



## REVIEW ON THE ROLE OF NANOPARTICLES IN OVERCOMING DRUG RESISTANCE IN CANCER: MECHANISTIC AND THERAPEUTIC PERSPECTIVES

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### ABSTRACT

Nanoparticles have emerged as a transformative platform in cancer therapeutics due to their unique physicochemical properties and ability to overcome the limitations of conventional chemotherapy. This review offers a thorough explanation of nanoparticles, their categorization, and their molecular functions in the fight against cancer treatment resistance. Metal-based, ceramic, and carbon-based nanostructures are examples of the organic and inorganic forms of nanoparticles, each of which offers unique physicochemical properties for targeted drug delivery. While inorganic and metallic nanoparticles offer better stability, controlled release, and imaging potential, organic nanoparticles like liposomes and polymeric carriers improve biocompatibility and drug solubility. Targeted drug delivery, improved permeability and retention effects, and regulated intracellular release that reduces systemic toxicity are the processes of nanoparticle-mediated cancer therapy. Both intrinsic and extrinsic mechanisms, such as altered drug efflux, apoptotic inhibition, tumor hypoxia, and enzymatic degradation of anticancer medicines, can lead to drug resistance in cancer. Collectively, this review highlights the pivotal role of nanotechnology in redefining strategies to overcome cancer drug resistance and enhance treatment outcomes.

## **INTRODUCTION TO NANOPARTICLES**

Nanoparticles are small solid particles that range in size from 10 to 1000 nanometers. In these systems a drug can be dissolved, trapped, enclosed or adhere to the surface of the nanoparticle matrix. Depending on how they are made, they can exist in different forms such as nanoparticles, nanospheres or nano capsules each designed to control how the drug is transport and released in the body (1). A nanoparticle is the building block used to create nanostructures. It is far smaller than the objects we see in daily life which follow Newton's laws of motion yet larger than individual atoms or simple molecules which are governed by the rules of quantum mechanics (2). Nanotechnology holds enormous potential to improve the quality of air, water and soil in our environment. It can make pollutant detection and monitoring more accurate and efficient while also supporting the development of new methods to clean and restore contaminated areas (3). Nanomedicine presents exceptional prospects to enhance the diagnosis and treatment of various human diseases. Using microorganisms to produce nanoparticles is an eco-friendly and sustainable approach. Nanotechnology has the ability to transform biotechnology tools making them more personalized, compact, affordable, safe and easy to use for both researchers and patients (4). The special characteristics and usefulness of nanoparticles come from several unique features one being that their size is comparable to biomolecules like proteins and nucleic acids. Nanoparticles are made up of metals or semiconductor materials giving them crucial properties such as fluorescence and magnetic behavior which make them highly versatile in scientific and medical applications (5). Nanoparticle-based treatments are developed for many serious conditions including Methicillin-Resistant *Staphylococcus aureus* (MRSA), Alzheimer's disease, lung and liver cancers and coronary artery disease. As their use continues to grow

scientists are carefully studying their safety and long-term effects to ensure they are both effective and harmless for human health (6). A range of materials including polymers, lipids, metals and ceramics have been used to design different particulate drugs and drug delivery systems (DDS) (as shown in Fig. 1). Nanoparticles can be divided in many ways they may be organic or inorganic or categorized based on their shape, size, surface charge and physicochemical properties. These variations allow scientists to tailor nanoparticles for specific medical and technological purposes (7).

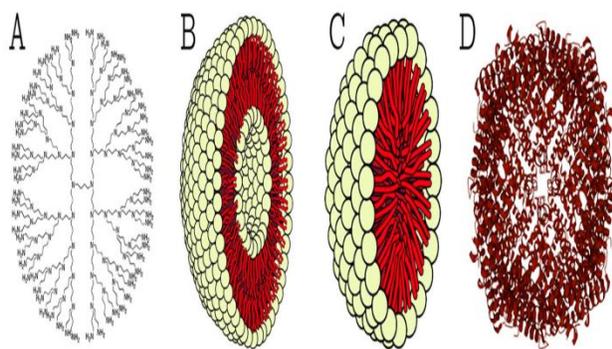
### **Nanoparticles Classification**

Nanoparticles (NPs) are categorized into different types which are based on their shape, size and physical or chemical characteristics. Generally, they are divided into three main groups organic nanoparticles, inorganic nanoparticles and carbon-based nanoparticles each with unique structures and applications.

