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# A REVIEW ON LATEST TRENDS IN ONCHO NANOTECHNOLOGY

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**ABSTRACT**

Amongst various cancer therapies, chemotherapy is one of major treatment modalities along with debulking surgery. Major challenges in chemotherapy are linked to toxicity on healthy proliferating cells and multidrug resistance against anticancer drugs. However, these approaches failed because of significant heterogeneity in both solid tumour cell types and cell surface markers. However, in most tumors the pH gradient is reversed. The low pH in tumour extra cellular space or in various sub cellular organelles is a significant signal for targeting which is the basis for the pH targeting nanotechnology a novel anticancer drug delivery .This abstract highlights recent progress of the pH sensitive tumour targeting nano carriers.

**Keywords:** Chemotherapy, pH, nanotechnology.

## INTRODUCTION

Cancer is a multifaceted disease caused by genetic instability and accumulation of multiple molecular alterations [1]. It is multifaceted because it involves many cellular physiological systems like cell signaling and apoptosis. Survival of cancer patient largely depends on early detection followed by effective therapy. Nanotechnology deals with particles ranging in size of 1-100nm which are emerging as a class of therapeutics in cancer treatment. Very sensitively designed devices constructed from nanoscale components such as nano cantilevers, quantum dotes, nano tubes, fullerene's, and nano shells offer high potential to detect even the smallest molecular signals associated with malignancy [2]. These nanotechnological tools help in designing early imaging agents and diagnostics that will allow clinicians to detect cancer in earliest, most easily treatable, presymptomatic stage. Multifunctional targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations with physiologically appropriate timing directly to cancer cells .nanotechnology also enables the technology of developing research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance [3]. Nanoparticles offer the potential to overcome drug resistance, since nanoparticles can bypass the P-glycoprotein efflux pump, one of the main drug resistance mechanisms, leading to greater intracellular accumulation.

## NANOPARTICLES FOR CANCER TARGETING AND DELIVERY: NANOVECTORS

Nanovectors act as carriers for the therapeutic and imaging payloads, or their constituent materials might also possess image-enhancement properties, such as in case for iron oxide for MRI, and semi-conductor or nanocrystals or quantum dots for optical imaging. . A typical nanovector consists of a nanoparticle core coated with a targeting agent specific to the target cells and a biomolecule with designated functionality. The nanovector must be detectable by at least one characterization technique to validate its location in vivo and to evaluate its therapeutic effects in a time course. The nanovector specifically targets cancer cells and thus imposes minimal side effects to healthy tissue. For therapeutic payload delivery, a mechanism must be established to release the drug from the nanovector after entry to the target cell to induce cellular apoptosis or inhibit cell migration or proliferation. The molecular targeting of nanovectors containing active agents might be attained by the conjugation of active recognition moieties to the surface of nanovector. Specificity is then increased, at the expense of added complexity in the nanoparticle preparation, increased particle size and the risk of biological adverse reactions to the targeting agent.

A hydrophobic interaction between the core of polymeric nanoparticle and the drug molecule allow the drug to be entrapped in the nanoparticles core .A proper linker is very much important to drug-polymer conjugate as the stability of linker affects the release of nanoparticles.

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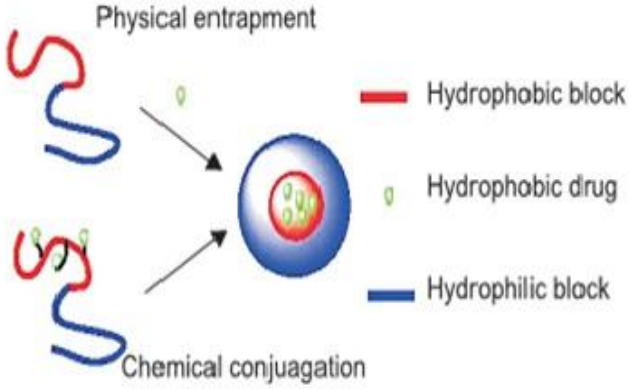
If linker is too stable the drug release is delayed while if the linker is too unstable, drug may be released before the nanoparticles reaches the tumor a variety of pH-sensitive linkers have been developed such as hydrozone and cis aconity [4]. Molecularly targeted nanovectors have several advantages like, providing selectivity enhancement, carry multiple and potentially different targeting agents, delivery of much higher therapeutic payloads per target misrecognition etc. The delivery of multiple agents results in targeted combination therapy. Nanovector modules like nanocantilever, nanowire and nanotube enable the transition from single-biomarker to multiple-biomarker cancer diagnostic, prognostics and treatment selection. nanoparticles, each with one of many different colours might be conjugated with antibodies to different molecular targets. When irradiated with a light beam of single wavelength, a precise map of the distribution of many molecular markers in a single cell, cell population or tissue is generated.this offers the potential advantage to readily identify conjugate markers and yielding specific information on their tissue distribution. This also introduces new protocols which include cell surface, endocellular and micro-environmental antigens in the same test. Nanovectors used for anticancer drug delivery can be made from a variety of materials, including polymers, liposomes, carbon nanotubes, gold and iron oxide nanoparticles, dendrimers etc. Most of the nanoparticles delivery systems that have been approved by FDA or that are in clinical trials are based on polymers or liposome technologies.

