Virtual Issue on Nanomaterials for Drug Delivery

As the development of nanotechnology has extended to the world of biomaterials, a revolution has occurred in the design of nanomaterials systems for drug delivery that have the potential to impact drug efficacy and patient outcomes significantly for some of our most critical medical challenges, including cancer, infectious disease, and a broad range of genetic disorders. As chemists, materials scientists, engineers, and others begin to apply their expertise and capabilities toward biomedical applications, our ability to manipulate nanotechnology to address these important problems has led to the establishment of a burgeoning new field that has been heavily represented in *ACS Nano* since the journal's first issue in 2007. From the start, these have been among our most exciting and highest impact papers. In this virtual issue,[1] we cover a subset of these articles that address some of the most important aspects of this new world of nanomedicine, as well as many of its challenges and future directions. Some of the most critical themes in the field are addressed in the *ACS Nano* Perspective on the "Impact of Nanotechnology on Drug Delivery", by Farokzhad and Langer.[2] This short article gives insight from the unique perspective of a team that has worked closely at the threshold of translation of nanomaterials from the laboratory to the clinic. At the time of publication of this issue, we are seeing the first active, or molecularly targeted, polymeric nanoparticles enter clinical trials, a promising sign for the future of the field. The use of nanomaterials has enabled us to address a number of problems with traditional delivery systems, as outlined in the Perspective, including increased bioavailability of the drug, a means of targeting drug delivery to desired cells or tissues, and the potential to combine functionalities within a nanomaterial, such as imaging and delivery.

From the start, papers in *ACS Nano* have addressed nanomaterials for drug delivery. Now, we collect a series of papers in a virtual issue on the topic.

Drug delivery nanoparticles have become key vehicles for the encapsulation and delivery of a range of drugs, including cancer drugs, because their small size enables them to accumulate through the leaky tumor vasculature into the tumor as a means of passive targeting. Both organic and inorganic materials have been examined for nanoparticle delivery, each with its own set of advantages. Inorganic materials systems often have inherent electrical, optical, or other electromagnetic properties that can be used for multifunctionality—for example, imaging and delivery—or manipulated to facilitate the delivery and release of drugs in the body. Over the past few years, one of the inorganic materials of great interest has been mesoporous silica, a low-cost, relatively nontoxic, and readily accessible inorganic system that can easily incorporate other inorganic materials for magnetic or

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optical properties, while exhibiting surfaces that are easily modified using a range of different surface chemistries. The power and potential of drug delivery using mesoporous silica vehicles was presented by Liong *et al.*,[3] who demonstrated the incorporation of hydrophobic cancer drugs within the pores, while creating hydrophilic exterior surfaces with low aggregation and the ability to add a range of inorganic components in these systems. Noble metals, in particular, gold, also present relatively bioinert surfaces that can be readily modified for specific functions; Ghosh *et al.*[4] demonstrated that modification of gold nanoparticles with thiolated-lysine-based functional groups enables the optimization of positive charge on the particles for DNA condensation and delivery; once uptake occurs, however, the gold−thiolate bonds used to modify the particles are reversed in the presence of the naturally occurring glutathione present inside the cell. The group thus takes advantage of the gold−thiol bond to yield the effective unwrapping of the DNA in the intracellular environment for high gene transfection and low cytotoxicity. Gold and similar metal nanoparticles can also exhibit unique properties due to the combination of their size and electro-optical properties. Hamad-Schifferli and co-workers[5] used the fact that gold nanoparticles of different shape and size absorb light at different wavelengths as a means of selectively melting away gold nanorods with different DNA plasmids bound to their surfaces with ultrafast laser irradiation at the resonance peak of the desired nanoparticle. The ability to deliver a set of different nanoparticle systems intravenously and have them release different cargos at different times by "remote control" is an appealing concept enabled by the unique properties of materials at the nanoscale.

Our ability to manipulate nanotechnology to address these important problems has led to the establishment of a burgeoning new field.

Many newer materials to enter the nanomedicine arena are carbon-based. The use of carbon nanostructures has been extensive in areas such as energy and electronics due to their electrical and optical properties; however, their unique size and structure can also be highly advantageous in drug delivery. Hongjie Dai and co-workers[6] illustrated that the graphene sheet composition and high surface area of single-wall carbon nanotubes (SWNTs) enables the use of aromatic π stacking to adsorb large amounts of small-molecule drugs, dye molecule tags, and shield poly(ethylene glycol) (PEG) chains to the surfaces. This noncovalent attachment can be disrupted at lower biologic pH, and the degree and extent of adsorption is controlled by the diameter of the nanotube, which determines the strengths of these interactions and thus the rate of molecule release in the body. New concepts such as these enable the nanoparticle community to use carbon nanotubes as a new platform for drug delivery. Newer papers have just been published that explore different aspects of carbon nanocarriers. Bhirde *et al.*[7] demonstrate that SWNTs that are covalently conjugated with quantum dots and an anticancer agent, along with a molecular targeting peptide that binds with a receptor overexpressed on tumor cells can lead to targeted tumor cell death, tumor remediation, and simultaneous tumor imaging in animal models. Sengupta and coworkers[8] have compared the effect on shape of carbon nanocarrier by studying high-aspect-ratio carbon nanotubes and spherical modified fullerene molecules with similar diameter when conjugated with an antitumor drug both *in vitro* and *in vivo*. It was found that shape matters a great deal in modulating the angiogenesis of tumors—the growth and maturation of blood vessels—and that this fact can greatly impact the efficacy of drugs delivered by these two vehicles.

