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Editorial

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Nanoparticles as Targeted Drug Co-Delivery in Cancer Therapeutics

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Nanoparticles can cross the blood–brain barrier (BBB) following the opening of endothelium tight junctions by hyper-osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors [1]. Tween 80-coated nanoparticles have been shown to cross the BBB as well [2]. Submicron nanoparticles, but not larger microparticles, are taken up by the majority of cell types [3]. Indeed, 100 nm nanoparticles had a 2.5-fold greater uptake rate than 1 μm microparticles, and a 6-fold greater uptake than 10 μm microparticles by Caco-2 cells [4]. In a similar study, nanoparticles are shown to penetrate throughout the sub mucosal layers of a rat intestinal loop model, while microparticles were predominantly localized in the epithelial lining [5]. This indicates that particle distribution can, in part at least, be tuned by controlling particle size.

Various methods can be used to study the release of drug from the nanoparticle: (1) side-by-side diffusion cells with artificial or biological membranes; (2) dialysis bag diffusion; (3) reverse dialysis bag diffusion; (4) agitation followed by ultracentrifugation/centrifugation; or (5) ultra-filtration. Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred. However, these methods prove difficult to replicate and scale-up for industrial use.

Cancer is a difficult disease to treat due to its heterogeneous disease manifestation as well as pathogenic path ways. This necessitates tailored and sophisticated therapeutic modalities for effective treatment. Polymer-based chemotherapeutic drug or anti- cancer gene delivery systems have been extensively studied and have the potential to offer many advantages. In particular, polymeric nano- particles are able to effectively load drugs and/or package genes in order to increase cargo solubility, enhance cargo efficacy compared with free cargo, and prolong the circulation half-life.

Drug delivery in cancer is important for optimizing the effect of drugs and reducing toxic side effects. Several nanotechnologies, mostly based on nanoparticles, can facilitate drug delivery to tumors. Drug delivery systems based on polymeric nanoparticles have emerged as one of the most promising carriers for targeted and controlled delivery of cancer therapeutics in recent years. .Ideal characteristics of nanoparticles include a high drug loading capacity, safe delivery of drug to specific pathological tissues without premature drug leakage and efficient drug unloading at the site of action. Stimuli-sensitive drug delivery systems, also known as “smart” drug delivery systems,

particularly suits this need as they can release drugs at the tumor sites at the desired time on an "on-demand" basis in response to numerous chemical (pH, redox), physical (temperature)and biological (enzymes) stim- uli. The association of a drug to conventional carriers leads to modification of the drug bio distribution profile, as it is mainly delivered to the mononuclear phagocyte system (MPS) such as liver, spleen, lungs and bone marrow. Nanoparticles can be recognized by the host immune system when intravenously administered and cleared by phagocytes from the circulation. Novel nanosystems can be pre-programmed to alter their structure and properties during the drug delivery process, allowing for more effective extra- and intra-cellular delivery of encapsulated drug [6]. Nanoparticles also can be formulated to deliver drugs across several biological barriers [7, 8]. Anti-neoplastic, anti-viral drugs, and several other types of drugs are markedly hindered because of inability of these molecules to cross the BBB. The application of nanoparticles to deliver across this barrier is extremely promising. It has been reported that nanoparticles can cross the BBB following the opening of tight junctions by hyper-osmotic mannitol, which also may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors [9]. Tween 80-coated nanoparticles also have been shown to cross the BBB [10].

Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [11]. However, particles >200 nm are not heavily pursued and nanomedicine often refers to devices < 200 nm (i.e., the width of microcapillaries). Typically, the drug of interest is dissolved, entrapped, adsorbed, attached and/or encapsulated into or onto a nano-matrix. Depending on the method of preparation nanoparticles, nanospheres, or nanocapsules can be constructed to possess different properties and release characteristics for the best delivery or encapsulation of the therapeutic agent [12-14].

The development of a wide spectrum of nanoscale technologies is beginning to change the scientific landscape in terms of disease diagnosis, treatment, and prevention. These technological innovations, referred to as nanomedicines by the National Institutes of Health, have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients. Nanoparticles can mimic or alter biological processes (e.g., infection, tissue engineering, de novo synthesis, etc.). These devices include, but are not limited to, functionalized carbon nanotubes, nanomachines (e.g., constructed from interchangeable DNA parts and DNA scaffolds), nanofibers, self-assembling polymeric nanoconstructs, nanomembranes, and nano-sized silicon chips for drug, protein, nucleic acid, or peptide delivery and release, and biosensors and laboratory diagnostics.

It is important to consider both drug release and polymer biodegradation when developing a nanoparticulate delivery system. In general, the drug release rate depends on: (1) drug solubility; (2) desorption of the surface-bound or adsorbed drug; (3) drug diffusion through the nanoparticle matrix; (4) nanoparticle matrix erosion or degradation; and (5) the combination of erosion and diffusion processes. Hence, solubility, diffusion, and biodegradation of the particle matrix govern the release process.

Biodegradable polymers have been studied extensively over the past few decades for the fabrication of drug delivery systems. Considerable research is being directed towards developing biodegradable polymeric nanoparticles for drug delivery and tissue engineering, in view of their applications in controlling the release of drugs, stabilizing labile molecules (e.g., proteins, peptides, or DNA) from degradation, and site-specific drug targeting.

