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Applications of Nanoparticles for Drug Delivery in Cancer Treatment: A Review

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Abstract Anticancer drug resistance virtually always arises and poses major hindrances on the way to curative treatment of numerous human malignancies.

Numerous cancer patients have hopeful response to 1st line chemotherapy but end up with cancer advancement or cancer relapse, which needs additional management. Response to consequent chemotherapy using different agents typically decreases considerably because of challenging resistance against chemotherapy. Numerous mechanisms had been proposed which may be responsible for cancer resistance against chemotherapy or poor response to chemotherapy. Best-studied mechanism of resistance is mediated via modification in drug efflux proteins accountable for elimination of various generally utilised anti-cancer medications. Therapeutic Nano-Particles have developed as an innovative as well as encouraging substitute of traditional small molecule chemotherapies to fight drug resistance against chemotherapy. These have displayed greater therapeutic efficiency as well as less side effects as matched to their small molecule counterparts. This targeted approach offers assurance in paving approach for introduction of extremely effective nanoscopic vehicles for cancer therapies while overcoming resistance.

Keywords Nanoparticles, Drug Delivery, Cancer

Cancer is a major health issue in modern world, which is growing day by day. Currently it is 2nd main reason of mortality and till date many currently available therapies are not adequate [1-4]. Chemotherapy is widely used as conventional method in treatment of cancer [5-6]. Chemotherapy leads to vigorous killing of rapidly growing cells (infected as well as normal) thus one hand benefits the patient by killing malignant cells whereas on the other hand shows side effects in form of loss of hair, GI reactions, suppression of bone marrow etc [7-10]. There is prerequisite to develop new drugs or systems for delivery of drugs which may target specific cells (to lower the side effects) [11-12].

Drug resistance developed against drugs that are used in cancer is also increasing day by day and is challenging researchers to find new ways to stop, overcome, or reverse this resistance [13-15].

Currently known mechanisms of resistance against chemotherapy include

a. defective apoptotic pathways
b. overexpression of drug efflux transporters
c. hypoxic environment [16-18]

As new mechanisms of cancer drug resistance are explored: increasing researches to target these mechanisms [19-20].

Researches to treat cancer has leads to development of many novel drugs & innovative techniques [21].

Nanoparticles: usage has increased in last few decades. As name indicates they have very small size measured in nano-meters (10^{-9}) (nm) [22-23]. Their size may range from 10 nm to few hundred nm (depending on purpose of using it). Nano particles are available in variety of shapes also for ex. spheres, rods, tubes, wires, fullerenes (cluster),

branched structures etc [24-25]. Active pharmaceutical ingredient (drug which has intended therapeutic action) may be attached/linked with these nano particles by various techniques surface attachment, encapsulation or entrapping etc. Nanoparticles for drug delivery come in a wide range of compositions, shapes, as well as sizes. Capacity of drug loading, particle along with stability of drug, drug release rates, and capability for delivery at targeted site are all different for each particle [26-28]. Nanoparticles are being used in many fields in medicine like diagnosis, treatment and in drug delivery systems for targeting specific cells (tumour cells) [29-30]. Few Nanoparticles, which are currently approved by various agencies (like USFDA), include pegylated liposomal doxorubicin, liposomal daunorubicin, on pegylated liposomal doxorubicin, abraxane [31-33].

Many researches are also currently are under process because of its promising outcomes. Many of researches are in clinical stage, which may join the commercial market soon.

Targeted Drug Delivery

Mechanism of Targeting specific cells (tumour cells) may be

1. **Active Targeting**: Nanoparticles carry Ligands, which directly interact with receptors (molecules, which are overexpressed on surface of cancer cells) thus ligands can differentiate tumour cells easily. This interaction between Ligands and receptors of targeted cells includes receptor-mediated endocytosis thus therapeutic drugs are released inside the targeted cells. This type of Targeting is used when:
    a. **Ligands include:** Amino Acids, Vitamins, peptides, carbohydrates, monoclonal antibodies
    b. **Receptors include:** Glycoproteins, folate receptor, epidermal growth factor receptor, transferrin receptor
2. **Passive Targeting:** When specific receptors or ligands (widely investigated) are not available, which can be utilized for targeted delivery then drug delivery is done via differentiating different characteristics of tumour cells and normal cells. These include
    a. **Enhanced Permeability and Retention Effect (EPR Effect):** New blood vessels are formed at fast rate because of high proliferation of cancer cells (to cater increased nutrient needs for tumour cells). Vascular walls of these newly formed blood vessels have large pores (100-780 nm) which decreases their ability to discriminate between anions and cations as compared to normal cells. This allow Nano Particles to enter & accumulate in tumour cells from these rapidly & defectively generated new blood vessels. Here they can release the drug contents carried with them. This is supported by enhancing their retention in tumour cells caused due to poor drainage of lymphatic system because of cancer.
    b. **Microenvironment of Tumour cells:** In cancer cells, proliferation leads to increased glycolysis (to cater increased needs of energy for tumour cells) thus in tumour tissue pH is reduced leading to acidic environment so Nanoparticles which are pH sensitive can deliver the carried drug in this area where pH is less [34-37].

