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Targeting nanotherapeutics to the tumor microenvironment: how accurately can we aim?

“As a growing body of experimental data are available, we are becoming aware of many hurdles that therapeutic nanotechnologies must overcome before entering the clinic.”

Keywords: cancer ■ metastasis ■ nanoparticle ■ nanotechnology ■ nanotherapeutics ■ targeting ■ theranostics ■ triggered release ■ ultrasound

The scientific and medical communities generally agree that targeting drugs to diseased organs, at therapeutically relevant doses, is key for a successful treatment. Nanotechnologies are playing an important role in realizing this goal. With more than 40 nano-sized drugs on the market [1], and many others in the bench-to-bedside pipeline, we can look proudly at the evolution of this field. However, as a growing body of experimental data are available, we are becoming aware of many hurdles that therapeutic nanotechnologies must overcome before entering the clinic [2].

Liposome-encapsulated doxorubicin (Doxil[®]) highlighted two major advantages that nanoscale drug-delivery systems present: tumor targeting and reduced cardiotoxicity [3]. Utilizing the enhanced permeability and retention effect, these 100-nm liposomes infiltrate solid tumors via their discontinuous vasculature [4]. From a formulation point of view, Doxil combined two important concepts: remote loading and stealth properties. The former ensures a high concentration of the drug inside each nanoparticle [5], while the latter utilizes PEG to avoid reticuloendothelial clearance and to increase circulation time of the nanoparticles [6]. However, Doxil also raised nano-associated clinical complications, including severe hand and foot syndrome and complement activation in many patients [7,8]. These issues were addressed clinically by limiting the administered dose and by screening patients for their complement activity before beginning a treatment cycle. Recently, Barenholz (an inventor of Doxil) and colleagues reported the development of a new liposomal formulation that alleviates hand and foot syndrome [9]. Interestingly, social networks (such as [10]), in which patients

share their treatment experiences, are playing an important role in identifying and dealing with these issues. Failed attempts to reproduce the clinical and financial success of Doxil, using identical liposomes loaded with different drugs, emphasized the need for drug- and disease-specific tailoring of nanotherapeutics.

The next major milestone in the field was Abraxane[®], 130-nm particles composed of albumin-coated paclitaxel, which was approved for the treatment of breast and lung cancers. Unlike Doxil, this system utilizes receptor-mediated transport mechanisms to penetrate tumor cells [10]. This achievement highlights the importance cell-surface ligands can have in the targeting process; giving enthusiasm to the many groups that are developing nanoparticles decorated with disease-specific ligands. Such efforts matured recently with the clinical evaluation of nanoparticles targeted to the prostate-specific membrane antigen [11].

Another way to direct nanoparticles towards disease sites is by conjugating them to metallic components and subsequently controlling their biodistribution with magnetic fields. To penetrate the tissue, researchers used micron-scale gas bubbles conjugated to therapeutic nanoparticles. Once at the target site, the bubbles are disrupted with ultrasound, thereby creating a forceful jet that propels the nanoparticles into the tissue. However, targeted therapies must improve, specifically, new systems need to be capable of autonomously detecting, targeting and treating malignant cells deep inside tissue [12].

While targeting strategies can help direct nanotherapeutics towards the disease site, they are limited in their ability to control the drug-release profile at the target. Focused drug



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release can have many clinical advantages, such as reducing off-target effects and side effects, pulsating drug release over prolonged periods of time, or, alternatively, flushing the target tissue with a high-drug dose to treat severe conditions.

Nanocarriers that are sensitive to external stimuli have attracted great interest. A popular trigger is ultrasound, due to the fact that it is clinically available and that it can induce thermomechanical effects in most soft tissues. However, despite the great promise, these systems are intimidating to potential investors that envision a drug/device combination and the regulatory challenges associated with it. Alliances between active pharmaceutical ingredient manufacturers and medical device companies, as well as an open dialog with the regulatory agencies, will refuel these important efforts. From a scientific perspective, creating drug/device combinations will address unmet clinical needs and grant a significant therapeutic advantage over existing treatments. For example, releasing a highly toxic drug from nanocarriers at the target site, thereby avoiding damage to vital organs, can meet these criteria. Another promising approach is to use this mode to deliver delicate or degradable compounds, such as siRNA and proteins. Different energy sources, such as microwaves, infrared rays and radiowaves are being developed as new triggers that have the capacity to interact with organic and inorganic nanomaterials [13]. These triggers will enable co-stimulating multiple processes, such as drug release and tissue ablation [14].

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Future nanotherapeutics must exhibit improved targeting and enhanced therapeutic efficacy. The approach being used to meet these requirements is the development of ‘hybrid’ nanoparticulate systems that integrate multiple functions, such as one or more drugs (therapeutic), a metallic structure (for magnetically controlled spatial positioning, thermal tissue ablation and as a radiopaque contrast agent for imaging), a targeting ligand (for accuracy), and

an onsite chemical or biological indicator of the efficacy of the treatment (theranostics, i.e., coupling diagnostics to the therapy). Bhatia and co-workers have moved such concepts several steps forward by constructing nanoparticles that communicate intelligently with each other, resulting in the recruitment of a nanoparticle ‘community’ to the disease site [15]. Douglas and Bachelet used DNA origami to construct nanotherapeutics that respond logically to specific biomarkers [16], and Langer, along with the present author and others, developed nanoparticles with integrated protein-producing molecular machines that have the capacity to autonomously synthesize a drug from amino acids onsite in response to stimuli [17]. These and other inventions will mark a new era in targeted drug delivery [18]; an era in which smart nanosensors, integrated within nanotherapeutics, will respond to a disease biomarker by delivering the proper active agent where, when, and at the needed dose. On the one hand, engineering such systems must address concerns regarding toxicity [19], and on the other, our understanding that a one-size-fits-all approach in nanomedicine is passé.

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Our collective research and understandings in the field of nanotechnology are converging into sophisticated multicomponent systems [20]. Not just the work of a single group, but a global effort in the fields of material science, chemical engineering, biomedicine and biology will facilitate new medical capabilities that will impact our lives for the better.

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