



Nanomedicines in Cancer Therapy- An Overview

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Abstract:

Cancer is the leading cause of death worldwide. Despite all the advancements in cancer research, the year 2020 witnessed about 10 million deaths by Cancer. The conventional treatment modalities are often accompanied by unwanted side effects because of their non-specific nature. Nanotechnology has contributed to all sectors of science including medical science. Nanotherapy allows the manipulation, regulation and control of physicochemical properties of nanoparticles thus facilitating early diagnosis, targeted drug delivery and improved efficiency of conventional therapies. This review article gives an overview of clinical applications of nanomedicines for cancer, their mechanism of action and prime challenges faced during the formulation and internationalization of these nanosystems.

Keywords: Cancer; Nanotechnology; Nanomedicine; Targeted drug delivery

List for abbreviations:

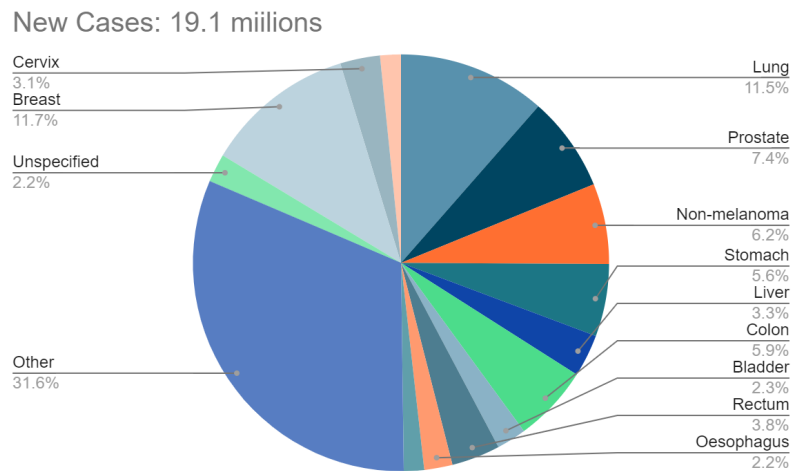
1. Nanoparticle: NP
2. Multidrug Resistance: MDR
3. Polyethylene glycol: PEG
4. Multifunctional Nanoparticle: MNP
5. Gold Nanoparticle: AuNP
6. Quantum Dot: QD
7. artificial Antigen- presenting cells: aAPCs
8. Tumor- associated antigen: TAA
9. EPR: Enhanced Permeation and Retention
10. IV : Intravenous
11. PLGA : Poly Lactic-co-Glycolic Acid

1. Introduction

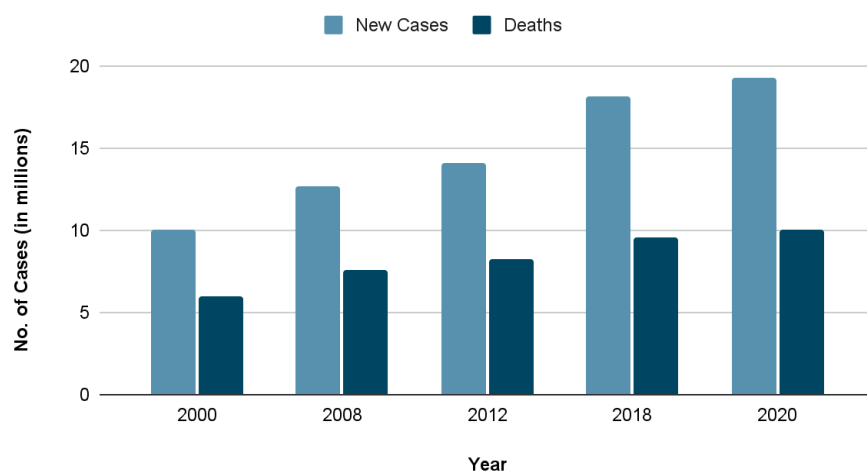
Cancer is a disease that arises from the uncontrolled proliferation of malfunctioning and miscommunicating cells. DNA in eukaryotic cells undergo continuous damage, repair and resynthesis. A homeostasis equilibrium exists which balances DNA damage and repair. Disruption of this balance leads to the accumulation of multiple mutations which causes cancer¹. 19.3 million cases and 10.0 million deaths due to cancer were estimated worldwide in the year 2020² and according to a study by The International Agency for Research on Cancer, 1 in 6 people are expected to develop cancer in their lifetime and WHO expects this number to rise.³

Chemotherapy and radiotherapy are conventional therapies targeting the disease. Apart from being

non-specific, these therapies are responsible for many adverse side effects as they kill all rapidly dividing cells. In the past few years, *in vivo* imaging for diagnosis and targeted therapies aided by nanotechnology are seen to roll in promising better efficiency in terms of diagnosis, screening and treatment with fewer side effects. Cancer is caused by alterations at the molecular level or at the nanoscale. Nanotechnology is defined as the 'intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1 to 100 nm).⁴ Nanoparticles (NPs) have wide application in medicine and nanomaterials are now used for clinical diagnosis (nano diagnosis), controlled drug delivery (nanotherapy), and regenerative medicine.



(a)



(b)

Figure 1: Total Deaths in year 2020

- a. Graphical comparison of new cases in different types of cancer in 2020.³
- b. Graphical comparison of number of cancer cases and deaths from the year 2000 to 2020

1.1 Introduction to Nanomedicines

Nanomedicine is a widely implemented form of nanotherapy in which NPs loaded with drugs act as carriers and are used as drug delivery systems. Nanomedicine has ushered in a new era for drug delivery by improving therapeutic indices of Active Pharmaceutical Ingredient (API).⁵ The major objective of this system is to increase the drug efficacy and shrink the toxic effects while reducing the loss of the drug administered. Anti-cancer drugs loaded with NPs can be administered through different routes including intravenous and oral administration, intraperitoneal injection, inhalation, depending on the effect desired. Early screening and diagnosis, which is another application of nanotherapy have facilitated more effective treatment of cancer. The potential of nanomedicine can be further extended to monitoring, combination therapies and targeted drug delivery at the site of the tumor which could promise more efficient treatment. Nanomedicines also encompass different types of nanosystems including nanofibers, nanodevices and nanoscale microfabrication-based entities. A wide range of systems including lipid-based⁶, metal-based, polymer-based, inorganic, antibody and drug-conjugated NPs are being analyzed as nanocarriers to aid in cancer treatment⁷. The efficacy of drugs administered via nanocarrier depends on

the properties and certain parameters of the nanocarrier like their size, surface-to-volume ratio, favorable drug release mechanism, route of administration, etc.