Hybrid Nano-Particles: these are hybrid systems, which include pooled properties of diverse nano-particles thus increase the stability & functions of DDS.

When related to conventional medications, drug delivery based on nanoparticles has specific benefits which includes:

- ✓ exact targeting of specific cells (tumour cells)
- ✓ Good pharmacokinetics
- ✓ better stability
- ✓ improved permeability
- ✓ enhanced retention effect
- ✓ improved biocompatibility
- ✓ overcoming cancer-related drug resistance (there are reports on the potential of overcoming multi drug resistance in some types of cancer (like prostate, breast, ovarian)

- ✓ decrease in side effects
- ✓ provide platform for combination drug therapies
- ✓ can be loaded with a variety of therapeutic agents [38-40]

Nanoparticles, which are utilized in Drug delivery systems, are selected on basis of many characteristics like:

- ✓ Size of particles
- ✓ Shape of particles
- ✓ Surface characteristics of particles
- ✓ Pathophysiology of targeted cells

Drug delivery systems based on nanoparticles are supposed to improve immunotherapy, and reverse tumour microenvironment, which is immunosuppressive.
Researches are in progress to examine role of nanoparticles in immunotherapy [41-45].

Drug Resistance

Despite the fact that there are numerous options available, drug resistance is still a significant issue in treatment of cancer. Multidrug resistance causes different cancer treatments to fail, resulting in progression of cancer as well as poor prognosis. Mechanisms of tumour treatment resistance involve both physiological and cellular elements, like an acidic and hypoxic tumour microenvironment, an overexpression of ATP binding cassette (ABC) transporters, in addition to malfunctioning apoptotic machinery. It has been demonstrated that using nanotechnology to deliver drugs for the treatment of cancer can significantly help overcome medication resistance.
Key modalities of anti-tumor drug resistance might be clustered in minimum 5 main classes:

1. better drug efflux mainly through ATP-driven extrusion pumps commonly of ATP-binding cassette (ABC) superfamily
2. reduced drug influx
3. activation of DNA repair
4. inactivation of apoptosis pathways with parallel activation of anti-apoptotic cellular protection modalities
5. metabolic modification besides detoxification

P-glycoprotein (P-gp/ABCB1), multidrug resistance proteins (MRPs/ABCC), and breast cancer resistance protein (BCRP/ABCG2) are all members of the ABC superfamily that act as ATP-driven drug efflux transporters and provide a special defence against chemotherapeutics besides several exo- and endotoxins [13-20].

Role of Nanoparticles in cancer immunotherapy

Cancer treatment has entered a new era due to introduction of immunotherapy. The usage of NPs in immunotherapy demonstrated significant promise, in addition to their critical function in the administration of chemotherapy. The primary method of cancer immunotherapy is to stimulate anti-tumor immune response. Synthetic antigen-presenting cells (aAPCs), Nanovaccines, besides targeting immunosuppressed tumour microenvironment (TME) are all components of Nano-Particles-associated immunotherapy. Tumor-related antigens (TAAs) as well as adjuvants are delivered to APCs like dendritic cells via nanovaccines. Moreover, Nano-Particles can operate as adjuvants by themselves to boost APC antigen presentation as well as to encourage DC maturation, which will activate cytotoxic T cells' anti-tumor ability. TAAs can be delivered into DCs' cytoplasm by Nano-Particles like liposomes, gold Nano-Particles, PLGA Nano-Particles, micelles, and dendrimers, which improves the immune response against tumour cells. Inorganic NPs, like mesoporous silica, and polymers, like acetylated dextran (AcDEX), have been demonstrated to serve as an adjuvant in immunotherapy, stimulating immune response. Contrary to nanovaccines, artificial APCs work by activating T cells by the direct binding of co-stimulatory molecules to co-stimulatory receptors on T cells and MHC-antigen complexes to T cell receptors (TCRs). Targeting regulatory T cells (Tregs), myeloid derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), all of which are significant

cell types in TME, is the major way to combat the immunosuppressive TME. Additionally, Nano-Particles are typically treated with PEG to reduce interactions with the reticuloendothelial system [46-55].

