# "*Yin-Yang* philosophy" for the design of anticancer drug delivery nanoparticles

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**Key Words:**
*in vivo* drug delivery; nanoparticle design; on-demand drug release; targeting strategy; "*Yin-Yang* harmony"

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## ABSTRACT

*Understanding the in vivo transport process provides guidelines for designing ideal nanoparticles (NPs) with higher efficacy and fewer off-target effects. Many factors, such as particle size, morphology, surface potential, structural stability, and etc., may influence the delivering process of NPs due to the existence of various physiological barriers within the body. Herein, we summarise the distinct influences of NP physicochemical properties on the four consecutive in vivo transport steps: (1) navigating with bloodstream within blood vessels, (2) transport across vasculature walls into tumour tissues, (3) intratumoural transport through the interstitial space, and (4) cellular uptake & intracellular delivery by cancerous cells. We found that the philosophy behind the current consensus for NP design has certain similarities to the "Yin-Yang" theory in traditional Chinese culture. Almost all physicochemical properties, regardless of big or small sizes, long or short length, positive or negative zeta potentials, are double-edged swords. The balance of potential benefits and side effects, drug selectivity and accessibility should be fully considered when optimising particle design, similar to the "Yin-Yang harmony". This paper presents a comprehensive review of the advancements in NPs research, focusing on their distinct features in tumour targeting, drug delivery, and cell uptake. Additionally, it deliberates on future developmental trends and potential obstacles, thereby aiming to uncover the ways these characteristics influence the NPs' biological activity and provide theoretical guidance for the targeted delivery of NPs.*

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## Introduction

"*The miniature crafts cruise silently through the blood vessels. Sneaking through holes in the vascular wall, they dive into the tumour and use on-board antibody keys to gain entry into cancer cells. Once inside, their anti-cancer cargoes are deployed for cancer destroying. Mission accomplished.*" This is the vision of nanomedicine depicted in animations in the early 2000s, which promised nanotechnology as a magical bullet against cancer.[1] Nanomedicine's overarching aim is precision medicine: delivering the correct drugs to the precise pathological sites at the optimal time, eliminating only the targeted cells in the intended individual.[2, 3] To accomplish this, numerous innovative drug delivery systems (DDSs) have been meticulously designed for overcoming pharmacokinetic limitations of conventional drug formulations.

For delivering anticancer cargo into cancerous cells, intravenous nanoparticles (NPs) must traverse four consecutive steps: circulation within blood vessels; penetration of vascular walls to enter tumour tissues; intratumoural transport through the tumour microenvironment (TME), and finally, being endocytosed by cancer cells.[4, 5] Due to the increased vascular permeability and impaired lymphatic drainage, NPs can target to tumours via enhanced permeability and retention (EPR) effect, demonstrating the potential to increase macromolecular accumulation and opening exciting avenues for tumour-specific drug delivery.[6] Besides, unique physicochemical properties (such as particle size, surface charge, morphology, and etc.), which play crucial roles in determining the *in vivo* fate of NPs, can be regulated as needed, enabling them effectively

reach and release delivered biomolecules in intended sites.[7, 8]

However, the *in vivo* microenvironment in which NPs exert their biological functions remains quite complicated, making it difficult to precisely define the optimal parameters for their physicochemical properties. Therefore, a large number of researchers focus on the innovation of traditional NPs and try to build composite NPs with more comprehensive properties to overcome biological barriers. The surface of these composite NPs often combines some active targeting molecules, such as antibodies, peptides, transferrin, folate, and aptamers to specifically enhance the uptake capacity of cells.[9] At the same time, some components capable of stimulating reactivity release (such as temperature stimulation, pH stimulation, ultrasound stimulation, etc.) are often designed for controlling the release of delivered payloads.

However, particle design is not a one-fit-all scenario. Whether large or small particle sizes, positive or negative surface charges, and relatively stable or unstable structures, are all double-edged swords. The balance of potential benefits and side effects should be fully considered when optimising particle design. In this review, we focus on several major physicochemical properties of NPs and their implications for efficacy and uniform delivery. In addition, this review summarises the tradeoffs based on comprehensive considerations to optimise the properties of nanoparticles, as well as advanced strategies developed to address the dilemmas encountered during particle design. The process of dealing with these contradictions is like the balancing of "*Yin-Yang*", which is one of the essences of traditional Chinese culture.

## Particle Size: Large or Small?

Among a number of factors affecting the *in vivo* efficacy of NPs, particle size plays a key role due to the presence of various particle size thresholds within the body. These thresholds include endothelial junctions of approximately 10 nm in normal blood capillaries, widened intercellular gaps in malformed tumour vasculature, 100–150 nm vascular fenestrations in the liver, a glomerular filtration threshold of around 6 nm in the kidney, and tight junctions measuring less than 1 nm in the blood-brain barrier.[10-12] Because of these distinct size cutoffs, the interaction between nanoparticles and biological components is usually size-dependent. Particle size determines not only the *in vivo* biological drug distribution, release and clearance, but also the tumour drug aggregation and penetration.[12-14] A crucial question that preoccupies many researchers is determining the optimal size for NPs in anti-tumour drug delivery.

