoration of various biomolecules including carbohydrates, proteins, and DNA molecules.

Zhong et al. leveraged a modular genetic strategy to develop functional amyloid adhesives based on the rational integration of amyloid protein CsgA, the major protein component of *E. coli* biofilm, with Mfp-3/5, major interfacial adhesive proteins from mussels [Fig. 8(a)]. Molecular dynamic modeling showed that the Mfp-3/5 domains either in the monomer or fibril structure were random coil structures exposed on the exterior of CsgA amyloid cores [Fig. 8(c)]. The mixture of the two proteins at different monomer ratios led to hierarchically co-assembled fibrous bundles. The copolymer fibers displayed the highest underwater adhesion among the protein-based underwater adhesives reported thus far [Fig. 8(d)]. In addition, the fibrous structures also showed enhanced tolerance to oxidation compared with Mfp-3/5.

To achieve strong underwater adhesion, it is important that tyrosine residues in the rationally designed proteins are purposely converted to Dopa residues by tyrosinase. Conventional approaches for enzymatic modification with tyrosinase are often carried out *in vitro* after protein purification,
resulting in low yield or heterogeneous distribution of modified residues along the molecules. An alternative approach is based on in vivo site-specific incorporation of non-standard amino acids (NSAAs). Cha et al. reported an in vivo technique that relied on Dopa competitively binding endogenous tyrosyl-tRNA synthetase and allowed for the incorporation of a significant amount of Dopa residues into adhesive proteins.\textsuperscript{68} The resultant adhesive proteins, with over 90% of the tyrosine residues replaced with Dopa, exhibited superior surface adhesion in water. This approach therefore provided a practical way to incorporate Dopa into adhesive proteins in de novo design engineering. The technique however has several limitations such as low protein yield and the difficulty in simultaneous incorporation of multiple post-translationally modified amino acids (such as phosphoserine and Dopa) into the molecules.

The recent development of genetically modified hosts and cell-free expression techniques may provide alternatives to solve the above technical bottlenecks. For example, the Church group recently had utilized engineered E. coli as a genomically recoded organism (GRO) to accommodate the incorporation of NSAAs. They developed a customizable system for large-scale design and assembly of synthetic organisms.\textsuperscript{69,70} This approach mainly depends on the heterogeneous pairs of aminoacyl-tRNA-synthetases (aaRS) and tRNAs that enable the co-translational incorporation of non-canonical amino acids in a host organism.\textsuperscript{71} In parallel, a cell-free protein expression system had been used to

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FIG. 7. (a) Structure of Cyclic Trichrysobactin (CTC), a natural bacterial catechol siderophore. (b) Structures of catechols showing the difference between 3,4-dihydroxyl catechol (Dopa or 4-methylcatechol) and 2,3-dihydroxycatechol, which is commonly present in tris-2,3-dihydroxybenzoyl (DHBA) containing siderophores. (c) SFA force-distance interaction for CTC-mediated adhesion between two mica surfaces in buffer (50 mM phosphate buffer + 150 mM KNO\textsubscript{3}) at pH 6.7. (d) Structure of Tren-Lys-Cam (TLC), a synthetic analog of the natural siderophore CTC. (e) SFA force-distance interaction for the TLC-mediated adhesion between two mica surfaces in buffer (50 mM acetate buffer + 150 mM KNO\textsubscript{3}) at pH 3.3. The open and solid circles are for data measured on approach and separation, respectively, of the mica surfaces. The inset images showing the interacting surfaces throughout the SFA experiments. Reprinted with permission from Maier et al., Science \textbf{349}(6248), 628 (2015). Copyright 2014 American Association for the Advancement of Science.
allow the incorporation of NSAA s in multiple sites with high yield. These promising techniques can be leveraged in advancing fundamental understanding and technical applications of Dopa-based underwater adhesives in the future.

