

# Cancer therapy with nanotechnology-based platforms

## Introduction

Targeted drug delivery has received lots of attention in cancer research and therapeutics due to its advantage of eliminating the affected cells and reducing the toxic side effects associated with systemic administration. Nanoformulations of these encapsulations have chalked appreciable successes in the targeting abilities. A myriad of nanotechnology platforms are either in advanced stages of basic research or clinical trials to assess and facilitate the effective delivery of payloads to tumors. This minireview discusses some of the more commonly used nanotechnologies, and summarizes recent progress in developing these platforms for cancer diagnosis and treatment. Future prospects are also highlighted.

## Hydrogels

Hydrogel-nanoparticles use hydrophobic polysaccharides to encapsulate and deliver proteins, peptides, and drugs. Hydrogels are highly absorbent, and could be natural or synthetic polymers possessing appreciable degree of flexibility, depending on their surface structure. The designation of hydrogels as “smart materials”, stem from the fact that the cross-linked polymers with hydrophilic groups can alter their structure in response to varying salt concentrations, pH and temperature. By virtue of their carboxylic acid groups on the polymers, the negatively charged polymer chains repel each other when the sodium ions are removed, allowing the chains to uncoil. In this state the hydrogel can absorb more than 500% its own weight of water. It is the ability to absorb this quantum of water that makes the hydrogel very useful in encapsulation. Hydrogel-nanoparticles are immuno-stimulatory and readily taken up by dendritic cells (DCs). DCs are considered key regulators of immunity based on their unequalled ability to take up, process, and present antigens compared with other antigen presenting cells (APCs). The use of hydrogels to encapsulate tumor antigens to be presented to antigen-presenting cells, including DCs, would therefore be an attractive strategy, owing to the urgent need for an efficient system for cancer vaccines and immunotherapy toward tumor antigens. Furthermore, this would be a promising strategy since the tumors themselves generally evade immune detection. Recognizing this, extensive efforts have also been made to significantly improve upon the short lives of DCs in order to achieve optimal protective immunity.

## Micelles

Copolymer micelles are lipid molecules that arrange themselves in spherical super-molecular assemblies in aqueous solutions. Micelle formation is a response to the amphipathic nature of fatty acids i.e. the core contains hydrophobic chains while the shell is hydrophilic thereby making the micelle water-soluble, and allowing delivery of the poorly soluble contents. Micelles have several advantages over other drug delivery systems, including increased drug solubility, prolonged half-life circulation, targeted accumulation at tumor sites, and lower toxicity. However, at the present time this technology falls short of tumor specificity and efficient release-control features of the entrapped agents. Consequently, the focus of nanomedicine strategies

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is no longer passive targeting systems (e.g., micelles), but rather, active targeting. Currently, SP1049C and NK911, have been approved for clinical use.<sup>1</sup> SP1049C is formulated as doxorubicin (DOX)-encapsulated micelles whilst NK911 is DOX-encapsulated micelles from a copolymer of PEG-DOX-conjugated poly (aspartic acid).

## Dendrimers

Dendrimers are highly branched, nanometer-sized macromolecules having a central core, an interior dendritic structure, with an exterior surface having both active and functional groups. The functionalized surfaces yield themselves to different shapes and sizes, making them amenable to several chemical and biological applications including drug delivery, gene delivery, and peptide delivery. Previously, dendrimer-based drug delivery systems which were mainly based on drug encapsulation, had woefully poor drug release profiles. Recent results from empirical research in dendrimer chemistry have however yielded a new class of more improved molecules called dendronized polymers, which are linear polymers bearing dendrons at each repeat unit. This new class of polymeric dendrimers provides numerous drug delivery advantages because of their enhanced circulation time. Classic examples include an mPEGylated peptide dendrimer-doxorubicin (dendrimer-DOX) conjugate-based nanoparticle which has been formulated and characterized as a drug delivery vehicle.<sup>2</sup> The DOX which was conjugated to the periphery of the dendrimer can self-assemble into a nanoparticle. At equal dose, mPEGylated dendrimer-DOX nanoparticle resulted in significantly high antitumor activity. The in vivo toxicity evaluation demonstrated the remarkable ability of nanoparticles to avoid DOX-related toxicities that presents side effects to normal organs. Thus, the mPEGylated dendrimer-DOX presents a potential drug delivery nanoparticle formulation for cancer therapy.

