REVIEW

Selection of Biomolecules Capable of Mediating the Formation of Nanocrystals

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ABSTRACT Biopolymers in the biosphere are well known to mediate the formation of a wide array of inorganic materials, such as bone, shells, lenses, and magnetic particles to name a few. Recently, *in vitro* experiments with biopolymers such as peptides, RNA, and DNA have shown that templating by these macromolecules can yield a variety of materials under mild reaction conditions. The primary sequence of the biopolymer can be viewed as a proteomic or genomic signature for the templating of an inorganic material from defined metal precursors and reaction conditions. Together with the rapid advances in inorganic particle synthesis by other combinatorial methods, these bioinspired *in vitro* materials experiments may provide additional insights into possible inorganic materials yet to be discovered and subsequently synthesized by conventional methods. Some of the concepts important to understanding the crystallization phenomena occurring during biopolymer mediation are discussed. A simple kinetic model is provided in the context of known biopolymer-mediated inorganic crystallizations.

KEYWORDS: nanocrystal · nanoparticle · SELEX · phage display · biomineralization · RNA · DNA · crystallization · mediation

Biological systems are capable of synthesizing a remarkably diverse range of inorganic materials. These systems are resourceful and assemble a vast assortment of materials using precursors that are readily available and abundant in the biosphere. In addition, these materials must be synthesized under a relatively narrow set of reaction conditions, typically in aqueous solutions, near ambient temperatures and pressures, and at neutral pH. Biological systems have adapted within these constraints by applying a large and dynamic combinatorial approach to materials synthesis, resulting in protein enzymes that catalyze inorganic reactions and mediate the formation of growing crystals. As a consequence, evolution and natural selection have resulted in organisms capable of synthesizing materials with controlled compositions, microcrystalline shapes, and long-range organization.[1–3] In addition to affording an organism structural integrity and protection against predation, many materials found in nature have more sophisticated physical properties, such as magnetism[4,5] and light focusing.[6]

Biomaterials have inspired a growing research effort in which biomolecules are used to synthesize and assemble materials in the laboratory.[1,2,7–21] In an attempt to mimic natural evolutionary processes, *in vitro* selection methods (Figure 1) employing large random-sequence RNA, DNA, peptide, and even whole-cell libraries are now being used to discover biomolecules that bind to or mediate the formation of materials.[15,22,23] In addition to potentially affording more environmentally friendly routes to inorganic materials, the sometimes highly selective recognition capabilities of biomolecules selected *in vitro* can facilitate the assembly of nanoscale materials into more complex functional assemblies and devices.[24–26]

This exciting work has prompted us to consider many fundamental questions concerning *in vitro* selection as applied to materials synthesis and crystal growth: How might the presence of a biomolecule affect crystal growth? What terminology is appropriate in describing this behavior? How should "catalysis" be distinguished from "mediation"? And finally, how do selection methods for protein binding sequences compare/contrast with those designed to isolate sequences capable of forming materials?

In addressing these questions, it is informative to consider *in vitro* selection (*e.g.*, phage display for peptides and systematic enrichment of ligands by exponential enrichment (SELEX) for RNA) first in the broader context and then specifically as it applies to materials synthesis. Historically, *in vitro* selection methods have been predominantly applied to the search for biomolecules with high protein binding

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affinities[27–33] or catalytic activities toward organic reactions.[34–46] When applied to materials chemistry, *in vitro* selection can produce apparently similar results. Biomolecules with high binding affinities and specificities for certain inorganic crystal faces[23,47,48] or for catalytic activities toward the synthesis of materials have been isolated.[49,50] In materials *in vitro* selections, however, a third outcome may be anticipated. Biomolecules may be isolated that alter the formation of a spontaneously growing crystal such that the size, size distribution, shape selectivity, growth rate, and polymorph selectivity of the resulting crystals are affected. A biomolecule with such ability is commonly referred to as a "template" or "mediator". This is how we phenomenologically define crystal growth mediation.

