



Nanotechnology in Oncology

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Almost all chemotherapy agents act on healthy tissues along with cancerous tissues, resulting in the adverse effects and suboptimal doses to the tumor sites. The advent of nanotechnology in medicine enabled us to encapsulate the drugs with a nano-sized particle, thereby delivering these drugs with high precision to the tumor site. This technology has opened a new vista of opportunities in clinical medicine, Medical Oncology in particular.

Richard Feynman way back in 1959 mentioned in his famous lecture and advised the scientific community to think small for future innovations in science. This laid foundation stone to a new era in science and technology that is today's nanotechnology. The term "Nano" literally means a dwarf in the Greek language.¹ Nanotechnology is a branch of science dealing with particles ranging from the size between one and one thousand nanometers. Nanomedicine is a subspecialty of nanotechnology exploring its applications in the medical field.²

Nanoparticle/Nanocarrier Properties

1. Size: The first property is their smaller size that enables them to reach and accumulate more in tumor tissues, as the vasculature of the tumors is leaky with imperfect basement membrane due to neoangiogenesis.
2. Shape: The spherical shape of this particle leads to a higher ratio of surface to volume that leads to more uptake in tumor tissues.
3. Surface: With the advent of newer technologies, the surface of these particles can be modified in such a way that their half-life in the blood can be more than conventional drugs and their uptake is preferably done by certain tissues through the process of cellular endocytosis and pinocytosis.
4. Charge: The charges over these particles can be made to be variable in various tissues. For example, they can have

a positive charge at infusion so that they target blood vessels immediately after infusion, and they can be made to switch to neutral charge after entering the tissues allowing faster diffusion into tumor tissues.

5. Solubility, degradation, and clearance: Hydrophilic nanoparticles improve water solubility, prevent degradation and clearance by the reticuloendothelial system, thereby increasing the stability and bioavailability of the drug. The application of polyethylene glycol over nanoparticles achieves this property of hydrophilicity.
6. Targeting: The main advantage in the nanoparticle-mediated drug-delivery systems is the release of drug after reaching the target. This can be achieved through three different mechanisms³:
 - i. Active targeting: By ligand (on nanoparticle)–receptor (on tumor cell surface) binding.
 - ii. Passive targeting: Accumulation of Nab-paclitaxel in pancreatic tumor tissue is a typical example of this mechanism where enhanced permeability and retention effect are achieved because of the neoangiogenesis in tumor tissues with leaky blood vessels.
 - iii. Triggered release: This can be achieved by release systems operating upon specific stimulus or trigger acting at the target site. This trigger can be internal in the tissue like changes in pH compared with intravascular space, differences in the redox potential of tissues, changes in charges and ionic strength, etc. In specific conditions, external stimuli can be used to mediate drug or chemical release from the nanoparticle. Some technologies are using physical stimuli like hyperthermia to dislodge drug in a particular tissue and also the infrared and ultraviolet wavelength of light for the release of drugs in superficial tissues such as skin and subcutaneous tissues.

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Types of Nanoparticles

1. Organic substances like proteins, lipids, protein-lipid polymers, liposomal particles, and gelatins such as hydrogels are commonly used.
2. Inorganic substances like silica, hafnium oxide, gold, magnetic particles.
3. Drug conjugates with antibodies.
4. Viral nanoparticles.

Applications of Nanotechnology in Oncology

Coming to the uses of nanoparticles in oncology, they are used extensively in diagnostic applications, therapeutic purposes, and a combination of both referred to as theranostic applications (► **Table 1**).⁴

Diagnostic

Nanoparticles have large surface area to volume ratio, due to which they can be densely covered with antibodies, small molecules, peptides, aptamers, and other moieties. These moieties can bind and recognize specific cancer molecules. Quantum dots, gold nanoparticles, and polymer dots are three common nanoparticle probes used in diagnosing cancer.

Detection of Biomarkers

- A zinc oxide quantum dot-based immunoassay was developed for the detection of carcinoembryonic antigen in predicting tumor recurrence after the completion of colorectal cancer treatment.
- Gold nanoparticles for the detection of human epidermal growth factor receptor 2 in breast cancer.
- Various nanoparticles are used to detect DNA, RNA, miRNA sequences, methylation of histone proteins, and extracellular vesicles.