B. Coacervate-inspired molecular design

In parallel to the development of Dopa-based biomimetic adhesives, recent research efforts have also been directed towards engineering underwater adhesives inspired by the coacervate structures involved in biological adhesion. For example, Stewart et al. have designed polyacrylate glue containing phosphate, primary amine, and catechol side chains, with molar ratios similar to their natural counterparts. Fluid mixtures of the polyelectrolytes can concentrate into liquid complex coacervates under a neutral pH value. The adhesive material was applied to glue wet cortical bone specimens, showing that the bond strength was around 40% of the commercial cyanoacrylate adhesives. Similarly, Cha et al. demonstrated complex coacervates by combining recombinant mussel adhesive proteins, fp-151 or fp-131, with hyaluronic acid (HA). They showed that the bulk adhesion strength of the coacervate phases based on Mfp-151/HA and Mfp-131/HA were much stronger than the sole Mfps.

Waite and co-authors have recently developed a new molecular design approach towards coacervate-enabled adhesives. The adhesives were based on versatile microporous structures formed by polyelectrolyte complexation via solvent exchange (Fig. 9). Specifically, they pre-mixed catechol-containing poly (acrylic acid) with a quaternized chitosan (QCS), ion-paired with bis(trifluoromethane-sulfonyl)imide (Tf₂N) in dimethyl sulfoxide (DMSO). The water–DMSO
solvent exchange actuated the electrostatic complexation, phase inversion, and rapid setting of the complexed catechol-rich polyelectrolytes, therefore promoting quick (∼25 s) and strong (Wad ≥ 2 J m⁻²) underwater contact adhesion to a variety of substrates including plastics, glasses, metals, and biological materials. The solvent exchange method, enabling spatial and temporal coordination of complexation, inversion, and setting, provided a new pathway for producing underwater adhesives with quick setting. In addition, the same group also designed a novel mussel foot protein homologue (Mfp-3s-pep) in recapitulating important characteristics of Mfp-3s in mussels such as appropriate isoelectric point (PI), polyampholyte nature, hydrophobicity, and self-coacervation. The coupling of Dopa with a coacervate phase in the synthetic peptide significantly improved adhesion in wet environments by displacing surface-bound water molecules, therefore allowing for direct bonding with the substrates, such as hydroxyapatite (HAP) and TiO₂.

Park et al. demonstrated a re-moldable and injectable coacervate-based hydrogel, formed by the interaction between dopamine conjugated hyaluronic acid (HA-DN) and lactose modified chitosan. The complex coacervate structures strengthened with catechol cross-linking and cyclization led to a physically stable and strong interpenetrating hydrogel. This system is the first example of a bio-inspired coacervate hydrogel system that owns injectable/moldable property with long-term physical stability in water settings.

The Stupp group reported the formation of self-assembled macroscopic sacs and membranes formed at the interface upon addition of a negatively charged hyaluronic acid (HA) solution into a peptide amphiphile (PA) aqueous solution (Fig. 10). The simple process could produce structures
of variable shapes that were mechanically robust in both dry and hydrated states and exhibited self-sealing feature. The soft gel-like sacs and membranes indeed possessed all the typical characteristics of coacervate structures, even though the authors did not claim the formation of coacervates in their study. Inspired by the above study, Mata et al. recently developed a dynamic system based upon co-assembly of an elastin-like polypeptide (ELP5) and a peptide amphiphile (PAK3), with pI 3.4 and 10.3, respectively. Strong electrostatic forces of the ELP/PA interactions enabled the creation of a robust membrane. The authors demonstrated that such structures had potential in generating complex bioactive scaffolds for applications in tissue engineering.

Collectively, the above studies manifested the great potential of coacervate-based structures as strong underwater adhesives. Notably, the coacervation phenomena are found beyond underwater adhesion in nature. In fact, many natural protein systems harness coacervates for functional purposes. For example, the low-complexity (LC) sequences, frequently found in many RNA-binding proteins in eukaryotic cells, can also form liquid-like droplets at low ionic strength in vitro. The highly concentrated LC sequence droplets exhibited dynamic fluid behaviors, as assessed by fluorescence recovery after photobleaching (FRAP). The fluidic behaviors of droplets are similar to those of complex coacervates. It would be interesting to probe whether these structures also exhibit underwater adhesion towards various substrates. If so, these proteins may provide new clues to develop coacervate-based underwater adhesives in the future.