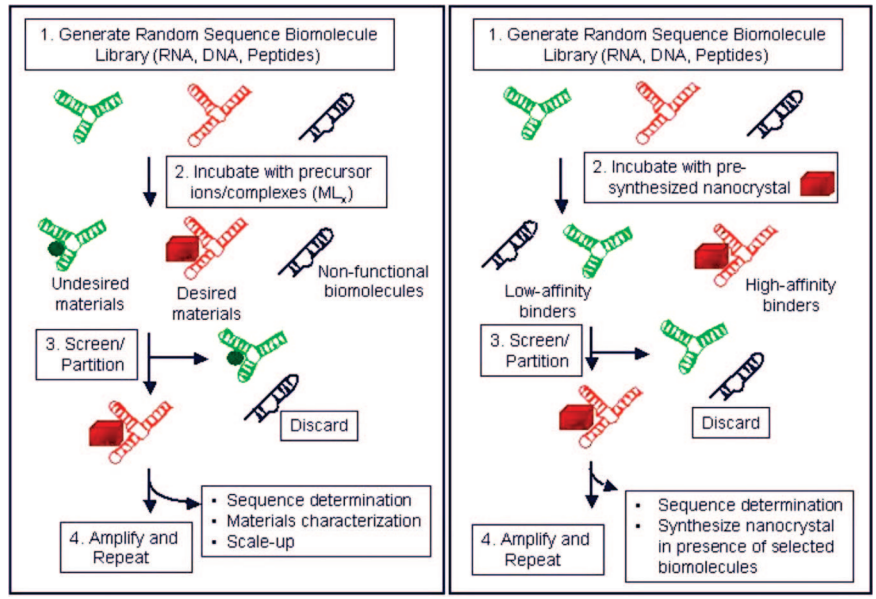

Figure 1. Generic *in vitro* selection schemes for exploring possible biomolecule–inorganic materials interactions. (Left) Selections designed to isolate sequences capable of assembling monomeric metallic precursors into nanocrystals with desired properties. (Right) Selections designed to isolate sequences that bind to nanocrystals synthesized using other, often high-temperature, synthetic methods. Once isolated, these sequences can subsequently be tested for their ability to direct the synthesis of the identical nanocrystal at lower temperatures.

The process of mediation—within the context of biomolecule-mediated growth of metal crystals from solutions containing a generic metal complex precursor $[M(L)_x]$—is perhaps best illustrated by the set of reactions shown in Figure 2. These reactions represent a minimalist view of the fundamental stages in crystal growth. In order for a crystal to grow, monomer units must be generated and combined to form a stable crystal (critical) nucleus. These are shown as $[M(L)_{x-y}]$, where y represents the number of ligands lost in generating the crystallizing monomer unit. The case in which $y = x$ represents just one possibility in which a free metal atom is generated and becomes the monomer. Crystal nuclei can then grow *via* monomer addition or nuclei aggregation. In many cases, the nucleation event controls the final particle size, size distribution, and polymorph. For example, in LaMer's sulfur sol formation mechanism from the 1950s,[51] the average size and size dispersity of the resulting crystals are influenced by the rate at which crystal nuclei are generated. A rapid "burst" of nuclei separated in time by monomer addition produces the most narrow size distributions. Alternative kinetic schemes have been described in the literature in which slow nucleation followed by rapid growth can also result in relatively monodisperse crystals. In Finke's synthesis of Ir clusters,[52,53] the generation of critical nuclei is slow, and growth is autocatalytic and rapid.

Once a crystal nucleus has formed, the resulting crystal shape is determined by a growth phase that could be either thermodynamically or kinetically controlled. In a thermodynamic growth regime, monomers will add to the highest energy facets of the growing crystal until they merge into the more stable crystalline facets. For example, PbS nucleates into a tetradecahedral shape terminated by {100} and {111} facets. In the rock salt structure, the {111} facets are higher in energy; ions therefore add preferentially to these facets, resulting in the formation of cube-shaped PbS crystals bounded by {100} facets.

In a kinetically controlled growth regime, the relative rates of monomer addition to different facets dictates the resulting shape. These rates can be altered by changes in precursor concentration; for example, in the synthesis of Pt particles from the precursor complex $[Pt(acac)_2]$ (acac is acetylacetonate), where low $[Pt(acac)_2]$ concentrations produced sharply faceted and polydisperse Pt cubes while high concentrations yielded monodisperse yet poorly faceted structures.[54]

The presence of a biomolecule (or any molecule introduced intentionally or accidentally) can also change the course of crystal nucleation or growth. A biomolecule can speed or slow the rate at which a monomer is generated, changing its concentration and, in turn, its solubility equilibria or crystal nucleation and growth rates. A biomolecule that coordinates strongly to a metal center could, of course, prevent crystallization altogether. Alternatively, a biomolecule can bind selectively to certain facets, speeding or slowing monomer addition to that facet relative to others (changing the relative magnitudes of k_4–k_7 in Figure 2), which results in non-thermodynamic and often highly anisotropic crystal shapes.