Extravasation serves as the initial process for NPs to penetrate malignant tissues. The presence of larger pores in tumour blood vessel walls, typically ranging from 50 to hundreds of nm, notably enhances vascular permeability and hydraulic conductivity in cancers, being the basis for EPR effect.[2, 15] Relatively large NPs are able to aggregate at the tumour site with higher specificity.[16] For achieving best treatment effects, NPs must accumulate in tumours with sufficient amounts for tumour killing while producing minimal adverse effects in normal tissue.

Nevertheless, it is widely accepted that smaller NPs tend to exhibit superior ability in traversing the initial tumour-associated barrier and infiltrating the TME with a higher efficiency.[17, 18] However, smaller particles (< 10 nm) often extravasate into most normal tissues, leading to undesired off-target effects.[2] Therefore, increasing particle size will provide selectivity at the expense of limited accessibility to and within malignant tissues, and *vice versa*.[19, 20] Researchers also found that smaller NPs might be more likely to return back to tumour vasculature via the leaky vascular wall, thereby reducing tumour accumulation.[10] While large NPs encounter difficulty crossing the tumour endothelium, but once passed the endothelium, they are prone to retain in the TME.[21, 22]

The efficiency of an ideal DDS in targeting tumours is also positively correlated with its size-dependent blood retention, this is because the longer the NPs circulate in the blood, the more chance they have to enter the malignancies.[23] For instance, the tumour accumulation of poly(ethylene glycol) (PEG)-coated gold NPs with hydrodynamic diameters of 20, 40, 60, 80, and 100 nm was investigated in MDA-MB-435 xenograft tumours by Perrault et al.[24] The results showed tumour accumulations of respectively 0.3%, 15.8%, 26.5%, 20.4%, and 17.9% ID·h/g.[24] These findings suggest that among the tested NPs, the 60 nm particles exhibited the longest blood elimination half-life, which corresponded to the highest tumour accumulation. Studies have also demonstrated that NPs measuring less than 5–6 nm cannot be retained by the glomeruli and are quickly cleared by the kidneys.[25] Choi et al.[26] found that rigid spherical NPs could be cleared by the kidney when the particle size was about 5.5 nm, with a plasma half-life less than 4 hours. Abellan-Pose et al.[27] compared the *in vivo* distribution of NPs with particle sizes of 100 and 200 nm after intravenous injection, and found that 100 nm NPs were able to accumulate in lymph nodes more quickly. The conclusion is also consistent with Blanco's study,[13] who proposed that NPs could better enrich at the target site at 100–200 nm, but with particle sizes larger than 150 nm, more and more NPs are trapped by the liver and spleen. It is generally noticed that NPs with a diameter of > 100 nm are more difficult to escape from the capture by Kupffer cells in liver, and those with size larger than 200 nm are more likely to be captured by the reticuloendothelial system (RES), which acts as a blood filtration system in the spleen.[28, 29]

It is currently suggested that the optimal diameter for therapeutic NPs falls within the range of 10–100 nm. This size range allows NPs to resist rapid blood clearance by the RES and renal systems, and passively accumulate in tumours with high specificity and efficiency.[2, 10, 30] For instance, Doxil, which was approved by U.S. Food and Drug Administration-approved in 1995, is a liposomal doxorubicin preparation with a particle size ranging from 90 to 100 nm.[31] However, both

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large and small particle size owned respective advantages and disadvantages during the transport process (**Figure 1**). This so-called optimal size is just a compromise after considering both the specificity and efficiency of drug delivery. The advantages and disadvantages associated with particles of different sizes have motivated researchers to devise innovative strategies, including the development of size-shrinkable NPs, in order to enhance the efficient delivery of nanomedicines into tumours.[22]