#### **Organic Nanoparticles**

This type includes nanoparticles composed of organic materials such as proteins, carbohydrates, lipids, polymers and other carbon-based compounds (8). These particles are mainly biodegradable and non-toxic and some are like micelles and liposomes having a hollow core that can be used to carry drugs or other molecules (9). Both micelles and liposomes feature a hollow core commonly referred to as nano-capsules and they are sensitive to heat and electromagnetic radiation (10). The surface of a dendrimer has multiple chain ends that can be chemically modified to carry out specific functions making them particularly useful in catalytic applications (11). Nanoparticles (NPs) tend to be less toxic when used at low concentrations and for short exposure periods. These characteristics make them suitable for a variety of uses, such as commercial, residential, industrial, medical, energy-related research, and environmental

cleaning. In recent years, the pharmaceutical industry has been at the forefront of research on organic nanoparticles with the growing field of nanomedicine driving the development of new materials and the improvement of existing technologies (12).



**Figure 1: Types of organic NPs. A Dendrimers; B liposomes; C micelles; and D ferritin (13)**

### **Inorganic Nanoparticles**

This category includes nanoparticles that are not made from carbon or other organic materials. Typical examples include metal, ceramic and semiconductor nanoparticles. Metal nanoparticles are composed entirely of metal precursors which can exist in different forms monometallic (single metal), bimetallic (two metals) or polymetallic (multiple metals) depending on their composition and intended use.

### **Metal based nanoparticles**

Metal nanoparticles are minuscule materials made entirely of one kind of element. They can occur as clusters of several atoms or as single atoms. Some of the most commonly produced metal nanoparticles include gold (Au), silver (Ag), platinum (Pt), copper (Cu), palladium (Pd), rhenium (Re), zinc (Zn), ruthenium (Ru), cobalt (Co), cadmium (Cd), aluminum (Al), nickel (Ni) and iron (Fe) (14). Copper nanoparticles (Cu NPs) are

increasingly being used in many industrial applications. They reduce friction, act as catalysts on activated carbon to lower nitrate levels in water, and function as fillers to improve electrical conductivity, flexibility, and wear resistance. Like silver nanoparticles (Ag NPs) copper nanoparticles also exhibit strong antibacterial properties effectively inhibiting the growth of bacteria such as *Escherichia coli* and *Bacillus subtilis* (15). Metal nanoparticles exhibit distinctive optoelectronic properties due to their plasmon resonance behavior. Their synthesis can be carefully controlled by adjusting factors such as shape, size and crystal facets. In fact, nanoparticles can be synthesized from almost all types of metals.

### **Metal oxide-based nanoparticles**

Metal oxide nanoparticles (metal oxide NPs) are metal-based nanoparticles that have been converted into their respective oxides. When compared to their pure metal counterparts these nanoparticles have better qualities. Due to their remarkable characteristics metal oxide NPs are widely used in various fields such as catalysis, sensors, optoelectronic materials and environmental cleanup (16). At present different types of metal oxide nanoparticles (MONPs) are being used in clinical applications such as antibacterial and wound-healing dressings, biosensors, anticancer therapies and imaging contrast agents. Among them zinc oxide (ZnO NPs), cerium oxide (CeO<sub>2</sub> NPs), iron oxide (Fe<sub>2</sub>O<sub>3</sub> NPs), silver oxide (AgO NPs), magnesium oxide (MgO NPs), titanium oxide (TiO<sub>2</sub> NPs), nickel oxide (NiO NPs), zirconium oxide (ZrO NPs) and cadmium oxide (CdO NPs) are considered some of the most promising candidates for biomedical use (17).

### **Ceramic Nanoparticles**

Ceramic nanoparticles are inorganic materials known for their porous structure. Because their size and porosity can be precisely

controlled, they have recently gained significant attention as potential drug delivery vehicles. These nanoparticles are made from materials that exhibit properties between those of metals and non-metals. Typically, they have low electrical and thermal conductivity, a high elastic modulus and excellent stiffness making them highly resistant to corrosion and harsh environments (18). Ceramic nanoparticles can exist in various forms including polycrystalline, porous, dense and hollow structures. These different forms make them suitable for a wide range of applications such as photocatalysis, catalysis, imaging and the photodegradation of dyes (19).