C. Future bio-inspired design

In view of new strategies towards developing better or optimized underwater adhesives, we argue that this not only calls for deeper knowledge of marine underwater adhesion but also requires sophisticated learning of nature from a more comprehensive picture building upon existing knowledge. Within this scenario, we underline that future bio-inspired research should take into account those important but ignored aspects of biological adhesion and we highlight several potential research opportunities in future bio-inspired research: (1) linking molecular context with Dopa-based adhesives; (2) tuning coacervate-enabled adhesives with depicted phase diagrams; (3) constructing multi-component complex integrating interfacial and cohesive strength; (4) recapitulating dynamic and multi-scale adhesion; and (5) engineering conceptually new types of adhesives that bond on demand, self-heal, and adapt to environments.

(1) Linking molecular context with Dopa-based adhesives: Dopa is peculiar but abundant of catecholic amino acid in the adhesives of several marine organisms. However, Dopa alone cannot create the strong adhesion of marine organisms. Exemplified by the “one-two punch” synergistic interplay between abundant Dopa and lysine residues in mussel adhesive foot proteins, increasing evidence suggests that the molecular context in local chemical environment shows importance in the catechol-mediated adhesion. Future Dopa-based bio-inspired research therefore would include those neglected aspects into the design. For example, interfacial adhesive protein Mfp-3 or Mfp-5 is rich in multiple post-translationally modified residues such as phosphoserine or 4-hydroxyarginine. Since detailed understanding of their specific roles of these residues is still lacking, research opportunities exist in the context of taking those post-translationally residues into the bio-inspired design and evaluating how such residues contribute to the catechol-mediated adhesion.

(2) Tuning coacervate-enabled adhesives with depicted phase diagram: phase diagrams that depict the biological adhesives as a function of optimizing pH, ionic strength, and polyelectrolyte concentration for coacervation would be beneficial for understanding the detailed molecular mechanism of biological adhesives based on coacervates. Similarly, future bio-inspired coacervate-enabled adhesives’ design can build upon the existing depicted phase diagram. In particular, correlating the specific phase structures with their corresponding adhesion performance would eventually help engineer coacervate-enabled adhesives with tunable adhesion performance.

(3) Constructing multi-component complex integrating interfacial and cohesive strength: the adhesive molecules utilized by marine organisms may vary from one species to another, but
one common feature that these adhesive molecules share is that they seamlessly integrate interfacial adhesion with cohesion to achieve efficient underwater adhesion. Adhesive molecules associated with marine organisms are often multi-protein complexes, in which each component fulfills one or multiple functionalities through diverse molecular interactions. Biomimetic strategies that integrate both interfacial and cohesive strength in a multi-component complex have not been much explored yet and would represent new research opportunities in future bio-inspired research. In particular, the barnacle cement, currently having less impact on materials science, deserves more attention in the bio-inspired research area, as the cement serves an ideal multi-protein complex model, in which the multifunctionality in the cement can be dissected and might be applied to each single function. In addition, the multi-protein complex in barnacles also provides an attractive resource for decoding diverse molecular self-assemblies based on intra- or intermolecular interactions, which in turn would inspire new design principles of adhesive materials.

(4) Recapitulating dynamic and multi-scale adhesion under appropriate conditions: marine organisms regulate the reactivity of their adhesive proteins under special conditions at different lengths and time scales. For example, to implement wet adhesion, mussel creates an insulated reaction chamber with a low pH, low ionic strength, and high reducing poise. These conditions ensure that adhesive proteins undergo controlled fluid-fluid phase separation, surface absorption and spreading, microstructure formation, and eventually hardening. Although knowledge regarding how they spatiotemporally govern the dynamic processing of adhesive molecules remains largely unknown, such dynamic processing necessarily involves diverse molecules of different features, enzyme activities, and well-controlled catechol chemistry. Future research opportunities in mimicking the dynamic feature of adhesion will require the rational integration of disparate adhesive molecules in a spatiotemporally controlled fashion under appropriate conditions. Strategies that recapitulate dynamic features of biological adhesion, to be implemented either in a cellular or non-cellular context, will be useful in engineering novel underwater adhesives towards more broad and practical applications.

