Chapter 04

Use of Nanoparticles for Drug Delivery in Cancer Treatment

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ABSTRACT

Enhancing treatment techniques against cancer is highly promising due to the rapid advancement of nanotechnology in the invention of nanomedicine agents. The recently discovered method for injecting medications into cancer cells with the least amount of drug leakage into healthy cells is using Nanoparticles (NPs). A highly effective therapeutic strategy for treating cancer disorders is the coupling of NPs with ligands of tumor biomarkers unique to cancer. The ideal size and surface properties of NPs have been engineered to enhance their biodistribution and maintain their blood circulation. Nanotherapeutics make use of the distinct pathology of tumors, which includes increased permeability and retention effects, to precisely deliver active drugs to cancer cells. Apart from the passive targeting method, the efficacy of these pharmaceutical NPs is enhanced by active targeting tactics that employ ligands or antibodies that are directed against specific tumor sites. Different nanostructures have been studied as carriers in drug delivery systems, including polymer compounds, dendrimers, silicon or carbon compounds, magnetic NPs, and liposomes. This chapter addresses the use of NPs as delivery vehicles for anticancer medication compounds. Drug carrier systems and target specificity have been investigated for a range of NPs with varying structural and chemical compositions.

KEYWORDS
Nanoparticles, Cancer, Drug delivery

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INTRODUCTION

Every year, about 10 million new instances of cancer are diagnosed, making it one of the most deadly diseases in the world (Stewart et al., 2003). However, in the last two years, death has decreased as a result of technological developments in diagnostic tools and therapies as well as an improved understanding of cancer. Surgical procedures, radiation therapy, and chemotherapy are being used to treat cancer. These therapies frequently result in the death of healthy cells and damage to the patient. The non-specific distribution of conventional chemotherapeutic agents in the body limits their ability to influence both cancerous and normal cells. This leads to suboptimal treatment outcomes because of excessive toxicities and a lack of targeted action within tumor cells (Ross et al., 2004).

In the world, cancer is the second-greatest cause of mortality and one of the major public health issues. By the conclusion of 2021, 1.9 million new cases are expected, as estimated by the American Cancer Society (Gavas et al., 2021). Many nanotherapeutic medications have been developed and are now extensively marketed as a result of breakthroughs in nanotechnology, and since 2010, numerous more have reached the clinical stage. Drug combinations and the repression of mechanisms that contribute to drug resistance are two areas where nanotherapeutic medicines have made advances in the domains of drug delivery methods and anti-cancer multidrug resistance (Palazzolo et al., 2018). The capacity to operate at the atomic, molecular, and supramolecular levels (on a scale of around 1-100 nm) is known as nanotechnology.

It allows us to develop and comprehend material structures, devices, and systems with essentially unique characteristics and capabilities due to their microscopic structure (Roco et al., 2000). Due to nanotechnology, we can now create materials with whole new and desirable properties. The benefits and scientific limits of using NPs as medication delivery methods are being thoroughly studied worldwide. The development of the use of NPs as efficient medication delivery methods has advanced remarkably throughout the past ten years. Currently being researched are a variety of nanoparticle forms that can be used as drug delivery systems, such as ceramic NPs, polymeric micelles, dendrimers, liposomes, and polymeric biodegradable NPs, including nanospheres and nanocapsules (Yih et al., 2006). This chapter will focus on the various types and characteristics of NPs, their application as vehicles for drug delivery to more effectively kill cancer cells and remove drug resistance, and how advancements in nanoparticle technology in the future will improve the efficacy of their therapy and utility in cancer treatments.

Nanoparticles

According to scientific definitions, NPs are single-dimensional particles smaller than 100 nm with special qualities typically absent from larger amounts of the same substance (Boisseau et al., 2011). NPs can be categorized as 0D, 1D, 2D, or 3D, depending on their overall shape (Laurent et al., 2008). The relatively complicated fundamental composition of NPs is made up of the surface stratum and core which is basically the center of the nanoparticle and is often known as the nanoparticle itself (Tiwari et al., 2012). Due to their remarkable characteristics, such as their high surface-to-volume ratio, difference, sub-micron size, and improved targeting mechanism, these materials have become increasingly important in interdisciplinary sectors. Permeability and absorbance (EPR) impact is said to be enhanced by NPs' deep tissue penetration. Moreover, the surface characteristics effectively overcome epithelial fenestration, which affects solubility and half-life (Shin et al., 2016).