2. Nanomedicines in Cancer Therapy

NPs are comparable in scale to biological molecules and systems, moreover, they can be designed to possess controlled and desired properties, hence, nanotechnology potentially has clinical applications as ‘nanomedicines’. Nanomedicines due to distinct advantages over conventional therapies⁸ have found their applications in cancer therapy as a carrier for the drug for controlled and targeted drug delivery systems and may even as a therapeutic agent. A drug delivery strategy that selectively targets the cancerous tumor promises a sophisticated pathway for treatment and diagnosis. This pathway is facilitated by the use of nanomedicine in cancer treatment. Nanomedicines on account of nanosize, surface functionalization and stability provide a unique ability to target tumor sites. This approach allows the administration of multiple drugs to the tumor sites without mutilating normal tissues and cells. Nanomedicine formulations help in increasing the solubility and bioavailability of the administered drug. The key benefit of using nanomedicine over other therapies is less toxic

side effects due to the property of targeted delivery. NPs with a diameter less than 200 nm are not screened out of circulation and hence stay in the system for a longer time. Thus, nanomedicines have arisen with benefits with efficient therapies and collateral reducing side effects like undesired damage and Multidrug Resistance (MDR).

Drugs are conjugated or loaded on the nano-sized particles for their intervention into the system giving therapeutic or diagnostic output. Drug loading strategies

broadly involve adsorption: either on the surface or in the matrix (nanogels), encapsulation in a cavity (hydrophobic inner cavity of CD), complexed or chemically bonded with a macromolecule or polymer⁹ (figure 2). Covalent linking enables controlling the number of drug molecules linked to the nanocarrier which gives covalent bonding an advantage over other types. Targeting tumors and ensuring the bioavailability of drugs can be achieved by surface functionalization and modification of NPs.

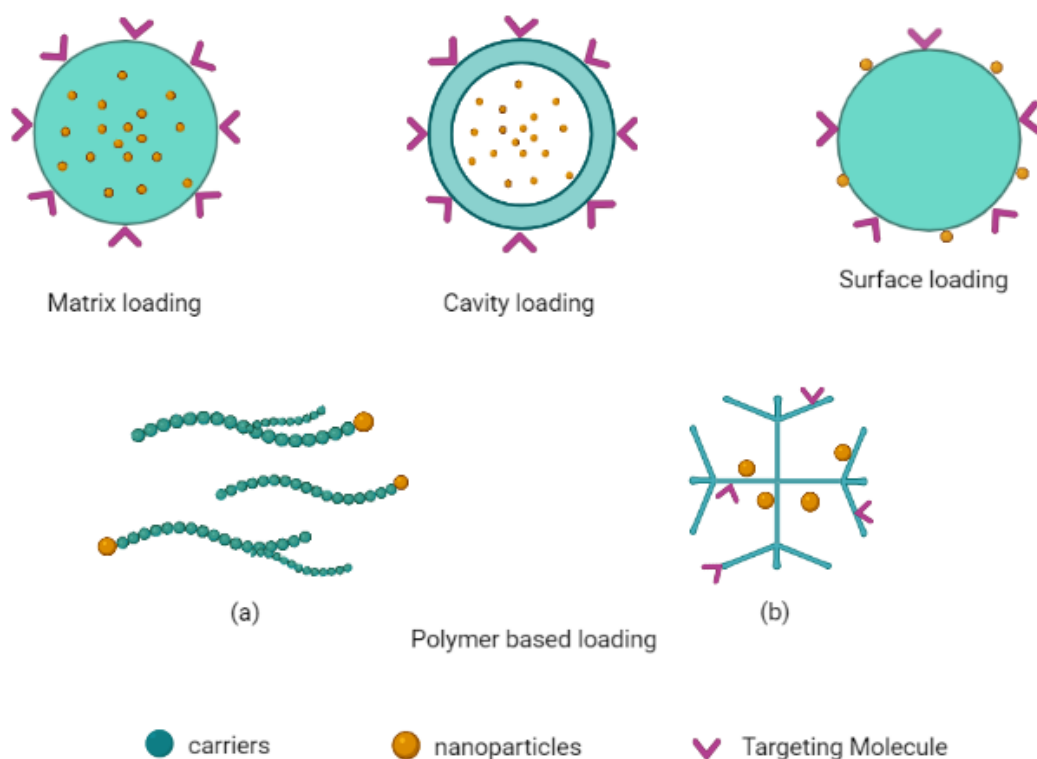


Figure 2: Drug loading strategies

Schematics illustrating four different drug loading strategies i.e matrix loading, cavity and polymer-based loading. Created using Biorender.com