A promising method of treating cancer is the combination of chemotherapy and immunotherapy. One study, for instance, demonstrated that co-loading the cytokine GM-CSF and the chemotherapeutic drug Nutlin-3a in spermine-modified AcDEX NPs increased the proliferation of cytotoxic CD8(+) T cells and stimulated the immunological response, causing tumour cell death without damage in immune cells. Co-delivering chemotherapeutics and monoclonal antibodies into porous silicon nanoparticles is an alternative method of combination chemo-immunotherapy that has been successful in triggering complement activation, antibody-dependent cell cytotoxicity (ADCC), and an immunological response against cancer cells [46, 56-57].

Properties of nanoparticles for drug delivery

Nanoparticles are affordable, environmentally friendly structures that can be produced using a variety of chemical and biological processes. By interacting with particular biological components, nanoparticles can easily diffuse into cells, allowing for selective targeting and accumulation in particular cells or tissues. Additionally, because nanoparticles are pH-labile structures, they can quickly lose their drug-carrying capacity in cells with low pH by deactivating, degrading, or decomposing.

Polymeric polyethylene-glycol and other biodegradable nanoparticles are some examples of drug delivery systems that utilise them. Nanoparticles are appropriate for use in drug delivery systems because they can endure for weeks or more in the microfluidic environment of a cell without degrading [6]. Carbon nanotubes, for instance, have numerous uses and can last for a longer time [6]. Since they are compatible with the body's immune system and are non-immunogenic, nanoparticles do not cause an immunological reaction when they are ingested [6, 7]. The following list of benefits of nanosized medicines is provided:

- Improved surface area
- Improved solubility
- Improved dissolution rate
- Improved oral bioavailability
- Fast onset of therapeutic action
- Lesser dosage requirement
- Reduced fed/fasted variation
- Reduced case-to-case variation [58-63].

Protocols used for the synthesis of nanoparticles

The methods used to create nanomaterials can be divided into bottom-up, top-down, or a mix of methods. Building up molecules is a component of bottom-up methods. For the production of nanoscale materials, some processes use bottom-up strategies. These include molecular self-assembly, chemical vapour deposition (CVD), sol-gel processing, and liquid phase procedures based on inverse micelles. The covalent forces that hold the components created by bottom up methods together make them substantially stronger than macroscale components. When creating nanomaterials using top down procedures, materials are micronized through cutting, carving, and shaping. Milling, physical vapour deposition, hydrothermal methods, electroplating, and nanolithography are a few examples [64-68].

Classification of nanoparticles

Based on their forms, nanoparticles can be broadly divided into the following four groups. First, depending on how many dimensions are present at the nanoscale, nanostructures can be classified as zero-, one-, two-, or three-dimensional structures.

Zero-Dimensional Nano Structures

Nanoparticles and dendritic structures that have functionalized nanoparticles are included in zero dimensional nanostructures, which are objects with zero dimensions that are outside nanoscale, ex. spheres and clusters (fullerene).

One-Dimensional Nano Structures

These are only one dimension, outside of the nanoscale, and include things like fibres, wires, and rods. These have been employed in nano-devices, nanoscale fibrils, and the creation of polymer nanocomposites to boost stability. The nanoscale is only one dimension; therefor nanomaterials with needle-like shapes, such as nanotubes, nano-rods, and nanowires, are produced. Amorphous or crystalline, single crystalline or polycrystalline, chemically pure or impure, and independent materials or immersed within another medium are just a few of the characteristics that one-dimensional nanoparticles often exhibit. One-dimensional nanoparticles are employed in a wide variety of applications, including corrosion-resistant materials, hydrophobic and self-cleaning materials, dirt-repellent materials, antibacterial and antimicrobial agents, catalytically active materials, and chemically functionalized materials.

