

## Cancer Therapy with the Aid of Nanotherapeutics

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### Introduction

The utilization of polymeric micelles in providing optimal drug delivery against cancer has been thoroughly investigated and exhibits many promising facets, as evidenced by many research scientists all over the globe. The acceleration in the rapid development of these micelles as a robust delivery platform is primarily dictated by the fate of these micelles *in vivo*, which ultimately governs their stability profile and efficacy in the blood stream [1]. As a result of this ever-evolving interest in developing nanotherapeutics, several micellar based anti-cancer treatments are currently in advanced stages of clinical development [2]. Chemotherapeutic medications suffer from various limitations such as dose-limiting toxicities, unfavorable bio distribution profile and lack of therapeutic efficacy at the target site of action [3]. These inherent drawbacks can be alleviated by the judicious use of nanotherapy, particularly polymeric micelles. The therapeutic strategy of “magic bullet”, as envisioned by Paul Ehrlich, proposed that the delivery system will usher the pharmacologically active molecule to the site of interest with maximum accuracy and minimal distribution to the peripheral organs of elimination [4,5]. These nano particulate therapies have exhibited similar characteristics to this binding principle of magic bullet.

### Passive and Active Targeting

Various hurdles are encountered by nanoparticles, while making their foray towards the target with their therapeutic payloads. To circumvent these barriers, a proper understanding of the internal tumor biology along with the structure and composition of the polymeric nanocarriers needs to be leveraged to build a robust delivery system [6]. The most prominent features of tumors include leaky blood vessels, ineffective lymphatic drainage along with a compromised vascular architecture [7]. Nanoparticles can accumulate in the tumor regions through permeation into the leaky, vascular regions, while a chemotherapeutic drug may simply diffuse through the fenestration. This phenomenon of accumulation of these nanocarriers along with their specific payloads is known as Enhanced Permeation and Retention Effect (EPR) [8]. The compromised lymphatic drainage allows significant retention of these nanocarriers along with the distribution of the drugs in the regions adjacent to the tumor [9]. However, there are limitations to this method as not all types of tumors may display similar vascular scaffolds and also permeation characteristics may vary throughout these irregular, leaky regions within the tumor [10,11]. To avoid these potential shortcomings with passive delivery of nanotherapeutics, the nanocarriers can be programmed to bind to particular cells with the introduction of suitable targeting ligands on the surface of these nanoparticles [12]. These surfaces can be optimally tailored to facilitate the incorporation of suitable targeting ligands by adjusting the ratio of ligand density to the polymeric end groups, which are constructively employed for the attachment of these targeting ligands. After achieving this,

nanocarriers will suitably recognize and bind to target cells through ligand-receptor interactions, when the receptors on the surface of these tumor cells have been significantly over-expressed [13]. This is a major factor that contributes to the maximal employment of the target cell-nanocarrier interactions, thus facilitating active targeting [14].

### Polymeric Micelles

One such example of nanoparticles that can be briefly discussed in the context of nanoparticulate delivery are polymeric micelles. These are self-assembled core-shell structures that consist of a hydrophobic core and a hydrophilic shell [15]. This hydrophobic core can be employed to solubilize highly hydrophobic cargos while the hydrophilic shell can be used to prevent opsonization of these nanoparticles by the circulating immune cells in the blood stream [16]. This affords maximum protection, stability and prolonged circulation times to these nanocarriers in the blood stream. These characteristics confer desirable attributes to these polymeric micelles and they can be conceptually developed as a robust nanocarrier. These polymeric micelles are formed above certain concentrations of the polymer, also known as critical micellar concentration (CMC) and above a certain temperature, which is also known as the critical micellar temperature (CMT) [17]. A suitable example of this polymeric micelle, under clinical evaluation, is the NK911. The composition consists of Doxorubicin (~45%) attached to a block copolymer of Polyethylene Glycol (PEG) and aspartic acid. This formulation was evaluated for metastatic pancreatic cancer treatment. Similar micellar formulation, NK105, which consisted of Paclitaxel was clinically studied for pancreatic, colonic and gastric tumor treatment [18].

### Conclusions

It is very difficult to make a judicious selection of an appropriate nanocarrier because several factors may influence the overall biodistribution profile and the therapeutic efficacy of these nanocarriers at the tumor sites. Concurrently, there are very few reliable methodologies that provide optimal screening of these nanocarriers that can be tailored to facilitate delivery to specific types of tumors with varying inherent characteristics. Therefore, developing these strategies to actively or passively deliver nanotherapeutics is a time-consuming process that needs to be evaluated differently for different cases. However, with the amount of research and thorough investigative processes being carried out in the last decade, nanoparticulate therapy remains a favorable option to deliver chemotherapeutics safely coupled with minimal toxicities and higher therapeutic efficacies.

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