Targeted Polymeric Nanotherapeutics

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The field of drug delivery has had significant impact on patients' lives with approaches that offer improved efficacy, safety and compliance of existing medicines or that enable the successful development of new drugs. Generally, these improvements are accomplished by changes of formulation leading to, for example, increased duration of action or changing the route of delivery (e.g., transdermal, inhalation).

Particle-based drug delivery, and in particular polymeric particle systems wherein delivery is achieved by encapsulation of a drug within the particle matrix has been a very active approach which has resulted in several successful products. One example is Risperdal CONSTA®, which is indicated for the treatment of schizophrenia. It delivers the drug risperidone encapsulated in poly(lactic-*co*-glycolic acid) (PLGA) biodegradable polymeric microspheres with a particle diameter of around 100 □m via intramuscular injection once every two weeks. The mechanism by which this drug delivery system works is that the drug is released over time by slowly diffusing through the polymeric matrix as water diffuses in and as the polymer chains degrade via hydrolysis. Risperdal®, the original risperidone product, on the other hand is taken orally by patients on a daily basis. For schizophrenia patients, taking a pill on a daily basis can be problematic, whereas an intramuscular injection administered by a doctor or nurse once every two weeks has shown both improved compliance and efficacy resulting in significant improvement in the treatment of schizophrenia patients with Risperdal CONSTA.

Nanoparticle delivery systems, in which particle sizes can range from about 20 nm to 200 nm, offer the opportunity for systemic administration of drugs by intravenous injection. The

small particle size allows nanoparticles to circulate through the blood stream and passively diffuse across the leaky vasculature found in inflammatory and infectious diseases, as well as cancer, to deliver drugs directly to the disease site. Optimization of nanoparticle properties, particularly size and surface characteristics, is critical to the development of a successful nanoparticle drug delivery system to avoid rapid clearance of the particles from the blood by the phagocytic cells of the reticuloendothelial system (RES). One approach to minimize RES clearance is to construct nanoparticles with the biocompatible polymer poly(ethylene glycol) (PEG) on the surface (Gref et al. 1994). The hydrophilic, uncharged nature of PEG reduces RES uptake and can prolong circulation time. DOXIL® is a liposomal formulation of the drug doxorubicin that utilizes a PEG surface to prolong circulation times. DOXIL is approved for several disease indications including ovarian cancer. By encapsulating doxorubicin in the PEGylated liposome nanoparticles, DOXIL diminishes doxorubicin absorption into unwanted tissues and allows longer circulation times until the particles diffuse into the tumor vasculature.

Although effective, passive nanoparticle targeting does have its limitations such as non-specific nanoparticle deposition in other parts of the body as well as the possibility of passive diffusion back out of the disease site. Considerable research efforts are focusing on further improvement of nanoparticle drug delivery systems by actively targeting the nanoparticles to the diseased cells (Allen 2002; Heidel et al., 2007; Peer et al., 2007). These approaches take advantage of the presence of unique or highly up-regulated cell surface receptors found on the diseased cells and functionalizing the surface of nanoparticles with ligands that promote cell-specific recognition and binding.

This paper will overview the important steps being taken by BIND Biosciences in translating innovative discovery research from MIT and Harvard into the pharmaceutical development of novel targeted polymeric nanotherapeutics.

BIND Biosciences (BIND) is a biopharmaceutical company that was founded upon the research of two pioneers in the nanoparticle drug delivery field: Dr. Robert Langer of MIT and Dr. Omid Farokhzad of Harvard Medical School. Their research represents a convergence of advances in the field, the result of which is targeted nanoparticles composed of biodegradable and biocompatible polymers with precise biophysicochemical properties optimized to deliver drugs for specific therapeutic applications (Gu et al., 2008). A schematic diagram of the targeted nanoparticles is shown in Figure 1 and the critical components of the nanoparticle delivery system are described below.