Two-Dimensional Nano Structures

Films, plates, and networks are examples of two-dimensional structures with two dimensions outside the nanoscale. These are employed in optoelectronics, electronics, and sensing. Particles of the two-dimensional variety are not restricted to the nanoscale. Nanofilms, nanolayers, and nanocoatings are examples of 2-D nanomaterials that have plate-like structures. Two-dimensional nanoparticles are coated on a substrate and integrated into the surrounding matrix material as single layer or multilayer structures.

Three-Dimensional Nano Structures

These have three dimensions outside the nano-range. These, can be in tri or tetra pod forms and nanocombs and have been used in the separation, catalytic, biomedical, and heat transfer. Materials that are not restricted to the nanoscale in any dimension are referred to as bulk nanomaterials. These materials may be identified by their three arbitrary dimensions that are more than 100 nm. Examples include nanoparticle dispersions, clusters of nanowires, fullerenes, multinanolayer nanotubes, dendrimers, and nanowire bundles. Three-dimensional nanoparticles have diverse configurations of nano-sized crystals, a noncrystalline structure, and various orientations [69-74].

Types of nanostructures used for drug delivery

- Metallic nanoparticles

Metallic nanoparticles have been employed in medication delivery, especially in cancer therapy, as well as biosensors. Gold, silver, nickel, and iron oxide are examples of metallic nanoparticles that have been explored for targeted cellular delivery. Metal nanoparticles can also form conjugates with polymers and have anticancer, antitumor, and antibacterial properties. Metallic nanoparticles can contain a significant amount of medication due to their enormous surface area. The metal may be processed to get the required size between 0.8 to 200 nm. The surface may be changed with various functional groups for gene transfection, conjugated into a gene delivery vector, and targeted at the cell nucleus with proteins and peptides. The toxicity of metallic nanoparticles is a problematic aspect of their use [75-78].

- Carbon-based nanomaterials

Carbon nanotubes are structures that resemble tubes made of carbon. These are arr anged as a graphite sheet that has been rolled up into a cylinder and has a bucky ball on one or both ends. These are hexagonal carbon atom networks that have lengths between 10 and 100 nm and a diameter of around 1 nm. Recent years have seen a lot of interest in two carbon-based configurations: single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs). As the name indicates, MWNTs are made up of several concentric tubes, while SWNTs only have one tube [79-82].

- Liposomes

Due to their tiny size ie between 50 and 200 nm, these nano carriers are the most developed nano-carriers for innovative and targeted delivery of drugs. Closed vesicles are created when dry phospholipids are moistened. Liposomes have a high entrapment efficiency, are adaptable, and are biocompatible. Liposomes' principal benefit, which makes them a key target for drug delivery, is their biocompatibility. Additionally, liposomes have the ability to carry a range of medicines, including hydrophobic, amphiphilic, and lipophilic ones. The quick removal of the medication from circulation through the reticuloendothelial system or mononuclear phagocyte system is a disadvantage of the liposome drug delivery technology. By adding "PEGylated Stealth®" liposomes, which divert protein absorption and, as a result, are detected and actively transported across the PEG surface, the aforementioned limitation can be minimized [83-86].

- Fullerenes

A carbon allotrope with at least 60 carbon atoms and a polygonal structure is called a fullerene. Spherical cages called fullerenes contain 28 to more than 100 carbon atoms. These can also termed "bucky balls." Alkali-doped fullerenes, exohedral fullerenes, endohedral fullerenes, endohedral metallofullerenes, and heterofullerenes are among the several forms of fullerenes. They are able to withstand enormous pressures and return to their original shape once the pressure is released. These molecules have a significant potential for use as lubricants since they do not combine with one another [87-90].

- Dendrimers

Hyperbranched, tree-like nano structures are known as dendrimers. They are made up of 3 parts which are: the core moiety, ranching units, and densely packed surface. They are less than 10 nm in size, have a globular structure, and enclosed interior cavities. Dendrimers are a special type of nano polymers with highly controllable size and structure, and chemical polymer compartmentalization. These regularly branching polymeric nanostructures can have any number of branches, which determines their size. These well defined nanostructures have the monodispersity of size, surface functionalization ability, and stability characteristics that make them desirable drug carrier agents [91-93].

- Graphene

The allotrope of carbon known as graphene has exceptional thermochemical characteristics as well as a high tensile strength. Its unique hexagonal structure permits the conversion of infrared energy into heat. Medicine delivery is made possible by the increased surface area of malignant cells, but because the drug is hazardous, surface shielding is necessary [94-96].

