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Current Opinion in Biotechnology

Advances in the clinical translation of nanotechnology

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The use of novel materials in the nano-scale size range for applications in devices, drugs and diagnostic agents comes with a number of new opportunities, and also serious challenges to human applications. The larger size of particulate-based agents, as compared to traditional drugs, allows for the significant advantages of multivalency and multifunctionality. However, the human use of nanomaterials requires a thorough understanding of the biocompatibility of the synthetic molecules and their complex pharmacology. Possible toxicities created by the unusual properties of the nanoparticles are neither well-understood, nor predictable yet. A key to the successful use of the burgeoning field of nanomaterials as diagnostic and therapeutic agents will be to appropriately match the biophysical features of the particle to the disease system to be evaluated or treated.

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Current Opinion in Biotechnology 2017, **46**:66–73

This review comes from a themed issue on **Nanobiotechnology**

Edited by **Benjamin G Davis** and **Christopher Serpell**

For a complete overview see the Issue and the Editorial

Available online 7th February 2017

http://dx.doi.org/10.1016/j.copbio.2017.01.002

Introduction

The field of nanotechnology, which is the study and application of materials on the nanometer scale, is rapidly expanding its reach into many areas that will have great impact on computing, electronics and power, and healthcare. The nanomedicine field encompasses the development of new materials and their manipulation for devices, drugs and diagnostics. In this brief review, we will focus on recent translational advances in the use of nanometer-scale materials to develop diagnostic and therapeutic agents for human disease, focusing on drug and nucleic acid delivery, imaging, and sensors. Other comprehensive reviews of this enlarging field have been published [2–7].

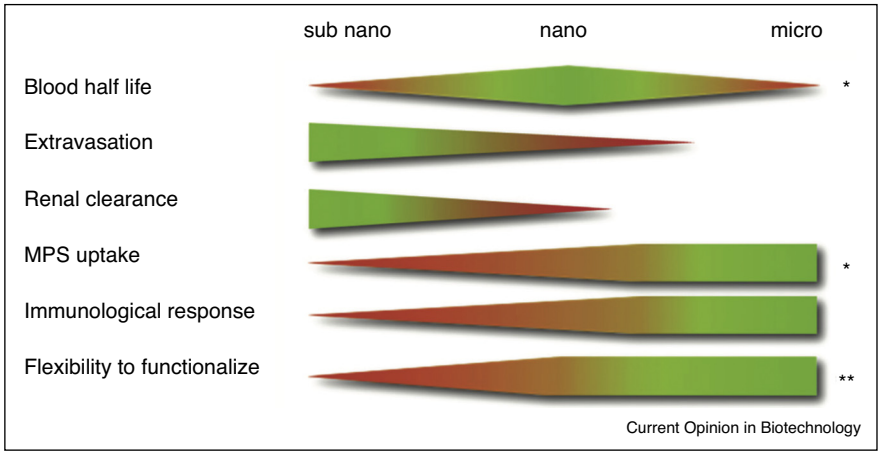
Traditionally the materials that define this technology ranged from 1 to 100 nm in a single dimension. At this size range, particles may take on new bio-physical characteristics not revealed in the same materials at a larger or smaller scale. Importantly, it is also within this size range that most cellular machinery operates. This includes the organelles, motility machinery, and other protein and chromatin complexes within cells, the signaling pathways, the viruses that infect cells, and the secreted molecules that communicate with other cells, or cause their destruction.

The larger size of particulate-based agents, as compared to traditional drugs, allows for the significant advantages of multivalency and multifunctionality. Multivalency can confer both important changes in affinity and potency, which may lead to stronger signals at the cellular level and amplification of both diagnostic and therapeutic effects. Valency also causes differences in pharmacokinetics, such as longer off-rates at targets sites leading to prolongation of effects. Multivalency may additionally allow cross-linking of targets to achieve different effects than what would be observed with monovalent drugs. The enormous increases in avidity conferred by multivalency can also transform an ineffective signal into an effective one.

Multifunctionality, on the other hand, allows for the creation of more complex drugs that might be used simultaneously for both diagnosis and therapy within a single molecule. Such agents are known as 'theranostics.' Appropriately designed multifunctional particles could have components that allow selectivity to the target *in vivo*, tracing of its location in real time within the patient, and a therapeutic warhead effector.