**Fig 1. Polymer based nanoparticles**




**POLYMERIC NANOPARTICLES**:

Generally the polymeric material that is used for nanoparticles preparation falls under two major categories.

**NATURAL POLYMERS**

Eg: dextran, heparin, chitosan, alginates, gelatin, collagen have been investigated.

**SYNTHETIC POLYMERS**

Eg: Polyethylene glycols (PEG), polycarprolactone (PCL), polylactic acid (PLA), N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) have been exploited. Generally the polymer contains two parts a hydrophobic core which serves as container for anticancer drug and a hydrophilic shell which stabilizes the nanoparticles in aqueous environments [6].

**How to detect Cancer**

**Conventional**

Conventional detection of the cancer is done by observing the physical growth/changes in the organ by Xrays and/or CT Scans and is confirmed by biopsy through cell culture. However the limitation of this method is that it is not very sensitive and the detection is possible only after substantial growth of the cancerous cells. Often the treatment is also not possible once the cancer is in such an advanced stage.

**Nano Technology Detection**

As mentioned before, nanoparticles (NP) are of a few of nm and the cells are of the size of few microns. So NP can enter inside the cells and can access the DNA molecules/Genes and, there is a possibility that the defect in the genes can be detected. DNA molecules can be detected in their incipient stage. This could be possible in vivo or in vitro. It will be shown latter that NP does show potential of cancer detection in its incipient stage.

**Cancer Treatment**

**Conventional**

One of the treatment options is surgery. That is, remove the cancerous part. However, the limitation is that one loses the organ and the cancer may appear again. Further, the surgery is not possible for all types of cases of the cancer. Second option is radiation therapy. In this the cancerous cells are burnt by radiation of specific frequency band and the intensity. The limitation of this method is that even the healthy cells get burnt, cancerous cells burning is not uniform and the burnt part may become dead and nonfunctional. The third option is chemotherapy. That is, cancerous cells are killed by drugs toxic to cells or by stopping cells from taking nutrients needed to divide the cells or stop the mechanism responsible for division of the cell. Normally a combination of drugs is given so that drugs affect all the three aspects of the cancer treatment. The limitation of this approach is that treatment is harmful to healthy cells, approach is gross and rarely successful if the cancer is in advanced stage.

**Nanotechnology**

Certain nano particles can particles can be designed to absorb preferentially certain wave length of radiation and gets heated. Such a NP if enters in the cancerous cell will burn it if irradiated by suitable wavelength radiation. This is kind of the analogue of radiation therapy. As mentioned before, nanotechnology can be used to create therapeutic agents that target specific cells and deliver toxin to kill them. The NP will circulate through the body, detect cancer associated molecular changes, assist with imaging release a

therapeutic agent and then monitor the effectiveness of the intervention.

## NANOTECHNOLOGY TOOLS IN MEDICINE

Different methods for the synthesis of nano-engineered materials and devices can accommodate precursors from solid, liquid or gas phases and encompass a tremendously varied set of experimental techniques. Detailed presentations of these are beyond the scope of this review. (microcontact printing) techniques begin with a macroscopic material or group of materials and incorporate smaller-scale details into them, whereas "*bottom-up*" (organic- synthesis, self-assembly) approaches, begin by designing and synthesizing custom-made molecules that have the ability to self-assemble or self-organize into higher order mesoscale and macroscale structures [7]. A myriad of studies is available for applications of micro- and nanotechnologies in chips for medical molecular diagnostics. For the subsequent readout detection either fluorescence- or radionuclide-based markers, or surface plasmon resonance spectroscopy can be applied [8] scanning probe microscopy (STM, AFM) that allow three dimensional-type topographical atomic and molecular views or optical responses (SNOM) of nanoscale structures ; in situ monitoring techniques that allow the monitoring and evaluation of building block assembly and growth [9] ellipsometry, an optical method, with the capability of measuring in liquid environment (e.g, protein solution) to study protein and cells adsorption on solid surfaces6, it has been employed to discriminate and identify bacteria at the species level, and is very promising for analytical purposes in biochemistry and in medicine[10,11]Not only to image surfaces of molecules or sub-cellular compartments, but also to measure molecular forces between molecules. This is substantially increasing our knowledge of molecular interactions [12].