If the rate of monomer production (Figure 2, k_1) is increased by a biomolecule, one could reasonably posit that "catalysis" has occurred. The recognition of $[Pd(L)_x]$

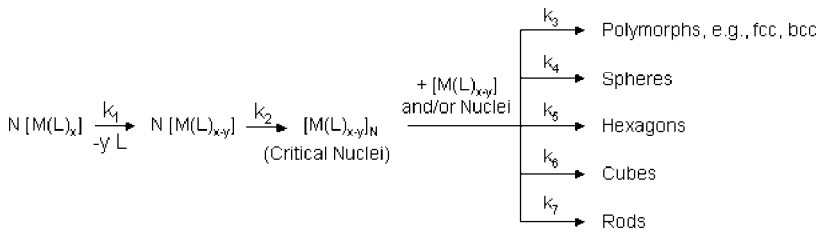

Figure 2. Illustration of the fundamental steps required to generate metal crystals from the generic complex $[M(L)_x]$. k_1 and k_2 result in the generation of critical nuclei, k_3 represents competing routes to different polymorphs, and k_4–k_7 represent face-dependent rates of monomer addition or crystal aggregation that would yield different crystal shapes. A change in any one of these *k*'s in the presence of a biomolecule would likely result in a change in crystal size, size dispersity, or shape.

by an RNA or peptide sequence, such that the displacement of L from Pd atoms is accelerated, would be one example. It is certainly reasonable and common in the crystal growth literature to conclude that if *any* of the rate constants shown in Figure 2 changes in the presence of a molecule, then "mediation" of crystal growth by that molecule has occurred. That is, if the crystal formation rate, polymorph, size, size dispersity, or shape distribution changes, then mediation has occurred.

Most inorganic crystallizations mediated by biomolecules have been performed using cationic metal complexes. An alternative possibility exists for forming metallic crystals when using zerovalent organometallic metal precursors (Figure 2). Loss of L, either mediated or occurring spontaneously under the reaction conditions, could yield a coordinatively unsaturated species $[M(L_{x-y})]$, where $x > y$. These coordinatively unsaturated metals could then either combine to form metal–metal bonds in solution or within the biomolecule structure. Of course, functional groups within the biomolecule could serve as metal ligands and dictate the mechanistic path to be followed. Loss of any amount of L would be expected to give M–M bonds, and complex structures could be formed with and without inclusion of remnants of L in the crystal structure formed. Some of the Pd and Pt "giant clusters" reported by Oleshko would appear to fall into this category.[55] It seems reasonable to propose that biomolecule-mediated crystallization will sometimes include both inorganic and organic components, depending on the organometallic precursor, biomolecule structure, and reaction conditions.

Catalytic activity is, however, not a prerequisite for a biomolecule to influence crystal growth. A wonderful illustration of the effect that a biomolecule can have on nanocrystal size was recently provided by Kelley.[22] The Kelley group was able to assess the role of RNA secondary structure on the growth of CdS nanocrystals. They showed that a folded wild-type tRNA (wtRNA) and an unfolded mutant tRNA (mtRNA) of identical length were both able to mediate the formation of CdS during its spontaneous precipitation from solution, but they saw differences in the average nanocrystal size and size distribution. A unimodal distribution of 6 nm diameter particles was found for particles grown with wtRNA, while mtRNA yielded a bimodal distribution of 7 and 11.5 nm diameter particles. CdS will precipitate even in the absence of RNA, and so it is unclear, in the absence of kinetic measurements, if either sequence "catalyzed" the transformation $Cd^{2+} + S^{2-} \rightarrow CdS_{(s)}$. It is also not the case that this is the only way to synthesize CdS nanoparticles, as many other routes exist to this same product. Yet both the wtRNA and mtRNA were able to control the size of the resulting CdS crystals, and both can legitimately be said to mediate CdS crystal growth. Moreover, it follows that the wtRNA has some as-yet unknown but unique property that enables it to mediate CdS growth differently than the mutant. Thus, while perhaps subtle, this is a clear example of how folded RNA structure can affect the trajectory of the crystallization events depicted in Figure 2.

Interestingly, it appears that specific RNA folding is not a requirement for particle growth to be mediated. Recently, Kumar and Jakhmola reported the RNA-mediated synthesis of PbS quantum dots.[56] In these experiments, specific RNA sequences were not employed, but a mixture of yeast RNA was sufficient to provide PbS synthesis. They found that this mixture of RNA sequences could be used to control the size, stability, and even the electronic properties of PbS quantum dots. It is also important to note that, in contrast to work on DNA-mediated synthesis of CdS quantum dots, DNA was found to not be effective at mediating PbS synthesis.