Liposomes¹⁰, polymers, dendrimers¹¹, silicon or carbon materials, magnetic and metal nanoparticles¹² are a few nano-systems¹³ evaluated and approved for clinical applications in oncology. Liposomes were the first nanoparticles to be used in cancer therapy. Liposome-based nanoparticles are spherical nanoparticles constructed using lipid bilayers. Apart from being

self-aggregating, biocompatible, biodegradable liposome NPs can pass easily through cell membranes and show an affinity for nuclear components. Doxil was the first nanotechnology-based cancer liposomal carrier containing an active drug- Doxorubicin, used for the treatment of Kaposi's sarcoma, multiple myeloma and cancer of the breast, ovaries, bladder, etc.¹⁴ Nanotherm therapy is a

therapy that involves the introduction of magnetic liquid containing Iron oxide NPs to the tumor site which is then activated using a suitable magnetic field.¹⁵ As a result, the oscillation of these particles tends to release the active drug and eventually causes cell death. This Iron oxide NP is used for glioblastoma treatment. Magnetic NPs¹⁶ may improve the accuracy of cancer imaging and their magnetic properties aid targeted delivery. Polymeric micelles are one of the effective delivery systems for poorly water-soluble anticancer drugs. The nanosize and hydrophilic shell of PEG-coated polymeric micelles

facilitates prolonged blood circulation time and also enhances tumor accumulation. Genexol-PM is a polymeric micelle NPs containing the active drug paclitaxel used for the treatment of breast cancer, lung cancer and ovarian cancer. Dendrimers come as the smallest organic particle with the advantages of surface functionality which increases target selectivity. Dendrimer conjugated AZD4320 contains the active drug AZD0466 used to treat advanced solid tumors, lymphoma, multiple myeloma, hematologic malignancies.¹⁷

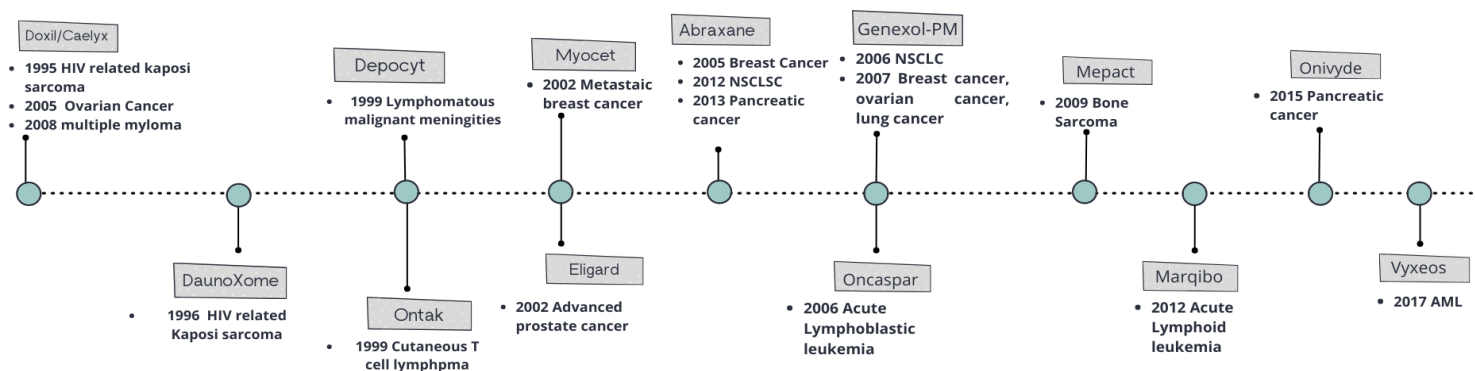


Figure 3: Timeline of FDA approved nanomedicines
Schematics illustrating updated FDA approved nanomedicines in cancer.^{9, 17-18}

2.1 Multifunctional Nanoparticles (MNPs) in Cancer Therapy:

MNPs have the ability to carry one or more therapeutic agents, imaging agents or diagnostic agents. They can even be engineered to carry multi-functional agents at a time. These MNPs are designed to detect cancer cells, deliver therapeutic agents, and monitor treatment response, thus integrating diagnosis and treatment instantaneously. Other than therapeutic agents, targeting moieties, image contrast agents and permeation enhancers are also encapsulated to make it multifunctional. MNPs

offer the feasibility to engineer anti-cancer drug combinations in a single drug delivery system for maximum efficiency and low toxicity. Aurimune® is the first MNP system to enter the clinic. Aurimune has both imaging and therapeutic functionalities. Aurimune® is composed of a colloidal-gold nanoparticle conjugated to the tumor growth inhibitor tumor necrosis factor-alpha to achieve theranostic properties¹⁹.

Table 1: General classification and types of nanoparticles


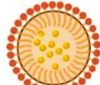



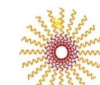




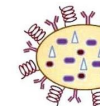
	Nanoparticle	Materials used	Medicinal use	Example of formulation for Cancer therapy	STRUCTURE
LIPID BASED NANOMEDICINE	Liposomes	Phospholipids , non-ionic surfactants	Drug, gene therapy, Cosmetics	Doxil , Onivyde	
	Solid lipid nanoparticle (SLN)	Solid Lipid + stabilizer	Drug, gene Delivery , Cosmetics	Ramipril- loaded SLN	
	Nanostructured lipid carrier (NLC)	Solid lipid + Liquid , Lipid + Stabilizer	Drug, gene therapy, Cosmetics	Docetaxel- loaded NLC	
	Lipid micelle	Polymer, Phospholipid Surfactant	Drug, gene therapy, Surface cleaning, Cosmetics	Genexol-PM, Nanoxel-PM	
POLYMER BASED NANOMEDICINE	Polymeric nanoparticle	Polymer	Drug, gene delivery	Zinostatin stimalamer	
	Polymeric micelle (PM)	Hydrophilic polymer Block + Hydrophilic polymer core	Drug Delivery	Genexol- PM	
	Dendrimer	Branched Polymer	Drug, gene delivery	Dendrimer conjugated AZD4320	
METAL BASED NANOMEDICINE	Iron oxide nanoparticle	Surfactant + metals	magnetic resonance imaging, tissue repair, magnetic hyperthermia and drug delivery	NanoTherm	
	Gold Nanoparticle	Hydrogen tetrachloroaurate (HAuCl4) with citric acid	Drug, gene delivery	AuroShell	
	Carbon Nanotube	Carbon+ Substrate	Drug delivery and biosensing methods for disease treatment and health monitoring	Single walled carbon nanotubes (SWCNT) loaded with paclitaxel	
	Multifunctional Nanoparticle	Imaging agents / Diagnostic agents/ therapeutic agents	Diagnosis , drug delivery, imaging	Aurimune ®	

Table illustrating general classification and types of available nanoparticles along with their structures, medicinal uses, materials used and some examples of available formulation of each type of nanoparticle.

