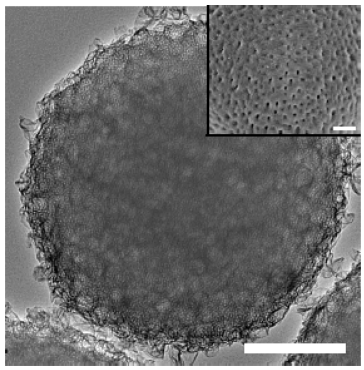
Protocells Prove Their Worth in Drug Delivery

Systemically delivering cancer therapeutics that hone in on their targets remains one of the holy grails of medicine. However, systemic delivery has many drawbacks. For example, many potentially useful drugs are poorly soluble or unstable in the body. Additionally, some therapeutic macromolecules, including nucleic acids and proteins, degrade through enzymatic digestion or an immune response. To overcome these drawbacks, researchers are exploring using nanoparticles to encapsulate therapeutic molecules. These vehicles isolate molecules from physiological conditions and protect them from degradation. Although some promising constructs have been developed, these nanoparticles have been hampered by limited cargo capacity and premature degradation.

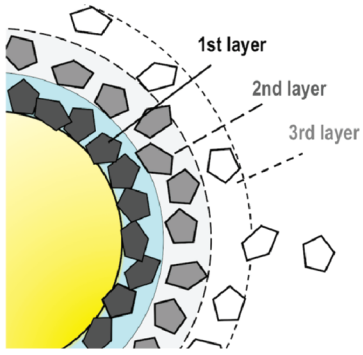
In a step toward this goal, Ashley *et al.* (DOI: 10.1021/nn204102q) developed nanoparticles consisting of mesoporous silica-supported lipid bilayers, which they deemed "protocells" due to their likeness to reductionist cells. In proof-of-principle experiments, they showed that these constructs can aptly deliver siRNA, a class of therapeutic nucleic acid that can control gene expression, to hepatic cancer cells with the aid of targeting molecules attached to the protocells' surfaces. Results show that protocells have a significantly increased carrying capacity compared to lipid nanoparticles and are more stable when incubated in solutions that mimic biologic conditions necessary for cellular delivery. When loaded with siRNA that targets genes that control the cell cycle, the protocells effectively silenced the expression of those genes and reduced protein expression, leading to growth arrest and apoptosis. The researchers suggest that protocells may eventually serve as carriers not only for siRNA but also for other broad classes of therapeutic macromolecules.



Protein and Nanoparticles: Measuring Attraction

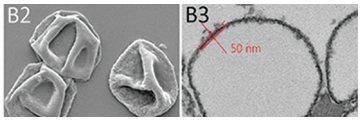
Nanoparticles have the potential for a vast array of applications in nearly every sector of science and technology, including many biomedical fields. Before these tools can be useful, researchers must verify their safety and understand how they interact with living organisms. Previous studies have shown that nanoparticles' surface chemistry is key in defining their effects on cells and tissues. Biological fluids coat nanoparticles with biomolecules, including proteins, creating a corona that ultimately defines how these nanomaterials interface with cells. Scientists have undertaken a variety of studies to understand protein adsorption on nanoparticles. However, these studies have typically failed to incorporate the fact that protein binding on nanoparticles can be reversible. Although some research has suggested that proteins form two layers on nanoparticles—a hard, irreversibly bound corona and a soft, reversibly bound corona—protein exchange on the soft corona had not yet been quantified.

Using a method known as fluorescence correlation spectroscopy, Milani *et al.* (DOI: 10.1021/nn204951s) measured protein molecules adhered to sulfonate- and carboxyl-polystyrene nanoparticles. Using transferrin, an abundant blood glycoprotein, as a model protein, the researchers found that free transferrin molecules continue to bind to the nanoparticle surfaces as long as those surfaces are not fully covered. Once this saturation point is reached, a second, more weakly bound layer (aka the soft corona) forms. Further experiments show that this second layer maintains a continuous, dynamic exchange with other nanoparticles. Blood plasma protein almost completely removed this soft corona. The authors suggest that these findings add to a more complete model of protein adsorption to nanoparticles, which could be used in the future for biomedical applications.