Polymeric nanoparticles made from natural and synthetic polymers have received the majority of attention due to their stability and ease of surface modification [15, 16]. They can be tailor-made to achieve both controlled drug release and disease-specific localization by tuning the polymer characteristics and surface chemistry [17-20]. It has been established that nanocarriers can become concentrated preferentially to tumors, inflammatory sites, and at antigen sampling sites by virtue of the enhanced permeability and retention (EPR) effect of the vasculature. Once accumulated at the target site, hydrophobic biodegradable polymeric nanoparticles can act as a local drug depot depending on the make-up of the carrier, providing a source for a continuous supply of encapsulated therapeutic compound(s) at the disease site, e.g., solid tumors. Polymeric nanoparticles have interesting advantages with respect to other non-viral

carriers for siRNA delivery: they are easy to scale-up, have improved stability and better safety regarding both to the materials used and to the manufacturing processes [21]. Smaller particles also have a greater risk of aggregation during storage, transport, and dispersion. Polymer degradation also can be affected by particle size.

In early studies, dendrimer-based drug delivery systems focused on encapsulating drugs. However, it was difficult to control the release of drugs associated with dendrimers. Recent developments in polymer and dendrimer chemistry have provided a new class of molecules called dendronized polymers, which are linear polymers that bear dendrons at each repeat unit. Their behavior differs from that of linear polymers and provides drug delivery advantages because of their enhanced circulation time. Another approach is to synthesize or conjugate the drug to the dendrimers so that incorporating a degradable link can be further used to control the release of the drug.

Targeted treatments are aimed to block specific biologic transduction pathways or cancer proteins that are involved in tumor growth and progression, i.e. molecular targets (receptors, growth factors, kinase cascades or molecules related with apoptosis and angiogenesis) that are present in normal tissues, but are found overexpressed or mutated in cancer. The idea of these revolutionary therapies is either to block the signals that help malignant cells to grow and divide uncontrollably, produce the death of cancer cells. By means of induction of apoptosis, stimulate the immune system, or target the delivery of chemotherapy agents specifically to cancer cells, minimizing the death of normal cells and avoiding the undesirable side effects [22, 23]. The importance of these new anticancer drugs can be deduced looking at the FDA-approved drugs in the oncology area in the last fourteen years. Among the 19 anticancer drugs approved in the 2000–2006 period, 14 were targeted therapies. These data increased between 2007 and 2012 when 40 drugs were approved for the treatment of different types of cancer, and 30 of them targeted specific cancer molecules. It should be noted that among 19 cancer drugs approved by the FDA between 2012 and 2014, 18 were targeted cancer drugs based on inhibiting or blocking biologic transduction pathways and/or specific cancer proteins [24–26].

Active targeting is achieved by attaching specific ligands to the nanoparticle structure, allowing a selective recognition of different receptors or antigens overexpressed in the tumor cell surfaces, increasing the cytotoxicity of the anticancer agents in tumors and avoiding most of their side effects, since the exposure of healthy cells to the drug is minimized [27]. The functionalization of the surface of the polymer nanoparticles, not only provides active targeting characteristics to the particles, but also improves therapeutic efficacy of cytotoxic drugs and overcomes the multidrug resistance (MDR) [28, 29].

Another challenge of loading drugs and genes together in the same carrier is to ensure that the presence of one therapeutic agent does not affect the other, in terms of loading capacity and functionality. Furthermore, depending on the drug and gene combination selected, co- encapsulation might not be feasible when their combined presence jeopardizes the loading capacity of the co-delivery carrier. Indeed, this has been the limitation for many co-delivery carriers which have been reported [30-33]. These systems in general can be used to provide targeted (cellular or tissue) delivery of drugs, improve bioavailability, sustain release of drugs or solubilize drugs for systemic delivery. This process can be adapted to protect therapeutic agents against enzymatic degradation (i.e., nucleases and proteases) [34]. Thus, the advantages of using nanoparticles for drug delivery are a result of two main basic properties: small size and use of biodegradable materials. Nanoparticles, because of their small size, can extravasation through the endothelium in inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or penetrate microcapillaries. In general, the nanosize of these particles allows for efficient uptake by a variety of cell types and selective drug accumulation at target sites [19, 20, and 35]. Many studies have demonstrated that nanoparticles have a number of advantages over microparticles (>1 μm) as a drug delivery system [36]. Nanoparticles have another advantage over larger microparticles because they are better suited for intravenous delivery. The smallest capillaries in the body are 5–6 μm in diameter. The size of particles being distributed into the bloodstream must be significantly smaller than 5 μm, without forming aggregates, to ensure that the particles do not cause an embolism.

Finally, it is important to highlight the use of active targeting nanoparticles for the treatment of multi-drug resistant (MDR) cancers that commonly overexpress the epidermal growth factor receptor (EGFR). For example, to overcome the MDR Milane and co-workers [37] modified nanoparticles with an EGFR-specific peptide (GE11) and loaded them with a drug combination of paclitaxel, that prevents cell division, and lodinamine, that induces apoptosis and decreases MDR.

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