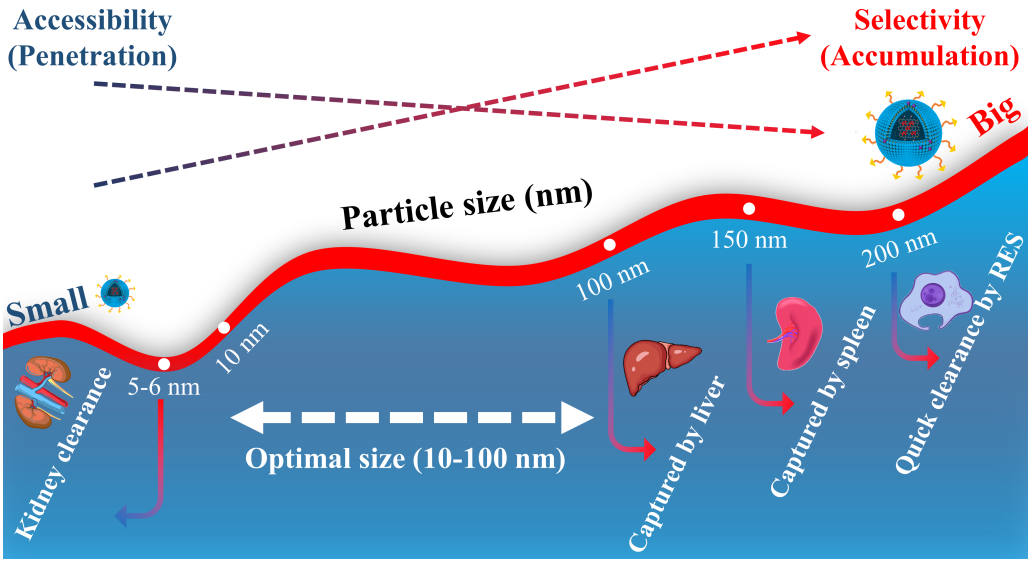


**Figure 1.** Schematic representation of the size dependence of NP delivery *in vivo*. Both large and small particle sizes owned respective advantages and disadvantages during the transport process. Smaller nanoparticles (< 10 nm in diameter) can permeate through most tissues with high efficiency, but NPs smaller than 5–6 nm are quickly cleared by the kidneys. NPs larger than 100 nm are easy to be captured by the liver, spleen, etc. When the diameters exceed 200 nm, the NPs are more likely to experience quick clearance by the RES. It is reported that the optimal diameter of therapeutic NPs should be in the range of 10–100 nm. Created with Microsoft PowerPoint (version Microsoft 365). NP: nanoparticle; RES: reticuloendothelial system.

## Surface Charge: Positive or Negative?

Surface charge, as indicated by the zeta potential, is another important factor significantly impacts the *in vivo* behaviour of NPs.[4] When entered the blood vessels, serum proteins may adsorb onto NPs creating protein coronas (termed as opsonisation), speeding up their clearance by RES.[32] Due to the alkaline pH of human plasma (7.35–7.45), plasma proteins are more likely to lose positive charges and become negatively charged. Therefore, cationic NPs are more attractive to plasma proteins, resulting in reduced circulation time.[33, 34] The greater the positive surface charge, the higher the macrophage scavenging rate.[35, 36] He et al.[33] demonstrated that mouse macrophages were easy to phagocytic NPs with higher surface charge and larger particle size, while NPs with slight negative charge and particle size of 150 nm showed the best targeting and retention effects. Studies also demonstrated that neutral NPs diffuse more rapidly within the tumour interstitial space than either cationic or anionic counterparts, this is because the latter may aggregate with positively (such as collagen) or negatively (such as hyaluronan) charged molecules in the TME.[2] Given that the existence of a variety of negatively charged components on surface of malignant cells, researchers have confirmed that cationic NPs have a higher degree of cellular internalisation than anionic ones in certain cancers.[37-39] Cho and colleagues[40] found that cationic Au NPs was absorbed into SK-BR-3 breast cancer cells at more than five times the rate of anionic Au NPs. The authors also report that in addition to endocytosis, half of cationic gold particles but not their anionic and neutral counterparts, can also diffuse into cells by generating pores in the cytomembrane.[40]

Taking into account all the aforementioned factors, most *in vivo* and *ex vivo* studies suggest that neutral NPs (±10 mV), especially those with a slight positive charge (ranging from 0 to 10 mV), may be preferred for anticancer drug delivery (**Figure 2**).[2, 19, 36]

## Rod-Shaped Nanoparticles: Long or Short?

Recent studies on the role of particle morphology in drug delivery have garnered considerable attention.[41] NPs with non-spherical morphologies often demonstrate distinctly different behaviours compared to spherical counterparts *in vivo*.[4] The structural anisotropy of non-spherical particles leads to asymmetric forces exerted on NPs, affecting ways the particles move during systemic circulation and penetration within the tumour, thus influencing their cytotoxicity and therapeutic efficacy.[41, 42]

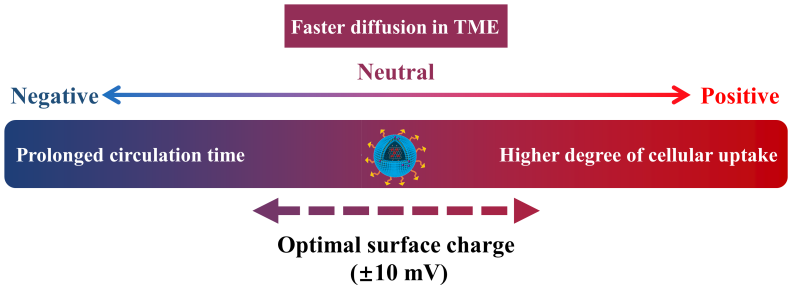


**Figure 2.** Schematic representation of the surface charge dependence of NP delivery *in vivo*. Cationic NPs have a higher degree of cellular internalisation than anionic ones in certain cancers, but they are more attractive to plasma proteins, resulting in a shorter circulation time. Neutral particles diffuse more rapidly within the tumour interstitial space than either cationic or anionic counterparts. It is suggested that neutral NPs (±10 mV), especially those with a slight positive charge (between 0 to 10 mV), may be preferred for anticancer drug delivery. Created with Microsoft PowerPoint (version Microsoft 365). NP: nanoparticle.

