



## **A Review of Nanoparticles in Medication Delivery and Their Role in Mitigating Drug Resistance in Cancer Treatment**

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### **Abstract**

The major cause of death worldwide is cancer. Chemotherapy, radiation therapy, immunotherapy, and targeted therapy are examples of conventional cancer treatments. However, there are significant obstacles to effective cancer treatment, including cytotoxicity, lack of selectivity, and multidrug resistance. Cancer diagnosis and therapy have radically changed with the development of nanotechnology. Through lessening its side effects, nanotechnology has particular advantages in cancer treatment. Nanoparticles (1–100 nm) can be utilized to treat cancer because of their unique benefits, which include improved permeability and retention (PR), decreased toxicity, increased stability, biocompatibility, and precise targeting. The unique drug delivery method using nanoparticles makes use of the properties of the tumor and its surroundings. Nanoparticles not only overcome multidrug resistance but also address the shortcomings of traditional cancer treatment. Additionally, nanoparticles are being studied more thoroughly as new multidrug resistance mechanisms are discovered and examined. Being able to bypass the drug efflux mechanism linked to such a phenotype and directing drugs to target cancer cells specifically gives them an additional means of avoiding multidrug resistance. There has been a comparison of the effectiveness of active and passive nanoparticle (NP) targeting techniques in cancer theranostics. New cancer therapeutics were developed and improved using a variety of nanomaterials, including inorganic or organic, and synthetic polymers. This review addresses the function of NPs in cancer treatment, including targeting mechanisms and various drug delivery techniques for cancer therapy.

**Keywords:** Nanotechnology; nanoparticles; cancer treatments; drug delivery; passive and active targeting

## Introduction

Colloidal NPs were successfully incorporated into biological liquids by utilizing the optical and magnetic properties of inorganic materials. The advantages of using nanoparticles as effective delivery vehicles are demonstrated by the unique properties of nanoparticles in drug delivery [1][2]. Furthermore, the catalytic activity regarding NPs has garnered much attention because of its ability to modify the biological microenvironment [3]. Nano-technology development has resulted in changing the treatment and diagnosis of cancer because treatments for cancer, which include radiation treatment, chemotherapy, individualized treatment, and immunotherapy, suffer from multiple limitations, including lack of specificity, cytotoxicity, and multidrug resistance. Chemotherapy as well as radiation therapy are often related to severe adverse impacts as well as a considerable recurrence chance, despite their capacity for cytotoxicity and cytostasis [4]. NPs (1–100 nm) could be utilized for treating cancer, because of their unique benefits, like decreased toxicity, biocompatibility, increased patient compliance, increased permeability and retention effects, and enhanced pharmacokinetics of the biologics as well as small molecules, which have

otherwise short half-lives in vivo and precise targeting [4,5].

Biocompatible nanocarriers include polymers, liposomes, tailored multifunctional antibodies, and nanoparticles (NPs) composed of metals (such as gold and silver), quantum dots, other biological molecules, or combinations of these materials. Nanoparticles not just overcome multi-drug resistance, but also address the drawbacks of traditional treatments of cancer. Nanoparticles are also being studied more vigorously as new multi-drug resistance mechanisms have been discovered and examined [5][6]. Nanoparticles are utilized in bio-medical applications because of the unique chemical and physical properties of such nanomaterials. When formulating nanotherapeutics, for instance, design features that could be controlled include geometry, size-to-volume ratio, surface area, surface charge, shape, and stimuli-responsive characteristics. Following their creation, the NPs could be functionalized with extra chemical components, including antibodies or ligands for cell surface receptors, to selectively target specific sites, stop blood clearance, and confer other desired functional characteristics. It may be possible to create targeted nanocarrier systems that deliver cargo to cancer cells preferentially while avoiding dose-limiting adverse effects on healthy organs, because they are adaptable in terms of shape and size [7][8]. Numerous therapeutic implications of nano-formulations opened up new avenues for the

treatment of cancer. Although many useful functions in biomedicine have been realized as a result of substantial study in NP synthesis, integrating numerous functionalities onto a single platform and maximizing their combined performance remains a difficulty. This calls for constant work and advancements.