### **Carbon Based Nanoparticles**

Carbon-based nanomaterials (NMs) possess significant properties and play an important role across various interdisciplinary fields. Carbon, a solid element exists in several forms such as graphite, amorphous carbon and diamond. Carbon-based nanoparticles (NPs) appear in different structures including graphene, fullerene and carbon black. Fullerene (C<sub>60</sub>) has been one of the most researched carbon nanomaterials since its discovery in 1985. Water soluble and hydrophilic derivatives of fullerene C<sub>60</sub> are important in biomedical sciences. Fullerenes easily undergo addition reactions involving their double bonds due to their special structure rich in  $\pi$ -electrons (20). Fullerene is a remarkable nanomaterial with valuable applications in biomedicine. Its strong antioxidant properties make it an excellent component in products like sunscreens, skin-whitening creams and anti-aging formulations. Additionally, due to their fluorescent interaction with specific biomolecules protein-encapsulated nanotubes are being utilized as implantable biosensors. Moreover, nanoscale robots and motors made with nanotubes are being explored for studying

cellular functions and biological systems at the microscopic level (21).

### **Mechanism of action of Nanoparticles in cancer therapy**

Scientifically, nanoparticles (NPs) are particles with a single dimension smaller than 100 nm and unique properties that are typically lacking in larger amounts of the same compound. Cancer is one of the leading causes of illness and death due to its complicated pathophysiology. Common cancer treatments include immunotherapy, targeted therapy, chemotherapy, and radiation therapy. Cytotoxicity, lack of selectivity, and multi-drug resistance are a few barriers to effective cancer treatment. The advent of nanotechnology has revolutionized the realm of cancer diagnosis and treatment. There are numerous uses for nanoparticles (NPs) in various scientific fields. In recent years, there have been numerous reports on the significance of NPs in modern medicine. They have been investigated for a variety of clinical uses, including contrast agents in imaging, gene delivery to malignancies, and medication carriers. For the development and creation of new cancer treatments, a variety of nanomaterials based on organic, inorganic, lipid, or glycan compounds as well as synthetic polymers have been employed (22).

The unique nanoparticle drug delivery system makes use of the features of the tumor and its surroundings. In addition to overcoming multidrug resistance nanoparticles address the shortcomings of traditional cancer treatment. Research on nanoparticles is intensifying as new pathways of multidrug resistance are discovered and examined. Many therapeutic applications of nano formulations have opened up entirely new avenues for the treatment of cancer (23). Worldwide, cancer is the most common cause of death. Chemotherapy, which has a number of harmful effects, is the mainstay of the typical

therapeutic strategy. Nanoparticle-based anti-cancer medicine delivery has certain appealing advantages over conventional chemotherapy drugs. Functional nanoparticles have made significant strides in cancer treatment thanks to the interdisciplinary application of nanotechnology in the biomedical arena. Cancer diagnosis and targeted, customized treatment have been aided by nanoparticles (24).

A wide range of compounds can be utilized to create nanoparticles, which can be employed to give special optical, magnetic, and electrical properties for imaging and therapy, or to encapsulate or solubilize chemotherapeutic drugs for better administration *in vivo*. The mechanism underlying tumor regression and the *in vivo* fate of these systems following intravascular or tumoral injection are examined. The supply, effectiveness, and safety of therapeutic drugs can now be improved because to nanotechnology, which has emerged as a revolutionary field in cancer treatment (25).

By taking advantage of the tumor's poor lymphatic drainage and leaky vasculature, nanoparticles (NPs) which are tiny materials with special physicochemical characteristics preferentially concentrate within tumor tissues. This would enhance the medicinal medicines targeted delivery. Targeted therapy is a customized method to treating molecular pathways involved in the development and spread of tumors. The presence or lack of particular markers in the tumor tissues determines how targeted therapy works (26). The targeted activity of the NPs is altered by the ligands that bind to receptors produced on the surface of cancer cells. The receptor mediated intake of NPs by the cancer cells and the drug transport systems selectivity enhanced. Antibodies or peptides that target the P-selectin receptor which is overexpressed in malignancies can also functionalize the NPs (27).

The increased permeability retention (EPR) effect, which causing NP accumulation at the tumor spot and the mechanism underlying passive NP targeting. Since NPs grow up in the tumor environment during OC treatment, this development is important. Drug exposure to healthy cells is decreased when NPs build up at the target site. NPs with a size of 10 nm to 100 nm penetrate tumor tissue more important and the shape of NPs affects cellular uptake and bioavailability (28).