Delivering Vaccines in Tiny Packages

Historically, the vast majority of vaccines have been composed of biological material, often live, attenuated bacteria or viruses. However, these have the potential to impose serious safety issues and often do not generate the desired immunity. Consequently, vaccine research has shifted from using whole microorganisms to using recombinant antigens. Because many of these antigens are poorly immunogenic, they are typically delivered with an adjuvant designed to increase response. Yet, adjuvants currently approved for human use do not induce the necessary immune cell responses for some important pathogens, such as HIV, malaria, and tuberculosis. Additionally, they do not generate a response in immune cells that can fight cancer, a growing area of cancer therapeutics research.

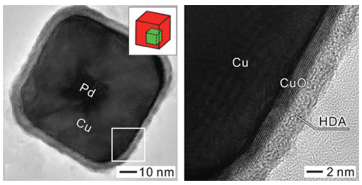


To combat these issues, De Geest *et al.* (DOI: 10.1021/nn205099c) encapsulated antigens in micrometer-sized capsules composed of polymer multilayers that more readily mimic the size of biologic pathogens, potentially improving cellular uptake and immune response. Using ovalbumin as a model antigen, the researchers encased this antigen in a bilayer membrane using a sacrificial core of calcium carbonate. Experiments showed that dendritic cells readily internalized these polymeric multilayer capsules (PMLC) and delivered their antigen cargo to draining lymph nodes. There, they successfully enhanced antigen presentation in T and B cells. Immune cells of mice immunized with these PMLC attacked ovalbumin-transduced melanoma cells that had been injected into the animals. Similarly, the vast majority of mice immunized with a component of influenza A survived a lethal challenge with the virus. The authors suggest that PMLC could form the basis of more effective antigen delivery systems.

Published online March 27, 2012
10.1021/nn3010894

Matchmaking Metals, Despite Their Differences

Bimetallic core–shell nanoparticles are a growing area of research, with a range of applications in catalysis, plasmonics, and surface-enhanced Raman spectroscopy. Typically, these dual material particles are formed by growing one metal on the surface of a seed particle made of a different metal. Previous research has suggested that epitaxial growth only occurs when the lattice mismatch between the metals is below 5%. Generating bimetallic core–shell nanoparticles epitaxially with lattice mismatches greater than this amount has had only partial success, often producing polycrystalline structures with spherical shapes and no control over the thickness of the shells.

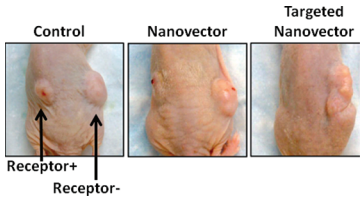


Hoping to change this paradigm, Jin *et al.* (DOI: 10.1021/nn2050278) developed core–shell nanocubes using Cu epitaxially layered onto Pd, two metals with a lattice mismatch of 7.1%. The researchers started with Pd nanocubes, then added $CuCl_2$ reduced in glucose with hexadecylamine (HDA) as a capping agent. Findings showed that the Cu formed an asymmetrical coating around the Pd seeds, forming new bimetallic nanocubes with Pd seeds situated off-center. Reducing the concentration of Pd seeds resulted in larger nanocubes with thicker Cu shells. Various analytical methods suggest that Cu growth on the Pd nanocubes was epitaxial. By studying the reaction at different time points, the reseachers found that Cu atoms first nucleated and grew on only one or two facets of the Pd nanocubes. However, as time progressed, growth also occurred on other faces of the Pd nanocubes, eventually encasing the Pd with Cu. The authors suggest that their findings could expand the realm of bimetallic nanoparticles into other epitaxial combinations, despite large lattice mismatches between components.

Cooking Up Cancer Drugs Noncovalently

Nanovectors offer the potential for targeted cancer therapeutics, with the ability to carry several drugs at once, along with targeting ligands and imaging agents that can guide the nanovector to its destination and allow it to be visualized in the body. Previous studies have demonstrated that these vehicles offer better efficacy with fewer side effects compared to conventional chemotherapies that operate in a systemic fashion. However, for targeting nanovectors to join other conventional therapies, their assembly must be facile and modular, providing a timely way to prepare personalized therapies quickly for individual patients.