Experiments with RNA have also shown how the presence of biomolecules can alter the distribution of crystal morphologies. RNA sequences have been selected from a random RNA sequence library that mediate the growth of crystals from the precursor complex $[Pd_2(DBA)_3]$ (DBA is dibenzylidene acetone).[57] In exploring the behaviors of individual sequences isolated from the selection, it was found that the presence of certain RNA sequences resulted in the formation of crystals

VOCABULARY: SELEX – **s**ystematic **e**nrichment of **l**igands by **ex**ponential enrichment, the experimental process by which large libraries (*ca.* 10^{14}) of unique single-stranded RNA or DNA sequences are subjected to iterative cycles of screening, selection, and amplification; the process results in the isolation of sequences in the library that perform a desired task, for example, high-affinity binders to a certain protein · **phage display** – an *in vitro* selection method employing a random-sequence peptide library, which is "displayed" on the surface of a bacterial virus (phagemid); in this method, phage selected from the library because of their ability to perform a certain task (*e.g.*, binding to a material) are amplified by allowing the phage to infect a bacteria · **template or mediate** – the interaction of any chemical species with a growing crystal such that the crystal formation rate(s), polymorph, size, size dispersity, or shape distribution is altered · **polymorph** – two or more solids with the same chemical composition but different crystal structures · **morphology** – the three-dimensional shape of a crystal; two or more solids of the same chemical composition may have identical crystal structures (*i.e.*, identical polymorphs) but different morphologies (cubes *vs* hexagons)

with hexagonal morphology while another sequence yielded cubes.[58] The possibility exists that these sequences either facilitate formation of crystal nuclei that lead to hexagons or cubes or bind to nuclei that formed spontaneously and control the resulting growth, or both. For example, the RNA sequence for hexagons could accelerate k_1 in Figure 2 to generate nuclei that lead exclusively to hexagons, or it could accelerate k_5 relative to k_4, k_6, and k_7 (or alternatively decelerate k_4, k_6, and k_7 relative to k_5) to provide hexagons to the exclusion of other morphologies.

With this description of crystal growth mediation in mind, we now examine the materials *in vitro* selection experiment itself. The most critical element of any *in vitro* selection is the selection pressure. This is designed by the experimenter with the intent of driving a random-sequence library toward a desired goal. For example, if RNA aptamers with a high binding affinity for a certain protein are sought, then solution conditions can be adjusted to favor the isolation of even extremely rare tight binders.[59] Likewise, if sequences that bind to a known material are sought, one may synthesize the material using an existing method and then perform cycles of amplification where the selection pressure is binding the material in a manner analogous to RNA–protein aptamer *in vitro* selection. In contrast to selections for protein binders, however, individual sequences that emerge from such an experiment can then be tested for their ability to catalyze or mediate the formation of crystals as defined above (Figure 1, right). Consider the pioneering work of Belcher and coworkers as an example. They employed phage display to isolate peptides with high binding affinities to preformed solid FePt nanoparticles.[60] Upon chemical reduction of $FeCl_2$ and H_2PtCl_6 in the presence of these peptides—expressed as fusion proteins on the tip of a virus—FePt nanoparticles formed on the virus. Notably, the FePt nanoparticles used in the selection were synthesized and annealed at high temperatures to produce the preferred ferromagnetic crystalline phase. When Fe and Pt ions were reduced in the presence of the FePt-binding peptides, however, the preferred phase was synthesized directly, obviating the need for high-temperature annealing.

In addition to providing environmentally benign routes to materials, biomolecules have been used to assemble nanoparticles on surfaces or into thin films. Peptides displayed on phage appear to be excellent scaffolds in this regard. One-dimensional chains of gold nanoparticles have been assembled along the virus long axis.[24] Individual gold nanoparticle-coated viruses were then connected in predetermined ways by modifying the viral ends with a second peptide that recognized streptavidin-coated gold or CdSe nanoparticles. A similar strategy was used to synthesize hybrid Co_3O_4/Au nanoparticle-coated phage, which were then assembled into thin films and tested as flexible anodes in Li ion batteries.[26]

