PERSPECTIVE

Impact of Nanotechnology on Drug Delivery

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ABSTRACT Nanotechnology is the engineering and manufacturing of materials at the atomic and molecular scale. In its strictest definition from the National Nanotechnology Initiative, nanotechnology refers to structures roughly in the 1—100 nm size regime in at least one dimension. Despite this size restriction, nanotechnology commonly refers to structures that are up to several hundred nanometers in size and that are developed by top-down or bottom-up engineering of individual components. Herein, we focus on the application of nanotechnology to drug delivery and highlight several areas of opportunity where current and emerging nanotechnologies could enable entirely novel classes of therapeutics.

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The application of nanotechnology to drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future.[1−7] The pipelines of pharmaceutical companies are believed to be drying up in many cases, and a number of blockbuster drugs will come off patent in the near-term.[8] There has also been a concurrent increase in the utilization of the Hatch−Waxman Act by generic drug companies, which allows them to challenge the patents of branded drugs, further deteriorating the potential revenues of pharmaceutical companies.[8] The development of nanotechnology products may play an important role in adding a new armamentarium of therapeutics to the pipelines of pharmaceutical companies. Using nanotechnology, it may be possible to achieve (1) improved delivery of poorly water-soluble drugs; (2) targeted delivery of drugs in a cell- or tissue-specific manner; (3) transcytosis of drugs across tight epithelial and endothelial barriers; (4) delivery of large macromolecule drugs to intracellular sites of action; (5) co-delivery of two or more drugs or therapeutic modality for combination therapy; (6) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities;[9] and (7) real-time read on the *in vivo* efficacy of a therapeutic agent.[3] Additionally, the manufacturing complexity of nanotechnology therapeutics may also create a significant hurdle for generic drug companies to develop equivalent therapeutics readily. These are just a few of the many compelling reasons that nanotechnology holds enormous promise for drug delivery.

Nanotechnology: Both Evolutionary and Revolutionary. Among the first nanotechnology drug delivery systems were lipid vesicles, which were described in the 1960s and later became known as liposomes.[10] Subsequently, a variety of other organic and inorganic biomaterials for drug delivery were developed. The first controlled-release polymer system for delivery of macromolecules was described in 1976.[11] More complex drug delivery systems capable of responding to changes in pH to trigger drug release,[12] as well as the first example of cell-specific targeting of liposomes,[13,14] were first described in 1980. The first long-circulating liposome was described in 1987, and the concept was later named "stealth liposomes".[15] Subsequently, the use of polyethylene glycol (PEG) was shown to increase circulation times for liposomes[16] and polymeric nanoparticles[17] in 1990 and 1994, respectively, paving the road for the development and subsequent approval of Doxil (doxorubicin liposome) in 1995, for the treatment of AIDS-associated Kaposi's Sarcoma.

There are over two dozen nanotechnology therapeutic products that have been approved for clinical use to date.[18] Among these first-generation products, liposomal drugs and polymer−drug conjugates are two dominant classes. The majority of these therapeutic products improve the pharmaceutical efficacy or dosing of clinically approved drugs, which in some cases also provides life-cycle extension of drugs after patent expiration. There have been significantly fewer clinical examples where nanotechnology has enabled entirely new therapeutics that would otherwise not exist; we see this as an important area of promise for nanotechnology in the future. With nanotechnology therapeutic products now validated through the improvement of previously approved drugs, increasing interest is expected among academic and industry investigators to revisit pharmaceutically suboptimal but biologically active new molecular entities (NMEs) that were previously considered undevelopable through con-

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ventional approaches. Indeed, we expect the emergence of nanotechnology platforms to enable development and commercialization of entirely new classes of bioactive macromolecules such as those involved in RNA interference pathways (*e.g.*, siRNA or microRNA) that need precise intracellular delivery for bioactivity. Nearly all of the major pharmaceutical companies now have a RNAi franchise, and the obstacle to their broad clinical translation is the development of robust delivery platforms, an area where nanotechnology can make significant strides.[19]

Targeting: Necessity or Luxury? The current clinically approved nanotechnology products are relatively simple and generally lack active targeting or triggered drug release components. Interestingly, the products that are currently under clinical development also lack complexity. In fact, nearly 29 years after the first examples of targeted liposomes were described in the literature,[13,14] this technology has not made a significant clinical impact on human health; the question is why? The answer is complex and needs to be explored on a case-by-case basis while considering at least the following points: (1) Delivery vehicle—were the combination of biomaterials and the processes to develop targeted drug delivery system optimal for product development? (2) Drugs—were the properties of the therapeutics as well as their site and mode of action suited for targeting to confer an advantage? (3) Diseases and indications—were the diseases for which targeted drug delivery systems were previously explored the correct "killer apps" for targeting to confer an advantage?