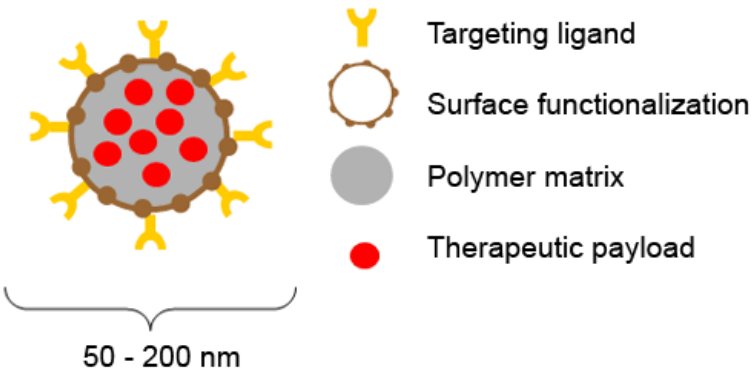

Figure 1. Schematic diagram of targeted polymeric nanoparticle.

The **targeting ligand** provides active targeting capabilities, enabling the targeted nanoparticles to recognize specific proteins or receptors that are found on the surface of cells involved in disease or the surrounding extracellular matrix and bind with high specificity and avidity to their intended cellular target site. **Surface functionalization** imparted by a PEG

component shields the targeted nanoparticles from RES immune clearance, while providing an attachment site for the targeting ligand on the particle surface at precise and controlled levels through proprietary linkage strategies to ensure the drug is delivered efficiently and consistently. The **polymer matrix** encapsulates the drug in a matrix of clinically safe and validated biodegradable and biocompatible polymers that can be designed to provide the appropriate particle size, drug loading, drug release profile and other critical nanoparticle properties. A variety of drugs or **therapeutic payloads** can be incorporated into the targeted nanoparticles, including small molecules, peptides, proteins and nucleic acids, such as siRNA.

When a start-up company is founded based upon academic research, the initial scientific efforts focus on the transfer of the technology from the academic labs into the hands of the company to establish the capabilities within the company and reproduce the results. Shortly thereafter, with the baseline understanding of the technology in hand the translational aspects begin. The company focus shifts to opportunities for improvement as well as the regulatory requirements dictated in the United States by the FDA (Food and Drug Administration) for pharmaceutical development of the drug product candidates. Since its inception in early 2007, for its lead targeted polymeric nanotherapeutic candidate BIND has made a number of improvements to the nanoparticle formulation as well as the nanoparticle production process.

The next phase of development focuses on further optimization efforts for the nanoparticle formulation and process. This includes in vitro cell-based and in vivo preclinical testing. In addition, for a targeted polymeric nanotherapeutic candidate, there are several CMC (Chemistry, Manufacturing and Controls) requirements mandated by the FDA to assure among other things batch to batch reproducibility and shelf-life stability that require testing of a variety

of properties such as particle size, targeting ligand content, drug loading level, and particle/drug stability under storage and in-use conditions. Through the course of development, the CMC requirements become more stringent, however it is at this early stage where the company first begins testing these critical parameters.

In order to establish an acceptable level of safety and tolerability to support dosing the drug product candidate in humans, the FDA requires formal safety testing in animal models. This is the first major step into the FDA-regulated area of pharmaceutical development. It also represents the first efforts at scaling up the formulation and process capabilities. Whereas the research at MIT/Harvard and the initial efforts at BIND were conducted on nanoparticle batches of 100-500 mg, the BIND nanoparticle production scale has been scaled three orders of magnitude to batch sizes of 500 g to enable the animal safety/tolerability testing to support moving our lead targeted polymeric nanotherapeutic candidate into human clinical studies.

The critical and long-term stage of pharmaceutical development is clinical testing. Through a progression of studies the safety, tolerability and efficacy of a drug product candidate is established and is accompanied by a series of submissions and discussions with the FDA. For BIND targeted polymeric nanotherapeutic drug candidates that are based upon improving the performance of an existing marketed drug, the clinical development process will likely be shorter than for a completely new drug candidate, as the history and data established for the existing drug are valuable reference points for BIND and the FDA. Nonetheless, several clinical studies will be required, all CMC requirements must be fulfilled and the nanoparticle production process must grow to the kilogram-scale in order to supply the clinical studies and eventual supplies to doctors and patients. Thus, it is a long, hard and very exciting pathway that lies ahead for BIND Biosciences to translate the novel targeted polymeric nanoparticle drug delivery research from

MIT and Harvard into medicines that improve and save the lives of patients afflicted with serious diseases.

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