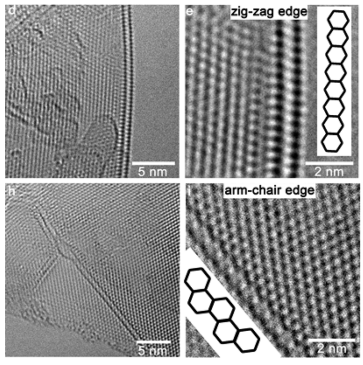
In a new proof-of-principle study, Sano *et al.* (DOI: 10.1021/nn204885f) demonstrate a novel combination of nanovector, drug, and targeting antibody, all joined noncovalently. The researchers started with hydrophilic carbon clusters functionalized with the biologically friendly molecule poly(ethylene glycol). They created their targeted chemotherapeutic by mixing this vector with paclitaxel, a drug used to treat a variety of cancers, and cetuximab, a monoclonal antibody that exclusively binds to epidermal growth factor receptor—a protein overexpressed in most head and neck squamous cell carcinomas. This combination showed similar toxic effects *in vitro* compared to other nontargeted formulations of paclitaxel. However, the targeted nanovector showed significantly greater effects *in vivo* in mice with grafted human tumors and enhanced the effects of radiation, a clinically significant therapy model often used in human patients. The authors note that in future studies it will be necessary to optimize the formulation for maximum radiosensitization before this therapy is ready for clinical use.



Nanotubes Bursting at the Seams

Graphene continues to be a popular subject for nanotechnology research because of its unique electrical, thermal, and mechanical properties, which could prove useful in a variety of applications. Thin strips of this material, known as graphene nanoribbons (GNRs), have semiconducting properties that may eventually provide an alternative to silicon semiconductors. Graphene nanoribbons have been synthesized in a variety of ways, including mechanical cleavage followed by lithography, etching, and chemical stripping, as well as chemical vapor deposition. However, these methods all have the drawback of producing GNRs with rough edges that significantly affect their electronic properties and chemical activities. No method yet exists to synthesize bulk quantities of GNRs with atomically smooth edges.

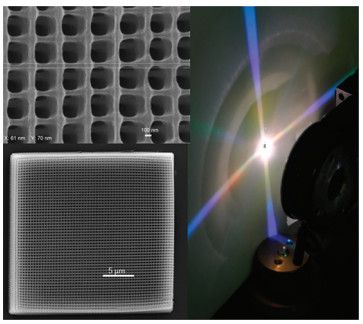
In a new study, Morelos-Gómez *et al.* (DOI: 10.1021/nn2043252) reveal a novel method to synthesize large numbers of smooth-edged GNRs. Their technique relies on inserting molecular nitrogen into multiwalled carbon nanotubes, then rapidly expanding the tubes with a fast thermal shock. The researchers first treated the nanotubes with a mild acid solution, which opens the nanotubes' ends and allows introduction and diffusion of liquid N_2 inside and within surface defects. Exposing these N_2-impregnated nanotubes to boiling water subsequently led to fractures, efficiently unzipping them into one of three different structures: partially unzipped nanotubes exhibiting a V-shape, curved nanoribbons, or flat nanoribbons. Nearly half the nanotubes in a large sample were unzipped with this simple technique, all with atomically smooth edges exhibiting either zigzag or armchair terminations. The authors suggest that this method could be used to unzip other carbon nanostructures into graphene, as well as intercalated layered materials, including BN, MoS_2, and WS_2.



A New Way To Write in Hi Res

Several studies have proven the potential of a recently developed method, known as direct laser writing (DLW), to fabricate three-dimensional (3D) microstructures and nanostructures for a variety of applications. Direct laser writing involves using the beam of an ultrafast laser on a photosensitive material, polymerizing it within the focused beam volume, and creating arbitrary patterns. Later, the bulk material can be immersed in a solvent, dissolving away unpolymerized material and revealing a 3D structure. This method can produce structures readily and efficiently. However, it lacks the resolution of other competing technologies, such as e-beam lithography. While this latter technique can produce structures with resolution on the order of tens of nanometers, the resolution of DLW currently hovers around hundreds to thousands of nanometers.