## Quantum dots

Quantum dots (QDs) are generally fluorescent nanoparticles typically between 10 to 100 atoms in diameter that consist of a semiconductor material such as silicon, cadmium selenide, or cadmium sulfide. Their special and unique optical characteristics, such as high brightness, long-term stability, and simultaneous detection of multiple signals, make them attractive as imaging and therapeutic systems in

cancer therapy. Moreover, their surface structure makes coupling the QDs with drugs, peptides and antibodies attractive payloads for tumor therapy. One of the major problems initially associated with QDs was their instability owing to their dispersability in water, but this was resolved by using various surface coatings, which markedly improved the stability of the QDs and allowed incorporation of desirable tumor-targeting ligands.<sup>3</sup> Single-particle quantum dots conjugated to tumor-targeting anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody (Mab) have been used to target tumors. These systemic conjugates not only bound HER2, but was also able to permeate the tumor vasculature, allowing an in-depth in vivo imaging of the binding.

## Nano-formulations

An interesting focus in nanomedicine has been the development of new nanoparticle methodologies and formulations in order to increase the overall effectiveness as agents of cancer therapy. Manipulation of nanomaterials to create a new water-soluble drug delivery formulation, as opposed to the current water-insoluble suspensions anticancer drugs has been a research area of particular interest. While most anticancer drugs require the addition of solvents in order to aid absorption into cancer cells, most of these solvents not only dilute the potency of the drugs, but create an appreciable level of toxicity. A report generating a novel approach using silica-based nanoparticles to deliver the CPT anticancer drug and other water-insoluble drugs to tumor cells<sup>4</sup> has received positive reviews. The method incorporates the CPT drug into the silica nanoparticles and delivers the nanoparticles into a variety of human cancer cells to induce cell death. Clearly, these results suggest that the porous silica nanoparticles could be potentially effective vehicles to overcome the insolubility of most anticancer drugs.

## Nanocells

A nanocell refers to a drug delivery architecture comprising a polymer-bound chemotherapeutic drug combined with a lipid-bound anti-angiogenesis drug. The nanocell in effect, allows the sequential delivery of two different therapeutic agents with different modes of action. A nanocell is formed by encapsulating a nanocore with a first agent inside a lipid vesicle containing a second agent. In treating cancer, an antineoplastic agent is contained in the outer lipid vesicle, while the antiangiogenic agent is loaded into the nanocore. This arrangement allows the antineoplastic agent to be released and delivered first to the tumor before the tumor's blood supply is cut off by the antiangiogenic agent. Targeting of nanocells via bispecific pathways to receptors on cancer cells results in the destruction of the angiogenic integrity and drug release. For equivalent tumor regression, doses of drugs delivered via nanocells are approximately 1,000times less than the dose of the free drug, an essential factor for reducing systemic toxicity.

## Nanotubes

A carbon nanotube (CNT) is a miniature carbon allotrope having a cylindrical structure of rolled-up sheets of graphene that form hollow strands, with graphite molecules attached at the edges. A number of nanoparticles have been investigated to overcome the limitation of reduced targeting ability, which stems from attaching varying drug molecules directly to antibodies. Incidentally, the numerous chemical bonds seems to have a negative effect on antibody activity. A single-walled carbon nano-tube (SWCNT), is a new class of nanoparticles, that have been specially synthesized for tumor targeting in order to

overcome the limitation of covalently attaching multiple copies of tumor-specific monoclonal antibodies (MAbs).<sup>5</sup> This has also led to the synthesis of a class of nanotubes based on the 'Fullerene' structure (an anticancer compound containing both tumor-targeting antibodies and nanoparticles). This delivery platform can be loaded with different molecules of anticancer drugs.<sup>6</sup> The real advantage of fullerene-based therapies vs. other targeted therapeutic agents is most likely to be fullerene's potential as a multifunctional drug-carrying agent. The elegance of the fullerene payload method comes from the fact that cancer cells can become drug resistant, and therefore one can drastically reduce the possibility of their "ducking" by bombarding them with a plethora of different drugs at the same time. The first fullerene payload has been prepared and characterized as an initial step towards the development of fullerene-based cancer therapy.

## Conclusion

While a paucity of information still exists regarding the safety of nanocarriers, nanoparticle platform for drug delivery holds great promise in overcoming most of the impediments in targeting different cell types. A couple of challenges however remain, for example, the precise characterization of molecular targets in order to ensure that the molecules only target cancerous organs and not the 'innocent' cells; the fate of the delivered drugs within the nucleus; and the structural and functional characterization of the ligand-receptor interactions in order to achieve effective targeting. As these new drug delivery systems are brought to clinical trials, however, it is hoped that the negative side effects associated with these compounds would all come to the fore. Further, considering the countless potential applications of nanoparticles in cancer research, there is an urgent need for the development of safety guidelines by the mandated regulatory bodies. Taken together, nanoparticles have tremendous potential in applications involving multifunctional systems combining targeting, diagnostics and cancer therapy.

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## Conflict of interest

The author declares no conflict of interest.

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