Nanorods (NRs) are one of the most attractive particles for biological applications. It has been shown that mechanical forces such as haemodynamic, buoyantly, and van der Waals forces applied to the NRs drive them drifting laterally as they circulate in the blood stream (termed as margination).[43] Due to the tortuous nature of the tumour vasculature and its slow blood flows, margination is increased within tumour vessels. This enhancement results in specific adhesion to the walls of tumour capillaries, facilitating a more rapid transport of tumour cells out of the circulation compared to spherical NPs.[41, 44]

It has been reported that rod-shaped NPs are less likely to be cleared by RES, which is responsible for their advantageous circulation behaviours when compared with their spherical counterparts.[45, 46] Zhou et al.'s study[47] demonstrated that the 500 × 60 nm and 1000 × 100 nm NRs exhibit circulation time three times longer than nanosphere counterparts. NRs have demonstrated their ability to deliver therapeutics into deeper regions within tumours compared to their spherical counterparts. This enhanced penetration can be attributed to their elongated structures, which facilitate diffusion through the dense tumour interstitium.[48, 49]

The aspect ratio (AR), being defined as the ratio of length to width of the NRs, plays a vital role in the *in vivo* fate of NRs.[4] To some extent, long NRs with high AR exhibit long circulation time, whereas the shorter ones had a more rapid *in vivo* clearance.[50] However, NRs with low AR have a chance of exiting the systemic circulation and accumulating in tumour tissue greater than their long counterparts, leading to a totally different story.[51] Chariou and colleagues[52] compared the intratumoural penetration of NRs with distinct ARs, and found higher penetration efficiency of NRs with the least AR. However, Agarwal et al.'s study[41] demonstrated that the penetration of NRs was primarily governed by their smallest dimension rather than their AR.

AR also has important effects on endocytosis, which depends on the contact point of anisotropic particles with the cytomembrane.[4] Shorter NRs are more likely to be taken up by cells than NPs with higher ARs because longer rods tend to form larger aggregates with loose and irregular structures that may be difficult to internalise, and the internalisation process may require more energy.[53] Chariou and colleagues[52] found that the cellular uptake of PEGylated and RGD-coated NRs increased with the rise of AR. Interestingly, Dasgupta et al.[54] also found that long and short NRs cross the cytomembrane through different mechanisms. Short NRs penetrate tip-first, resembling a "rocket" mode of entry, whereas NRs with a high AR enter side-first, with their long axis parallel to the membrane, akin to a "submarine mode" (**Figure 3**). The internalisation process proves more efficient when rod-shaped NPs are aligned perpendicularly to the cytomembrane, as opposed to a parallel alignment.[52] Wang and colleagues[55] found that gold NRs alienate in a discontinuous and force-rebound rotation, termed "intermittent rotation". This is because the diffusion rate of receptors involved in the endocytosis process. As the AR increases, more receptors are required for internalisation via the "submarine mode", and peripheral receptors spread to the endocytic site more quickly. This rotation behaviour pauses until a sufficient number of receptors are recruited to the endocytic site. In addition, intermittent rotation from a horizontal to a vertical direction serves to minimise energy dissipation during the internalisation process.[55]

Despite the desirable properties of anisotropic nanoparticles described above, few non-spherical NPs have reached the clinical stage so far.[4, 56] Unfortunately, these anisotropic particles have not received adequate attention in investigations, and studies related to the effects of particle properties (such as rigidity, morphology, AR, and etc.) on targeted drug delivery and biocompatibility are still in its infancy. For clinical translation, attention should be paid to limit the potential toxicity induced by these heavy metal particles. Moreover, the explanation for the emerging phenomenon of non-spherical particle targeting remains inadequate. Only when these questions are answered can anisotropic particles be developed for clinical use. In any case, one thing we can be sure of is that spherical and non-spherical particles do own pros and cons for cancer drug delivery, just like the other physicochemical properties we have just discussed.

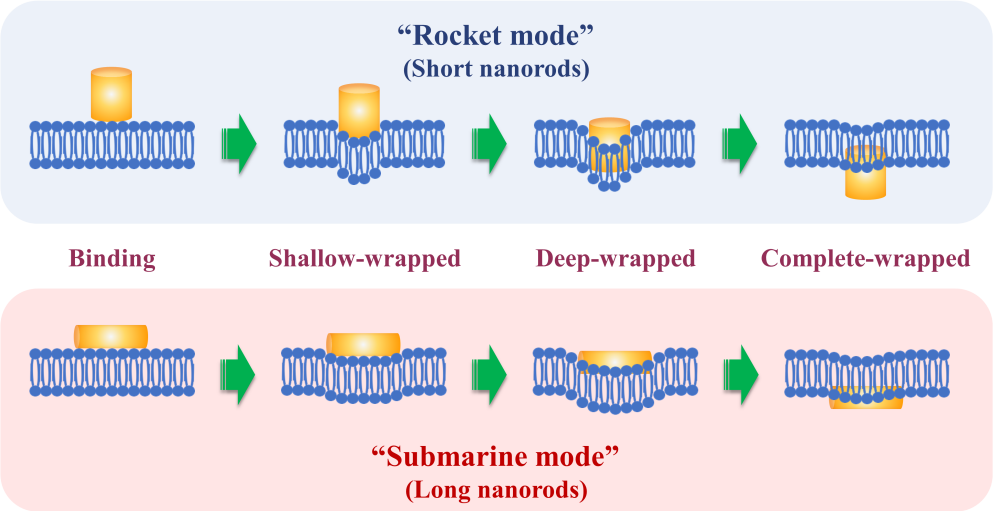


**Figure 3.** Schematic representation illustrating various modes of entry for nanorods with diverse aspect ratios. Short NRs penetrate tip-first, resembling a "rocket" mode of entry (upper panel), whereas NRs with a high AR enter side-first, with their long axis parallel to the membrane, akin to a "submarine mode" (lower panel). Created with Microsoft PowerPoint (version Microsoft 365). AR: aspect ratio; NR: nanorod.

