PERSPECTIVE

Nanoparticulate Alternatives for Drug Delivery

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ABSTRACT The ability to apply nanomaterials as targeted delivery agents for drugs and other therapeutics holds promise for a wide variety of diseases, including many types of cancer. A nanodelivery vehicle must demonstrate *in vivo* efficacy, diminished or no toxicity, stability, improved pharmacokinetics, and controlled-release kinetics. In this issue, Lee *et al.* construct polymer nanobins that fulfill these requirements and demonstrate effective delivery of doxorubicin *in vivo* to breast cancer cells. This Perspective explores the outlook for these nanobins as well as other technologies in this field and the challenges that lie ahead.

The development of an effective, versatile nanodelivery option for the targeted delivery of therapeutic compounds has the potential to radically improve disease outcomes. Most front-line drugs are untargeted, toxic compounds that act in a nonspecific fashion, often eliciting unwanted, dose-limiting, and often debilitating side effects. The ability to use nanotechnology to alter the characteristics of a drug to increase solubility, decrease degradation during circulation, and concentrate the drug at the desired site of action promises to increase efficacy while decreasing unwanted side effects. The enormity of this opportunity has spurred much funding and research aimed toward the development of various nanoparticulate drug delivery systems.

However, all nanotechnologies are not created equally, especially for nanotechnologies that are being contemplated as targeted drug delivery solutions. This is evidenced by the fact that growing work in the field of drug delivery over the past 30 years has yielded only a few nanodrug formulations, such as Doxil and Abraxane, which have reached the clinical market. Even those formulations that have reached the clinical market represent only marginal improvements, often increasing circulation time but falling short in terms of targeted and controlled delivery. Even though size matters, it is becoming increasingly evident that optimal nanoscale *in vivo* drug delivery and imaging formulations must have certain critical physical and chemical attributes to ensure success in the clinic. Satisfying all of these attributes in simple, scalable, broad-based nanodelivery carrier platforms that can meet the rigors of Food and Drug Administration (FDA) requirements, provide delivery for many different pharmaceutical drugs, and scale to clinical production levels is no small task. The present Perspective describes the desired physiochemical characteristics of nanomaterials essential for *in vivo* efficacy and diminished toxicology. In the accompanying article in *ACS Nano* by Lee *et al.*, a polymer-caged liposomal formulation, known as nanobins, is evaluated in breast cancer models.[1] The increased therapeutic efficacy of encapsulated doxorubicin within nanobins, as compared to free doxorubicin, can be directly linked to these optimal physiochemical characteristics.

As described in detail below and outlined in Table 1, successful nanoscale formulations must incorporate or engineer the following properties into their design: biocompatibility, biodegradation, encapsulation (protection) of active therapeutic, colloidal stability, improved pharmacokinetics, and controlled-release kinetics. Although these properties are relatively intuitive from a pharmaceutical point of view, many nanotechnologies that do not meet these criteria have been tested in biological models. The nanobin technology described by Lee *et al.*[1] successfully integrates all of these properties. Nanobins are engineered to encapsulate and protect doxorubicin from the physiological environment, minimizing metabolism and degradation during transit. Just as importantly, a pH-responsive trigger is incorporated into the polymer cage that enables release of the active drug in the acidic environment of the tumor. Therapeutic efficacy in several orthotopic models of breast cancer may be based upon these physiochemical properties. Many nanoparticle compositions (reviewed by Yih and Al-Fandi[2]) have been studied for pharmaceutical delivery; however, few, if any, meet all of these demands (Table 2).

Two other near ideal nanoparticle delivery systems are shown in Figure 1. The nanoliposome is representative of the organic-based systems, while the calcium

