Expert Opinion

Nanotechnology for drug delivery: the perfect partnership

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The pipelines of pharmaceutical companies are in many cases believed to be drying up and many blockbuster drugs are expected to be coming off patent in the near term. The application of nanotechnology to drug delivery is widely expected to create novel therapeutics capable of changing the landscape for pharmaceutical and biotechnology industries. This editorial highlights the nanotechnology platforms that are under development or in clinical use today, and points to exciting areas of opportunity where nanotechnology may enable the development of more effective and safer targeted therapeutics for a myriad of clinical applications.

Nanotechnology is the engineering and manufacturing of materials at the atomic and molecular scale. One important application of nanotechnology is for developing safer and more effective therapeutic modalities. In its strictest definition from the National Nanotechnology Initiative, nanotechnology refers to structures roughly in the 1 – 100 nm size in at least one dimension. To put this size range in perspective, a small molecule, a virus, a bacterium, and the cross-section of a human hair are around 1, 100, 1000 and 100,000 nm, respectively. 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 [1-4].

The earliest forms of nanotechnology for drug delivery were lipid vesicles that were described in 1965, which later became known as liposomes [5]. Subsequently, the first controlled-release polymer system for delivery of macromolecules was described in 1976 [6]. These early discoveries had an enormous impact on drug delivery and laid the foundation for the development of next-generation nanotechnologies that are capable of: i) controlled delivery of water soluble or poorly water soluble drugs; ii) targeted delivery of drugs in a cell- or tissue-specific manner; iii) delivery of large macromolecule drugs to intracellular compartments; iv) co-delivery of two or more drugs or therapeutic modality for combination therapy; v) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities; and vi) real-time read on the *in vivo* efficacy of a therapeutic agent.

More than two dozen nanotechnology therapeutic products have been approved for clinical use to date [7]. Among these first-generation products, liposomes and polymer–drug conjugates are two dominant classes. The majority of these products were developed to improve the pharmaceutical properties or dosing of clinically approved drugs, which in some cases also provided life cycle extension of drugs after patent expiration. Another promising application of nanotechnology to drug delivery is the re-exploration of pharmaceutically suboptimal, but biologically active, new molecular entities that were previously considered undevelopable through conventional approaches. Particularly exciting are the recent efforts to apply supramolecular engineering of multifunctional nanoparticles to potentially enable the development and commercialization of new classes of bioactive macromolecules capable of RNA interference (i.e., siRNA or microRNA) that

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need precise intracellular delivery for bioactivity, thus creating entirely novel classes of RNAi-nanotherapeutics. 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. The first clinical translation of targeted RNAi-nanotherapeutic was recently announced by Calando Pharmaceutical, which initiated Phase I tolerability evaluation of CALAA-01: a targeted nanoparticle system for solid tumor therapy delivering siRNA to reduce the expression of the M2 subunit of ribonucleotide reductase (R2). Older technologies including non-targeted cationic lipids for siRNA delivery have also been under investigation for many years with limited success.

The application of nanotechnology to drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future [8]. The pipelines of pharmaceutical companies are in many cases believed to be drying up and many blockbuster drugs are expected to be coming off patent in the near term [9]. The loss of revenue from patent expiration is expected to top $45 and $80 billion in 2008 and 2011, respectively. During the past 7 – 9 years there has also been a concurrent increase in the use of the Hatch-Waxman Act by generics drug companies, which allows them to challenge the patents of branded drugs, thus further deteriorating the potential revenues of pharmaceutical companies [9]. The development of nanotechnology products may play an important role in adding a new armamentarium of therapeutics to the pipelines of pharmaceutical companies, while the manufacturing complexity of nanotechnology therapeutics may also create a significant hurdle for generic drug companies to readily develop equivalent therapeutics.