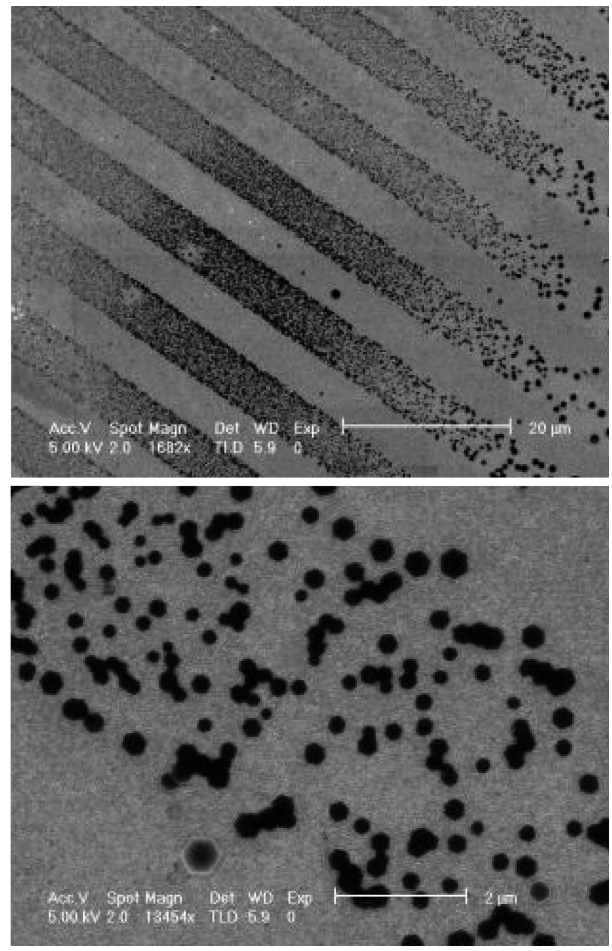

Figure 3. Scanning electron microscope images of line patterns of hexagonal nanoparticles grown from a gold surface. The entire gold surface was first modified with a maleimide-terminated oligoethyleneglycol thiolate monolayer.[61] The RNA sequence code known to mediate the formation of hexagonal nanoparticles from the precursor complex $[Pd_2(DBA)_3]$ was then deposited in the form of a line pattern using microcontact printing. The RNA was modified with a 5′-guanosine monophosphorothioate for coupling to the maleimide monolayer.

Biomolecule mediators of crystal growth can also be patterned on surfaces to enable spatially resolved materials synthesis. An example is illustrated by Figure 3, which shows a scanning electron microscope image of crystals grown on a gold slide. The sample was prepared by microcontact printing previously reported RNA Pd017[58] onto the slide in the form of a stripe pattern and then immersing the entire slide into a solution of $[Pd_2(DBA)_3]$. Note that crystals grew in the form of the printed stripe pattern, which suggests that RNA Pd017 mediated their growth. Note further that the spontaneous growth rate between the lines is very near zero and that hexagons were the predominant morphology observed.

CONCLUSIONS AND FUTURE PROSPECTS

The elegant examples described above illustrate how biomolecules, peptides, and nucleic acids, can be

utilized to synthesize nanoparticles of specific composition, shape, and size. In all of these examples, known materials were formed by the biomolecule in the presence of specific metal precursors and crystallization medium. The ability to replicate either peptides *via* phage display, or nucleic acids by *in vitro* selection methods, makes these biopolymer platforms especially attractive for the discovery of new nanomaterials with desired physical, chemical, or optical properties. Since the desired nanoparticle can be recreated by using specific sequences, or a mixture of sequences, these biopolymers can be thought of as "structurally" encoding for the composition and crystalline form of the nanoparticle of interest. This equivalent to a genetic or proteomic archive is a powerful concept for inorganic structures and, in fact, has shaped the biosphere. We have a long way to go in emulation of this bioinorganic phenomenon, but excellent progress is being made by many research groups around the world.

In the future, will *in vitro* selection methods for peptides and nucleic acids be able to find not only known but also new materials? Can these methods of selecting biomolecules that mediate nanoparticle growth be advanced such that enhanced magnetic materials, optical materials such as quantum dot semiconductors, and new inorganic catalysts are discovered? The key to success will be the efficient exploration of inorganic composition, shape, size, and even concomitant crystalline phase-space. Advances in nano-array technologies for the selection of desired nanoparticles and microscopy for their identification are likely to play an essential role.[62] In addition, the techniques of molecular biology and new enhancements in biophysical characterization, including single-molecule spectroscopy, will allow us to approach nanoparticle formation from an alternative perspective. The merger of both physical and biochemical methods may provide a powerful synergy that takes us to a higher level of understanding of inorganic chemistry and nanomaterials.

