Multifunctional Micro- and Nanoparticles – *Quo vadis*?

The synthesis of functional polymer particles has been a long-standing interest for materials scientists and — without a doubt — substantial progress has been made in recent decades. The materials used for particle synthesis resulted in a plurality of different types including inorganic materials, polymers, biomolecules, and semiconductor materials. In addition, there have been broad efforts in surface modification of particles to render their surfaces biofunctional. These methods resulted in immobilization of stealth polymers, such as poly(ethylene glycol), to render particle surfaces protein-resistant, or strategies to introduce targeting molecules on the surface of particles to control their biodistribution after administering them to the human body. The virtue, with which some of these syntheses have been performed, has been simply astonishing. Still, biological function has been mostly generated through intelligently designed synthetic methods and controlled surface modifications. These efforts have to some extent ignored other aspects of particle design, such as particle shape, architecture, texture, or mechanical stiffness.

By recognizing that physical properties of particles may be as important as their chemical make-up, scientists are currently launching a new area of multifunctional particles that takes advantages of a redefined and widely enlarged design space. It is the intent of this *Special Issue* to share some of the enthusiasm and excitement that is associated with what might become a radical change in how we think about particles for biomedical applications.

Shape

Shape is one of the most essential properties of multifunctional particles controlling cellular responses. Recently, several methods have emerged to fabricate particles of diverse shapes. Initially, nanocrystals with a wide range of shapes were prepared. A number of different approaches have been put forward control shape of nano- and microparticles, which include mechanical stretching, soft lithography, microfluidics, and self-assembly to name just a few examples.

Here, Weitz et al. used droplet microfluidics to create non-spherical particles. A major feature of this approach is the high degree of control provided by microfluidic technologies, which is instrumental in creating monodisperse emulsion droplets. Through subsequent processing steps, such as arrested coalescence, asymmetric polymer solidification, polymerization in microfluidic flow, and evaporation-driven clustering, an astonishing range of non-spherical particles that are defined in both size and shape can be prepared. Alternatively, Urban et al. synthesized particles with acorn-shaped morphologies based on two distinct phase-separated copolymers within the same colloidal particle. In this example, the authors used poly(methyl methacrylate)/*n*-butylacrylate and poly(*n*-butylacrylate)/pentafluorostyrene phases.

Doyle et al. report an intriguing photolithographic approach towards particles that mimic red blood cells in some of their key properties. Mimicking natural cells, such as blood cells, is believed to be a highly promising strategy towards the synthesis of particles with extended circulation times. As in the paper of Doyle et al., the Discher and Christian groups have recognized the importance of mechanical flexibility by developing stable and flexible polymersomes. In their Communication, copolymer-based vesicles were designed that combine in unique ways extended in vivo circulation times with the capability for controlled release of drugs. Taking advantage of the fact that red blood cells carry negative charges, the groups devised a strategy that mixed polyanionic block copolymers into polymersomes.

Why is shape actually so important for biomedical applications? The contribution by Mitragotri et al. sought to address exact this question. Their motivation was to elucidate whether particle shape influences the rates of particle endocytosis and their intracellular distribution in endothelial cells. The authors first synthesized poly(lactide-*co*-glycolide) particles with spherical and elliptical shapes. They found that elliptical disks with an aspect ratio of 5 were endocytosed at a slower rate compared to 1.8-μm-diameter spheres of the same volume, suggesting that the non-spherical shape may result in unusual kinetics and equilibrium distributions within cells.

Interfacial Anisotropy

The nano- and microstructure of surfaces has been established as a decisive factor related to particle–cell interactions. These and other aspects have sparked a keen interest in particles with interfacial anisotropy. Among the most widely investigated systems are so-called Janus particles. The review by Kretzschmar et al. highlights common approaches towards Janus particles including particle and nanosphere lithography and glancing angle deposition. This in-depth Review demonstrates the structural richness of this emerging field, but also critically addresses current shortcomings, such as the need for scalable particle production processes. In an interesting variation of existing processes towards Janus particles, Li et al. report that polymer single crystals can serve

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as generic substrates to create Janus particles by spatially controlled immobilization of nanoparticles. Here, single crystals of poly(ethylene oxide), polycaprolactone, and polyethylene-*block*-poly(ethylene oxide) have been successfully used to template a range of nanoparticles, such as gold, magnetite, and semiconductor nanoparticles.