With complexity and increased size, however, there are also potential complications that must be overcome. In particular, the systemic pharmacology of these new particles is still poorly understood (Figure 1). In part, this is due to the novel nature of many of the materials under study. For example, polymers, bearing repetitive charge motifs, or highly hydrophobic materials such as carbon nanotubes, will interact in unusual ways with cells within the body. This can have dramatic effects on their systematic clearance, retention in different regions of the body, and penetration into target sites. The sheer size of the particles alone, in the majority of cases, can reduce diffusion and extravascular access. Unusual pharmacokinetic properties as a result of the EPR effect (enhanced permeability and retention) must also be addressed.

Figure 1



Blood half-life, extravasation, renal clearance, uptake in the mononuclear phagocytic system (MPS), immunologic response, and flexibility to functionalize are important characteristics of imaging probes and theranostic compounds. These properties usually change depending on probe size. * = strongly depends on surface properties of particles. ** = option to increase detection sensitivity by attaching multiple imaging markers per molecule or strong endogenous imaging properties of the particle (*e.g.*, IONP's or microbubbles). Reprinted with permission from Ref. [8].

Key components of the immune system and other cells or enzymes within the body, responsible for surveillance of the blood contents, such as endothelial cells in the liver, spleen, and marrow, along with nucleases, are often designed to clear particulate matter, perhaps as a defense against viruses, immune complexes, or damaged normal cells. Therefore, a key hurdle to the use of nanoparticle-based drugs has been understanding these rapid clearance mechanisms and manipulating them to advantage.

Nanoparticles for medical imaging

The use of contrast agents for diagnostic imaging enables non-invasive detection of pathologies. However, despite rapid technological advancements in medical imaging technologies, such as positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), the number of medical contrast media available to clinicians remains limited. Many contrast agents, enhance image contrast between tissue types, based mostly on different physical properties (mainly perfusion), but less frequently rely on disease-specific molecular signatures. Nanoparticles represent a promising and versatile new approach for the development of new and highly specialized contrast media [9].

With the exception of agents used in nuclear medicine, virtually all contrast media in current use passively accumulate as dictated by the physiochemical properties of the contrast medium; biodistribution of these agents is perturbed by factors associated with a particular disease. However, the diversity and flexibility of nanoparticles enables both passive and active targeting. For passive targeting of nanoparticles in cancer, the EPR effect is exploited [3]. The EPR effect is responsible for the accumulation and retention of particles in the interstitial space due to the leaky nature of the tumor neovasculature and the lack of effective lymphatic drainage; the mechanics are similar to size exclusion chromatography. However, the EPR effect will be dependent upon the species (*e.g.*, mouse versus human), particle size, and tumor type [10], among other factors. For active targeting, the biodistribution of a particle is specifically biased towards a particular tumor biomarker of interest, and can be achieved by functionalization with targeting moieties, such as small molecules, peptides, aptamers, or antibodies. This enables the development of highly-specific molecular probes from particle-based contrast agents.

Investigational nanoparticles may incorporate a diverse array of molecular constructs (Figure 2). To provide image contrast, these particles may be functionalized with various imaging moieties. For example, nanoparticles may incorporate chelated gadolinium (MR contrast), isotopes (nuclear imaging), or fluorophores (optical imaging). For some nanoparticle platforms, contrast is an intrinsic property; for example, iron oxide nanoparticles (IONP) provide contrast in T2-weighted MR images, and bismuth particles add contrast in CT scans [11]. Functionalization with yet an additional contrast moiety (*e.g.*, appending an IONP with a PET radiotracer) allows for multimodal imaging, which could permit increased resolution and sensitivity in diagnostic procedures [9]. Additionally, inclusion of β particle-emitting radiotracers allows for use of Cerenkov imaging, an investigational medical imaging modality, which can be utilized independently (via electron-emitting radionuclides) or multimodally with PET (via positron-emitting radionuclides) [12]. By combining several imaging moieties into one particle, 'smart' imaging agents have been created which