Seeking to improve on this standard, Sakellari *et al.* (DOI: 10.1021/nn204454c) developed a new method based on quencher diffusion, which mops up radicals

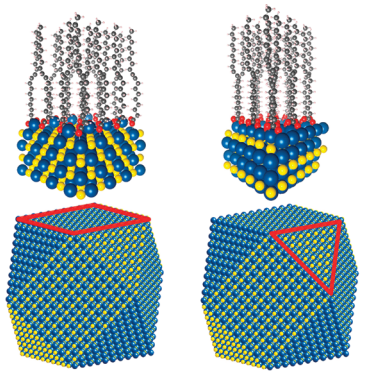


generated by the laser beam and significantly improves resolution of the resulting polymer structures. The researchers used 2-(dimethylamino)ethyl methacrylate as their scavenger, a photopolymerizable amine-based monomer built into the backbone of the photosensitive starter material. Using a slow laser scanning speed, the researchers created woodpile structures of various periodicities, the smallest of which had 400 nm interlayer spacing. This spacing is the smallest to date in woodpile structures using a single laser beam. The same material crafted without the quencher showed a periodicity limit of 900 nm for the same woodpile structure. The authors suggest that this method offers an attractive alternative to other 3D photopolymer structuring methods.

Ligands on Nanoparticle Surfaces: A Shape Changer

Nanocrystals have a broad range of electronic, optical, and catalytic properties that are currently being exploited for a variety of applications. These properties are highly tunable through adjustments of nanocrystal shape, which also plays a key role in how nanocrystals self-assemble and pack. Although researchers have long known that several factors influence nanocrystal shape, including the capping layer of organic surface ligands used to synthesize these materials, how capping ligands exert their influence has remained unknown. Additionally, investigators have been unsure of whether it might be possible to take advantage of this effect to predict or to influence shape through the use of these ligands.

To answer these questions, Bealing *et al.* (DOI: 10.1021/nn3000466) used density functional theory calculations to determine the binding energy of the capping ligand oleic acid on PbSe nanocrystals, a material that has been widely explored as a candidate for photovoltaic and optoelectronic applications. Results showed that binding energies differed significantly between the {100} and {111} facets of these nanocrystals, leading ligands to bind more strongly to the {111} surfaces. Modeling experiments based on Wulff construction suggest that this difference in binding has real consequences for the shape of PbSe nanocrystals. Namely, at low concentrations of ligand, only the {111} surface is passivated, leading the nanocrystals to develop an octahedral shape. As concentrations increase, the nanocrystal cores progress through a full range of shapes, ending at cubic at the highest ligand concentrations. Experimental evidence using transmission electron microscopy supports these theoretical findings. The authors suggest that using these findings to control nanocrystal shape could hold significant advantages in customizing these materials for desired applications.



A Logical Result for Chemically Assembled Single-Electron Transistors

Single-electron transistors (SETs), which allow flow of only a few electrons at a time, are attracting increasing attention as viable alternatives to field-effect transistors. These nanodevices provide low power consumption, high charge sensitivity, and the potential for multigate logic operation, which could prove beneficial in a variety of applications. One of their best advantages is size. Because SETs are only tens of nanometers wide, these transistors are orders of magnitude smaller than their traditional silicon transistor counterparts. One drawback to SETs is their need for exacting construction. With double-barrier tunneling junctions using Coulomb islands and gates, developing a method to fabricate stable SETs with a precise structures in bulk is key to their applied use.

In a step toward that goal, Maeda *et al.* (DOI: 10.1021/nn3003086) fabricated double-gate SETs using chemical assembly. To forge the source and drain electrodes and two side gates, the researchers used electroless gold plating. In the 10 nm gap between the electrodes, they placed a single 9 nm Au nanoparticle by chemisorbing it to the substrate surface. When current was applied to either gate, results showed periodic and stable Coulomb oscillations. Operating the nanodevices at 9 K, further experiments showed that the SETs could successfully perform all two-input logic operations, including XOR, XNOR, NAND, OR, NOR, and AND. Each of these operations was performed with an on/off ratio of 10^2. The authors note that this chemically assembled SET could prove useful in devices that perform these logic gate operations with precision and stability.