### **Nanoparticles (NPs)**

NPs are particles with one dimension of no more than 100nm and special features typically absent from bulk samples of one material. NPs could be classified as 0D, 1D, 2D, and 3D based on the general NP shape. The complex structure of nanoparticles consists of the shell layer, the surface layer, and the core, which is the central section of the nanoparticles [9]. The remarkable properties of such materials, like their dissimilarity, sub-micron size, high surface-to-volume ratio, and improved targeting mechanism, have made them greatly significant in multi-disciplinary sectors [10][11][12]. Deep tissue penetration of NPs has been shown to promote the increased effect of permeability and retention (EPR). In addition, surface properties influence bioavailability and half-life by effectively crossing the epithelial fenestrae [13]. Nanoparticles are used to deliver drugs to target cells or organs, enhancing treatment efficacy while limiting negative effects. In diagnostics, nanoparticles detect diseases, such as cancer, through fluorescent biomarkers or by improving contrast

in MRI. Nanoparticles can be used to create three-dimensional tissue structures, contributing to the repair of damaged organs. Nanoparticles are used in cancer treatment to deliver heat therapy to tumors (hyperthermia) or to increase the effectiveness of chemotherapy [14].

### **Synthesis of NPs**

NPs have a variety of shapes, sizes, and structures. Many synthesis approaches are utilized to accomplish this. Those techniques could be divided into two general groups: (1) top-down and (2) bottom-up approaches. Depending on their reaction and operation conditions, such methods could be further divided into several subclasses (Figure 1).

#### **Bottom-up Approach**

This process is called the constructive method since it builds material from atoms to clusters, then to NPs [15]. Sol-gel [16], Chemical vapor deposition (CVD) [17], and spray pyrolysis (SP) [18] are chemical techniques for NPs synthesis. In contrast, physical vapor deposition (PVD) [19], laser ablation in liquid (LAL) [2], and molecular beam epitaxy (MBE) [20] are generally classified as physical methods.

#### **Top-Down Approach**

Also known as a destructive approach, it synthesizes NPs by break down bulk material or

substance. NPs are created when a bigger molecule disintegrates or decomposes into nano-sized units [21][22]. It encompasses methods including chemical etching, thermal decomposition, sputtering, laser ablation, nanolithography, mechanical milling, and electro-explosion. The alteration of reaction conditions and other synthesis factors could change

the NP morphological characteristics, including their shape, charge, and size [23][2]. Furthermore, the growth method also determines NPs' chemical characteristics. This is why it is highly important to comprehend the growth mechanism to synthesize the necessary NPs.