## Structure: The More Stable, the Better?

Currently, researchers are committed to fabricating NPs with stable structures to ensure the long-term blood circulation and prevent undesired burst release or leaking of cargos.[57, 58] However, for an excellent DDS, it is not simply the case that the more stable the better. Although stable structure of NPs can prolong their circulation time, it would be more difficult to release their encapsulated agents within or at the vicinity of tumours, and *vice versa*.[59-61] The compromise between long time circulation and drug release in target tissues & cells remains a vital point to resolve for enhanced tumour suppressing efficacy.

Facilitated by recent advances in materials science, stimulus-responsive DDSs delivering bioactive cargoes in a space, time, and dose-controlled manner, known as "on-demand drug delivery", have become feasible.[62, 63] On-demand drug delivery, which is a type of dynamic targeting strategy, requires the applied biomaterials dynamically undergo a specific protonation, a hydrolytic cleavage, or molecular conformational shifts in response to extracorporeal physical stimulations, endogenous stimuli, or both.[63, 64] Since firstly proposed in late 1970s by Yatvin and colleagues,[65] a variety of stimuli-responsive DDSs been developed, taking into account different pathological characteristics of normal tissues, intracellular compartments, and the TME.[66, 67]

The external stimuli, such as thermal, electronic field and light, could facilitate enhancing the tumour accumulation of NPs, intracellular drug delivery, controlled drug release, as well as activated imaging and therapy of bioactive agents in desired sites.[67] The greatest advantage of external-stimuli responsive drug delivery is that the position, intensity, time, and frequency of a given stimulus can be precisely controlled according to treatment requirements.[66, 67]

Thermo-responsive drug delivery is one of the most investigated strategies. The NPs are designed to be stable during circulation and within normal tissues with a normothermia of up to 37°C, and responsive to a higher temperature with significantly alterations in their properties by responding to the narrow temperature shift.[68] Previously, we successfully fabricated a smart DDS, the high serum stability and longer circulation time was successfully achieved by the crosslink in liposomal bilayers after ultraviolet irradiation. Besides, temperature controlled ON-OFF drug release within tumours can be accomplished by the employment of thermos-responsive biomaterials in the liposomal bilayer.[61] Incorporate thermal-unstable materials inside nanocarriers is another strategy. For instance, the $NH_4HCO_3$ incorporated DDS could generate $CO_2$ in the environment of local hyperemia, making liposome swollen and collapse, and sufficient drug release in desired tumour tissues.[69]

However, the application of external stimuli directed drug delivery are impractical for treating metastatic lesions, the location of which are usually uncertain. While the specific biological factors in TME or inside malignant cells, such as tumour specific enzymes, low pH, redox-potential and hypoxia, etc., could be employed as specific triggers for on-demand drug release or prodrug activation.[64, 66, 70] Meng et al.[71] constructed a NP for targeting metabolic redox circuit with a pH- and adenosine 5′-triphosphate-responsive zeolitic imidazolate framework-8 as a porous core coated with a spatial stabiliser (poloxamer 407). Due to the abnormal pH and adenosine 5′-triphosphate conditions in the TME, the nanocarriers release drugs at specific locations and produce good efficacy in hepatocellular carcinoma HepG2 tumour bearing mice.[71] Liu et al.[72] designed a reactive oxygen species responsive DDS, which can achieve reactive oxygen species response to stimulant decomposition at the tumour site, the tumour inhibition rate of which was enhanced by two times when compared with that of free encapsulated agents.

However, high biological heterogeneity exists within a single tumour (intra-tumour heterogeneity), or within distinct tumours in the same patient or among patients (inter-tumour heterogeneity), which may affect their therapeutic efficacy.[64, 67]

Stimuli-sensitive drug release has been proven to be an ideal solution for the contradiction between longtime circulation in the bloodstream and sufficient drug release within tumours. Currently, many stimulus-responsive DDSs have been developed, showing preclinical therapeutic efficacy better than conventional formulations (**Table 1**).[72-78]

**Table 1. Summary of preclinical studies on stimuli-responsive DDSs**

| Stimuli | NP type | Drug release strategy | Reference |
|---|---|---|---|
| **Exogenous stimulus response** | | | |
| Temperature | Lipid based nanoparticle | This temperature-sensitive liposome containing the photosensitiser IR 820 can generate heat and ROS after NIR irradiation, which greatly improves the therapeutic effect on cancer cells. | 73 |
| Magnetic stimulation | copolymer micelle | The magnetic nanocarriers can target tumour efficiently under external magnetic field. Subsequently, high heat is generated under the stimulation of the alternating magnetic field, which causes the carrier to release the anti-cancer cargoes. | 74 |
| Ultrasound stimulation | Composite nanoparticle | The composite NP can receive external ultrasound stimulation and specifically release drugs in tumours. | 75 |
| Photostimulation | Inorganic nanoparticle | The constructed poly(ethylene glycol)-modified, diselenide-bridged mesoporous silica nanoparticles can break the diselenide bond and release drugs to treat breast cancer under low dose red light irradiation. | 76 |
| **Endogenous stimulus response** | | | |
| pH | Lipid based nanoparticle | The biomimetic "platesome" incorporates the pH-sensitive lipid DSPE-PEOz, which accelerates the release of the drug in an acidic environment. | 77 |
| ROS | Lipid based nanoparticle | Nanocarrier can achieve ROS response to stimulant decomposition at the tumour site, and the tumour inhibition rate of ROS-responsive nanomedicine is three times higher than that of free monotherapy. | 72 |
| Redox | Inorganic nanoparticle | This novel hybrid hollow PDA sphere is coated with manganese oxide ($MnO_2$), which shows effective response to GSH and specific drug release. | 78 |

Note: DDS: drug delivery system; DSPE-PEOz: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly (2-ethyl-2-oxazoline); GSH: glutathione; IR: infrared radiation, NIR: near-infrared ray; NP: nanoparticle; ROS: reactive oxygen species; PDA: polydopamine.

