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# Combating Cancer with Novel Technologies

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## Short Communication

Drug developers recruit and combine principles, procedures and strategies from chemistry, pharmacology, nanotechnology and biotechnology, focusing on the generation of functional vehicles as nano-carriers of drugs for improved stability and enhanced intracellular delivery.

The nanostructured drugs for cancer treatment that have so far reached the oncology market largely rely on passive targeting (p.e.: Abraxane, Doxil, Daunoxome, Oncaspar, DepoCyt), meaning that they are not empowered by specific mechanisms to recognize specific cell types or tissues. Preferential but still passive accumulation into tumor tissues is thus favored; in addition the increase in circulation time is promoted by the nanoscale size of the drug-vehicle conjugate contributing to the enhanced permeability and retention effect (EPR) [1]. The amount of drug that reaches target cells is supposed to remain low rather insufficient to ensure the desired therapeutic response. Most of such conventional chemotherapeutic drugs (e.g., 5-fluorouracil) exert their antitumor effect by interfering with nucleic acid synthesis and inhibiting tumor cell proliferation. When the level of DNA damage in exposed cells exceeds their repair capacity, the induction for cell death follows. The low molecular weight of anticancer drug allows their free diffusion through the body, as a result they also reach normal tissues. Their greatest effect occurs, however, in highly proliferative normal cells (i.e., bone marrow and intestinal tract), often causing dose-limiting myelosuppression and gastrointestinal toxicities. The conjunction of this narrow therapeutic index and the considerable inter-individual differences in distribution, metabolism and excretion of these cytotoxic agents in humans, result in an increased risk of toxicity and also sub-therapeutic dosing in the individual patient [2]. This limitation as a problem may soon change since many actively targeted nanoparticles for drug delivery are being evaluated in clinical assays. Among them, polymer-lipid hybrid nanoconstructs, liposomes, reverse micelles and core shell nanoparticles are our present research area [3]. The polymeric NPs are colloidal particles, which are self-assembled in case of amphiphilic block copolymers when exposed to an aqueous media. They offer several benefits such as a higher drug pay load, prolonged blood circulation, and controlled release profiles. In polymeric NPs, the hydrophobic cytotoxic drugs can be easily encapsulated into the hydrophobic core. The outer exposed hydrophilic part provided the stable dispersion by imparting a steric stabilization that ultimately enhanced its blood residence time following intravenous injection. Poly lactic-co-glycolic acid (PLGA) is commonly exploited for drug delivery and in the biomedical field owing to its excellent biocompatible, biodegradable nature and well-established safety in clinic applications. However, the block copolymer of PLGA with poly ethylene glycol (PEG) as mPEG-PLGA offers an attractive option owing to PEGylated polymeric NPs diminishing the systemic clearance as compared to non-PEGylated particles. Further with similar size they are successfully employed for passive targeting. They accumulated the tumor site through enhanced permeability and retention (EPR) effects. The continual advancements in drug delivery science and biotechnology together offers various targeting options that specifically identify and bind the receptors that are overexpressed on angiogenic vessels within solid tumors and also on tumor cells [3].

Some specific types of tumor cells and tumor endothelial cells represent CD13 proteins and act as receptors for Asn-Gly-Arg (NGR) motifs containing peptide. These CD13 receptors can be specifically recognized and bind through the specific sequence of cyclic NGR (cNGR) peptide with more affinity and specificity toward them. The cNGR peptide was conjugated to the poly ethylene glycol (PEG) terminal end in the poly(lactic-co-glycolic) acid PLGA-PEG block copolymer. Then, the ligand conjugated nanoparticles (cNGR-DNB-NPs) encapsulating docetaxel (DTX) were synthesized from preformed block copolymer by the emulsion/solvent evaporation method and characterized for different parameters. The various studies such as *in-vitro* cytotoxicity, cell apoptosis and cell cycle analysis demonstrated the enhanced therapeutic potential of cNGR-DNB-NPs. The higher cellular uptake was also found in cNGR peptide anchored NPs into HUVEC and HT-1080 cells. However, free cNGR could inhibit receptor mediated intracellular uptake of NPs into both

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types of cells at 37°C and 4°C temperatures, revealing the involvement of receptor-mediated endocytosis. The *in-vivo* biodistribution and antitumor efficacy studies indicated that targeted NPs have a higher therapeutic efficacy by targeting the tumor-specific site. Therefore, the study exhibited that cNGR functionalized PEG-PLGA-NPs could be a promising approach for therapeutic applications to efficient antitumor drug delivery [4].