(5) Engineering conceptually new types of adhesives that bond on demand, self-heal, and adapt to different environments: biological adhesives are dynamic living materials with endowed functional properties that are far beyond the reach of synthetic counterparts. For example, they are able to bond on demand, self-heal, and adapt to different environments to achieve optimized adhesion. These represent conceptually new types of adhesives that have not been explored in current adhesive techniques. One possible strategy to fulfill some of these new functionalities is to introduce the functional properties into engineered cells that can spatially and temporally regulate the secretion, self-assembling, and solidification of adhesive molecules controlled via synthetic gene circuits. In addition, the state-of-the-art directed protein evolution technique can be applied to evolve new adhesive proteins that achieve optimized or adaptive adhesion at specially given conditions.

IV. SUMMARY AND OUTLOOK

The last decade has witnessed great advances in fundamental understanding of natural underwater adhesion phenomena. Despite important progress, current knowledge is still not sufficient to gain a thorough view about the underlying mechanisms of underwater adhesion associated with different marine species. For example, although large amount of information about molecular sequences of adhesive proteins secreted by several marine organisms has been acquired, their structure-function relationship, self-assembly, and how those different adhesive molecules interact with each other and synergistically contribute to underwater adhesion remain largely unknown and require further exploration in the future.

In addition to the molecular-level information of proteins, another important aspect towards understanding natural underwater adhesion lies in how biological organisms dynamically control the processing details of adhesive molecules in a precise spatiotemporal manner. Unfortunately, the dynamic processing details, including protein expression, translational modification, delivery,
deposition, self-assembly, and curing of corresponding adhesive components, remain poorly understood. Knowledge in these aspects would eventually inform us to obtain a more comprehensive picture about underwater adhesion and thus provide new opportunities for engineering better adhesives. For example, by learning how biological organisms utilize complex mechanisms to protect adhesion against premature hardening and rescue from oxidation, we may be able to design underwater adhesive molecules with the easiness for storage and use.

In the design of biologically inspired or biomimetic underwater adhesives, various small-molecule, polymer, peptide, or protein-based adhesive molecules have been created to recapitulate the diverse features of natural adhesive molecules found in nature. Some adhesive molecules have indeed exhibited great potential for applications in coating techniques and biomedicine and tissue engineering. Despite those important advances, there are still great needs for improving the performance of current artificial underwater adhesives and expanding their applications in different areas. For example, no protein-based adhesives have yet been designed to recapitulate the full features of post-translationally modified residues, particularly the specific incorporation of phosphoserine and Dopa residues within a protein chain in a site-dependent manner. Recent advances have shown that synthetic biology can recode the gene sequences of *E. coli* systems that allow the incorporation of non-standard amino acids (NSAAs) into proteins in a site-specific fashion. Such techniques, if harnessed, would significantly promote the development of underwater adhesives with precise post-translational modifications that may exhibit functional properties that have not been realized in current adhesives. In addition, such technique platforms can be borrowed to produce natural adhesive molecules, in which post-translationally modified residues are incorporated at appropriate sites, to assess the functional roles of those special residues in underwater adhesion.

We underscore the importance of viewing natural adhesives as dynamic materials, which fulfill underwater adhesion to various substrates following the processes of protein expression, transportation, extrusion, and curing inside or outside an organism body. As such, in addition to the molecule-structure-functionality relationship of adhesive molecules, information about the dynamic processes and how organisms govern such processes in a spatiotemporal precise fashion is critical to developing new design principles for synthetic underwater adhesives.