Note: this table is modified from Eskandari Z, Bahadori F, Celik B, Onyuksel H., *J. Pharm. Sci.* 2020²⁰

3. Mechanisms of Targeting and Release

The conventional therapeutic agents for cancer therapy show improper body distribution and pharmacological effects. These drugs show rapid clearance from the body system and lack the ability to accumulate in the tumor sites which results in inefficient treatment causing toxicity. The development of nanosystems for drug

delivery manifests efficient drug delivery and efficient pharmacokinetics at the whole body as well as the cellular level. This precise drug delivery and desirable pharmacology are achieved mainly via two mechanisms: Passive mechanism and Active mechanism (figure 4).

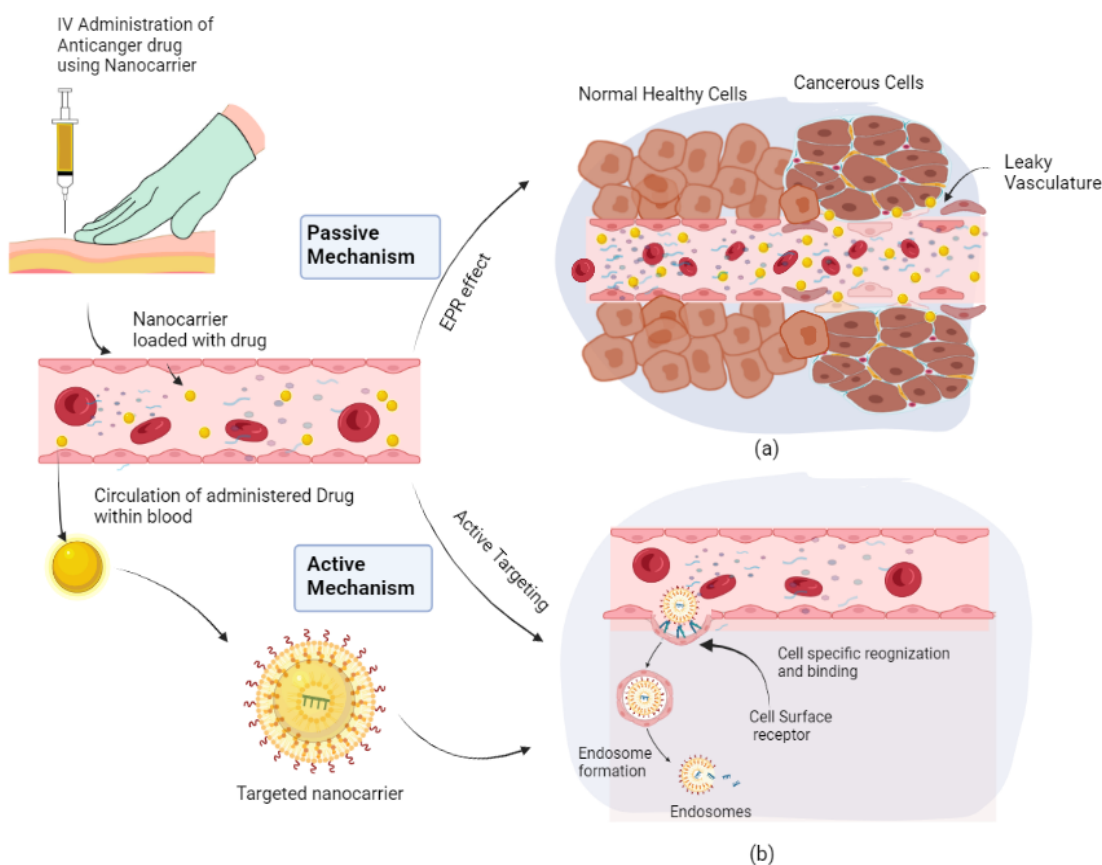


Figure 4: Mechanisms of action

Schematics illustrating the types of the mechanism of action of nanomedicines after intravenous administration by a. Passive mechanism b. Active mechanism. Created using Biorender.com

3.1 Passive Mechanism

In tumors, due to inflammation, the blood vessels become leaky and highly permeable; gaps among them increase from 100 nm to 800 nm. Tumor blood vessels are characterized by leaky vasculature, decreased lymphatic drainage. An effect indicating passive retention was identified by Maeda et al., which is called the 'Enhanced

Permeation and Retention (EPR) effect'. EPR is a mechanism attributing to which non-specific drugs may accumulate in leaky vasculature.²⁰⁻²¹ Accrediting their low molecular weight and nonspecific diffusion, free anticancer drugs tend to easily pass between the intercellular spaces. As a result, they remain in the bloodstream for a shorter time and the probability of reaching the drug to the tumor site decreases. Drugs anchored with nanocarriers bring larger sizes against

intracellular spaces, they sustain in the circulation for a longer time. As the blood vessels surrounding tumor tissues are defective and porous, nanocarrier containing anti-cancer drugs can permeate through blood vessels towards tumorous tissues, wherein they accumulate and show the desired pharmacological effect. Thus, nanomedicines, on account of the EPR effect, extravasate into the tumor environment.²² The EPR differs with types of tumor, their progression and location. Besides, the properties of the nanocarriers used, too affect the extravasation of nanomedicines.