There are, therefore, compelling reasons why nanotechnology holds enormous promises for drug delivery. The recent passage of the 21st Century Nanotechnology Research and Development Act in USA, authorizing $3.7 billion funding for nanotechnology research and development, and the allocation of $144 million by the National Cancer Institute and $54 million by the National Heart, Lung and Blood Institute in USA, for nanotechnology research, together with a sharp increase over the past 8 years in the number of patent applications in the area of nanotechnology, underscores the heightened level of interest by both academic and industry investigators in nanotechnology. So what is fueling this recent excitement over nanotechnology? The answer is multifactorial, but is related to the fact that recent success in the application of nanotechnology to medicine has heightened awareness in this area, which in turn has increased funding, thus accelerating the pace of discovery of more complex nanoscale systems, and this has fueled more excitement over nanotechnology.

While a variety of organic and inorganic materials have been used to generate nanoparticles for drug delivery applications, including polymeric nanoparticles, dendrimers, nanoshells, liposomes, nucleic acid based nanoparticles, magnetic nanoparticles and virus nanoparticles, the two most commonly used systems are polymeric nanoparticles and liposomes [10,11]. Controlled-release polymer technology has impacted virtually every branch of medicine, including ophthalmology, pulmonary, pain medicine, endocrinology, cardiology, orthopedics, immunology, neurology and dentistry, with several of these systems in clinical practice today such as Atridox, Lupron Depot, Gliadel, Zoladex, Trelstart Depot, Risperidol Consta and Sandostatin LAR. The annual worldwide market of controlled-release polymer systems, which extends beyond drug delivery, is now estimated at $100 billion and these systems are used by > 100 million people each year. Polymeric nanoparticles can deliver drugs in the optimum dosage over time, thus increasing the efficacy of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble, or relatively unstable drugs. These systems can also be used to co-deliver two or more drugs for combination therapy [12]. The surface engineering of these nanoparticles may yield them 'stealth' to prolong their residence in blood [13] and the functionalization of these particles with targeting ligands can differentially target their delivery or update by a subset of cells [14], thus further increasing their specificity and efficacy [15]. The successful clinical translation of therapeutic nanoparticles requires optimization of many distinct parameters including: variation in the composition of the carrier system, drug-loading efficiency, surface hydrophilicity, surface charge, particle size, density of possible ligands for targeting and so on, resulting in a large number of potential variables for optimization, which is impractical to achieve using a low-throughput approach. More recently combinatorial approaches have been developed to precisely engineer nanoparticles and screen multiple nanoparticle characteristics simultaneously with the goal of identifying formulations with the desired physical and biochemical properties for each specific application [16].

The other extensively studied drug delivery platform is liposomes, which form nanoparticles through the assembly of an amphiphilic bilayer membrane composed of natural or synthetic lipids [3,10]. The first liposome drug delivery system to gain FDA approval (in 1995) was Doxil (doxorubicin liposomes) for the treatment of AIDS-associated Kaposi's sarcoma. Other examples of lipsome drug delivery systems in clinical practice today include DaunoXome (daunorubicin liposomes), DepotDur (morphine liposomes) and Ambisome (amphotericine B liposomes). Cationic liposome systems have also been developed for delivery of nucleic acid-based therapeutics such as gene vectors, antisense, aptamers and RNAi delivery. Surface functionalized targeted liposomes are under investigation and the expectation is that targeted systems may further enhance the efficacy and safety profile of these drug delivery systems.

In the near and medium term we will see an increasing number of novel nanotechnology therapeutics that will emerge for a myriad of important human diseases. Central to rapid translation of nanotechnology therapeutics will be a concerted effort to overcome pharmacokinetic, biocompatibility, cost of goods, and manufacturing challenges associated with this class of therapeutics. Significant strides have been made by academic, government, and industry investigators to achieve these goals. These are exciting times for nanotechnology research and the pace of scientific discovery is beginning to gain momentum. It is widely accepted that with continued support, medicine and the field of drug delivery will be an important beneficiary of nanotechnology for years to come.

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