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REFERENCES AND NOTES

1. Fu, G.; Valiyaveettil, S.; Wopenka, B.; Morse, D. E. $CaCO_3$ Biomineralization: Acidic 8-Kda Proteins Isolated from Aragonitic Abalone Shell Nacre Can Specifically Modify Calcite Crystal Morphology. *Biomacromolecules* **2005**, *6*, 1289–1298.
2. Fu, G.; Qiu, S. R.; Orme, C. A.; Morse, D. E.; De Yoreo, J. J. Acceleration of Calcite Kinetics by Abalone Nacre Proteins. *Adv. Mater.* **2005**, *17*, 2678–2683.
3. Aizenberg, J.; Weaver, J. C.; Thanawala, M. S.; Sundar, V. C.; Morse, D. E.; Fratzl, P. Skeleton of Euplectella sp.: Structural hierarchy from the Nanoscale to the Macroscale. *Science* **2005**, *309*, 275–278.
4. Frankel, R.B.; Blakemore, R.P.; Wolfe, R.S. Magnetite in Freshwater Magnetotactic Bacteria. *Science* **1979**, *203*, 1355–1356.
5. Blakemore, R. Magnetotactic Bacteria. *Science* **1975**, *190*, 377–379.
6. Aizenberg, J.; Tkachenko, A.; Weiner, S.; Addadi, L.; Hendler, G. Calcitic Microlenses as Part of the Photoreceptor System in Brittlestars. *Nature* **2001**, *412*, 819–822.
7. Brutchey, R. L.; Yoo, E. S.; Morse, D. E. Biocatalytic Synthesis of a Nanostructured and Crystalline Bimetallic Perovskite-Like Barium Oxofluorotitanate at Low Temperature. *J. Am. Chem. Soc.* **2006**, *128*, 10288–10294.
8. Curnow, P.; Kisailus, D.; Morse, D. E. Biocatalytic Synthesis of Poly(L-Lactide) by Native and Recombinant Forms of the Silicatein Enzymes. *Angew. Chem., Int. Ed.* **2006**, *45*, 613–616.
9. Curnow, P.; Bessette, P. H.; Kisailus, D.; Murr, M. M.; Daugherty, P. S.; Morse, D. E. Enzymatic Synthesis of Layered Titanium Phosphates at Low Temperature and Neutral pH by Cell-Surface Display of Silicatein-Alpha. *J. Am. Chem. Soc.* **2005**, *127*, 15749–15755.
10. Kisailus, D.; Truong, Q.; Amemiya, Y.; Weaver, J. C.; Morse, D. E. Self-Assembled Bifunctional Surface Mimics an Enzymatic and Templating Protein for the Synthesis of a Metal Oxide Semiconductor. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 5652–5657.
11. Sumerel, J. L.; Yang, W. J.; Kisailus, D.; Weaver, J. C.; Choi, J. H.; Morse, D. E. Biocatalytically Templated Synthesis of Titanium Dioxide. *Chem. Mater.* **2003**, *15*, 4804–4809.
12. Bansal, V.; Rautaray, D.; Bharde, A.; Ahire, K.; Sanyal, A.; Ahmad, A.; Sastry, M. Fungus-Mediated Biosynthesis of Silica and Titania Particles. *J. Mater. Chem.* **2005**, *15*, 2583–2589.
13. Bharde, A.; Rautaray, D.; Bansal, V.; Ahmad, A.; Sarkar, I.; Yusuf, S. M.; Sanyal, M.; Sastry, M. Extracellular Biosynthesis of Magnetite Using Fungi. *Small* **2006**, *2*, 135–141.
14. Chandran, S. P.; Chaudhary, M.; Pasricha, R.; Ahmad, A.; Sastry, M. Synthesis of Gold Nanotriangles and Silver Nanoparticles Using Aloe Vera Plant Extract. *Biotechnol. Prog.* **2006**, *22*, 577–583.
15. Mandal, S.; Phadtare, S.; Sastry, M. Interfacing Biology with Nanoparticles. *Curr. Appl. Phys.* **2005**, *5*, 118–127.
16. Taton, T. A.; Mucic, R. C.; Mirkin, C. A.; Letsinger, R. L. The DNA-Mediated Formation of Supramolecular Mono- and Multilayered Nanoparticle Structures. *J. Am. Chem. Soc.* **2000**, *122*, 6305–6306.
17. Park, S.; Lazarides, A. A.; Mirkin, C. A.; Letsinger, R. L. Directed Assembly of Periodic Materials from Protein and Oligonucleotide-Modified Nanoparticle Building Blocks. *Communications* **2001**, *15*, 2909–2912.
18. Loweth, C. J.; Caldwell, W. B.; Peng, X.; Alivisatos, A. P.; Schultz, P. G. DNA-Based Assembly of Gold Nanocrystals. *Angew. Chem., Int. Ed.* **1999**, *38*, 1808–1811.
19. Sewell, S. L.; Wright, D. W. Biomimetic Synthesis of Titanium Dioxide Utilizing the R5 Peptide Derived from Cylindrotheca Fusiformis. *Chem. Mater* **2006**, *18*, 3108–3113.
20. Slocik, J. M.; Wright, D. W. Biomimetic Mineralization of Noble Metal Nanoclusters. *Biomacromolecules* **2003**, *4*, 1135–1141.
21. Slocik, J. M.; Naik, R. R.; Stone, M. O.; Wright, D. W. Viral Templates for Gold Nanoparticle Synthesis. *J. Mater. Chem.* **2005**, *15*, 749–753.
22. Ma, N.; Dooley, C. J.; Kelley, S. O. RNA-Templated Semiconductor Nanocrystals. *J. Am. Chem. Soc.* **2006**, *128*, 12598–12599.
23. Whaley, S. R.; English, D. S.; Hu, E. L.; Barbara, P. F.; Belcher, A. M. Selection of Peptides with Semiconductor Binding Specificity for Directed Nanocrystal Assembly. *Nature* **2000**, *405*, 665–669.
24. Huang, Y.; Chiang, C. Y.; Lee, S. K.; Gao, Y.; Hu, E. L.; De Yoreo, J.; Belcher, A. M. Programmable Assembly of Nanoarchitectures Using Genetically Engineered Viruses. *Nano Lett.* **2005**, *5*, 1429–1434.
25. Lee, S. K.; Yun, D. S.; Belcher, A. M. Cobalt Ion Mediated Self-Assembly of Genetically Engineered Bacteriophage for

