Biointerphases

EDITORIAL | DECEMBER 19 2016

Preface: In Focus Issue on Nanoparticle Interfaces

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Biointerphases 11, 04B101 (2016)
https://doi.org/10.1116/1.4972396

Preface: In Focus Issue on Nanoparticle Interfaces

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(Received 5 December 2016; accepted 5 December 2016; published 19 December 2016)
[http://dx.doi.org/10.1116/1.4972396]

Since 2000, the Web of Science reveals that the number of academic papers using the term "nanomedicine" has increased exponentially from only a few to over a thousand, and there are many examples of the creative use of nanoparticles for the purposes of medical imaging, disease diagnosis, drug delivery, and therapeutic applications such as targeted radiation and photothermal therapy. For example, in this issue, Cappitelli *et al.*,[1] Cortes,[2] and Meng[3] describe the use of nanoparticles (NPs) to address two of the most important health challenges facing society: the need for new antimicrobials and the treatment of cancer.

The translation of these promising studies into practical commercial endeavors is slowly gathering pace. There are now many tens of companies producing nanoparticle-enabled products for the life sciences. However, interactions of nanoparticles with living systems are particularly complex, and this has slowed the implementation of nanomaterials in medical products and clinical applications. Moreover, the scaling-up of lab bench products is sometimes not feasible or too costly from a commercial competitiveness point of view. This problem is widely recognized and was emphasized in a recent editorial for ACS Nano which called for standardization in measurement practice for academic publications.[4] Notably, although the editorial pointed to surfactants and trace impurities as a major barrier to progression, the examples of techniques which should form part of the standard characterization portfolio would generally be quite incapable of identifying such contaminants. It is often not the nanomaterial itself that is the issue, but what is attached to the interface that defines irreproducibility and biological performance. Exploitation of nanoparticles has been hindered by concerns over the toxicity of these new materials, where surface properties and chemistry are of critical importance, as highlighted by Mohanan *et al.*[5] in this issue. On the other hand, the development of reliable methods to detect and identify nanoparticles in complex matrices (e.g., food, biological media) and commercial products is also of a great importance both for manufacturers and policy makers as illustrated by Antonio, *et al.*[6]

The challenges of producing reliable nanomaterials are not confined to nanomedicine, and mechanisms should be put in place to ensure reproducibility and confidence in nanomaterial manufacture. This issue is explored by Baer *et al.*[7] in this In Focus issue, where potential solutions to variability in synthesis, change during storage and transportation and validation are outlined. One of the most important gaps in much of the early literature is appreciating the pivotal role of nanoparticle surfaces in their behavior and performance. The surface is tweaked, tuned, and adapted to provide a functionality, such as reduced protein adsorption or specific biological interaction. However, as noted above, validation of these procedures is often lacking and therefore the robustness and efficiency of the procedures are unknown. Many articles in nanomedicine are accompanied by seductive images of idealized nanoparticles with perfect and pure coatings of well-defined chemistry. Yet few not many of these images are backed up with experimental evidence. The functional performance of the particles is the usual test of the effectiveness of their design, but is this adequate? If only a small fraction of the particles work, the design may be deemed successful in many functional tests, but the majority of the particles may not be functional: it is our impression that such situations are common. Proof of principle will be shown, but efficiency and reproducibility will be inadequate for any practical use.

Measurement techniques for nanoparticle structure and interfaces are few and far between and it is a particular challenge to measure surfaces that consist of organic molecules. Rafati *et al.*[8] and Minelli *et al.*[1] describe how surface analytical techniques can be usefully applied to gold nanoparticles, and Dietrich *et al.*[9] shows the possibility of determining detailed chemical state measurements of individual particles using advanced synchrotron methods. Such methods require development to become part of the standard portfolio of characterization techniques for particles in which the surface chemistry is known to be important.

In the context of biomedical nanoparticles, it is usual to think of the surface as something that should be modified and controlled to achieve a desired property. For example, Lopez-Marin *et al.*[10] describe how coatings can be used to increase the effectiveness of drug delivery through sonoporation, Wei *et al.*[11] outline routes to use hydrophobicity to achieve specific targeting of particles, and Yingling *et al.*[12] demonstrate the use of cationic coatings to bind nucleic acids. Minelli *et al.*,[13] building upon the work of Sarikaya *et al.*,[14] show that peptides specifically adapted to interact with inorganic materials may be coated on surfaces and nanostructures, such as atomic force microscopy (AFM) tips.

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The selective interaction properties of these peptides appear to be retained and can be used to provide chemical contrast in AFM experiments and, potentially, to selectively capture nanomaterials. Moreover, Fu *et al.*[15] investigate adhesion forces of living cells by means of AFM tips modified with Ag and Au nanoparticles clusters. Results indicate that the adhesion forces depend upon nanoparticle size and charge and, for a given NPs size, AFM-Au NPs cluster tips interact strongly with cell membranes with respect to Ag NPs modified AFM-Tips.

In contrast to the use of coatings to change the properties and efficiency of nanoparticles, particles themselves can alter their surroundings through surface interactions: a property that has been exploited in catalysis for over a century. The size-dependent changes in chemical reactivity that have been exploited in that field for so long are not widely appreciated or used in nanomedicine. In this issue, Singh[16] reviews the catalytic properties of nanoparticles of ceria, arguing that their activity is similar to biological catalysts. Calzolai *et al.*[17] describe a quite surprising property of gold nanoparticles in retaining the structure of protein coatings even under conditions where the native protein is completely denatured. Such studies point to the possibility of tuning the biological interfacial reactivity of particles if their size, shape, and dispersity can be controlled, and these exciting properties may, in the future, be used to diagnose diseases with greater certainty and treat diseases through directed interactions.

Overall, this In Focus issue provides a snapshot of current challenges and opportunities for nanomaterials in biology and medicine. The articles highlight the need for reproducibility, traceability, control, and measurement of nanoparticles so that their unique properties, which are outlined herein, can be exploited for the benefit of humankind. It is our opinion that we are on the cusp of a revolution in disease diagnosis and treatment which exploits nanotechnology, and the impact of nanotechnology as a *disruptive technology* in medical applications will likely come in the next decades. In terms of the Gartner "hype cycle," we are crossing the "trough of disillusionment" where the initial inflated hopes of rapid exploitation have foundered. The realization that exquisite properties require exquisite reproducibility in nanomaterial manufacture has been made and, for some particles such as quantum dots, addressing this challenge has led to their incorporation in, and enhancement of, consumer products. Once this lesson is learned in nanomedicine, there is a bright future.

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