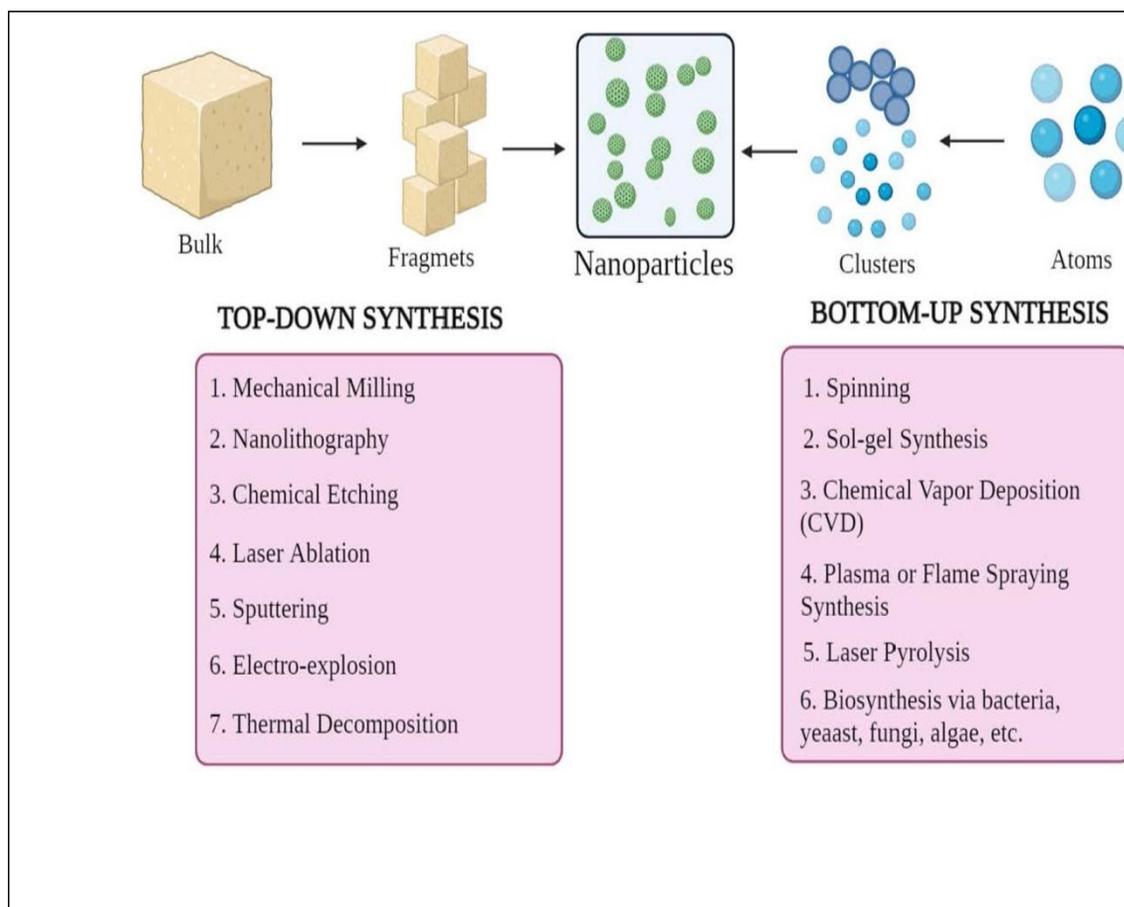


Figure (1): Nanoparticle synthesis classification[15].

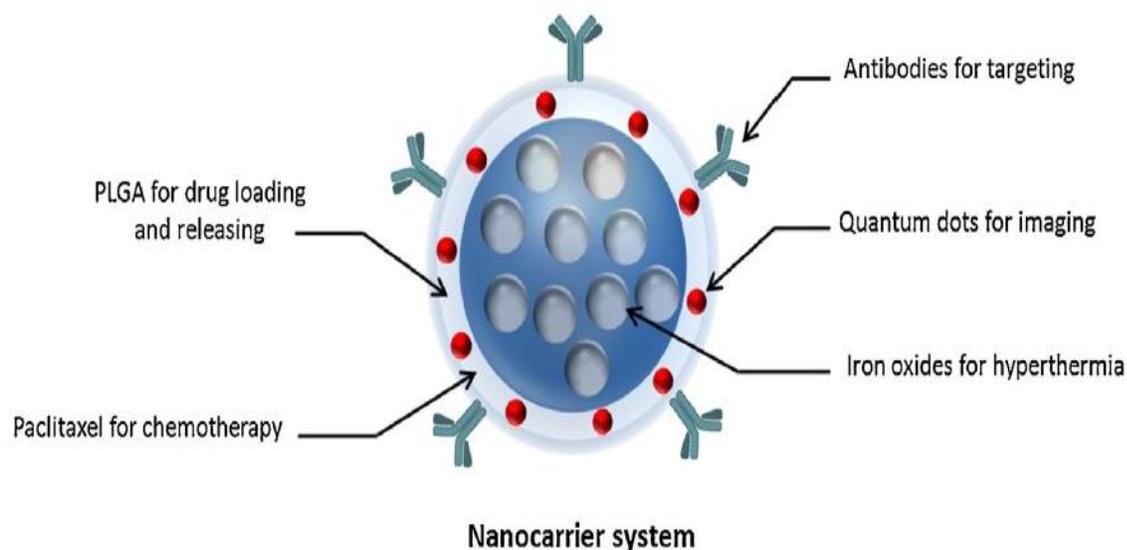
### Types of nanoparticles used in biomedical applications

Nanoparticles have received considerable recognition in biomedical investigation,

imaging, and treatment, thereby demonstrating their capacity to transform diagnostics and drug administration (Figure 2). This all-encompassing evaluation thoroughly examines

diverse categories of nanoparticles employed in biomedical contexts, drawing upon recent scholarly articles to emphasize their inventive

applications and prospective influence on healthcare [24].



**Figure (2): Multifunctional nanocarrier system (chemotherapy, hyperthermia, targeting, and fluorescent imaging) [24].**

### Nanoparticles in Cancer Therapy

Nanotechnology has shown promise in addressing the shortcomings of conventional molecular chemotherapeutic medications, including the incapacity to target, drug resistance, and serious side effects. A key benefit of treating cancers using nanoparticles lies in the fact that enhance their half-life and prevent payload medications from being eliminated or breaking down excessively quickly, increasing the possibility that they will reach and accumulate at metastatic locations. Because of their small dimensions, the NPs might penetrate deeply into

tumours to eliminate any remaining cancerous cells. Furthermore, nanoparticles (NPs) can target circulating tumour cells (CTCs), aggregate in the targeted tissue or lymph nodes that tumour cells have invaded, and prevent cancer cells from growing and spreading. Furthermore, recent research has shown a great deal of interest in theranostic NPs, which are multifunctional nano-systems that combine therapeutic as well as diagnostic capabilities in a single nanoparticle [25]. There are several types of nanoparticles for cancer treatment, including inorganic, organic, and hybrid nanoparticles used in drug delivery systems. Polymer-based NPs, dendrimers, and

liposome-based NPs are all found in the organic NPs. Carbon nanotubes, silver nanoparticles (AgNPs), gold NPs (AuNPs), silica NPs, and quantum dots are examples of inorganic nanoparticles [26]. Hybrid nanoparticles, such as polymeric lipid composite nanoparticles,

organically and inorganically synthetic nanoparticles, and nanoparticles covered with cell surface membranes [4], can combine the benefits of several nanoparticle types [4], as shown in Figure 3.