Another study from our lab was performed by Agrawal et al. [5]. The object of the study was to investigate the glioma targeting propensity of folic acid (F) decorated polymer lipid hybrid nanoparticles (PLNs) encapsulating cyclo-[Arg-Gly- Asp-D-Phe-Lys] (cRGDfK) modified paclitaxel (PtxR-FPLNs). The prepared PLNs were supposed to bypass the blood brain barrier (BBB) efficiently and subsequently target integrin rich glioma cells. The developed formulations were characterized for size, shape, drug entrapment efficiency, and *in vitro* release profile. PtxR-FPLNs demonstrated maximum *in-vitro* inhibitory effect, cell apoptosis and cell uptake. Pharmacokinetics and biodistribution studies showed efficacy of PtxR-FPLNs *in-vivo*. *In vivo* anti-tumor studies clearly revealed that the median survival time for Balb/C mice treated with PtxR-FPLNs (42 days) was extended significantly as compared to PtxR-PLNs (35 days), free PtxR (18 days), Ptx-FPLNs (38 days), Ptx-PLNs (30 days), free Ptx (14 days) and control group (12 days). From the results it can be concluded that the developed dual targeted nanoformulation was able to efficiently cross the BBB and could significantly deliver a higher amount of drug to brain tumor for better therapeutic outcome [5,6].

Active targeting by internalization prone cell-surface receptors, overexpressed by cancer cells, is to improve the cellular uptake of the nanocarriers. These are taken up by endocytosis, with later entry into the cytoplasmic matrix following diffusion through early or late endosomal or lysosomal membranes. However, the majority of such molecules are degraded in lysosomes without deterimenting the homoeostasis of the recipient cell, thus curtailing the intracellular (cytosolic) concentration of the drug. This necessitates the development of systems for effective cytoplasmic delivery. Recently, pH-sensitive systems and core shell nanoparticle having cationic material(s) have been appreciated as promising strategies for the cytoplasmic delivery of chemotherapeutic agents. These systems can directly fuse with plasma membrane and transfer the contained bioactive across the cellular membrane into the cytosol or attain cytosolic delivery via destabilization of endosomes by pH dependent/ proton sponge effect thereby avoiding the interaction of early endosome with late endosome what is called as endosomal escape. At present, our research group is exploring this type of carrier mediated drug delivery where the focus is on cytosolic anticancer drug delivery through targeted nanocarriers for effective tumor therapy. We formulated nanocarriers equipped or incorporated with moieties and functionality which results into their endosomal escape and they are being explored for anticancer potential and improved therapeutic index [7,8].

Cancer immunotherapy is another promising treatment strategy based on the stimulation of the immune system to attack tumor cells. To generate lifelong immunity against tumor cells, priming of tumor-specific cytotoxic effector as well as memory T-cells is essential. Currently, our research group is working on targeted immunization that deals with the development of effective immunotherapy/vaccine against carcinoma using sensitized dendritic cells (DCs) [9]. The antigen carrier system specifically target endosomal and cytosolic pathway f antigen processing and presentation. The results indicate that specific IL-2 and IL-4 titers in mice receiving nanovesicular system are higher and prominent. The studies also showed that pulsed dendritic cells using engineered nano-self assembled vesicular carriers are able to generate significant immune response against the melanoma in C57BL/6 mice and increase the life of animal by reducing the rate of progression of tumor. The vaccines demonstrated both the preventive as well as therapeutic(s) benefits. It is inferred that this type of approach may lead to the development of promising immunotherapy/vaccines against melanoma in mice, as a futuristic therapy of carcinoma.

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