3.2 Active Mechanism

Where passive targeting aims for localization of a nanosystem inside the tumor microenvironment, active targeting allows active ingestion of the nanosystem by the tumor cells. Active targeting of drugs is carried out by conjugating targeting agents with the NPs encapsulating the drug.²³ Target agents help the NPs identify certain genes and proteins in tumors and cancer environments and consequently either kill or inhibit the tumor growth, division or spread. Agents targeting angiogenesis - a process involving the growth of new vasculature from preexisting cells, are being developed for anti-angiogenesis imaging and therapies. Another class of chemicals that targets microtubules results in disruption of cell functions too, assures a promising therapy²⁴. Targeting agents can be determined for a process, cell stage, organ or tumor tissues. These target agents are hereby classified broadly as proteins, nucleic acids and receptor ligands. Antibody-based targeting approved by the FDA has shown greater feasibility.²⁵ This targeting component must show a strong affinity towards the receptors or proteins expressed in the targeted tumor site. As drug encapsulated NPs are administered in the bloodstream, the targeting agent assists in the identification of the tumor-specific antigens. Tumor cells are also characterized by increased expression of cell

surface proteins and receptors for example, transferrin receptor (TfR), and epidermal growth factor receptor (EGFR) which facilitate this recognition process. Once inside the cell, the polymeric nanocarrier degrades and the anti-cancer agent is thus free.²¹ This approach very conveniently avoids unnecessary cytotoxic effects of drugs on healthy cells and tissues and also eases cellular uptake of the drug by receptor-mediated endocytosis.

4. Properties of Nanoparticles

Particle size, shape and surface characters are the important parameters in determining the drug release profile of a particular NPs material.²⁶⁻²⁷ (figure 5). Smaller particles have a greater surface-area-to-volume ratio which causes faster drug release as the drugs associated with small particles would be at or near the particle surface. Particle size also affects clearance. Particles with diameters less than 5-6 nm are observed to be cleared at a faster rate whereas particles with a diameter of more than 200 nm stay in the system longer. Gao et al. observed cytotoxicity to be inversely proportional to particle size whereas NP size and its cellular uptake showed a linear relationship.²⁸ Uneven body distribution can cause toxicity and affect the concentration of drugs reaching the tumor sites.

NPs can be designed into different shapes viz. Spherical, rod-shaped, discoid, filamentous, etc. Cellular uptake of gold nanoparticles (AuNPs) was studied to be highest.^{27, 29} Studies show that when compared with spherical NPs, filamentous NPs are depicted to have better pharmacokinetics and homing capacity³⁰⁻³¹, rod-shaped NP has shown a better migrating tendency towards the blood vessels and better binding capacity is exhibited by rod-shaped and cylindrical-shaped particles. Shape and size correlations like aspect ratio and geometry influence the transport and interactions of nanomedicines.

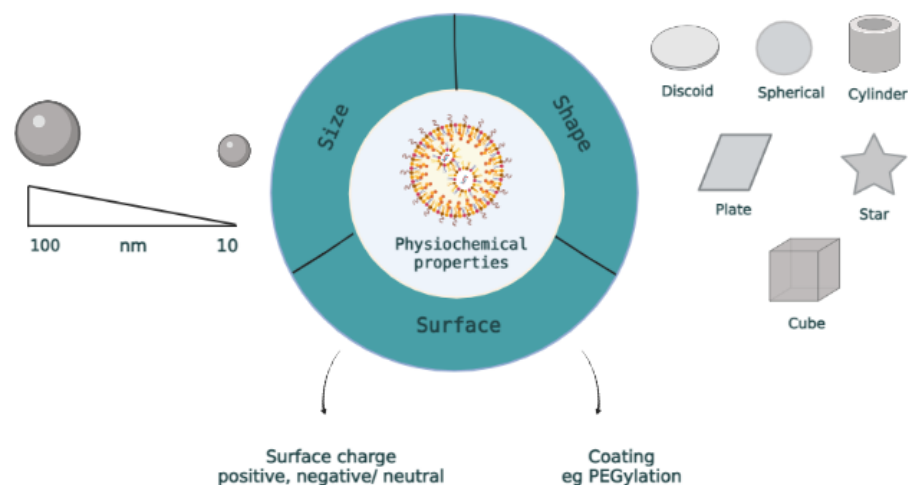


Figure 5: Physicochemical properties of nanoparticle

Schematics representing various physicochemical properties of nanoparticles affecting their therapeutic activity: shape (ranging from 10nm to 100nm), size (discoid, spherical, cylindrical, plate, star and cube) and surface properties (surface charge and coating). Created using Biorender.com

Coating (specifically PEGylation) enhances the desirable properties and therapeutic outcomes of the NPs. After the administration of nanomedicine into the body, the major problem faced with NPs is their recognition as foreign material and their elimination by opsonization. Opsonization is an immune response in which the complementary protein opsonin is released by the stimulation of entry of foreign material. The interaction between this protein and the foreign body causes the excavation of the foreign body by macrophages. In order to make the administered NPs unrecognizable as foreign bodies, these NPs are coated with hydrophilic polymer to suppress the release of this complementary protein²⁰. The process of coating the NPs with a hydrophilic polymer like polyethylene glycol is known as PEGylation. It is found that the PEGylated nanomedicines stay for a longer time in blood circulation than non-PEGylated nanomedicines. The surface charge of NP, which is measured as zeta potential, affects agglomeration and diffusion subsequently influencing the uptake, biodistribution and tumor penetration. Attributing to a higher diffusion coefficient, negative particles show rapid penetration^[32] whereas positively charged particles are evaluated to target tumor sites better³³.