Nanoparticles such as gold nanoparticles (AuNPs), silver nanoparticles, silica nanoparticles, quantum dots (QDs), and magnetic nanoparticles each present unique advantage. Organic nanoparticles (ONPs) have significant interest in cancer therapy due to their biocompatibility, biodegradability and ability to contain a diverse array of therapeutic agents including anticancer drugs, nucleic acids and imaging agents (29). These nanoparticles come in a variety of forms, including liposomes, polymeric nanoparticles, micelles, and dendrimers, each of which has special benefits for tumor targeting and medication delivery. To increase their accumulation and penetration in the TME, ONPs employ both passive and active targeting mechanisms. Passive targeting takes advantage of the EPR effect which promotes the causing of nanoparticles in tumors due to their leaky vasculature and impaired lymphatic drainage (30).

It is inappropriate to generalize nanoparticle radiosensitizer mechanisms due to the high degree of heterogeneity between nanoparticles. Formulations of nanoparticles should be seen similarly to pharmacological drugs and as a large class of therapeutic agents, requiring a high degree of uniqueness with regard to their interactions and final impact on radiobiological response. It is improbable that a single nanoparticle formulation will provide the greatest treatment results for every cancer just as there isn't a single anti-cancer drug.

There are significant opportunities for nanoparticle formulations to be adjusted for particular purposes because to the great degree of complexity and variety in molecular activity (31).

### Mechanism of Nanoparticles in drug Resistance

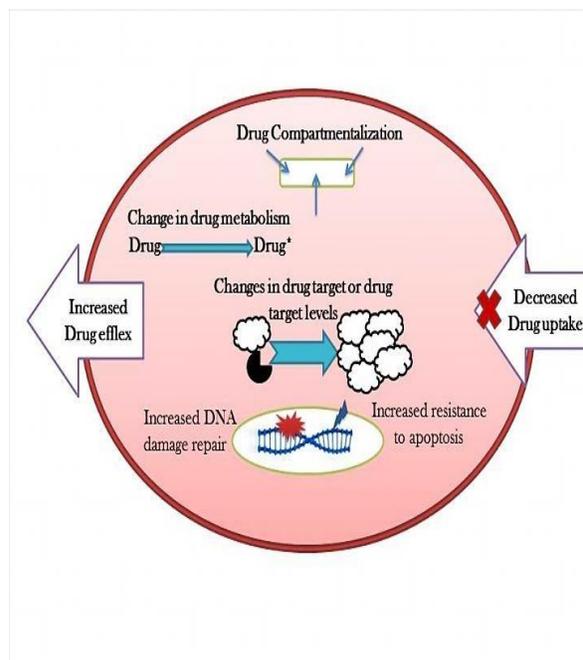
Despite an increase in cancer therapeutic techniques, drug resistance remains a significant issue in cancer treatment. When different cancer treatments fail due to multidrug resistance, the cancer progresses and the prognosis deteriorates. Cellular and physiological variables, such as overexpression of ATP binding cassette (ABC) transporters (e.g., efflux transporter), malfunctioning apoptotic machinery, interstitial fluid pressure, and acidic and hypoxic tumors, are among the reasons of tumor treatment resistance (32).

Because they enhance drug solubility, stability, and targeted distribution, nanoparticle-based drug delivery systems provide a viable remedy. These systems increase the effectiveness of therapy and decrease off-target toxicity by accumulating in tumor tissues through the Enhanced Permeation and Retention (EPR) effect. Coordination of pharmacokinetic and pharmacodynamic characteristics has been demonstrated to be possible using co-encapsulation techniques incorporating anticancer medications and resistance inhibitors within nanoparticles (33).

### Drug Resistance Mechanism in Cancer

The main treatments require on a deeper comprehension of the biology and molecular genetics underlying tumor growth. Common cancer treatments include radiation therapy, chemotherapy, combination therapy, laser therapy, and surgery. Despite these developments, chemotherapy remains the most promising cancer treatment available today. The invasion and spread of drug-

resistant cancers account for 90% of chemotherapy failures. Many patients' tumor cells develop drug resistance after receiving a specific medication during chemotherapy (34).