The emerging field of synthetic biology is becoming a broad important discipline to reprogram biological systems and processes. Synthetic biology tools, such as the recent optogenetic tools, can endow biological systems with controlled expression, secretion, and self-assembly of proteins in a spatiotemporal precise fashion. In addition, synthetic biology has recently inspired the advancement of living functional materials, which possess multifunctional, self-healing, and adaptable properties, created and organized in a distributed, bottom-up, and environmentally sustainable manner. Such concepts can be applied to engineering dynamic underwater adhesive systems that exhibit new functional properties such as bonding on demand and autonomous repairs. These are essential features of biological adhesion systems but are far beyond the reach of current adhesive systems. We therefore envision that synthetic biology would provide new opportunities not only in advancing fundamental understandings of natural underwater adhesives but also in engineering conceptually new types of underwater adhesives in the future, for example, adhesives that allow for rapid bonding and debonding on demand.

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1 H. Lee, S. M. Dellatore, W. M. Miller, and P. B. Messersmith, Science 318(5849), 426 (2007).
2 R. J. Stewart, Appl. Microbiol. Biotechnol. 89(1), 27 (2011).
3 R. J. Stewart, T. C. Ransom, and V. Hlady, J. Polym. Sci., Part B: Polym. Phys. 49(11), 757 (2011).
4 C. E. Brubaker and P. B. Messersmith, Langmuir 28(4), 2200 (2012).
5 L. Khande...
60. M. Lai, K. Cai, L. Zhao, X. Chen, Y. Hou, and Z. Yang, *Biomacromolecules* **12**(4), 1097 (2011).
61. Y. Ren, J. G. Rivera, L. He, H. Kulkarni, D.-K. Lee, and P. B. Messersmith, *BMC Biotechnol.* **11**(1), 63 (2011).
62. H. Ejima, J. J. Richardson, K. Liang, J. P. Best, M. P. van Koevenber, G. K. Such, J. Cui, and F. Caruso, *Science* **341**(6142), 154 (2013).
63. H. Ejima, J. J. Richardson, and F. Caruso, *Nano Today* **12**, 136 (2017).
64. Y. Ren, J. G. Rivera, L. He, H. Kulkarni, D.-K. Lee, and P. B. Messersmith, *BMC Biotechnol.* **11**(1), 63 (2011).
65. H. Ejima, J. J. Richardson, W. Zhu, M. Hu, Y. Ju, J. Cui, R. R. Dagastine, I. Yarovsky, and F. Caruso, *Nat Nanotechnol.* **11**(12), 1105 (2016).
66. H. Ejima, J. J. Richardson, and F. Caruso, *Nano Today* **12**, 136 (2017).
67. J. Guo, Y. Ping, H. Ejima, K. Alt, M. Meissner, J. J. Richardson, Y. Yan, K. Peter, D. von Elverfeldt, and C. E. Hagemeyer, *Angew. Chem., Int. Ed.* **53**(22), 5546 (2014).
68. J. Guo, B. L. Tardy, A. J. Christofferson, Y. Dai, J. J. Richardson, W. Zhu, M. Hu, Y. Ju, J. Cui, R. R. Dagastine, I. Yarovsky, and F. Caruso, *Nat Nanotechnol.* **11**(12), 1105 (2016).
69. H. Shao, K. N. Bachus, and R. J. Stewart, *Macromol. Biosci.* **9**(5), 464 (2009).
70. S. Lim, Y. S. Choi, D. G. Kang, Y. H. Song, and H. J. Cha, *Biomaterials* **31**(13), 3715 (2010).
71. Q. Zhao, D. W. Lee, B. K. Ahn, S. Seo, Y. Kaufman, J. N. Israelachvili, and J. H. Waite, *Nat. Mater.* **15**(4), 407 (2016).
72. H. Ye, M. D.-E. Baba, R.-W. Peng, and M. Fussenegger, *Science* **332**(6037), 1565 (2011).
73. D. Tischer and O. D. Weiner, *Nat. Rev. Mol. Cell Biol.* **15**(8), 551 (2014).
74. J. Fernandez-Rodriguez, F. Moser, M. Song, and C. A. Voigt, *Nat. Chem. Biol.* **13**(7), 706 (2017).
75. A. Y. Chen, C. Zhong, and T. K. Lu, *ACS Synth. Biol.* **4**(1), 8 (2015).