For sustainable drug release within the targeted tumor, NPs are synthesized using biodegradable materials. The diffusion and erosion rate helps in determining the drug release rate. When the drug is evenly distributed within the NPs, the degradation of biodegradable material and the diffusion are the two main parameters for determining the drug release rate. If the diffusion rate is faster than the degradation of material the drug release process is mainly governed by diffusion. In the initial stages, sometimes rapid and faster drug release is seen after administration which is termed as 'burst' release.²⁴

4.1 Approaches for the Preparation of Nanoparticles (figure 6)

1. Top-down method: Large molecules of micron size are converted into nano-sized particles using techniques like milling, homogenization, grinding, etc under controlled conditions.
2. Bottom-up method: Opposite to the top-down approach wherein different materials are constructed from molecular components (atoms).²⁰

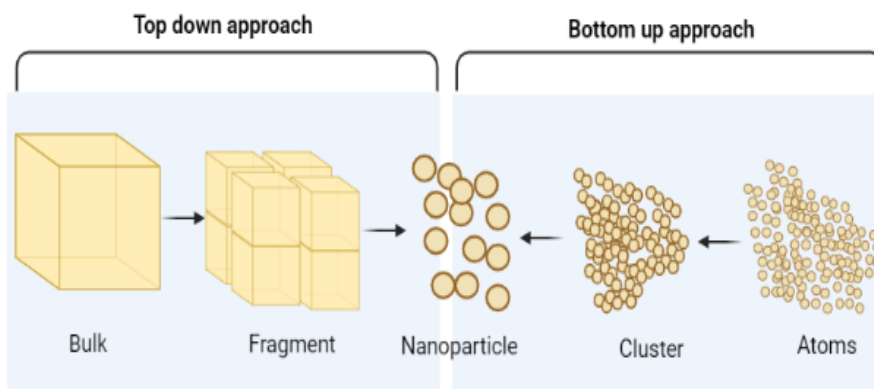


Figure 6: Approaches for preparation of nanoparticles
Schematics illustrating the approaches for the preparation of nanoparticles:
Top-down approach and Bottom-up approach. Created using Biorender.com

5. Applications

Owing to the adjustable biochemical and biophysical properties of NPs, these nanosystems aid in the early detection of tumors and efficient drug therapy for cancer.

5.1 Nanoparticles in Cancer Diagnosis

Nanomedicines with the help of NP between size range 1-100 nm provide a platform for early and precise diagnosis of tumor cells and tissues³⁴. Detection of cancer has become easier as NPs have begun to aid *in vivo* and *in vitro* imaging³⁵ of tumor tissues and cells. A wide range of technologies for imaging has been developed³⁶:

Optical imaging: Optical imaging uses the wavelength and intensity of the photon for detecting cancer environments applying phenomenon like fluorescence. Fluorescent imaging and Near-Infrared (NIR) imaging are two broad ways of optical imaging that are aided by NPs like AuNPs, magnetic nanoparticles, quantum dots (QDs emit fluorescence near the IR spectrum), etc.³⁷

Radio imaging: Radiography is another technique involving X-ray, computed tomography (CT) and positron emission tomography (PET) that even allows morphological detection of tumors. Colloidal NPs along with certain labeled nanosystems (Zr-labeled

phospholipids, ⁶⁴Cu Labeled) efficiently aids image-guided radiotherapy (IGRT).

Magnetic resonance imaging (MRI): MRI has navigated its way as a potent technique for tumor imaging where superparamagnetic iron oxide (SPIO) NPs along with are successfully used as probes for targeting tumors. MRI has great potential to identify morphological as well as functional alterations.

Ultrasound imaging: Despite lower stability and high clearance rate, nanostructures like iron oxide nanoparticles, gold nanostructures and graphene oxides can be used for ultrasound imaging by conjugating them with the drug through encapsulation. Proteins and microtubules can also be liganded with polymers to find markers in vasculature.³⁵

First-generation NPs for imaging were designed to be blood pool agents. Targeted imaging by NPs is either at the molecular level i.e., vascular and deep-tissue imaging and are mostly believed to be impacted by the EPR effect. Vascular targeting strategies generally devoid extravasation steps but the NPs should possess fairly well travel time through vessels and good binding avidity to the vasculature.

Precise imaging of tumors involves successful navigation of the probes in microenvironments through leaky

vasculature by crossing other biological barriers and this process is primarily governed by properties of the NPs like their shapes, sizes, surface functionality, etc. Studies have shown that longer circulation of NPs in blood circulation has shown a better extravasation rate, providing them the opportunity to accumulate at tumor sites.

5.1.1 Biomarkers

National Cancer Institute (NCI) defines biomarkers as ‘a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease’. These markers mark a healthy human from the diseased one and assess early detection and diagnosis processes. Molecular profiling studies help discover biomarkers. A variety of biomarkers comprises proteins, nucleic acid and even antibodies.³⁸⁻³⁹ p504S (α -methyl acyl CoA racemase, an enzyme involved in β -oxidation of fatty acids), hepsin (HPN, a transmembrane serine protease), are examples of few biomarkers successfully assessed for prostate cancer that indicates conditions like metastasis. NPs can be developed either into a probe that would detect extracellular and intracellular cancer biomarkers or into a system that would protect the biomarkers. NPs can be engineered into a biomarker to detect tumor niches or, biomarkers can be encapsulated in a nanosystem as organic fluorescent probes and inorganic biomarkers.⁴⁰

Quantum dots give promising results owing to their fluorescence property and good navigation rate through interstitial spaces. Silica nanoparticles, AuNPs, and conjugated polymer NP probes have also been used for fluorescence-based detection of cancer cells. Metal oxide-based NPs, e.g., ZnO, can be designed for biocompatibility and sensitivity to work as biomarkers.⁴¹ An ideal tumor biomarker is believed to have a decent sensitivity along with biocompatibility. Once the biomarkers are identified they can be detected and imaged under the aegis of NPs.⁴² Screening and measurement of biomarkers help understand the type and size of the tumor, progression of the disease and even aid risk assessment, management and monitoring of the therapy thus helping derive efficiency of the provided treatment.

