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EDITORIAL

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Chemistry at the Nano−Bio Interface

The interface of biology and inorganic materials represents one of the fastest growing and most promising areas of nanotechnology. The fifth issue of *JACS* Select contains 22 Communications and Articles from 2008 and early 2009 that illustrate the breadth and creative energy of this young field.

Although the use of colloidal particles of metals and semiconductors as pigments dates back many centuries, and although the recipe for stable 6 nm diameter particles of gold ("Ruby gold") was famously devised by Faraday in 1857,[1] the unique properties of nanomaterials and their promise for applications in biochemistry, cell biology, and medicine have only recently been appreciated. Prior to the 1990s, the principal role of inorganic colloids in biological research was as high-contrast stains for electron microscopy.[2] A paradigm shift occurred in 1996, when Mirkin, Alivisatos, and co-workers coupled metal nanoparticles to DNA.[3] Their experiments demonstrated not only that DNA could be used for the organization of nanostructures, as had been suggested in earlier experiments by Seeman,[4] but also that nanoparticles were highly sensitive spectroscopic reporters for the base-pairing of DNA. Advances in the synthesis of crystalline, size-selected, and epitaxially capped semiconductor quantum dots early in the 1990s[5] set the stage for their conjugation to antibodies that could target them to specific biological molecules in cells.[6] These experiments demonstrated that brightly luminescent quantum dots were effective for intracellular imaging and were potentially competitive in that role with fluorescent molecules and proteins. Almost simultaneously, techniques were devised for controlling the size and understanding the magnetic behavior of transition metal oxide and magnetic alloy nanoparticles. By the end of the 1990s, bioconjugated magnetic nanoparticles were used for sophisticated imaging experiments[7] as well as for the targeted destruction of cancer cells.[8] Carbon nanotubes were discovered in the early 1990s, and versatile techniques were also developed for growing semiconductor nanowires.[9,10] Nanotubes and nanowires, because of their extreme aspect ratio and sensitivity to charge-transfer interactions, proved to be very sensitive platforms for the detection of biomolecules.[11]

Research in the current decade has led to a much more sophisticated set of tools for controlling the size, shape, dispersity, and surface chemistry of nanoparticles. The complexity of nanoparticle structures — as nanoshells, prisms, Janus particles, derivatized nanotubes, core−shell particles, and striped nanowires, to name a few — offers new tools to tailor particles to specific problems in ultratrace detection, imaging, drug delivery, DNA/RNA delivery, and therapy. Sophisticated schemes for signal amplification, enhanced bioaffinity through multivalency, and cooperative binding highlight the synergy of nanoparticles as platforms for biological molecular recognition. The deliberate design of nanoparticles for biological applications, for example for drug delivery or for dual functions (such as imaging and magnetic manipulation of cells), has been enabled by these new advances in nanoparticle synthesis. In addition, nanoparticles and nanotubes, when properly functionalized, can be used as effective vehicles for controllable generation of

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singlet oxygen,[12,13] one of the most important cytotoxic agents for photodynamic therapy. The publications highlighted in this issue of *JACS* Select illustrate especially well how biocomposite nanoparticles are currently being designed for new and often unprecedented functions.

Nanoparticles can have several functionalities that enhance their effectiveness for drug delivery, including transport and targeting within cells and controlled release. The first six publications in this issue illustrate some of the new design principles that are being applied to this problem. **Feldheim**, **Margolis**, and **Melander** show that binding a weak inhibitor of HIV fusion to gold nanoparticles results in strong inhibition via multivalency.[14] The increased affinity that results from binding a CCR5 agonist to 2 nm gold nanoparticles is sufficient to overcome the need for a previously required quarternary ammonium group, which gave the agonist poor pharmacological properties. **Dai** and **Lippard** studied single-walled carbon nanotubes coupled via a Pt(VI) complex to a folic acid ligand.[15] The folate "oars" on the nanotube "longboat" enable it to target selectively tumor cells that overexpress folate receptors on their surface. The cisplatin "warhead" is armed inside the cell by reduction from Pt(IV) to Pt(II). Gene silencing by siRNA is a powerful tool both for understanding gene function and for targeted therapy, but its applications are limited by the instability and delivery problems of RNA. Two contributions describe new strategies for delivery of short-interfering RNA (siRNA) to cells using nanoparticles. **Nie** and **Gao** address the delivery problem by coating semiconductor quantum dots with proton-absorbing polymeric layers that allow the nanoparticle and its siRNA cargo to perform the functions of cellular penetration, endosomal release, carrier unpacking, and intracellular transport.[16] **Mirkin** shows that that the high packing density of siRNA on the surface of gold nanoparticles inhibits its degradation by nucleases and promotes its uptake by HeLa cells.[17] Two publications, by **Lin**[18] and **Férey**,[19] illustrate how porous metal−organic frameworks (MOFs), constructed by connecting metal ions with bifunctional linkers, can be made as nanoparticles and can carry therapeutic drugs such as cisplatin and ibuprofen for controlled delivery and release.