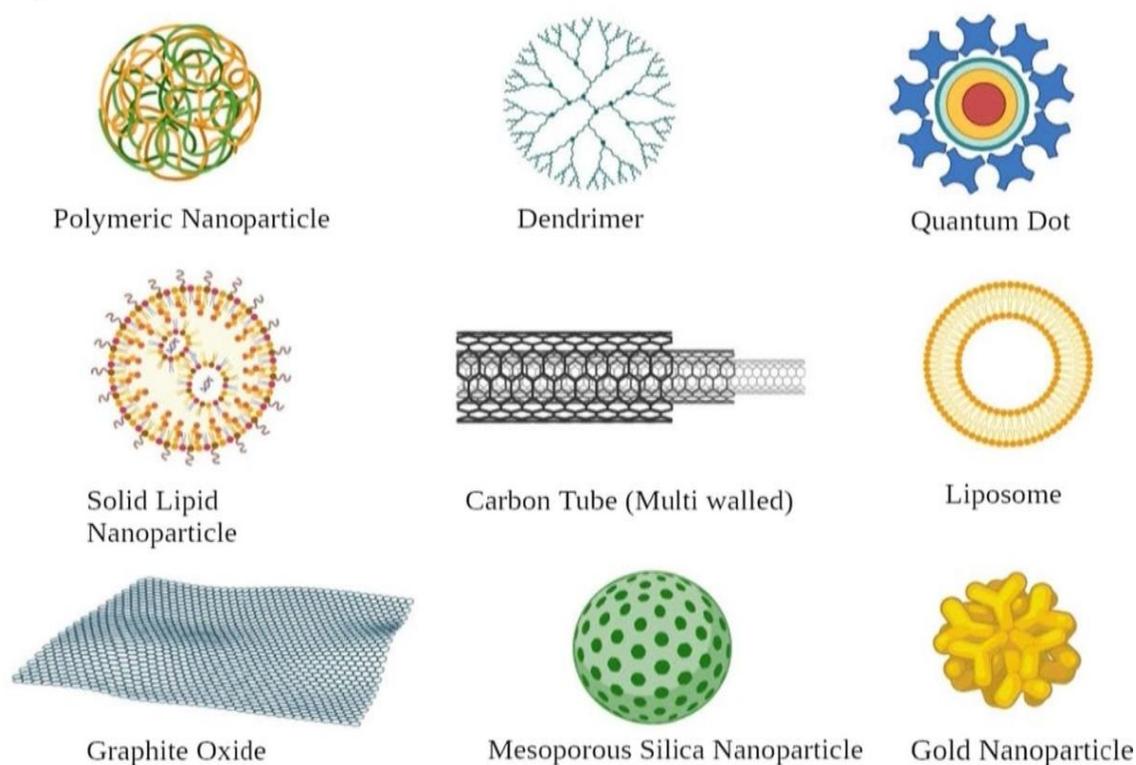
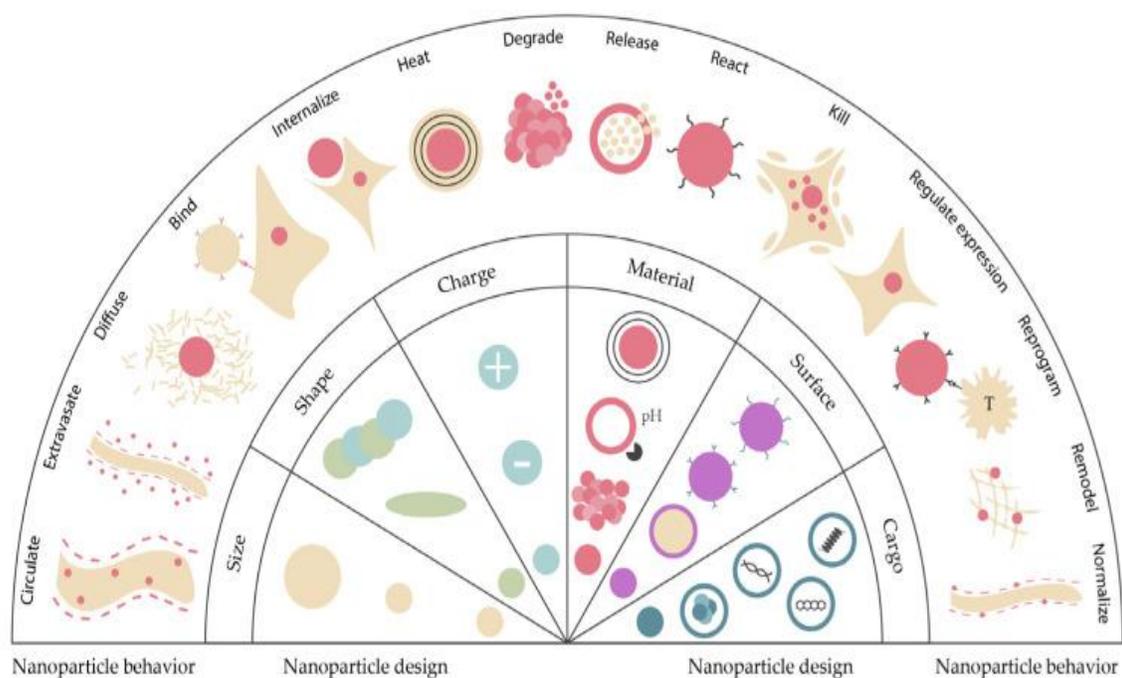