5.2 Nanoparticles for Targeted Drug Delivery

The size, engineered biological and physicochemical properties of NPs favor their use as efficient carriers for drugs aiming at targeted delivery. Conventional cancer therapies involve the diffusion of active metabolites and therapeutics freely in the bloodstream and the active agent reaches all parts, tissues and cells of the body causing toxicity to healthy cells and tissues. Targeted drug delivery targets the damaged cell and tissues, thus, reducing exposure to the non-cancerous parts of the body. This approach in a way helps to strategize precise dosing and collaterally reduce wastage, toxicity and side effects. NPs easily invade the vasculature, thereby increasing cellular uptake of the drug.²² These systems can be manipulated for controlled release and localized targeting of the drug. The release of drugs can be modulated under mechanisms namely, erosion, dissolution, diffusion and partitioning.⁴³

NPs are capable of storing drugs in them and releasing them at the targeted site at the desired time and for a sustained period. The release of NPs at the site can be through active or passive mechanisms. Another mechanism of release of the drug could be due to stimulus, i.e., Triggered release which may be governed by factors like pH and temperature. A wide spectrum of organic NPs like liposome-based NPs, carbon nanomaterials, nanogels and polymer-based NPs like polymeric micelles and dendrimers along with inorganic nanosystems like silica-based NPs and oxides of metals have been successfully used as tools for targeted drug delivery.⁴⁰ Apart from these, hybrid nanosystems have efficiently contributed to the targeted therapies.^{44,45}

5.3 Nanoparticles in Cancer Therapies

5.3.1 Chemotherapy:

Cytotoxic drugs hold the biggest share in chemotherapy of tumors. Chemotherapeutic agents cause toxicity to the cancerous cells resulting in termination of their growth or assassination. Though chemotherapy is the most promising form of treatment to date due to its convenient applications and availability of a variety of FDA approved drugs, patients still encounter complications of MDR. MDR is indicated by the reduction of sensitivity of drugs and their effectiveness in the patient's body. Administration of multiple drugs at the same time has proven to overcome this condition. NPs having the capability of carrying more than one chemical component

at a time successfully aid this process.⁴⁶ Drug loading for chemotherapy is mainly done by molecular (adsorption) and chemical conjugations. The presence of functional groups on the drugs as well as NPs gives the freedom of linking nanosystems with drugs via diverse chemical associations.^{47, 48} AuNPs chemotherapy conjugates are studied to implicate effective intracellular drug delivery.⁴⁹ Chemotherapy strategized using nanosystems gives an advantage of targeted delivery, overcoming biological barriers and co-delivery of drugs. Solid lipid nanoparticles have also proved to be potent vehicles for the delivery of chemosensitizers and cytotoxic agents. Thus, NPs facilitate co-targeted delivery of chemosensitizing and cytotoxic drugs, collaterally improving drug uptake and reducing adverse toxicity caused because of the treatment.

5.3.2 Radiotherapy:

Radiotherapy is killing or causing shrinkage of tumors by using a high dose of radiation involving X-rays, gamma rays, etc. Radiation therapy basically works by causing damage to DNA or disrupting cell functioning by administration of radioactive rays or by embedding radioactive nuclei into the system. Side effects and toxicity due to this therapy is primarily believed to be arising because of the therapy being non-specific. Radiations may sometimes not reach deep tissues and cells and also the cells may form resistance towards the radiation, this forms another limitation of radiation therapy.^{50, 51} NPs can be used to improvise the effectiveness of the external radiation or by loading NPs with radioisotopes and target delivery of radionuclides to the tumor site. NPs are being formulated to enhance the radiosensitivity of tumor cells and tissues. Metal-based nanoparticles, supramagnetic iron oxides, and QDs are promising NPs for radiotherapy. Nanomaterials with a high atomic number like iodine and gold are potent sensitizers for radioactive beams. Fullerene C₆₀, an allotrope of carbon, is found to have anti-cancer properties.⁵²

5.3.3 Immunotherapy:

Immunotherapy involves triggering the immune system to react and setting a defense mechanism by identifying the tumor environment. This treatment can work by either increasing the effector response, eventually leading to a decrease in suppressor mechanism and slowing down angiogenesis or by increasing their sensitivity to

immunologic defenses.^{27, 53} Nanovaccines and artificial antigen-presenting cells (aAPCs) are potentially applied to immunotherapy.⁵³ Tumor-associated antigens (TAA) are delivered at the site via nanovaccines. aAPCs can be engineered with NPs enhancing the delivery of TAA into the cytoplasm thus increasing the immune response. Liposomes, AuNPs, PLGA, micelles, and dendrimers are successfully used as NPs for immunotherapy.⁵³ Systems can be designed for direct targeting and stimulation of T-cells and activating the immune response in the tumor microenvironment. Biomarkers and targeting agents like monoclonal antibodies play a vital role in delivering targeted immunotherapy. Immunotherapy can be combined with chemotherapy for the co-delivery of chemical therapeutics and nanosystems for stimulating T-cells.⁵⁴

6. Challenges and Opportunities

Nanotechnology has its wide application in all fields of sciences along with medical sciences. Nanomedicines, besides all the advantages, still have some gaps that limit their all-inclusive applications. The key issue encountered while formulating these nanosystems is modulating their physicochemical properties for controlled pharmacokinetics, even biodistribution and formulating systems of nano-size.⁵⁵⁻⁵⁶ Besides these, the engineering NPs for clinical applications need addressing of certain challenges and problems, to name a few: system toxicity, reliability, production and cost optimization and production of easy to handle devices.

In vivo administration of NPs causes system toxicity especially in NP-based imaging for diagnosis. The potent toxicity of these NPs should be evaluated for their *in vivo* use. The physical and chemical properties of NPs can impact their toxicity and also govern their uptake. In addition to properties; the biodistribution, biodegradability and pharmacokinetic properties of NPs should be considered.⁵⁷ Another challenge faced in nanotechnology-based cancer therapies is reliability. To be applied clinically, it is essential to obtain reliable and quantitative detection results. Many factors can affect NP-based detection signals, including nonspecific binding of NP probes, NP interactions with biomolecules,

aggregation and unfit detection conditions. Due to the complex body fluid composition, fluctuation in the output signal can also be seen. From a clinical validation perspective, before NP-based clinical application, it is necessary to investigate assay reliability and reproducibility in large clinical sample pools.