## Endocytosis by Target Cells: The Easier, the Better?

Following bloodstream navigation, site-specific extravasation and intra-tumour penetration, NPs are expected to undergo cellular internalisation, after which bioactive agents can be released to exert therapeutic effects in target cells.[19, 79] Thus, the easier the NPs can be endocytosed into the cytoplasm, the better their therapeutic effects will be. However, the *in vivo* anti-tumour efficacy of NPs is not simply proportional to the endocytosis efficiency, which lack specificity in distinguishing between normal and malignant cells.[13, 79] Systemic exposure of easily engulfed NPs often leads to dose-limiting toxicity to normal tissues.[80, 81] Besides, the RES may also isolate a significant portion of NPs before reaching the tumour, leading to reduced tumour accumulation and diminished overall particle levels.[81, 82] This scenario may also result in potential damage to RES-rich organs, such as liver and spleen.[83] Whereas, if NPs are not readily to be recognised and phagocytosed, ensuring the targeted delivery of drugs with sufficient quantity becomes challenging. Although the EPR effect allows relatively high accumulation in cancerous tissues, this passive targeting strategy alone would not allow sufficient drug loading-NPs to reach and enter target cells.

Recent advances have shifted the targeting strategy from passive to active, achieved by attaching drug-loading NPs to the ligands of tumour-specific or tumour-associated antigens.[79, 84] Overexpression of multiple surface receptors is essential for the survival and proliferation of cancer cells.[84] By functionalising NPs with targeting molecules, they can be actively transported across cytomembranes via receptor-mediated transcytosis, thereby minimising off-target effects.[85-87] In addition, active targeting is important when drug delivery requires active endocytosis through physiological barriers such as the blood-brain barrier.[2, 85] **Table 2** lists some actively targeted NPs currently in clinical trials.[88-97]

Besides, the bionic strategy utilising natural cytomembrane camouflage technology has been extensively used in nanoformulation preparation.[98, 99] Current studies have demonstrated that adhesion molecules expressed on cancer

**Table 2. Summary of actively targeted NPs currently in clinical trials**

| NP | Target | Targeting molecule | NP type | Indications | Phase | Reference |
|---|---|---|---|---|---|---|
| MBP-426 | TRF | TF | Liposome | Gastroesophageal cancer | II | 88 |
| 2B3-101 | Glutathione transporters | Glutathione | Liposome | Recurrent high-grade glioma, breast cancer | II | 89 |
| ABT-888 | PARP | Small molecule | Liposome | Ovarian cancer, triple-negative breast cancer | II | 90 |
| Anti-EGFR-IL-DOX | EGFR | mAb | Liposome | Advanced triple negative breast cancer | II | 91 |
| BIND-014 | PSMA | Small molecule | Polymeric | Metastatic castration resists prostate cancer | II | 92 |
| CPC634 | Tubulin | Small molecule | Polymeric | Ovarian cancer | II | 93 |
| MM-302 | EGFR | mAb | Liposome | Breast cancer | I | 94 |
| SGT-53 | TRF | mAb | Liposome | Pancreatic cancer | I | 95 |
| SGT-94 | TRF | mAb | Liposome | Metastatic genitourinary cancer | I | 95 |
| LY01610 | TOP1 | Small molecule | Liposome | Advanced ESCC | I | 96 |
| PRECIOUS-01 | T-cell | Antigen | PLAG nanoparticle | Advanced NY-ESO-1 positive cancer | I | 97 |

Note: EGFR: epidermal growth factor receptor; ESCC: esophageal squamous cell carcinoma; mAb: monoclonal antibody; NP: nanoparticle; PARP: poly ADP-ribose polymerase; PSMA: prostate-specific membrane antigen; RARβ2: retinoic acid receptor β2; TF: transferrin; TOP1: topoisomerase I; TRF: TF receptor.

cell membrane can navigate and anchor cancer cells through receptor-ligand binding.[100] In addition, cancer cell membrane-camouflage endowing NPs with immunomodulatory self-markers, which can enhance their antiphagocytic abilities and prolong their circulation time *in vivo*.[101, 102] Previously, we have developed several cancer cell membrane-coated NPs for delivering anti-cancer bioactive molecules (including the surviving inhibitor YM155, the radiosensitizer Dbait, and the proteolysis targeting chimeras molecules), and all these versatile biomimetic DDSs hold great potential for the treatment of homologous cancers.[103, 104 105] Liu et al.'s study[106] demonstrated that mesenchymal stem cell cytomembrane coating not only improves endocytosis efficiency of the bionic NP, but also reduces systemic side effects as a result of its tumour homing tendency. Wei and colleagues[107] employed the exosomes of bone marrow mesenchymal stem cells as drug delivery vectors, which also showed better antitumour effects in osteosarcoma MG63 cells.