### PH responsive nanoparticles

Solid tumors have an acidic extracellular environment and an altered pH gradient across their cell compartments. Nanoparticles responsive to the pH gradients are promising for cancer drug delivery. Such pH-responsive nanoparticles consist of a corona and a core, one or both of which respond to the external pH to change their soluble/insoluble or charge states. Nanoparticles whose coronas become positively charged or become soluble to make their targeting groups available for binding at the tumor extracellular pH have been developed for promoting cellular targeting and internalization. Nanoparticles whose cores become soluble or change their structures to release the carried drugs at the tumor extracellular pH or lysosomal pH have been developed for fast drug release into the extracellular fluid or cytosol. Such pH-responsive nanoparticles have therapeutic advantages over the conventional pH-insensitive counterparts. The novel core-shell polymer nanoparticles are designed with their lower critical solution temperature (LCST) being dependent on the ambient pH. This value is above the nominal physiological temperature of 37°C at pH 7.4, but decreases to a temperature below the physiological temperature with a small decrease in pH. The resulting change in LCST causes the core-shell nanoparticles to deform and precipitate in an acidic environment, triggering the release the chemotherapeutics at low pH. In addition, a biological signal has been conjugated to the shell of the nanoparticles, which can recognize tumor cells. This system may be able to target drugs to tumor cells and release the drugs intracellularly [13-16].

## PATHWAYS FOR NANO PARTICLES IN CANCER DRUG DELIVERY

Nanotechnology has tremendous potential to make an important contribution in cancer prevention, detection, diagnosis, imaging and treatment. It can target a tumor, carry imaging capability to document the presence of tumor, sense pathophysiological defects in tumor cells, deliver therapeutic genes or drugs based on tumor characteristics, respond to external triggers to release the agent and document the tumor response and identify residual tumor cells. Nanoparticles are important because of their nanoscaled structure but nanoparticles[17] in cancer are still bigger than many anticancer drugs. Their "large" size can make it difficult for them to evade organs such as the liver, spleen, and lungs, which are constantly clearing foreign materials from the body. In addition, they must be able to take advantage of subtle differences in cells to distinguish between normal and cancerous tissues. Indeed, it is only recently that researchers have begun to successfully engineer nanoparticles that can effectively evade the immune system and actively target tumors. Active tumor targeting of nanoparticles involves attaching molecules, known collectively as ligands to the outsides of nanoparticles. These ligands are special in that they can recognize and bind to complementary molecules, or receptors, found on the surface of tumor cells. When such Nanotechnology - A Recent approach in Cancer Treatment[18] targeting molecules are added to a drug delivery nanoparticle, more of the anticancer drug finds and enters the tumor cell, increasing the efficacy of the treatment and reducing toxic effects on surrounding normal tissues. Although the past 30 years of innovation in nanotechnology has removed much of the "magic" to yield 21st century "smart bombs" capable of carrying a whole host of new anticancer drugs directly to tumors, we are still searching for the ideal delivery nanosystem. Nanotechnology studies [18] are not new. In essence, all drug molecules can be considered as Nanoengineered structures. What is new is the inclusion of a number of other Nano-based approaches to medical studies.

## FUTURE IMPLICATIONS

Nanotechnology will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer.

Nanotechnology can provide the technical power and tools that will enable those developing new diagnostics, therapeutics, and preventives to keep pace with today's explosion in knowledge. With nanomedicine, we might be able to stop cancer even before it develops. With such technology, nanomedicine has the potential to increase the life span of human beings.

## CONCLUSION

Nanotechnology will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Although most of the technologies described are promising and fit well with the current methods of treatment, there are still safety concerns associated with the introduction of nanoparticles in the human body. These will require further studies before some of the products can be approved. The most promising methods of drug delivery in cancer will be those that combine diagnostics with treatment. These will enable personalized management of cancer and provide an integrated protocol for diagnosis and follow up that is so important in management of cancer patients. There are still many advances needed to improve nanoparticles for treatment of cancers. Future efforts will focus on identifying the mechanism and location of action for the vector and determining the general applicability of the vector to treat all stages of tumors in preclinical models.

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