Both self-assembly and various forms of directed assembly have played key roles in developing nanoparticles for delivery; here, a number of organic nanoparticles have often been used to great advantage due to their ability to exhibit a broad range of interactions to generate complexes that can be made permanent or reversible. In the first edition of *ACS Nano*, the cover featured the work of Cortez *et al.*[9] on the development of electrostatic multilayered vesicles that can be designed to contain a broad range of hydrophobic or hydrophilic cargo; the layer-by-layer membrane can serve to protect the cargo on the interior and to regulate its release over time. Cortez *et al.* demonstrate that the size and the charge of the outer surfaces of these membranes greatly regulate their interaction with cells,

and that antibodies or other targeting ligands can be attached to the outer surfaces of these layer-by-layer (LbL) core−shell structures to drive molecular targeting. This past year, Zhang *et al.*[10] demonstrated that two simple modified polymers—one exhibiting strong positive charge, and the other with strong hydrophobic interactions—can be designed to interact with each other through a cyclodextrin sugar molecule so as to create complexes that sequester a hydrophobic drug on the interior, and present sufficient positive charge in the exterior water-soluble shell of the resulting complexes as to allow gene complexation. Reversible hydrophobic interactions that can be introduced with increased temperature were used by the Chilkoti group[11] to create dynamic ligand-assembling nanoparticles that arrange into more organized structures when heated slightly above body temperature. When the ligand-presenting elastin block copolymers used in this study are heated, the ligand is presented at the surface of the drug complex in high numbers, thus converting the nanoparticle from a low-binding species in the bloodstream to a high avidity targeting nanoparticle once it reaches the tumor, which is heated during treatment, thus avoiding undesired interactions of the nanoparticle while on its way to the targeted tissue.

This set of papers is a strong sampling of the range of chemistries and nanomaterials synthesis techniques used to generate drug delivery nanoparticles.

Along with the use of reversible interactions and molecular assembly, the synthetic capabilities of the chemistry community have had a large impact on the design of new nanomaterials. An example of a more complex chemistry that has enabled the mimicry or amplification of naturally occurring molecules is the highly branched dendrimer. Landmark *et al.*[12] demonstrated the use of the highly functional dendrimer as a means of presenting molecular targeting ligand with high efficacy and control on the surfaces of iron oxide nanoparticles, demonstrating the use of these highly functional molecules for ligand presentation and particle stabilization. Agrawal *et al.*[13] used positively charged amino dendrimers to functionalize the surfaces of iron oxide nanoparticles in a manner that forms linear functionalized nanoparticle aggregates, or "dendriworms", that are highly effective in the encapsulation and release of siRNA. Hamilton and Harth[14] used dendritic molecules with lysine, guanidine, and related functionality to create molecular transporter macromolecules that act much as cell-penetrating peptides in disrupting the cell membrane sufficiently to provide entry of short peptides directly to the cell's cytoplasm.

The ability to mimic the behavior of biological molecules can be particularly enabling when designing routes for cell entry and intracellular release of the drug contents, particularly when it is important to avoid or lessen exposure to the highly acidic environment of the endosome. Bale *et al.*[15] have recently shown the use of silica nanoparticles that have been directly conjugated with protein cargos for rapid cellular uptake *via* endocytosis; however, these particles rapidly exit the endosome and enable access of the protein in its active form to the cytoplasm. This capability is particularly important for the release of proteins and siRNA, and understanding the mechanisms of release will be one of the future challenges in this field. Finally, although most of the work on nanoparticle delivery has relied on the natural sequestration of nanoparticles in the desired tissue and/or on molecular targeting methods to gain accumulation and uptake by the desired cells, another approach to nanoparticle delivery is to let other cells carry the nanoparticle to the targeted tissue. This concept is very new and relies on the ability to modify the surfaces of cells as well as nanoparticles to generate attachments that are stable and do not interfere with the function of the carrier cell. Anderson and co-workers[16] demonstrated this concept through the direct attachment of nanoparticles to cell membranes using a pH-sensitive neutravidin−biotin conjugation; stem cells modified in this fashion were able to migrate toward tumors and deliver their cargo within the tumor region.

This set of papers is a strong sampling of the range of chemistries and nanomaterials synthesis techniques used to generate drug delivery nanoparticles. They provide some of the strongest examples of the integration of surface chemistry and its impact on drug delivery efficacy, as well as demonstrations of the use of organic, inorganic, and hybrid materials systems that are designed to assemble—or disassemble—under desired conditions within tumors. Finally, we give examples of basic findings regarding the impact of

charge, size, and shape on the delivery of these nanoparticle systems. These are but a few examples of the ever-expanding work in nanoparticle systems being published in *ACS Nano*—providing our readers with a guide to some of the exciting new and important directions and laying out the critical upcoming challenges for nanoparticle delivery and nanomedicine.