## Conclusion and Future Perspective

A positive prognosis for patients with cancer relies heavily on physicians' ability to direct anti-cancer agents to specific sites. However, bioactive therapeutics usually diffuse and distribute freely throughout the body, leading to undesirable off-target effects and limiting the achievement of appropriate dose required for effective responses.

This inability to reach target tissues and cells remains the principal cause of new chemical entity failure in clinical studies and gives rise to exceptionally high attrition rates of new chemical entities, with only one in nine gaining regulatory approval worldwide.[108] Targeted drug delivery is the process through which a therapeutic agent is transported within the body to achieve its intended effect, and NPs are rapidly reshaping the landscape of this process. With the discovery of EPR effect, Maeda and colleagues[81, 109] illustrated the prospect of increased NP accumulation via extravasation through porous tumour vessels, opening exciting avenues for the site-specific localisation of anticancer agents. However, current studies demonstrated that it is difficult to achieve sufficient amounts of NPs in cancer cells simply through this passive strategy alone. To this end, different targeting strategies have been developed to the design of smart DDSs, which can be broadly classified as dynamic & static targeting, active & passive targeting from two distinct dimensions.

**Figure 4** illustrates the schematic representation of the current classification of tumour targeting strategies. The abscissa represents the dimension of active and passive targeting, and the ordinate represents another dimension of dynamic and static targeting. Through the EPR effect, NPs can be passively accumulated in cancerous tissues owing to the leaky vascular walls and dysfunctional lymphatics, the whole process of which is relatively stable and does not involve too many alterations. In contrast, through the surface functionalisation with targeting ligands, NPs can actively accumulate in cancer tissues via receptor-ligand recognition and combination, being the basis for active targeting. Through this strategy, the cellular internalisation can also be promoted. In contrast to the dynamic targeting strategy, by which the scientists design NPs responsive to exogenous or endogenous stimuli and dynamically release their contents in desired sites, the EPR effect and surface ligand functionalisation can be categorized as static targeting, the concept we firstly proposed in 2018.[2] Thus, according to the above-mentioned classification, EPR effect (the combination of passive & static targeting) and surface ligand functionalisation (the combination of active & static targeting) should be arranged in the third and fourth quadrant, respectively. The exogenous stimuli, such as thermal, magnetic field and electronic field, can be actively added in desired time and sites. As for the endogenous stimuli responsive strategy, although the encapsulated cargoes can also be released in target


**Figure 4.** Schematic representation of the current classification of tumour targeting strategies. The abscissa represents the dimension of active and passive targeting, and the ordinate represents another dimension of dynamic and static targeting. Based on this description, different targeting strategies can be classified and localised in different quadrants. Created with Microsoft PowerPoint (version Microsoft 365). EPR effect: enhanced permeability and retention effect.

sites, these stimuli can only passively exert their influences as the NPs reaching the tumour tissues and cells. Therefore, as a representative of active and dynamic targeting, the exogenous stimuli-responsive targeting strategy should be arranged in the first quadrant, while the endogenous stimuli-responsive strategy (the combination of passive & active targeting) in the second quadrant, accordingly. The cytomembrane camouflage technology, by which NPs can be navigated and anchored to cancer cells through surface receptor-ligand binding, can also be ascribed to be active & static targeting, being localized in the fourth quadrant in the coordinate axis. However, for the design of an ideal NP, different targeting strategies should be employed in combination.

For purpose of cancer cell targeting, a great many researchers are devoted to investigating the optimal physicochemical properties of NPs for proper negotiation of biological barriers. As we discussed, NP design is not a one-fit-all scenario. Whether big or small sizes, long or short rods, cationic or anionic potentials, are all double-edged swords. The philosophy behind the current consensus for NP design has certain similarities with "*Yin-Yang* balance" theory in traditional Chinese cultures. Although "*Yin*" and "*Yang*" are opposite to each other, "*Yin-Yang* harmony" is a metaphor for sustaining adaptability and equilibrium.[110, 111] Taking the particle size as an example, both "*Yin*" (small) and "*Yang*" (large) own respective advantages and disadvantages (**Figure 5**), which should be weighted for ensuring "*Yin-Yang* harmony" before final decisions be made. This story is the same for the design of zeta potential and other properties. More importantly, for any ant-cancer therapeutics, the balance between potential benefit and side effects should also be carefully weighted. "*Yin*" and "*Yang*" are interdependent for existence. If we only pursue excellent therapeutic effects and ignore the potential side effects, it is unlikely that the NPs will be successfully applied in the clinic.

"*Yin*" might be transformed into "*Yang*" under certain conditions, and *vice versa*. This idea is also applicable during the development of NPs. The macrophage, which is one of the important members of MPS, is usually recognised as a major limitation for nanotherapeutic delivery. After entering the blood circulation, NPs, especially those with large particle sizes (> 150–200 nm), are easy to be sequestered and removed by macrophages, resulting in their inability to reach tumour sites.[10] In the extravascular space, TAMs often accumulate in the perivascular space of tumours and act as an important barrier to limit particle penetration.[112]

However, recent studies suggest that that nanotherapeutics harness TAMs for drug delivery, which has implications for the design of NPs.