Delivery of Nanoparticles with Selectivity

For anticancer medications to be successful in the treatment of cancer, they should ideally be able to pass through the body's barriers and reach the targeted tumor tissues with the least amount of volume loss or blood circulation activity. Second, medications should be able to attack cancer cells only while avoiding normal cells once they have reached their target. Because these two fundamental strategies immediately decrease dose-limiting toxicities and increase medication intracellular concentration, they are also linked to increases in patient lifespan and quality of life.

Characteristics of Nanoparticles Surfaces and sizes

For NPs to effectively carry medication to the target cancer tissue, they must be able to sustain extended circulation without being eliminated from the bloodstream. Both conventionally coated and unmodified NPs are frequently absorbed in the blood through the system of reticuloendothelial cells, including the liver and spleen, based on their dimensions and surface features (Moghimi et al., 2001). The surface features of NPs play a crucial role in dictating their life cycle and fate in the bloodstream concerning being engulfed by macrophages. For NPs to avoid being captured by macrophages, their surface should ideally be hydrophilic (Moghimi et al., 2003). This may be done in two ways: either hydrophilic polymers, such as Peg, are coated on the surface of the NPs to prevent opsonization, or blocking copolymers with hydrophobic and hydrophilic domains can be used to produce the NPs (Harris et al., 2001). Nanomaterials employed in drug administration must be large sufficient to before medications from spilling into the blood vessels too quickly, but they should also be small enough to evade capture by stable macrophages found in the liver and spleen, as well as other retinal endothelial system organs. In contrast, gaps between endothelial cells that exist in the leaky vasculature of tumors can have a diameter of 100 to 600 nm. The sinusoidal structures in the spleen's wall or the Kupffer cells in the liver are 150 to 200 nm in size. NPs need not be larger than 100 nm for them to get beyond these two distinct circulatory systems and into cancerous tissues (Wisse et al., 1996).

Types of Nanoparticles that are used in Drug Delivery Systems

In drug delivery systems, three types of NPs are frequently used: hybrid, organic, and inorganic NPs. Drug delivery methods with NPs submicron-sized particles (between 3 and 200 nm), systems that may be created utilizing a range of materials such as viruses (viral NPs), polymers (polymeric NPs), lipids (liposomes), and even organometallic compounds.

Organic Nanoparticles Polymeric-based Drug Delivery Systems

Natural polymers, including albumin, chitosan, and heparin, have long been used to carry medications as well as oligonucleotides, DNA, and proteins. To treat metastatic breast cancer, paclitaxel nanoparticle formulations have recently been used in clinical settings. According to Gradishar et al. (2005), this formulation uses nanometer-sized albumin-bound paclitaxel or serum albumin as a carrier. Polygl-glutamic acid (PGA) is the first environmentally friendly polymer utilized for the synthesis of conjugate. This was followed by polyethylene glycol (PEG), polystyrene-maleic anhydride copolymer, and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) (Li et al., 2002).

The method used to create a polymeric-based drug distributor determines whether the drug is covalently bucked to the polymer matrix or physically ensnared within it (Rawat et al., 2006). The resultant molecules might be amphiphilic core/shell polymeric micelles, capsule-shaped NPs of polymeric materials polymer-drug conjugates, or hyperbranched

macromolecules. Two types of polymers are employed as drug conjugates: natural polymers and synthetic polymers. According to a study, indomethacin-loaded nanocapsules significantly reduced tumor growth and increased survival in a rat model of xenograft glioma (Andronescu et al., 2017).

