

Cancer Nanotherapeutics: Small
Grenades Unleashing Big Catastrophe

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The ability to encapsulate chemotherapeutic drugs in tiny nanoparticles measuring anywhere between 1-100 nm in size is an emerging space with leading pharmaceutical companies spending billions of dollars on research to explore their potential. They have the advantage of being very small to reach sub-cellular levels to elicit anti-tumor response. They can be engineered for accurate drug delivery to increase their tumor-targeting capacity with fewer side effects. Recently, researchers have combined both treatment and diagnostics into their nanoparticle that has paved the way for a new approach called “theranostics” [1].

Nanotherapeutics falls under different categories based on their size, shape, and material composition [2]. Liposomes are artificially prepared spherical vesicles composed of a lipid bilayer [3]. They are front-runners in nanocarrier based drug delivery system with over 10 liposomal drugs approved by the U.S. Food and Drug Administration [4]. Liposomes are known for their biocompatibility and their ability to escape the phagocyte-based clearing mechanism often achieved by coating their outer surface with polyethylene glycol. Chemotherapeutic drugs can be encapsulated within the hydrophilic core of liposomes and therapeutic proteins can also be functionalized on liposomal surface. Taking a cue from body's natural defense mechanism, we showed that coating the surface of liposomes with apoptosis-inducing TRAIL protein and a targeting antibody against natural killer cells was able to target lymph node micrometastasis in vitro [5] and in vivo [6]. The spread of cancer to lymph nodes is a common occurrence, and negatively impacts patient survival. Lymph nodes are the first sites of metastasis and often the extent of tumor burden in the lymph nodes is used to stage disease progression in cancer patients [7]. We have described a liposome-based nanotechnology approach to coat the surface of the body's own natural killer cells with the anti-cancer protein TRAIL [6]. TRAIL-coated natural killer cells were found to effectively prevent lymph node metastasis of cancer cells in mice. This approach could be applicable to a range of cancers that are known to metastasize to the lymph nodes, and may represent a new avenue for the prevention of cancer metastasis to the lymphatic system. Liposomes can be further engineered using polymers to enable stimuli-sensitive release [8-12]. To this end, pH sensitive and temperature sensitive polymer-coated liposomes have been demonstrated to release their payload in response to specific stimuli within the tumor microenvironment.

The advent of self-assembling and stimuli-sensitive polymers has led to important strides in the development of novel class of micellar nanoparticles. Drug delivery systems based on micelles formed by amphiphilic PEGylated oligomer of Cholic Acids (CA) synthesized via peptide chemistry have been demonstrated [13]. Under aqueous condition, PEG5k-CA8 self-assembles into micelles with a size of 21 ± 4 nm [14]. The hydrophobic interior can be exploited to carry chemotherapeutic drugs such as Paclitaxel (PTX). It has been already demonstrated that such PTX-loaded micelles exhibit superior anti-tumor efficacy and lesser toxicity profile in xenograft models when compared to the FDA approved free drug (Taxol®) or albumin bounded PTX (Abraxane®) [15]. The molecular design enables stepwise addition of components to increase the flexibility of micelles. To further minimize premature release of drugs from the micelles during circulation, a Disulfide Cross-linked Micelle system (DCMs) that can be triggered to release drug at the tumor site and inside the cancer cells with high reductive potential has been developed [16]. In this novel nanopatform, four cysteines were first introduced onto the polylysine backbone of the parent telodendrimer and generated a thiolated telodendrimer (PEG5k-Cys4-CA8). The thiolated telodendrimers formed self-assembled micelles under aqueous conditions and inter-micellar disulfide cross linkages can be introduced via air oxidation. The protected amino groups adjacent to the dendritic core are reserved for the conjugation of fluorescent dyes, radionuclides, or additional drug molecules to the micelles. The DCMs retained their particle size for days and in response to FDA approved reducing agent N-Acetylcysteine (NAC) the drug release rate from the micelles can be increased. The release of the encapsulated paclitaxel from the cross-linked micelles was much slower than the non-cross-linked ones [13]. However, in the presence of 10 mM GSH, the release rate increased to approximately the same as that of the non-cross-linked micelles, indicating cleavage of the crosslinks [13]. As the vasculature in tumors is known to be leaky to macromolecules, and the tumor lymphatic system is also deficient, nanoparticles can preferentially accumulate in the tumor site via the Enhanced

Permeability and Retention (EPR) effects. Subcutaneous tumor xenograft bearing mice was chosen to compare the anti-tumor efficacy of intravenously administered clinical formulation of PTX (Taxol®), PTX-loaded DCMs and PTX-loaded Non-Cross-linked Micelles (NCMs) [13]. The in vivo anti-tumor efficacy of PTX-loaded DCMs was superior to NCMs (at both 10 mg/kg and 30 mg/kg PTX dosing) characterized by relative tumor volume and prolonged survival. Administration of NAC 24 h after each given dose of PTX-loaded-DCMs further increases the release of drug at the tumor site. The azide group at the distal terminus of the PEG displaying on the surface of the micelle can be used for ligation of targeting ligands or antibodies. Ligand targeted nanotherapeutics have been shown to be superior to non-targeted nanotherapeutics in an ovarian cancer xenograft mouse model [15].

Most recently, a smart 'all-in-one' micellar Nanoporphyrin (NP) platform with Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Photothermal Therapy (PTT) and Photodynamic Therapy (PDT) was demonstrated [17]. These nanoparticle-based theranostic agents are emerging as promising agents for personalized medicine for disease and patient specific diagnosis and treatment. Nanoparticle-based theranostic agents are at an early stage of development and the effective combination of PDT/PTT and chemotherapy shows great promise as a versatile multimodal platform for cancer diagnosis and therapy.

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