The special optical and electronic properties of nanoparticles have made them very useful platforms for sensitive molecular detection in complex, interfering media such as biological and environmental fluids. The next six contributions illustrate the range of new nanoparticle-based designs that are being developed for biosensing schemes. **Huo** has devised a method for detecting prostate-specific antigen (PSA) using complementary antibodies on spherical and rod-shaped gold nanoparticles.[20] The strong scattering properties of the nanoparticle conjugate formed in the presence of the antigen allow detection of PSA at 0.5 ng/mL. **Liu** exploits the highly cooperative base-pairing of DNA bound to gold nanoparticles, which results in sharp melting transitions, to develop a new colorimetric sensor for Hg^{2+} ions.[21] The binding of Hg^{2+} between mismatched thymine bases tips the balance in favor of hybridization and particle aggregation at room temperature. The folding state of DNA aptamers on gold nanoparticle surfaces modulates their electrostatic interactions and thus also affects the aggregation of particles. **Brook** illustrates how this effect can be used to make colorimetric biosensors based on gold nanoparticles.[22] The two following articles, by **Suzuki**[23] and **Yang**,[24] show how fluorescence resonant energy transfer (FRET) and luminescence quenching of bound fluorescent dyes can be used in biosensing schemes with quantum dots and carbon nanotubes, respectively. **Calvo** exploits both the scattering and electrochemical properties of core−shell gold−glucose

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oxidase nanoparticles to develop a surface-enhanced Raman-based sensor for glucose in the low millimolar concentration range.[25]

The next six publications in this issue report hybrid nanoparticles and nanoparticle conjugates that combine properties for cell targeting, imaging, and manipulation. Through increasingly sophisticated synthetic methods, these multifunctional particles are being made smaller so that they are less subject to nonspecific binding and can have enhanced extravascular transport properties. **Sun** reports ultrasmall (8 nm) peptide-conjugated Fe_3O_4 particles that accumulate preferentially in tumor cells and allow for high-contrast magnetic resonance imaging.[26] **Nocera**, **Ting**, and **Bawendi** report a new capping strategy for small semiconductor quantum dots that confers water solubility and allows for simple modification with both small molecules and proteins for FRET-based reporting of cellular microenvironments.[27] Cobalt ferrite nanoparticles were conjugated by **Zhang** to ligands that target receptors on ovarian cancer cells. Metastatic cancer cells could be magnetically separated from the peritoneal cavity and circulatory system of mice in vivo by this technique.[28] The next three contributions, by **Pellegrino**, **Roux**, and **Xu**, describe new designs for multifunctional nanostructures that combine optical and magnetic imaging components[29,30] and also allow for the physical manipulation of nanoparticles within cells through magnetic interactions.[31]

The last four Articles and Communications in this issue illustrate new ideas for using biomolecules to make complex nanostructures that contain inorganic nanoparticles. Although not yet applied to biological problems, these kinds of nanostructures highlight the similar sizes of their nanoparticle and biomolecular building blocks and show how the combination can result in tightly controlled assemblies that could have quite interesting biological, electronic, and plasmonic properties. **Rosi** used phage display to evolve dodecapeptides that nucleate the formation of gold nanoparticles coupled to an aliphatic chain at their C-terminus. The result is a self-assembling peptide double helix studded with nanoparticles at very regular spacing.[32] **Yan** and **Liu** developed a robust DNA−nanoparticle linking method that gives reliable nanoparticle binding to DNA-programmed assemblies.[33] **Alivisatos** and **Fréchet** used DNA ligases to develop a strategy for linking gold nanoparticles with single-stranded DNA.[34] Finally, **Niemeyer** developed a three-chromophore FRET system based on quantum dot−yellow fluorescent protein dyads bound to DNA, which bind a third chromophore through DNA base-pairing.[35] The dyad gives strong absorption and high quantum yield emission for FRET over very long distances.

We hope that this issue of *JACS* Select will give the reader a current snapshot of the scope of scientific activity at the nano−bio interface. What is most exciting about this field is that it continues to evolve very rapidly, driven by the practical need for improvements in biomedical analysis and therapy and by the fast pace at which the chemistry of nanomaterials continues to develop. We are certain to see many more exciting developments in this field over the next decade.

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