Dendrimers

There is a clear hyperbranched structure to the round polymeric macromolecules called dendrimers. A very branching architecture is what makes dendrimers unique. Dendrimers synthesis is often initiated by a reaction between acrylic acid and an ammonia core. This process yields a "tri-amine" GO product when it reacts with ethylenediamine to form a "tri-acid" molecule. According to Wang et al. (2008), this product undergoes another interaction with acrylic acid and generates the hexa-acid, which then generates "hexa amine", ET so off. Dendrimer's size ranges from 1 to 10 nm on average. However, according to Kim et al. (2017), it may be the size of up to 15 nm. The particular arrangement, which includes a set molecular weight, changeable branching, bioavailability, and charge, makes them useful for targeting nucleic acids. According to Lim et al. (2013), some frequently used dendrimers are Polyamidoamine (PAMAM), polyethyleneglycol, polypropylene imine (PPI), and triethanolamine, (TEA). To accomplish MDR management, a PAMAM dendrimer was first created. Many descriptions exist of PAMAM dendrimers assembled by DNA. The synthesized dendrimers considerably slowed the growth of epithelial carcinoma xenograft in mice treated with single-agent chemotherapy.

mAb Nanoparticles

Monoclonal antibodies have a specific targeting characteristic that makes them useful in cancer therapy (Kukowska-Latallo et al., 2005). These days, NPs and these mAbs are combined to form antibody-drug conjugates or ADCs. Compared to cytotoxic drugs or mAb alone, these have been demonstrated to be significantly more compelling and selective. In HER2+ mammary epithelial cell control, for instance, an antibody-drug NP with an outer layer modified by trastuzumab and a paclitaxel core showed better antitumor efficacy and less toxicity than either paclitaxel alone or as a single agent (Sievers et al., 2013).

Drug Delivery Systems based on Lipids

Liposomes

One of the earliest nanoparticle platforms used in medicine was liposomes, which were originally reported in 1965 (Bangham et al., 1993). More than 11 forms are now approved for use in clinical trials, while several others are being developed in preclinical and clinical stages. Liposomes are close colloidal shapes made of spherical lipid two layers with an outer lipid bilayer encircling a central aqueous region (Torchilin et al., 2005). Better kinetics and biodistribution are frequently found in drugs with liposomal compositions. Currently, this lipid-based technology is being applied to many types of cancer medications using a diversity of preparation procedures. Between them, liposomal forms of anthracyclines doxorubicin and daunorubicin were licensed for the treatment of the spread widely breast cancer and the Kaposi's sarcoma associated with AIDS (Markman et al., 2006).

Viral Nanoparticles

A wide range of viruses, including bacteriophages, canine parvovirus, the cowpea mosaic virus, and the cowpea chlorotic mottle virus, have been developed for usage in medical and nano utilization, including drug delivery and the process of tissue targeting. Using pharmacologic or genetic techniques, a wide range of targeted chemicals and peptides can be expressed on the viral surface in a physiologically significant fashion. Consequently, several ligands or antibodies, such as folic acid, transferrin, and single-chain immune globulin have been affixed to viruses to specifically target specific tumors in vivo (Hofheinz et al., 2005).

To optimize specificity, target cells should have higher levels of antigens or receptor surface markers compared to normal cells. To efficiently transport liposomes that to B-cell receptors using anti-CD19 monoclonal antibodies (mAb), for instance, the number of receptors should be around 104 and 105 copies per cell. It is less effective to target individuals with a lower density (Harris et al., 2001).

Receptor-mediated absorption is commonly needed for nano distributors to transport medicine in the cells and is caused by the way certain ligands react with their respective receptors (Alonso et al., 2004). An even more noteworthy therapeutic outcome was observed, for instance, if immunoliposomes target B-cell lymphoma, which is a kind of blood-related cancer, were tagged with an absorbing anti-CD19 ligand rather than a non-internalizing anti-CD20 ligand (Torchilin et al., 2005). Nevertheless, targeting nanocarriers towards non-internalizing receptors can sometimes be advantageous in solid tumors because of the effect of bystanders, which enables carriers to attach to surrounding cells and deliver medication to kill cells lacking the target receptor (Hobbs et al., 1998).

Inorganic Nanoparticles

Carbon Nanoparticle

Carbon is the building block of carbon NPs. They have found widespread use in health applications because of their mechanical ad optical, and electrical biocompatible characteristics (Swaminathan et al., 2010). Drugs can be encapsulated by carbon NPs via π-π stacking because of their intrinsic hydrophobic character (Ou et al., 2016). One can further classify

carbon NPs (NPs) into graphene, fullerenes, carbon nanohorns, carbon nanotubes, and graphene. Their form, morphology, and characteristics differ, even though they are all carbon-based.