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TABLE 1. Desired Characteristics for a Nanoparticle Drug Delivery Platform

desired characteristic	comments
Inherently nontoxic materials and degradation products	The initial material selection should be based on nontoxic materials especially with an aim toward human health care.
Small size (10−200 nm)	There is not a particular size that seems most efficacious, particularly based on *in vivo* studies. This is the range of particle diameters that have proven most effective for a wide variety of delivery systems. Also of note is the debate around the influence of particle shape.[13]
Encapsulation of active agent	To be effective, the active agent must be encapsulated within the nanoparticle vehicle. Surface decoration (*i.e.*, adsorption) will often be effective *in vitro* but falls short for *in vivo* studies because of the reticuloendoplasmic systems *in vivo*.
Colloidally stable in physiological conditions	The nanoparticle vehicle and surface functionalization must resist agglomeration for the solution pH values, ionic strength, macromolecular interactions, and temperature encountered in the physiological environment.
Clearance mechanism	The nanoparticle vehicle must have a ready clearance mechanism to avoid the cumulative and/or systemic effects of the drug-laden particles.
Long clearance times	Resistance to agglomeration and other effects that remove the nanoparticle-encapsulated drug from the patient must be avoided to promote long circulation times in the circulatory system for as many of the nanoparticles to find and sequester in the cancer cells as possible.
Biologically or extrinsically controlled release of therapeutic agents	There should be a trigger mechanism such as the acidic pH within the tumor or during endosome maturation designed into the nanoparticle platform to ensure the release of the encapsulated drug into the targeted tissue.
Can be targeted to cell/tissue of choice	The nanoparticle platform should be capable of surface bioconjugation to target molecules for the specific cancer to provide the greatest uptake with the lesions and fewest side effects with healthy tissue.

phosphosilicate is typical of bioresorbable inorganic systems.[3−8] Nanoliposomes encapsulate the drug as shown in the schematic and are capable, often with some difficulty, of bioconjugation of target molecules.[6] The encapsulation of siRNA has been accomplished in cationic nanoliposomes with multiple clinical trials currently being performed on these and other nanoparticle chemotherapeutic delivery platforms.[9] The calcium phosphosilicate nanoparticle (CPSNP) is a novel formulation that prevents the usual amorphous calcium phosphate to hydroxyapatite solution-mediated phase transformation by substituting silicate for phosphate.[4,10] Thus, drugs can be encapsulated at high concentra-

TABLE 2. Comparison of Nanoparticle Drug Delivery Systems (Updated from Yih and Al-Fandi[2])

nanoparticulate material	size (nm)	therapeutic agent(s) carried	advantages	limitations
Biodegrable polymers	10−100	Plasmid DNA, proteins, peptides, low-MW organic compounds	Sustained localized drug delivery for weeks	Exocytosis of undissolved nanoparticles. Fixed functionality after synthesis may require new synthetic pathways for alternate surface functionalities
Ceramic	<100	Proteins, DNA, chemotherapeutic agents, high-MW organic compounds	Easily prepared, water dispersible, stable in biological environments	Toxicity of materials, exocytosis of undissolved nanoparticles, time-consuming synthesis, surface decoration instead of encapsulation
Metals	<50	Proteins, DNA, chemotherapeutic agents	Small particles present a large surface area for surface decoration delivery	Toxicity of materials, exocytosis of undissolved nanoparticles, time-consuming synthesis, surface decoration instead of encapsulation
Polymeric micelles	<100	Proteins, DNA, chemotherapeutic agents	Suitable for water-insoluble drugs due to hydrophobic core	Toxicity of materials, fixed functionality after synthesis
Dendrimers	<10	Chemotherapeutic agents, antibacterial, antiviral agents, DNA, high-MW organic compounds	Suitable for hydrophobic or hydrophilic drugs	May use toxic materials, time-consuming synthesis, fixed functionality after synthesis may require new synthetic pathways for alternate surface functionalities
Liposomes	50−100	Chemotherapeutic agents, proteins, DNA	Reduced systemic toxicity, increased circulation time	Fixed functionality after synthesis, some leakage of encapsulated agent, lack of colloidal stability
PRINT	20−2000	Chemotherapeutic agents, proteins, DNA, imaging agents	Precise control over size, shape, and surface functionalization	Toxicity of materials depending on material
Calcium phosphosilicate	20−60	Chemotherapeutic agents, RNA, high- and low-MW organic compounds, imaging agents	Simple preparation, suitable for hydrophilic or hydrophobic drugs, colloidal stability in physiological environments, pH-dependent dissolution results in intracellular delivery of drugs, composed of bioresorbable material	Encapsulated materials limited to solubility in water or organic solvent