Biomimetic Co-Pt Hybrid Material. *Biomacromolecules* **2006**, *7*, 14–17.
26. Nam, K. T.; Kim, D. W.; Yoo, P. J.; Chiang, C. Y.; Meethong, N.; Hammond, P. T.; Chiang, Y. M.; Belcher, A. M. Virus-Enabled Synthesis and Assembly of Nanowires for Lithium Ion Battery Electrodes. *Science* **2006**, *312*, 885–888.
27. Ellington, A. D.; Szostak, J. W. In vitro Selection of RNA Molecules That Bind Specific Ligands. *Nature* **1990**, *346*, 818–822.
28. Eaton, B. E. The Joys of in Vitro Selection: Chemically Dressing Oligonucleotides to Satiate Protein Targets. *Curr. Opin. Chem. Biol.* **1997**, *1*, 10–16.
29. Bunka, D. H. J.; Stockley, P. G. Aptamers Come of Age—At Last. *Nat. Rev. Microbiol.* **2006**, *4*, 588–596.
30. Hermann, T.; Patel, D. J. Biochemistry—Adaptive Recognition by Nucleic Acid Aptamers. *Science* **2000**, *287*, 820–825.
31. Tuerk, C.; Gold, L. Systematic Evolution of Ligands by Exponential Enrichment—Rna Ligands to Bacteriophage-T4 DNA-Polymerase. *Science* **1990**, *249*, 505–510.
32. Hartig, J. S.; Najafi-Shoushtari, S. H.; Grune, I.; Yan, A.; Ellington, A. D.; Famulok, M. Protein-Dependent Ribozymes Report Molecular Interactions in Real Time. *Nat. Biotechnol.* **2002**, *20*, 717–722.
33. Cox, J. C.; Hayhurst, A.; Hesselberth, J.; Bayer, T. S.; Georgiou, G.; Ellington, A. D. Automated Selection of Aptamers Against Protein Targets Translated In Vitro: From Gene to Aptamer. *Nucleic Acids Res.* **2002**, *30*, 20.
34. Illangasekare, M.; Sanchez, G.; Nickles, T.; Yarus, M. Aminoacyl-RNA Synthesis Catalyzed by An RNA. *Science* **1995**, *267*, 643–647.
35. Lohse, P. A.; Szostak, J. W. Ribozyme-Catalysed Amino-Acid Transfer Reactions. *Nature* **1996**, *381*, 442–444.
36. Tarasow, T. M.; Tarasow, S. L.; Eaton, B. E. RNA-Catalysed Carbon-Carbon Bond Formation. *Nature* **1997**, *389*, 54–57.
37. Wiegand, T. W.; Janssen, R. C.; Eaton, B. E. Selection of RNA Amide Syntheses. *Chem. Biol.* **1997**, *4*, 675–683.
38. Nieuwlandt, D.; West, M.; Cheng, X. Q.; Kirshenheuter, G.; Eaton, B. E. The First Example of an Rna Urea Synthase: Selection Through the Enzyme Active Site of Human Neutrophile Elastase. *Chembiochem* **2003**, *4*, 651–654.
39. Seelig, B.; Jaschke, A. A. Small Catalytic Rna Motif With Diels-Alderase Activity. *Chem. Biol.* **1999**, *6*, 167–176.
40. Eisenfuhr, A.; Arora, P. S.; Sengle, G.; Takaoka, L. R.; Nowick, J. S.; Famulok, M A. Ribozyme with Michaelase Activity: Synthesis of the Substrate Precursors. *Bioorg. Med. Chem.* **2003**, *11*, 235–249.
41. Fusz, S.; Eisenfuhr, A.; Srivatsan, S. G.; Heckel, A.; Famulok, M. A Ribozyme for the Aldol Reaction. *Chem. Biol.* **2005**, *12*, 941–950.
42. Wecker, M.; Smith, D.; Gold, L. In Vitro Selection of a Novel Catalytic Rna: Characterization of a Sulfur Alkylation Reaction and Interaction with a Small Peptide. *Rna—Publ. RNA Soc.* **1996**, *2*, 982–994.
43. Wilson, C.; Szostak, J. W. In-Vitro Evolution of a Self-Alkylating Ribozyme. *Nature* **1995**, *374*, 777–782.
44. Huang, F. Q.; Bugg, C. W.; Yarus, M. RNA-Catalyzed CoA, NAD, and FAD Synthesis from Phosphopantetheine, NMN, and FMN. *Biochemistry* **2000**, *39*, 15548–15555.