Figure (3): Different types of NPs for cancer treatment [4].

### Broad Criteria for Drug Delivery Using Nanoparticles

For a cancer treatment system to function effectively, the used nanoparticles must possess certain characteristics, such as high bioavailability, stability in physiological

environments, and biocompatibility. Furthermore, once they reach the target area, they ought to be able to release the burden and only target the tumour cells, sparing the healthy cells in the area. Figure 4 illustrates the physical and chemical characteristics affecting NPs utilized as medication delivery [27].



**Figure (4): Physical and chemical characteristics of NPS, interactions within the body, and behaviors inside cells [28].**

Their size distribution significantly influences the performance of the NPs in cancer treatments. The NPs could be adjusted to be small enough to enter the tumor and large sufficient to stop extravasation from normal blood vessels, preventing agglomeration in other body areas. However, the size uptake specifications of various organs vary. Numerous studies were conducted to specify the appropriate size of NPs for cancer therapy. The results indicate that particles smaller than 50nm have higher rates of antitumoral efficiency when compared to those bigger than 50 nm [29]. Since shape affects fluid dynamics, among other impacts, it is another crucial aspect of NP design

for cancer treatment. The shape of a nanocarrier could regulate the interaction between NPs and the cell membrane. In addition to that, it has been mentioned that particle shape affects whether the reticuloendothelial system (RES) absorbs NPs [27]. A major barrier to the clinical translation of nanomedicines is the accumulation of these drugs in the RES organs, particularly the liver, because reticuloendothelial cells retain the majority of the delivered dosage, lowering the absorbed dose of the supplied NPs and increasing the associated immunogenicity and toxicity [30]. A complicated collection of procedures, including charge on the surface, imperfections, pore structure, and chemical grouping modifications,

make up surface chemistry, which affects many system aspects, including the rates of degradation and agglomeration, surface interactions, and cellular absorption. For example, some study suggests that a positive-

charge surface increases cellular uptake [31]. Different surface properties could be required for various cancer types or the same cancer type stages, as shown in Figure 5.