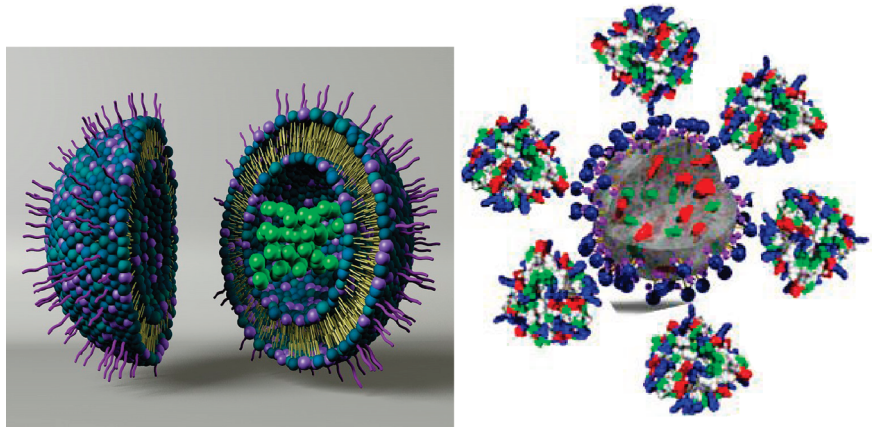

Figure 1. Schematic of near ideal drug delivery platforms. (Left) Schematic of a nanoliposomal nanoparticle drug delivery platform representative of many organic materials. The drugs are encapsulated within the bilayer amphiphilic capsule with polyethylene glycol surface functionalization shown. The nanoliposomes can deliver a variety of drugs including siRNA.[3] (Right) Schematic of an inorganic but bioresorbable drug delivery platform based on calcium phosphosilicate nanocomposite particles capable of targeted delivery of the drug *via* polypeptides or antigen bound to the surface of the nanoparticle.[3,5]

tions within the amorphous CPSNP and the nanoparticles functionalized with either polyethylene glycol (PEG) or a target molecule such as Gastrin 10 for pancreatic cancer or anti-CD71 for targeted delivery to breast cancer. The high solubility of calcium phosphates at low pH is maintained in the CPSNP, enabling this nanoparticle delivery platform to trigger intracellular delivery after endocytosis in the targeted tissue.[4,5,11,12]

OUTLOOK AND FUTURE CHALLENGES

So what is next for nanotechnologies such as nanobins? Cell-based cytotoxicity studies described in the accompanying article are suggestive of potential future applications but cannot substitute for a complete mean-tolerated dose study and toxicology profile. Additional hurdles include completion of a thorough absorption, distribution, metabolism, and excretion (ADME)/biodistribution study. Mechanistic questions concerning clearance mechanisms need to be addressed. Novel clearance mechanisms including enterohepatic biliary recirculation have recently been described for nanotechnologies.[4,8] The Nanotechnology Characterization Laboratory of the National Cancer Institute and various Contract Research Organizations offer essential pharmacokinetic analyses of nanotechnologies.[9] Additional mechanistic questions concerning the preferential and somewhat selective ability of certain nanotechnologies to affect oncogenic cells as compared to noncancer cells (see Figure 4 in the accompanying article) need to be answered. For example, does the enhanced permeability and retention (EPR) effect truly favor nanoscale particles? Is there a biological mechanism by which functionalizing with PEG or charge enhances EPR-dependent tumor targeting of nanoparticles? Do pH-responsive triggers release active agents from nanoparticles at the site of the tumor due to the hypoxic acidic environment of a necrotizing solid tumor or within the endolysosomal vesicle of a tumor cell? What mechanisms explain how these active pharmaceutical agents accumulate in the cytosol instead of being degraded within the lysosome? Fundamental questions concerning whether active targeting with small molecules or fragments of antibodies and so forth alter the pharmacokinetic profiles and therapeutic efficacy of untargeted "passive" nanotechnologies still remain unanswered. Questions concerning how the FDA would evaluate active *versus* passive targeted nanoparticles are still in flux. Rationally engineered nanotechnologies for clinical applications, including nanobins, will begin to address these questions and begin to fulfill the clinical promise of nanotechnology.

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