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REFERENCES AND NOTES

1. Virtual Issue on Nanomaterials for Drug Delivery. http://pubs.acs.org/page/ancac3/vi/2.
2. Farokhzad, O. C.; Langer, R. Impact of Nanotechnology on Drug Delivery. *ACS Nano* **2009,** *3*, 16–20.
3. Liong, M.; Lu, J.; Kovochich, M.; Xia, T.; Ruehm, S. G.; Nel, A. E.; Tamanoi, F.; Zink, J. I. Multifunctional Inorganic Nanoparticles for Imaging, Targeting, and Drug Delivery. *ACS Nano* **2008,** *2*, 889–896.
4. Ghosh, P. S.; Kim, C.-K.; Han, G.; Forbes, N. S.; Rotello, V. M. Efficient Gene Delivery Vectors by Tuning the Surface Charge Density of Amino Acid-Functionalized Gold Nanoparticles. *ACS Nano* **2008,** *2*, 2213–2218.
5. Wijaya, A.; Schaffer, S. B.; Pallares, I. G.; Hamad-Schifferli, K. Selective Release of Multiple DNA Oligonucleotides from Gold Nanorods. *ACS Nano* **2009,** *3*, 80–86.
6. Liu, Z.; Sun, X.; Nakayama-Ratchford, N.; Dai, H. Supramolecular Chemistry on Water-Soluble Carbon Nanotubes for Drug Loading and Delivery. *ACS Nano* **2007,** *1*, 50–56.
7. Bhirde, A. A.; Patel, V.; Gavard, J.; Zhang, G.; Sousa, A. A.; Masedunskas, A.; Leapman, R. D.; Weigert, R.; Gutkind, J. S.; Rusling, J. F. Targeted Killing of Cancer Cells *In Vivo* and *In Vitro* with EGF-Directed Carbon Nanotube-Based Drug Delivery. *ACS Nano* **2009,** *3*, 307–316.
8. Chaudhuri, P.; Harfouche, R.; Soni, S.; Hentschel, D. M.; Sengupta, S. Shape Effect of Carbon Nanovectors on Angiogenesis. *ACS Nano* **2010,** *4*, 574–582.
9. Cortez, C.; Tomaskovic-Crook, E.; Johnston, A. P. R.; Scott, A. M.; Nice, E. C.; Heath, J. K.; Caruso, F. Influence of Size, Surface, Cell Line, and Kinetic Properties on the Specific Binding of A33 Antigen-Targeted Multilayered Particles and Capsules to Colorectal Cancer Cells. *ACS Nano* **2007,** *1*, 93–102.
10. Zhang, J.; Sun, H.; Ma, P. X. Host-Guest Interaction Mediated Polymeric Assemblies: Multifunctional Nanoparticles for Drug and Gene Delivery. *ACS Nano* **2010,** *4*, 1049–1059.
11. Simnick, A. J.; Valencia, C. A.; Liu, R.; Chilkoti, A. Morphing Low-Affinity Ligands into High-Avidity Nanoparticles by Thermally Triggered Self-Assembly of a Genetically Encoded Polymer. *ACS Nano* **2010,** *4*, 2217–2227.
12. Landmark, K. J.; DiMaggio, S.; Ward, J.; Kelly, C.; Vogt, S.; Hong, S.; Kotlyar, A.; Myc, A.; Thomas, T. P.; Penner-Hahn, J. E..;*et al.*Synthesis, Characterization, and *In Vitro* Testing of Superparamagnetic Iron Oxide Nanoparticles Targeted Using Folic Acid-Conjugated Dendrimers. *ACS Nano* **2008,** *2*, 773–783.
13. Agrawal, A.; Min, D.-H.; Singh, N.; Zhu, H.; Birjiniuk, A.; von Maltzahn, G.; Harris, T. J.; Xing, D.; Woolfenden, S. D.; Sharp, P. A..;*et al.*Functional Delivery of siRNA in Mice Using Dendriworms. *ACS Nano* **2009,** *3*, 2495–2504.
14. Hamilton, S. K.; Harth, E. Molecular Dendritic Transporter Nanoparticle Vectors Provide Efficient Intracellular Delivery of Peptides. *ACS Nano* **2009,** *3*, 402–410.
15. Bale, S. S.; Kwon, S. J.; Shah, D. A.; Banerjee, A.; Dordick, J. S.; Kane, R. S. Nanoparticle-Mediated Cytoplasmic Delivery of Proteins To Target Cellular Machinery. *ACS Nano* **2010,** *4*, 1493–1500.
16. Cheng, H.; Kastrup, C. J.; Ramanathan, R.; Siegwart, D. J.; Ma, M.; Bogatyrev, S. R.; Xu, Q.; Whitehead, K. A.; Langer, R.; Anderson, D. G. Nanoparticulate Cellular Patches for Cell-Mediated Tumoritropic Delivery. *ACS Nano* **2010,** *4*, 625–631.