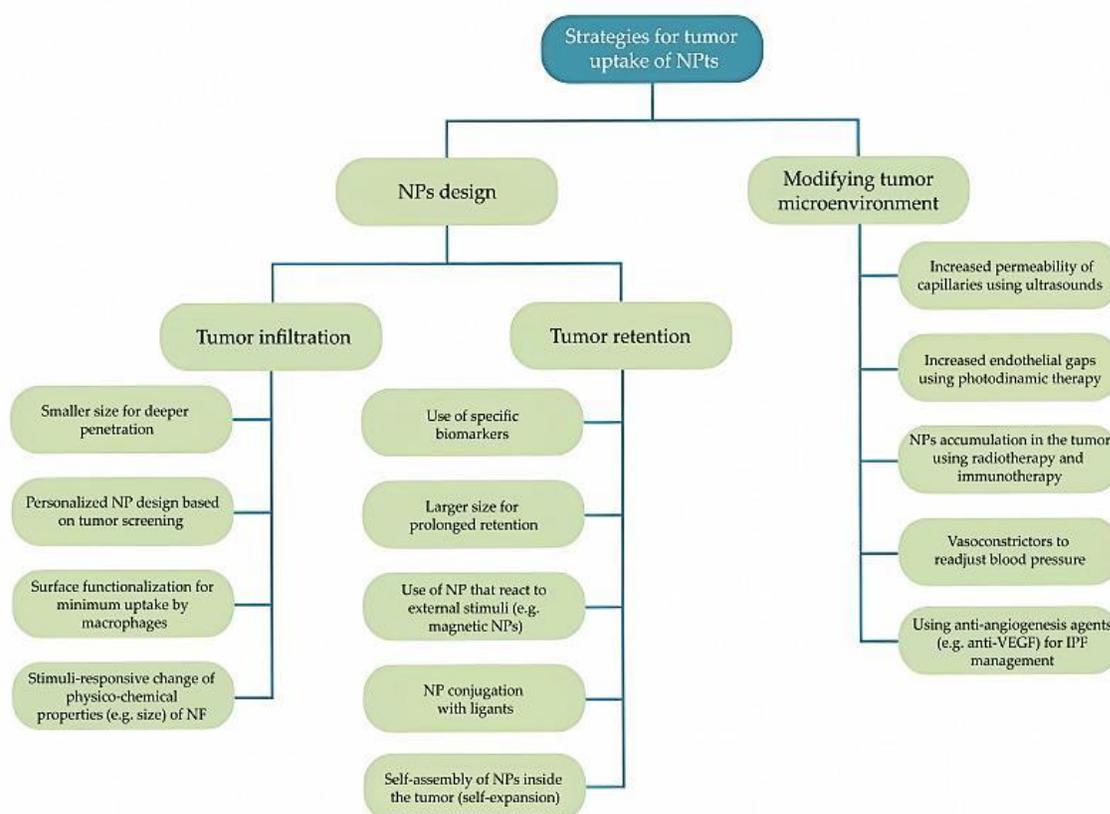


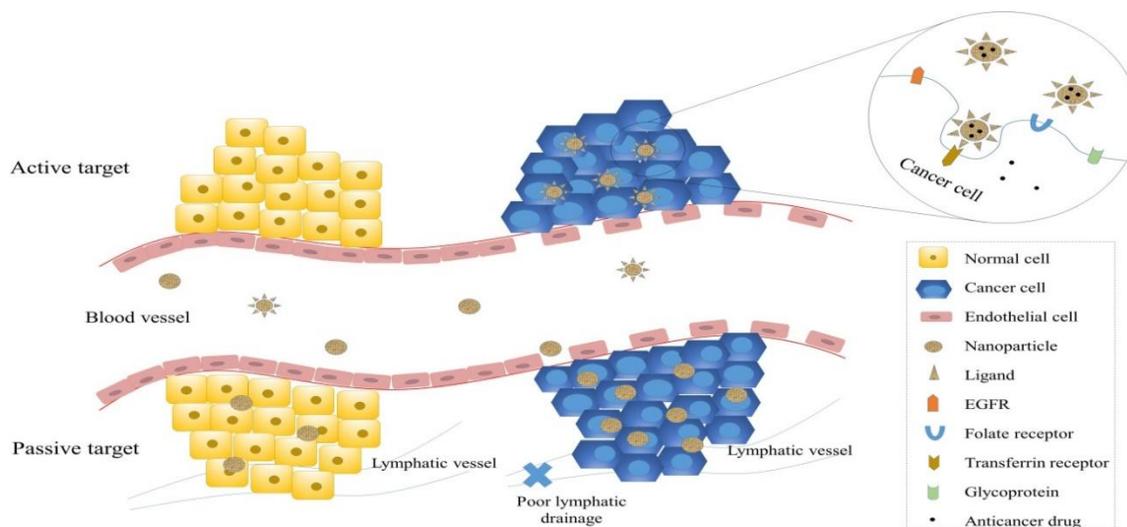
Figure (5): Different strategies for nanoparticle uptake in tumors [27].

### Mechanisms of Targeting

The ability of nano-carriers to selectively target cancer cells, enhance therapeutic efficacy, and protect healthy cells from toxicity is one of their key characteristics for drug delivery. The target selection strategy of nanoparticle-based drugs was the subject of

numerous investigations. Understanding cancer biology and the relationship between tumour cells and nano-carriers is essential for effectively addressing the difficulties associated with cancer treatment and nano-carrier system design. As illustrated in Figure 6, targeting

strategies can be broadly classified into two groups: targeted activity and passive.