Delivery Vehicle. There are a number of parameters that are important for the successful development and manufacturing of targeted drug delivery vehicles.[20] These include (a) the use of biocompatible materials with simple robust processes for biomaterial assembly, conjugation chemistry, and purification steps; (b) the ability to optimize in parallel the myriad of biophysicochemical parameters of targeted drug delivery vehicles important for pharmacokinetic properties and possible cell uptake; and (c) developing scalable unit operations amenable to manufacturing large quantities of targeted drug delivery systems needed for clinical translation. It has been shown that the development of targeted drug delivery vehicles by self-assembly of prefunctionalized biomaterials simplifies the optimization and the potential manufacturing of these systems.[20−23] The biophysicochemical properties of the vehicle, such as size, charge, surface hydrophilicity, and the nature and density of the ligands on their surface, can all impact the circulating half-life of the particles as well as their biodistribution.[20,21] The presence of targeting ligands can increase the interaction of the drug delivery system with a subset of cells in the target tissue, which can potentially enhance cellular uptake by receptor-mediated endocytosis. More recently, surface properties of nontargeted drug delivery vehicles such as ordered striations of functional groups[24] as well as their shape and size[25] have also been shown to enhance particle uptake (Figure 1).

Drugs. The choice of therapeutic for targeted delivery needs careful consideration. The delivery of therapeutics with intracellular sites of action for which cellular uptake is inefficient may be best achieved with targeted delivery vehicles. An example would be RNAi or antisense therapeutics. Conversely, if a therapeutic requires intracellular delivery for bioactivity, then therapeutic efficacy may require homogeneous tissue penetration and cellular uptake of the targeted drug delivery vehicle, which is difficult to achieve.[26] In some cases, it is believed that targeting may anchor drug delivery systems and decrease the efficiency of diffusion and uniform tissue distribution. The optimization of the ligand density on the drug delivery surface can facilitate the balance between tissue penetration and cellular uptake, resulting in optimal therapeutic efficacy. The targeting of cell surface receptors that participate in membrane recycling pathways facilitates the uptake of targeted drug delivery systems through receptor-mediated endocytosis. Understanding endosomal trafficking pathways, which are complex and can vary among receptors, can also facilitate the engi-

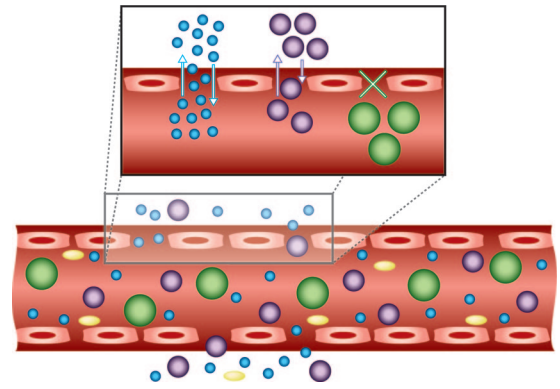

Figure 1. Efficacy of nanoparticles as delivery vehicles is highly size- and shape-dependent. The size of the nanoparticles affects their movement in and out of the vasculature, whereas the margination of particles to vessel wall is impacted by their shape.