**Figure 2:** The methods in which cancer cells resist drugs

### Factors in drug resistance (Intrinsic and extrinsic)

Intra-tumor heterogeneity may be attributed to many variables that mostly occur at the cellular level and can be seen at many distinct cancer levels. This indicates that different genetic, epigenetic, transcriptomic, and proteomic features are taken into consideration when variants naturally arise. In cancer, a high degree of intercellular genetic heterogeneity is produced by genomic instability (35,36). In addition to being influenced by main genotypic variations, epigenetic factors such as miRNA, transcriptome, and proteomic heterogeneity can also be a reflection of cell cycle stage, stochastic cell-to-cell variations, or the cancer stem cell theory's hierarchical cell organization. Extrinsic factors include pH, hypoxia, and paracrine signaling interactions with stromal and other tumor cells (37,38).

### **Deactivation of the anticancer drugs**

The effectiveness and efficacy of anticancer medications rely on intricate systems. Drugs molecular properties can be changed and eventually activated by interactions with various protein types (in vivo). By decreasing the effectiveness of medications, cancer cells develop resistance. AraC activity is decreased by down-regulation or mutations in the proteins and enzymes involved in this pathway (phosphorylation processes), which results in drug-resistant cancer cells (39).

### **Mechanistic Pathways by Which Nanoparticles Overcome Drug Resistance**

#### **Targeting Efflux Transporters**

Efflux transporters are members of the ABC transporter family, which has been shown to be crucial for drug resistance. By pumping the medication out of the cell efflux transporters lower intercellular drug concentration which results in treatment failure. One of the most extensively studied efflux transporters, P-glycoprotein (P-gp) is overexpressed in a number of drug-resistant cancers. P-gp-expressing multidrug-resistant cancer was defeated by nanoparticle-mediated drug delivery to the tumor neovasculature by concentrating on KDR receptors which are highly expressed in the tumor vasculature. This approach exhibited a stronger anti-tumor effect than combined therapy with chemotherapeutic drugs and P-gp inhibitors (40,41).

#### **Targeting Apoptotic Pathway**

Drug resistance in cancer is a because of defective apoptotic machinery, which allows cancer cells to avoid apoptosis and prolong their survival. Nuclear factor kappa B (NF- $\kappa$ B) and Bcl-2 deregulation frequently initiates the faulty apoptotic pathway. Numerous malignancies have high levels of Bcl-2, an anti-apoptotic protein that has been extensively studied. It also has a significant

role in treatment resistance, indicating that it may be a target for reversing drug resistance. An approach to combating medication resistance in cancer is the co-delivery of chemotherapeutics and Bcl-2-targeted siRNA by NPs, according to mounting data. Docetaxel and resveratrol-encapsulated folic acid-conjugated planetary ball-milled NPs are an effective treatment for multidrug-resistant prostate cancer. The results demonstrated down-regulated expression of anti-apoptotic genes and decreased ABC-transporter markers. Furthermore, NPs that targeted the mitochondria also had an impact on the apoptotic pathway and efflux transporters. Moreover, TPP-Pluronic F127-hyaluronic acid nanomicelles loaded with paclitaxel induced mitochondrial outer membrane permeabilization (MOMP), which released cytochrome C and activated caspase-3 and caspase-9, causing drug-resistant lung cancer cells to undergo apoptosis (42).

#### **Targeting Hypoxia**

A further factor that leads to multidrug resistance is hypoxia. There are numerous ways that hypoxia causes tumors to become resistant to drugs. For example, cytotoxic chemotherapeutics like alkylating chemicals and antibiotics can be evaded by slowly dividing cells in hypoxic environments. Hypoxia increases tumor heterogeneity and fosters a more aggressive phenotype by creating an oxygen gradient inside the tumor. Hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) is crucial to the process, and many human malignancies have been found to overexpress HIF-1 $\alpha$ . Thus, another treatment strategy for overcoming medication resistance is to target HIF-1 $\alpha$  (43, 44).

### **Advantages of Nanoparticles in Cancer Therapy**

A new phase in cancer diagnosis, therapy, and management has been brought about by the application of nanotechnology. NPs increase the intracellular concentration of medications

while avoiding harm in healthy tissue by active or passive targeting. To create and control the drug release, the targeted NPs can be modified to be either pH-sensitive or temperature-sensitive. ultrasonic waves and magnetic fields. The targeted drug delivery mechanism is significantly influenced by the physicochemical properties of NPs, including their size, shape, molecular mass, and surface chemistry (45).