**Figure (6): Targeting cancer cells by nanoparticles in their active and passive form [32]**

### Passive Targeting

The goal of passive targeting is to exploit the distinctions between healthy and cancerous tissues. With passive targeting, medications are effectively delivered to the intended location to carry out a therapeutic action. Large vascular wall holes weaken the permeability of the tumour vasculature in comparison to the normal vessels, and a high proliferative ratio of cancer cells causes neovascularisation. Macromolecules, like NPs, can leak from blood vessels that supply the tumor and accumulate within its tissue due to the fast and defective angiogenesis. In the meantime, the nanoparticle retention increases due to the poor lymphatic drainage linked to cancer, which permits the

nano-carriers to discharge their contents to the tumor cells. EPR effect is one of the factors that propels the passive targeting, which results from those processes [4][33]. NP size affects the effect of the EPR because, as numerous studies have shown, smaller NPs are more penetrable yet do not leak into normal vessels. However, the immune system is more possibly to eliminate bigger particles. along with the EPR effect, the tumor microenvironment has an important impact on the passive delivery of the nano-medicines. Cancer cells use glycolysis as their primary source of energy for proliferation, making it one of their metabolic traits [34]. Glycolysis reduces tumor micro-environment pH and produces an acidic environment. Therefore, a low level of pH triggers certain pH-

sensitive NPs, which might release drugs in cancer cells [35].

### **Active Targeting**

Active targeting uses direct interactions between the ligands and the receptors to target the cancer cells. Molecules that are overexpressed on the cancer cell surface are targeted by the ligands on the NPs surface, enabling them to differentiate between the targeted and the healthy cells. Internalized nanoparticles could effectively release the therapeutic drugs through receptor-mediated endocytosis, which is triggered by the interaction of the ligands on the NPs with the receptors on the cancer cell surface. Active targeting is therefore especially well-suited for macromolecular drug targets like siRNAs and proteins. Monoclonal antibodies, vitamins, amino acids, peptides, and carbohydrates can be listed as examples of targeting moieties [4].

Transferrin, which is a serum glycoprotein, works to carry iron to the cells. Receptors of transferrin are over-expressed in most solid tumor cells, while in normal cells, they are barely present. Therefore, drugs for treating cancer are delivered with the use of the transferrin-conjugated nanoparticles as one of the active targeting techniques [36]. Transferrin-modified nanoparticles were demonstrated to have an improvement in the

intracellular drug uptake and greater cell delivery efficiency than unmodified nanoparticles [37]. In addition to that, evidence indicates that the transferrin-conjugated polymeric nano-particles are crucial to defeating the drug-resistant chemotherapy [38].

### **Nanoparticle Advantages for Cancer Treatment**

The application has ushered in a new cancer treatment, diagnosis, and management age. The nano-particles increase the intracellular concentration of the drugs while preventing toxicity in the healthy tissue through either passive or active targeting. To create and control the drug release, the targeted nano-particles could be modified to be either temperature-sensitive or pH-sensitive. The pH-sensitive drug delivery system could deliver drugs within the acidic TME. Comparably, temperature variations introduced by some sources, like ultrasonic waves and magnetic fields, cause the temperature-sensitive nanoparticles to release the drugs at the target site [35]. Additionally, the targeted drug delivery mechanism is highly affected by the "physicochemical characteristics" of the nanoparticles, which include their shape, size, surface chemistry, and molecular mass. NPs have a high intracellular uptake as well as a surface-to-volume ratio. NPs could also target a specific moiety, which might be altered based on

the target [31]. Due to their cytotoxicity and uneven distribution, conventional chemotherapy as well as radiation therapy have many disadvantages in terms of effectiveness and negative effects. As a result, careful dosage that efficiently destroys cancer cells without causing severe toxicity is needed. The drug must meet many requirements to reach the target site. The process of drug metabolism is quite intricate. The drug should cross RES, TME, BBB, and the kidney infiltration under physiological conditions. Blood monocytes, macrophages, and other immune cells comprise the RES, or macrophage system [39]. A unique protective mechanism called the brain-blood barrier (BBB) is designed to shield the central nervous system (CNS) from toxic and dangerous agents. The "brain capillary endothelial cells" wall-like arrangement gives the brain vital nutrients. Currently available chemotherapy drugs for brain cancer are severely limited to the intraventricular or intracerebral infusions since the BBB's principal role is preventing toxic agents from reaching the brain [40].