Detection of Cancer Cells

Circulating tumor cells (CTCs) are already approved by the US Food and Drug Administration for prognostication in some cancers such as colorectal, breast, and prostate cancers. However, it is difficult to isolate CTCs in earlier stage due to their small number. Nanoparticles help in capturing and isolating CTCs by targeting some tumor-specific proteins among billions of cells, literally picking a needle in a haystack, for

Table 1 Applications of nanotechnology

Diagnostic	Therapeutic	Theranostic
1. Detection of biomarker	1. Targeted drug delivery	For both diagnostic and therapeutic purpose
2. Detection of cancer cells	2. Overcoming multidrug resistance	
3. In vivo tumor imaging		

example, detection of epithelial cell adhesion molecule using magnetic nanoparticles.

In Vivo Imaging

Nanoparticle probes preferentially accumulate in tumor tissues through active or positive targeting, thereby a very useful tool in radiodiagnosis.⁵ Ongoing clinical trials with nanotechnology-based applications in cancer diagnosis are listed below:

- Carbon nanoparticles as lymph node tracer in rectal cancer after neoadjuvant radiochemotherapy.
- Silica-hybrid nanoparticles for positron emission tomography imaging of patients with metastatic melanoma or malignant brain tumors.
- Nanoparticles are being evaluated as specific “immunosensors” to detect DNA, RNA, miRNA sequences, methylation of histone proteins, and extracellular vesicles.

Therapeutic

Targeted Drug Delivery

The main therapeutic application is to increase the efficacy and decrease the toxicity of conventional chemotherapeutic agents by targeted delivery. Some of the commonly used drugs are mentioned in ► **Table 2**.

Table 2 Nanomedicines in oncology

Type of nanoparticle	Active drug
Liposome	Doxorubicin, cytarabine
Liposome (PEGylated)	Doxorubicin, irinotecan
Liposome (Non-PEGylated)	Daunorubicin, vincristine, mifamurtide
Nanoparticle albumin bound	Paclitaxel
PEG protein conjugate	L-Asparaginase
PEG-PLA polymeric micelle	Paclitaxel

Abbreviation: PEG-PLA, polyethylene glycol-poly lactide.

Table 3 Advantages and disadvantages of nanotechnology

Advantages	Disadvantages
Increased solubility of highly lipophilic drugs	Lack of proper knowledge about the effect of nanoparticles on biochemical pathways and processes in human body
Tunable physical and chemical properties	Unpredictable genotoxicity due to insufficient toxicological assessment studies
Targeted drug delivery	Carcinogenesis
Drug release in a sustained and controllable manner	Elimination and metabolism vary with different types of materials used in nanoparticle synthesis
Good biocompatibility, bioavailability, and biodegradability	More expensive
Decreased toxicity or side effects of drugs	Short shelf life

Overcoming Multidrug Resistance

Of the many mechanisms of drug resistance in chemotherapeutic agents, one of the most important and common mechanism is the overexpression of P-glycoprotein (p-gp) over tumor tissues, which mediates the drug efflux and so-called multidrug resistance (MDR). Nanoparticles can help overcome this in the following ways: (i) Simultaneous delivery of the drug to tumors and inhibition of the MDR proteins. (ii) Partially bypassing the efflux pump as they are internalized by endocytosis; (iii) Downregulating the expression of p-gp using siRNA.

Abscopal Effect

Radiotherapy-activated hafnium oxide nanoparticles kill more cancer cells than radiotherapy alone in distant tumors due to increased CD8+ lymphocyte T-cell infiltrates—an abscopal effect.

Theranostics

Nanoparticles are to play a major role in personalized medicine by their application in the branch of theranostics where drugs are used simultaneously to diagnose and treat the medical conditions.

As with every new innovation, there are *pros and cons*⁶ for nanotechnology also as listed in ► **Table 3**.

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Conflicts of Interest

There are no conflicts of interest.

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