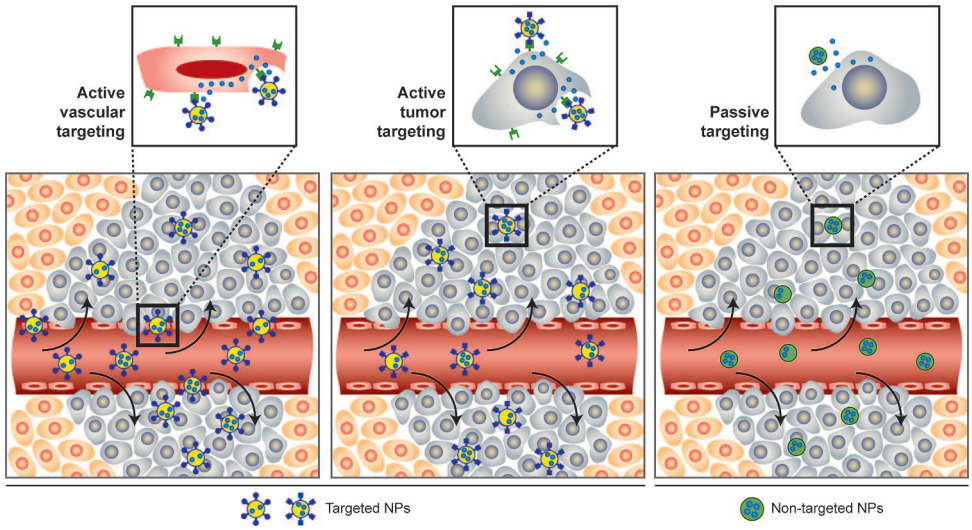

Figure 2. Passive *vs* active targeting. (Right) Particles tend to passively extravasate through the leaky vasculature, which is characteristic of solid tumors and inflamed tissue, and preferentially accumulate through the EPR effect. In this case, the drug may be released in the extracellular matrix and diffuse throughout the tissue for bioactivity. (Middle) Once particles have extravasated in the target tissue, the presence of ligands on the particle surface can result in active targeting of particles to receptors that are present on target cell or tissue resulting in enhanced accumulation and cell uptake through receptor-mediated endocytosis. This process, referred to as "active targeting", can enhance the therapeutic efficacy of drugs, especially those which do not readily permeate the cell membrane and require an intracellular site of action for bioactivity. (Left) The particles can be engineered for vascular targeting by incorporating ligands that bind to endothelial cell-surface receptors. While the presence of leaky vasculature is not required for vascular targeting, when present as is the case in tumors and inflamed, this strategy may potentially work synergistically for drug delivery to target both the vascular tissue and target cells within the diseased tissue for enhanced therapeutic.

neering of suitable targeted delivery systems.

Diseases and Indications. There has been increasing effort to identify new disease biomarkers and associated ligands for use in targeted drug delivery applications. While targeted drug delivery systems have been developed for a myriad of important diseases, the thrust of research has been focused on solid tumors, cardiovascular diseases, and immunological diseases. The currently approved nanotechnology therapeutic products for cancer therapy function by accumulating in tumor tissue through the enhanced permeability and retention (EPR) effect[27] and releasing their payload in the extravascular tumor tissue for antitumor efficacy. While these nontargeted drug delivery systems have been clinically efficacious, there have been contradicting data regarding the added benefit for the inclusion of targeting molecules to these systems.[20,28−31] Tumor tissue accumulation is a passive process requiring a long circulating half-life to facilitate time-dependent extravasations of drug delivery systems through the leaky tumor microvasculature and accumulation of drugs in the tumor tissue.[32] This process is largely mediated by the biophysicochemical properties of the nanoparticles and not by active targeting.[32] Therefore, even in the absence of targeting ligands, drug delivery systems can be engineered to better target a particular tissue, or nonspecifically absorbed by cells, by optimizing their biophysicochemical properties.[24,25] However, once particles extravasate out of the vasculature into the tumor tissue, their retention and specific uptake by cancer cells is facilitated by active targeting and receptor-mediated endocytosis (Figure 2).[30] This process can result in higher intracellular drug concentration and increased cellular cytotoxicity. While there is relatively modest improvement in tumor tissue accumulation of targeted drug delivery systems relative to nontargeted drug delivery systems,[29] the difference in cellular cytotoxicity is more pronounced.[20,30,34] In the case of vascular endothelial targeting for oncology or cardiovascular indications, ligand-mediated targeting is of critical importance as tissue accumulation is not a function of EPR.[35] Similarly, in the case of immunological tissue targeting, such as targeted drug delivery systems as vaccine where particles are transported through the lymphatic vessels to draining lymph nodes, size-mediated targeting has been shown to be important for efficient antigen presentation to cells in the lymph nodes.[36]

Nanotherapeutics are Gaining Traction. With recent scientific advances, it will be increasingly feasible to engineer targeted or multifunctional nanotechnology products for therapeutic applications. With the correct combination of an optimally engineered vehicle, a suitable drug, and a "killer app" disease, the benefit of a targeted drug delivery system over the equivalent nontargeted system is expected to be substantial. A case in hand is the recently announced completion of phase I tolerability evaluation of CALAA-01,[37] a transferrin-targeted RNAi-nanotherapeutic for delivering siRNA to reduce the expression of the M2 subunit of ribonucleotide reductase (R2) for solid tumor therapy.

In the near- and medium-term, we can expect the emergence of many nanotechnology platforms for drug delivery applications. While both organic and inorganic technologies are under development, controlled-release polymer technologies and liposomes will likely continue to have the greatest clinical impact for the foreseeable future. These are exciting times for nanotechnology research, and the pace of scientific discovery in this area is gaining momentum. It is

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widely accepted that with continued resources, medicine and the field of drug delivery will be an important beneficiary of nanotechnology for years to come.

Conflict of Interest. O.C.F. and R.L. have financial interest in BIND Biosciences and Selecta Biosciences, a biopharmaceutical company developing therapeutic targeted nanoparticles.

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