Due to their ability to facilitate the transport of drugs that cause apoptosis, Au-NPs are frequently employed. As carriers, the NPs lead to improving the stability of the drug by keeping the encapsulated cargo from degrading. Additionally, no chemical reaction is required to encapsulate a high volume of drugs. In comparison with the

nano-liquid formulations, dry solid dosage forms are more stable [41][42]. There are numerous ways to give NPs, including parenteral, intraocular, nasal, and oral. According to studies, NPs work better as drug transporters than microparticles [43]. Stabilizers could be applied to improve stability. Using porous nano-particles is yet another method for improving stability. Flawed vascular architecture, extensive angiogenesis, and impaired lymphatic drainage are some of the distinctive pathophysiological characteristics of tumors. Nanoparticles utilize these properties to target tumor tissue. The nano-particles are maintained efficiently in tumor tissue due to low lymphatic clearance and decreased venous return. EPR is the name given to this occurrence. Similarly, the tumor-targeting can be achieved by focusing on the surrounding tissues [44].

## **Conclusion**

A new cancer treatment era was ushered in by applying nanotechnology to cancer therapy. Both inorganic and organic NPs have already been extensively employed in the clinical treatment of several types of cancer. Numerous forms of NPs, which include metallic, polymeric, and hybrid NPs, showed improved efficacy of the drug delivery. Compared with conventional drugs, NP-based drug delivery systems are linked to better tumor targeting,

biocompatibility, pharmacokinetics, and stability. They significantly contribute to the reduction of systemic toxicity and the defeat of drug resistance. In addition, nano-carrier delivery systems offer better platforms for combination therapy, which helps overcome mechanisms of drug resistance. According to various MDR mechanisms, NPs loaded with various target agents in combination with cytotoxic agents could reverse the drug resistance. Despite the significant advancements in the field, it is important to remember that there are still a lot of obstacles to overcome before nanotechnology can be used for cancer therapy. More research is required to examine their possible long-term impacts in various biological systems to guarantee their scalable and safe use as nanomedicines. However, it is anticipated that significant advancements in cancer treatment and other medical specialties will be made shortly. The creation of sophisticated and potent NPs and their use in cancer treatment would aid in addressing the drawbacks of traditional cancer therapy and would give cancer patients hope for the future.

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## مقال مراجعة للجسيمات النانوية في توصيل الأدوية ودورها في الحد من مقاومة الأدوية في علاج السرطان

Jamal M. Rzaij, Hamsa A. Ali, Wissam Khayer Al-Rawi, Zena E. Slaiby

**الكلمات المفتاحية:** تقنية النانو؛ الجسيمات النانوية؛ علاجات السرطان؛ توصيل الأدوية؛ الاستهداف السلبي والنشط

### الخلاصة

السرطان هو السبب الرئيسي للوفاة في جميع أنحاء العالم. يُعد العلاج الكيميائي والعلاج الإشعاعي والعلاج المناعي والعلاج الموجه أمثلة على علاجات السرطان التقليدية. ومع ذلك، هناك عقبات كبيرة أمام العلاج الفعال للسرطان، بما في ذلك السمية الخلوية، وضعف الانتقائية، ومقاومة الأدوية المتعددة. شهد مجال تشخيص وعلاج السرطان تحولاً جذرياً مع تطور تقنية النانو. فمن خلال تقليل آثارها الجانبية، تتمتع تقنية النانو بمزايا خاصة في علاج السرطان. يمكن استخدام الجسيمات النانوية (1-100 نانومتر) لعلاج السرطان لما لها من فوائد فريدة، والتي تشمل تحسين النفاذية والاحتفاظ، وانخفاض السمية، وزيادة الاستقرار، والتوافق الحيوي، ودقة الاستهداف. وتستفيد طريقة توصيل الدواء الفريدة باستخدام الجسيمات النانوية من خصائص الورم ومحيطه. لا تتغلب الجسيمات النانوية على مقاومة الأدوية المتعددة فحسب، بل تعالج أيضاً عيوب علاج السرطان التقليدي. بالإضافة إلى ذلك، تخضع الجسيمات النانوية لدراسة أكثر شمولاً مع اكتشاف آليات جديدة لمقاومة الأدوية المتعددة وفحصها. إن القدرة على تجاوز آلية تدفق الدواء المرتبطة بهذا النمط الظاهري، وتوجيه الأدوية لاستهداف الخلايا السرطانية تحديداً، يمنحها وسيلة إضافية لتجنب مقاومة الأدوية المتعددة. لقد تم إجراء مقارنة بين فعالية تقنيات استهداف الجسيمات النانوية النشطة والسلبية في التشخيص العلاجي للسرطان. وقد طُوِّرت علاجات جديدة للسرطان وحُسِّنت باستخدام مجموعة متنوعة من المواد النانوية، بما في ذلك البوليمرات غير العضوية أو العضوية، والبوليمرات الاصطناعية. تتناول هذه المراجعة وظيفة الجسيمات النانوية في علاج السرطان، بما في ذلك آليات الاستهداف وتقنيات توصيل الأدوية المختلفة لعلاج السرطان.