Matsumoto and colleagues[22, 113] found that tumour vascular permeability exhibits a dynamic phenomenon marked by vascular bursts, followed by vigorous fluid outflows into the tumour interstitial space. This process facilitates NP extravasation from the tumour blood vessels, enabling even large NPs to penetrate the TME.[22, 113] Miles and colleagues[114] found that TAM is increased in tumour xenografts and tumour biopsies from patients after radiation therapy, while this radio-induced TAM localisation can elicit dynamic bursts of extravasation that subsequently enhances NP accumulation in adjacent tumour cells. TAMs have also reported to be employed as drug repositories to accumulate high levels of therapeutic NPs, with cytotoxic payloads gradually released to adjacent cancerous cells.[115] As we can see, although macrophages are considered as major obstacles ("*Yin*") for cancer drug delivery, the TAMs might be served as essential aids ("*Yang*") in certain conditions. The roles of macrophages in drug delivery can be a vivid example for "*Yin-Yang* transformation", just like a famous saying "*Yin* is within, but not against *Yang*".

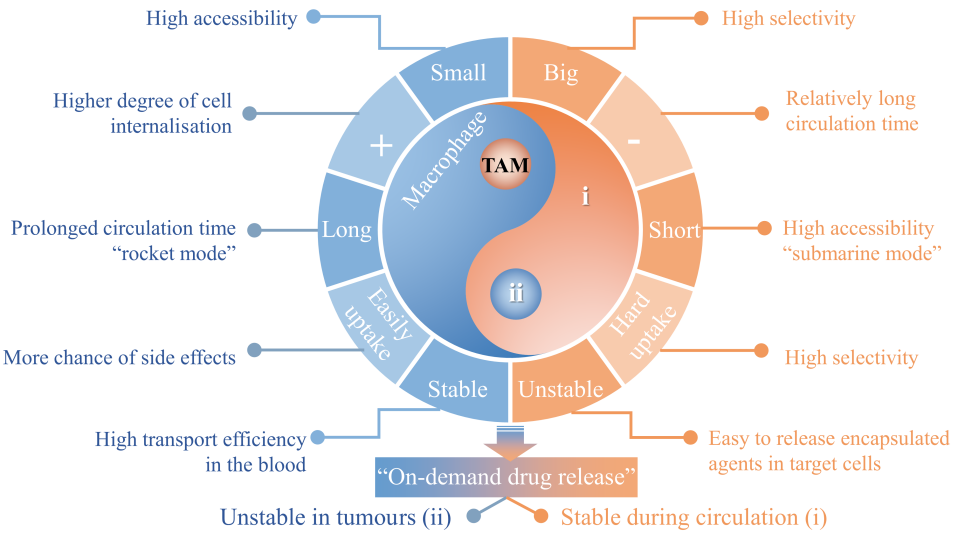


**Figure 5.** The philosophy behind the current consensus for NP design has certain similarities with "*Yin-Yang* balance" theory. Both "*Yin*" and "*Yang*" of each physicochemical properties have pros and cons for drug delivery, the balance of which should be considered before the final design. An ideal drug delivery system should be stable during circulation (i) while unstable when reach target tumour issues and cells (ii). Macrophages act as a major limitation for nanotherapeutic delivery, while TAM might be utilized for drug delivery, as "*Yin* is within, but not against *Yang*". Created with Microsoft PowerPoint (version Microsoft 365). NP: nanoparticle; TAM: tumour-associated macrophage.

The field of NP-based drug delivery is undergoing a significant evolution, moving beyond traditional boundaries and exploring innovative geometries and chemical modifications. This transformation aims to develop rationally designed nanoparticles capable of overcoming sequential biological barriers. Despite the intricacies involved in effectively delivering therapeutics to tumours, there is a growing realisation that these challenges are surmountable. As highlighted in this review, clinically promising nanoformulations necessitate a delicate balance of diverse factors. These include utilising unconventional geometries to enhance vascular dynamics, designing optimal sizes and zeta potentials to enhance targeted delivery efficiency, integrating biomimetic cytomembranes to evade phagocytic uptake, and formulating "on-demand" drug release strategies to maximise therapeutic outcomes. Although numerous smart NPs have exhibited promising anti-tumour effects in preclinical experiments, their intricate designs should still adhere to the principle that "simplicity is the essence of sophistication" when contemplating their clinical application potential. Overcomplicated designs can directly hinder scaling up and mass production, while also compromising biosafety. Additionally, an excess of design elements complicates the identification of crucial components that truly enhance drug efficacy during clinical trials. Depending on the specifics of the design, obtaining regulatory approvals for quality control, reproducibility, and toxicity may present further obstacles. We can anticipate that breakthroughs in the understanding of cancer biology and innovations in materials science will continue to drive the development of novel NPs for effective tumour-specific delivery, elevating NP-based therapies from a promising field to a viable strategy for the treatment of cancer.

**Author contributions**

HL conceived the idea of this review and outlined the review with YA and YT. YA and YT draft the manuscript. HL, JQ and CW systematically revised the whole review. HL contributes the conception and creation of figures. All authors discussed and commented on the manuscript, and approved the final version of the manuscript.

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**Conflicts of interest statement**

None.



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