Because of their unequal distribution and cytotoxicity, modern radiation therapy and chemotherapy have several drawbacks in terms of side effects and efficacy. Therefore, a cautious dosage that destroys cancer cells without causing them any significant harm is needed. The medication must pass through multiple fortifications in order to reach the intended place. The process of drug metabolism is quite intricate. The medication must cross the TME, RES, BBB, and renal infiltration under physiological conditions. The macrophage system, or RES, is composed of blood monocytes, macrophages, and other immune cells (46). When drugs interact with MPS in the liver, spleen, or lungs, the drug is quickly eliminated by macrophages or leukocytes. As a result, the drug's half-life is shortened. To get around this process, NPs with surface modification, such PEG, prolong the drug's half-life. An essential physiological mechanism is renal infiltration. Adequate renal infiltration reduces the toxicity that NPs induce (47).

The brain-blood border (BBB) is a special defense mechanism that keeps harmful and toxic chemicals out of the central nervous system (CNS). The brain capillary endothelial cells form a wall-like structure that provides the brain with important nutrition. Intraventricular or intracerebral infusions are currently the sole chemotherapy therapies for brain cancer because the BBB's primary function is to keep dangerous substances out of the brain. Numerous methods, such as transcytosis, peptide-modified endocytosis,

targeted ultrasound, and the EPR effect, are now used to transport NPs. Methotrexate-encapsulated glutathione PEGylated liposomes improved rats' absorption of the medication. Since Au-NPs have been shown to aid in the transport of drug that cause apoptosis, they are frequently employed (48).

Some of the particular pathophysiologic features of tumors include extensive angiogenesis, defective vascular architecture, and poor lymphatic drainage. The NPs employ these features to target tumor tissue. Due to reduced venous return and limited lymphatic clearance, NPs are effectively retained in tumor tissue. This phenomenon is known as EPR.

Likewise, focusing on the surrounding tissues can lead to tumor targeting. NPs can be given orally, nasally, parenterally, intraocularly, and in other ways. NPs have a high intracellular uptake and surface-to-volume ratio. According to studies, NPs work better as drug transporters than microparticles (49).

### **Challenges in clinical application of Nanoparticles**

Nanoparticles (NPs) have enormous potential for targeted medication delivery, imaging, and diagnostics, a number of obstacles have prevented them from being widely used in clinical settings. Since NPs' behavior in vivo is dependent on their size, shape, surface charge, and coating—all of which affect the formation of protein coronae, biodistribution, and clearance—the primary concern is biological complexity and safety. Standard animal models cannot predict toxicities that are caused by unpredictable immunological responses, complement activation, and off-target accumulation in the liver or spleen (50). Preclinical models' translational limitations make it more difficult to anticipate human outcomes, highlighting the need for improved large-animal and in vitro testing methods. Due to the difficulty and expense of precisely

controlling particle homogeneity, surface functionalization, and sterility under Good Manufacturing Practices (GMP), manufacturing and scale-up also present substantial challenges (Anselmo & Mitragotri, 2019). Additionally, characterization and quality control of nanoparticles remain technically difficult regulatory approval is complicated by variety in size distribution, aggregation, and payload release (51).

### Conclusion and Future prospectives

A major development in conventional oncology, nanoparticles (NPs) provide innovative solutions to the drawbacks of conventional cancer therapies. There are many types which include metal, metal oxide, ceramic, inorganic, organic, and carbon-based nanoparticles which provide modular system for accurate drug administration, imaging and modulation. (NPs) increase therapeutic efficacy while reducing systemic toxicity through mechanisms include enhanced permeability and retention (EPR) active receptor based targeting, and regulated drug release. One of the main challenges in the treatment of cancer is drug resistance and nanoparticles are important to overcoming this. NPs can increase drug susceptibility and stimulate cancer cell death by altering intrinsic and extrinsic resistance mechanisms including drug deactivation, efflux transporter upregulation, hypoxia, and apoptosis. Their therapeutic impact is further improved by targeted techniques such as modification of tumor hypoxia, blockage of efflux transporters and control of apoptotic pathways.

Despite significant advancements a number of obstacles still stand in the way of clinical translation such as complex tumor microenvironments, long-term toxicity and scaleup issues. Future research should focus on creating intelligent and multipurpose nanoparticles that can respond in real time stimuli specific to tumors and have combined

therapeutic and diagnostic features. Integration nanotechnology with genetics, AI, and medicine will lead to new possibilities for optimizing patient specific treatments.

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