Production of large-scale nanoprobe which are highly sensitive, highly reproducible, and have long-term storage stability at an acceptable cost can also be a limiting factor in the commercialization of nanomedicine. Even though the production of current nanoprobe is done in the very optimized condition, the production of these probes in batches is still a big challenge. Due to the variations in shape, size, composition, charge, and surface coating, the detection of the results varies great.⁵⁸ To minimize batch-to-batch changes, the synthesis steps and nanoprobe functionalization must be simplified. In addition, some of the np due to their size and composition may tend to aggregate during storage. Moreover, the cost-effectiveness

of developing a nanotechnology-based platform must be taken into consideration. In addition, difficulties could be experienced while manufacturing NP-based devices with high sensitivity that are easy to handle and cost-efficient.

Nanomedicines have revolutionized the treatment and diagnosis sector for cancer despite these challenges which may seem herculean to overcome. Gold-based nanoparticles⁵⁹ specifically, are being used to a very large extent in all provinces of the therapy owing to their unique properties of absorbance and greater stability. NP-based point of care devices and formulas of NP-based personalized medicines, as well as therapies, have a broad scope for development and clinical application in cancer diagnosis. Although only a few NP-based assays have advanced to clinical trials, with close collaboration among researchers, engineers, clinicians. Nanotechnology-based cancer diagnosis is poised to move into the clinic in the near futur

7. Overview of Nanomedicines

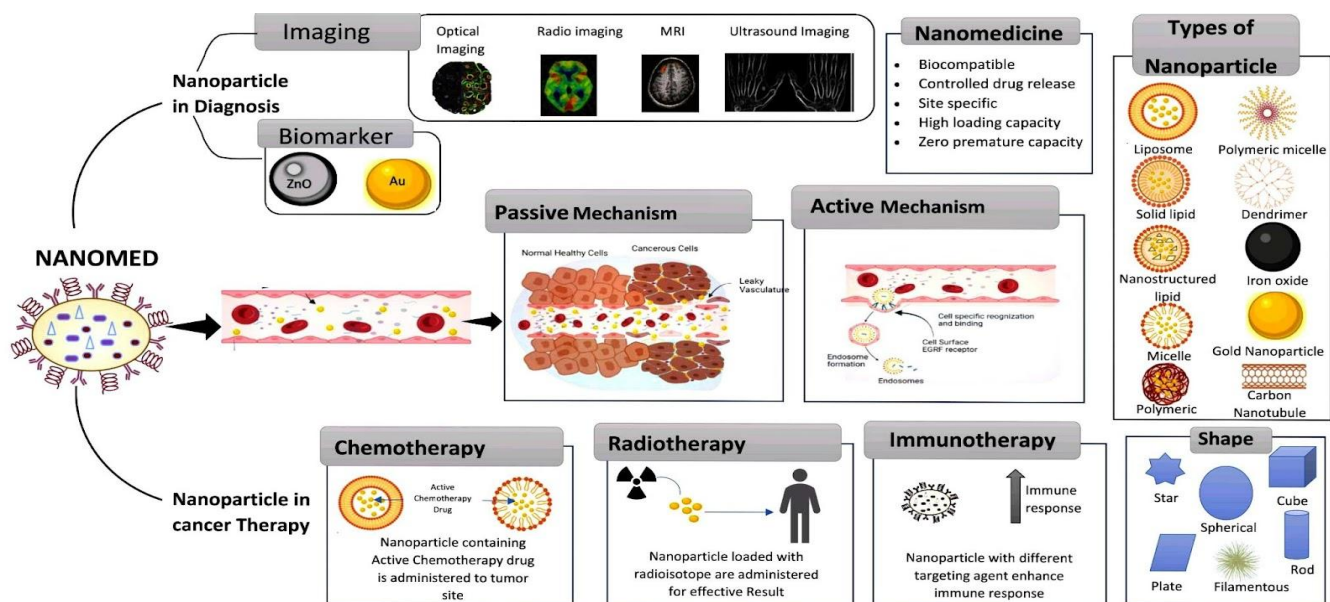


Figure 6: Overview of Nanomedicines

Schematics illustrating the Overview of Nanomedicines.

(Role of NPs in cancer diagnosis and therapy along with the mechanism of action and types)

8. Conclusion

Nanomedicine, which is a combination of nanotechnology and biological devices, is an emerging method for cancer therapy. Conventional strategies for the treatment of cancer are often limited by their non-specificity and toxic adverse effects. Nanomedicines have evidently showcased several advantages over the conventional strategies for diagnosis and treatment. Properties like high surface area to volume ratio which enables more loading of the drug to a particle along with tunable optical, electronic, magnetic and biological properties allow these particles to be modified into different sizes, shapes, structures giving them an edge over atoms and macroscopic materials used for treatment. Also, NPs can be incorporated into biological devices and drug delivery vehicles with greater convenience. Cancer, an aggressive disease, for many years has been the most devastating disease

and its treatment demands targeted delivery, controlled release, invasion through blood brain barrier which aligns with objectives behind the development of nanomedicines. The development of nanotechnology based assays for cancer diagnosis and treatment as well as in the field of nanotherapy has facilitated an increase in survival rate of cancer patients. When compared to the currently available cancer diagnostics in the clinic, a variety of NP-based assays are studied to show enhancement in terms of selectivity and sensitivity. Advancements in nanomedicines have the potential of contributing to precise, highly efficient and personalized medicines in the near future. Nanotechnology-based nanomedicine has unlocked new potential for cancer therapies and has opened a gateway that can be foreseen to make cancer a manageable ailment.

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