- Polymerosomes

Polymersome nanoparticles are spherical vesicular entities with synthetic amphiphilic building blocks that hold an aqueous solution. Hydrophobic and hydrophilic subunits, such as polylactic/glycolic acid and polyethylene glycol-block-polycaprolactone, make up the two halves of this special copolymer. These systems also provide improved flexibility and stability, allowing liposomes to take on features of a bilayer, such as chemical composition and thickness [97-101].

- Nanocrystals

Nanocrystals enable direct drug incorporation at the target site while reducing the buildup of carrier particles. Without stabilisers, nanocrystals are exceedingly stable in aqueous dispersions. They are effectively absorbed by tumour cells. The medication that needs to be injected into the cell is made at the nanoscale and is capable of acting as its own carrier. Due to their nano size, the drug particles are easily soluble in water. Polymeric macromolecules and non-ionic surfactants stabilise the surface when the drug particle is decreased to the nano size range. The drug's surface area has risen due to its reduced size. In the end, the plasma concentration increases and solubility dissociation is enhanced [102-105].

Nanotechnology in drug delivery

Recently, drug delivery methods have successfully used nanostructures. Paul Ehrlich, a German scientist, proposed the notion of employing "magic bullets" to more precisely target medication more than a century ago. This concept was employed once again, and researchers discovered nanoparticles to be acceptable in this respect and they may be used in the selective accumulation in the target organ or tissue and have been given the name of drug delivery system. To increase the therapeutic efficacy of medications, a variety of nanoforms have been used as drug delivery

systems, including liposomes, solid lipid nanoparticles, dendrimers, and solid metal-containing nanoparticles. In these ongoing efforts, liposomes have been employed to transport proteins since they were first reported in the 1960s. For instance, lymph drainage in tumour tissue is diminished or reduced due to the high permeability of walls of blood vessel.

Devices that have received approval utilise nanomaterials made from organic and inorganic materials as delivery systems to create potent medicines. More than 20 therapeutic medicines based on nanotechnology have been authorised for use in patients by the Food and Drug Administration (FDA), and numerous others are now undergoing clinical testing. The bulk of them are first generation nanotherapeutics since they are made of non-targeted delivery mechanisms (such polymers and liposomes). The first generation nanosystems provide several benefits over traditional medication delivery. In particular, they can increase the therapeutic action by extending the half-life of the medication, making hydrophobic medicines more soluble, lowering the possibility of immunogenicity, and/or releasing the drug either gradually or in response to stimuli. As a result, both the frequency of drug administration and its hazardous side effects can be decreased. In addition, due to increased permeability and retention, nanoscale particles can passively gather in some tissues (such as tumours). Beyond these therapeutically effective nanosystems, novel medicines and the creation of next-generation nanosystems for "smart" drug delivery have also been made possible by nanotechnology. The delivery mechanism effectively attaches to diseased tissue due to nanoparticles that contain "targeting molecules" (such as particular antibodies or folic acid). A few nanoparticles were discovered to carry medication across the blood-brain barrier to treat brain cancers when dealing with relevant targeting molecules. As a result, it can aid the immune system's detection. Endocytosis is the process by which cells take up the conveyance framework holding the dynamic substance. The delivery mechanism has been combined with a contrast agent, such as fluorescent or radioactive materials, and employed as needed in imaging techniques to track the delivery to the target [106-112].

Future perspectives of Nanoparticles for Drug Delivery in Cancer Treatment

Usage of nanoparticles aimed at drug delivery in cancer treatment is a relatively new field of research. Although much progress has been made in the development of nanoparticle-based drug delivery systems, there are still numerous challenges that need to be addressed. One major challenge is to improve targeting of nanoparticles to cancerous cells. Currently, most nanoparticles are not able to specifically target cancer cells and thus are not able to selectively deliver drugs to these cells. This limits the efficacy of nanoparticle-based drug delivery systems. Another challenge is to develop more effective and safe nanoparticles. Currently, many nanoparticles are not biocompatible and can cause side effects in patients. Additionally, many nanoparticles are not effective at delivering drugs to cancer cells. Finally, it is vital to improve strategies to prevent nanoparticles from being cleared by the body before they can reach the cancer cells. This is a major challenge because the body has several mechanisms to clear nanoparticles from the bloodstream. Despite these challenges, nanoparticle-based drug delivery systems have great potential in the treatment of cancer. These systems have the ability to specifically target cancer cells, increase effectiveness of medications, as well as reduce side effects [101-106, 107-109].