Compositional Anisotropy

Beyond the surface anisotropy of Janus particles, recent efforts have been aimed at creating particles with truly compositional anisotropy. In such particles, multiple compositionally different subcompartments coexist. Each of these compartments can, in principle, be made of different materials or loaded with different additives. Here, the Lahann and Stellacci groups demonstrate that gold nanocrystals can be selectively incorporated into only one hemisphere of compositionally anisotropic polymer particles. The authors used the electrohydrodynamic co-jetting process to formulate this novel type of multifunctional particles. This study describes a flexible approach towards inorganic/organic composite particles with precisely engineered distribution of inorganic nanocrystals. Using a related experimental approach, Loscertales et al. achieved encapsulation of poly(*N*-isopropylacrylamide)-based monodisperse microgels within microfibers of crosslinked poly(vinyl pyrrolidone) using electrospinning. Interestingly, the authors found an increase in absorbance that was substantially larger after swelling. In addition, the change in absorbance could be tuned by controlling external factors, such as temperature or pH of the medium.

Velev et al. conceptually combined these two strategies by synthesizing both shape-anisotropic (''doughnut'') and composition-anisotropic (''patchy magnetic'') supraparticles. In this effort, the shape is guided by the initially formed droplet meniscus. During subsequent solvent evaporation, shape transitions (concaving) occur that result in doughnut supraparticles. In addition, compositional anisotropy was achieved by using a mixed suspension of two types of particles: latex and magnetic nanoparticles, while exposing it to magnetic field gradients. Controlling the magnetic field results in a wide range of different particle architectures including bilateral or trilateral patched spherical particles.

An alternative approach towards unusual particle shapes is through self-assembly of multifunctional particles. As novel types of multifunctional particles with ever improved control over key properties emerge, they offer novel possibilities for self-assembly that truly distinguish them from conventional particles. By systematically varying the anisotropy dimensions of internal bond angles and chemical ordering, Solomon et al. identified interesting non-close-packed assemblies. They unambiguously relate the structure of the observed assemblies to building block anisotropy. An important aspect of this work is that it outlines a holistic approach based on synthesis, simulation, and assembly that ultimately may yield in design rules that can guide future particle fabrication efforts.

Biomedical Applications of Multifunctional Particles

Sasisekharan et al. review biological factors that govern the development of cancer and point out decisive aspects that emerge from such considerations. A specific emphasis is given to the potential of designer particles for cancer diagnostics and drug delivery. An important aspect of this highly informative Review is a critical perspective on the emerging role of macromolecular biophysics and computational nanotechnology in engineering spatiotemporally-regulated anti-cancer systems.

Putting another twist on microfluidics, Kumacheva et al. used a microfluidic set-up to produce spherical bubbles with diameters below 10 μm. To stabilize the bubbles, they were encapsulated with a protein–polysaccharide shell. Stable bubbles are of substantial interest to the biomedical community as contrast agents for medical imaging.

The study of Clark et al. investigated previously established sensor particles, so-called optodes, for monitoring cellular ion flux in cardiomyocytes. For this purpose, optodes were applied to a glass surface for fluorescent imaging of potassium ion flux during the repolarization phase of the cardiac action potential. They further demonstrated a decrease in the flux in response to a known inhibitor.

Finally, a novel type of multifunctional sensor particles is presented in the work by Kotov et al. Complex nanoparticle assemblies with magnetoplasmonic properties were in fact prepared from individual building blocks. The prepared superstructures are based on magnetic Fe_3O_4 nanoparticles encapsulated in silica shells (magnetic function), surrounded by gold nanoparticles (plasmonic function), and coated with poly(ethylene glycol) (protein-resistant function). Through a comprehensive set of experiments, the authors demonstrate both imaging and therapeutic functions of the nanoparticle assemblies in a cancer model system.

While by no means meant to be comprehensive, this issue provides selected snapshots on the exciting progress that the design and synthesis of multifunctional micro- and nanoparticles has witnessed today. Given the impressive pace of progress and the wide range of high-impact applications that can potentially be addressed by advanced particle

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designs (see Review by Sasisekharan et al. in this issue), the future of multifunctional micro- and nanoparticles seems almost beyond boundaries. By editing this *Special Issue*, it was my intent to convey some of the passion and excitement about this emerging field.

I hope you will enjoy reading it!

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