45. Tsukiji, S.; Pattnaik, S. B.; Suga, H. An Alcohol Dehydrogenase Ribozyme. *Nat. Struct. Biol.* **2003**, *10*, 713–717.
46. Zhang, B. L.; Cech, T. R. Peptidyl-Transferase Ribozymes: Trans Reactions, Structural Characterization and Ribosomal RNA-Like Features. *Chem. Biolo.* **1998**, *5*, 539–553.
47. Merzlyak, A.; Lee, S.W. Phage as Templates for Hybrid Materials and Mediators for Nanomaterial Synthesis. *Curr. Opin. Chem. Biol.* **2006**, *10*, 246–252.
48. Sarikaya, M.; Tamerler, C.; Schwartz, D. T.; Baneyx, F. O. Materials Assembly and Formation using Engineered Polypeptides. *Annu. Rev. Mater. Res.* **2004**, *34*, 373–408.
49. Ahmad, G. Rapid, Room-Temperature Formation of Crystalline Calcium Molybdate Phosphor Microparticles Via Peptide-Induced Precipitation. *Adv. Mater.* **2006**, *18*, 1759.
50. Naik, R. R.; Brott, L. L.; Clarson, S. J.; Stone, M. O. Silica-Precipitating Peptides Isolated from a Combinatorial Phage Display Peptide Library. *J. Nanosci. Nanotechnol.* **2002**, *2*, 95–100.
51. Lamer, V. K.; Dinegar, R. H. Theory, Production and Mechanism of Formation of Monodispersed Hydrosols. *J. Am. Chem. Soc.* **1950**, *72*, 4847–4854.
52. Watzky, M. A.; Finke, R. G. Transition Metal Nanocluster Formation Kinetic and Mechanistic Studies. A New Mechanism when Hydrogen is the Reductant: Slow, Continuous Nucleation and Fast Autocatalytic Surface Growth. *J. Am. Chem. Soc.* **1997**, *119*, 10382–10400.
53. Watzky, M. A.; Finke, R. G. Nanocluster Size-Control and "Magic Number" Investigations, Experimental Tests of the "Living-Metal Polymer" Concept and of Mechanism-Based Size-Control Predictions Leading to the Syntheses of Iridium(0) Nanoclusters Centering About Four Sequential Magic Numbers. *Chem. Mater.* **1997**, *9*, 3083–3095.
54. Ren, J.; Tilley, R. D. Preparation, Self-Assembly, and Mechanistic Study of Highly Monodispersed Nanocubes. *J. Am. Chem. Soc.* **2007**, *129*, 3287–3291.
55. Oleshko, V. P. Aperiodic Core Structures Of Pd and Pt Giant Clusters Chemically Stabilized with Diphenyl Phosphide Ligands. *J. Mol. Catal. A—Chem.* **2006**, *249*, 4–12.
56. Kumar, A.; Jakhmola, A. RNA-Mediated Fluorescent Q-PbS Nanoparticles. *Langmuir* **2007**, *23*, 2915–2918.
57. Gugliotti, L. A.; Feldheim, D. L.; Eaton, B. E. RNA-Mediated Metal–Metal Bond Formation in the Synthesis of Hexagonal Palladium Nanoparticles. *Science* **2004**, *304*, 850–852.
58. Gugliotti, L. A.; Feldheim, D. L.; Eaton, B. E. RNA-Mediated Control of Metal Nanoparticle Shape. *J. Am. Chem. Soc.* **2005**, *127*, 17814–17818.
59. Irvine, D.; Tuerk, C.; Gold, L. Selexion—Systematic Evolution of Ligands by Exponential Enrichment with Integrated Optimization by Nonlinear-Analysis. *J. Mol. Biol.* **1991**, *222*, 739–761.
60. Reiss, B. D.; Mao, C. B.; Solis, D. J.; Ryan, K. S.; Thomson, T.; Belcher, A. M. Biological Routes to Metal Alloy Ferromagnetic Nanostructures. *Nano Lett.* **2004**, *4*, 1127–1132.
61. Gugliotti, L. A.; Liu, D.; Tkachenko, A. G.; Shipton, M.; Eaton, B. E.; Feldheim, D. L. Shape-Controlled Synthesis of Metal Nanoparticles on Surfaces Using Catalytic RNA. *Langmuir* **2006**, *22*, 5862.
62. Hong, S.; Mirkin, C. A. Nanoplotter with Both Parallel and Serial Writing Capabilities. *Science* **2000**, *288*, 1808–1811.