The use of nanoparticles for cancer treatment is a rapidly evolving field with great potential. There are many different types of nanoparticles being investigated for use in cancer treatment, each with unique properties that may make them more or less effective for specific applications. In general, nanoparticles have potential to improve the efficacy and safety of cancer treatments by specifically targeting cancer cells and delivering therapeutics directly to them. Additionally, nanoparticles can be used to improve the delivery of imaging agents, allowing for more precise diagnosis and monitoring of cancer. Despite the great potential of nanoparticles for cancer treatment, there are still many challenges that need to be addressed. One of the major challenges is the development of safe and effective nanoparticles that can be used in humans. Additionally, it is important to optimize the delivery of nanoparticles to cancer cells so that they are maximally effective. Finally, it is important to continue to develop new and improved cancer treatments that can be delivered via nanoparticles. With continued research and development, nanoparticles have the potential to revolutionize cancer treatment and improve the lives of patients [105, 108-111].

Conclusion

Chemists, physicists, biologists, and pharmaceutical scientists have all contributed significantly to the development of new therapeutic approaches and diagnostic tools in the field of nanotechnology which makes it a truly multidisciplinary field. Advancements in diagnostic tests and treatments, as well as the treatment of cancer and many other diseases, have all been made possible by nanotechnology. Additionally, implanted delivery systems can be made possible by nanotechnology, which are typically preferred over the usage of injectable medications since injectables frequently exhibits first order kinetics (concentration of drug in blood increases rapidly and decreases exponentially with time). This paper demonstrates how the use of nanotechnology in drug delivery, nanomedicine, and therapy can open up new avenues for delivering flexible, safe, and efficient treatment alternatives [113-116].

The therapeutic approaches for cancer that are currently present have serious drawbacks that frequently lead to failure of treatment. The underlying causes of such failure are complex and include non-specific biodistribution, inadequate targeting of the therapeutic agents, a lack of oral bioavailability and water solubility, low therapeutic indices, dose-limiting toxicity to healthy tissues, and, most significantly, almost always developing drug resistance. Drug resistance is still a major barrier to cancer chemotherapy's effectiveness. New cancer nanotherapeutics are quickly developing and being used to get around some of these constraints. NPs have been created with the ideal size and surface properties to prolong the biodistribution of anticancer drugs and optimise their blood circulation. Both passive targeting techniques, like the EPR effect, and active targeting mechanisms employing ligands directed towards specific determinants significantly overexpressed on the surface of tumour cells are capable of carrying and delivering their active therapeutic payloads to cancer cells. It may be possible to use rationally designed NPs to overcome the drug resistance that hinders the effectiveness of traditional chemotherapy treatments. Accordingly, NPs endowed with the capacity to accumulate in cancer cells while eluding ejection by efflux pumps would lead to an increase in intracellular concentration and thereby an improvement in the drug cargo effectiveness. Additionally, NPs containing chemotherapeutic medications may also contain a protein inhibitor or a drug resistance gene modulator that will work together to increase the effectiveness of the treatments. In the end, NPs should also be loaded with a diagnostic-aid, enabling the precise localization of the tumour and its metastases, in addition to a cancer selective targeting moiety, a cytotoxic drug combination, and particular molecules targeting drug resistance proteins. This will make it easier to use supplementary treatment modalities including surgery, photodynamic therapy, and radiation. NPs that combine a cytotoxic drug with a substance that can neutralise a well-defined drug resistance mechanism have been investigated in vivo, but none of them have yet made it to clinical trials. It is anticipated that using such "theragnostic NPs" for cancer treatment will improve diagnoses, reduce the amount of chemotherapy required for a full recovery, reduce toxicity and adverse effects on healthy tissues, and raise the therapeutic index. Such nanovehicles may have specific configurations that target CSCs/TICs. Overall, "smart" theragnostic nanovehicles for combined drug delivery made up of four components that aim to specifically target the cancer cell, identify its location(s), destroy malignant cells with a cytotoxic drug(s), and simultaneously neutralise the relevant drug resistance mechanism(s) are among the most promising new treatment options in the near future for cancer therapy. We suggest calling these hypothetical four-element nanovehicles “quadrugnostic nanoparticles” [117-121].

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