Carbon nanotubes are cylinders that were originally discovered in the late 1980s; they are also referred to as rolls of graphite. There are two types of CNTs: single-walled and multi-walled. They may communicate with immune system cells to generate an immunological reaction, which will halt the tumor's growth because they are carbon-based. They were previously used as the DNA vector transport devices and in heat therapy of ablation. To target colon cancer cells, for example, a fluorescent single-walled CNT containing a mAb enclosing doxorubicin is employed. These CNTs combine to produce a complex that the cancer cells efficiently absorb, releasing doxorubicin intracellular while keeping the CNTs in their cytoplasm (Tabata et al., 1997)(Fig.1).

Quantum Dots

Biological imaging uses quantum dots extensively because they are semiconductors at the nanoscale scale that have a large variety of absorption, limited emission bands, and quality photostability (Heister et al., 2009). The three groups into which they are divided based on carbon are graphite quantum dots or carbon quantum dots, among others. Biological imaging with quantum dots is not the only application being explored by researchers. Cancer treatment is another. Graphene quantum dot quantum dots are the most widely used variety of quantum dots because they are rapidly eliminated from the body and are naturally biocompatible. Jamieson et al. (2007) reported that doxorubicin and quantum dots aptamer combo is effective against prostate cancer cells. However, the biggest obstacle is the absence of an ideal process for producing quantum dots.

Metallic Nanoparticles

Due to metallic NPs' exceptional optical, magnetic, and photothermal properties, they are being extensively investigated for "biological imaging" and focused DDS applications. Among the majority often utilized kinds of metallic NPs are those based on copper, iron, silver, and gold. According to (Bagalkot et al. 2007), NPs of gold (NPs) are utilized as internally extended drug carriers due to their easily controlled surface and size properties.

Magnetic Nanoparticles

When using metallic or metallic oxide-based medication delivery systems or magnetic resonance imaging (MRI), NPs with magnetic properties (NPs) are frequently employed. It is usually bound with the organic ingredients as fatty acids or polymers and increases their biocompatibility and durability (Castaneda et al., 2011). Breast cancer can be detected and visualized with the help of supermagnetic NPs of iron oxide and LHRH (Basoglu et al., 2018).

Nanoparticles of Calcium Phosphate

The substance known as "calcium phosphate NPs" is biodegradable, compatible with biology, and does not have any negative side effects. For this reason, they are employed as a delivery system for growth hormones, insulin, antibiotics, and birth control (Maurya et al., 2019). They are used in the transportation of oligonucleotides and plasmid DNA (Khosravi et al., 2010). Calcium phosphate NPs have been effectively used as delivery vectors for viral or non-viral cellular gene transfer veterinarians. The "liposomal nanolipoplex mixture" and magnesium or glycerol were shown to have reduced poisoning and better transfiguration characteristics (Mozafari et al., 2007).

Silica Nanoparticles

Silica has been studied in biology very recently, despite being a key element found in numerous natural materials. Silica NPs, also known as NPs, are widely used for gene transfer because of their ability to enhance their exterior with amino-silicanes (Katragadda et al., 2021).

Nanoparticle-mediated passive targeting

Improved Retention and Permeability

NPs that meet those prerequisites for size and surface properties in order to avoid being captured by the reticuloendothelial system can circulate in the circulation for extended periods and have a higher probability of reaching the targeted tumor tissues. Macrophages, including NPs, can aggregate in tumor tissues with selectivity due to the distinct path physiologic features of tumor vasculature (Maeda et al., 2001). In order to give oxygen and nutrients to rapidly proliferating cancer cells, existing arteries must be rerouted or recruited (a process known as revascularization) close to the tumor mass (Carmeliet et al., 2000). Tumor arteries become highly disordered and dilated, and numerous apertures show greater gaps in the junction between the endothelial cells and limited lymphatic outflow due to the resulting imbalance in angiogenic regulators, including matrix metalloproteinases and growth factors. These characteristics are referred to as the improved permeability and retention effect, and they are a crucial mechanism that allows macromolecules including NPs with molecular weights greater than 50 kDa to concentrate in the tumor interstitium in a targeted manner.

Microenvironment of Tumor

The distinct environment surrounding tumor cells, which differs from the surroundings of normal cells, also plays a

role in passive targeting. Cancer cells that proliferate quickly have a rapid metabolism, and they typically cannot sustain this pace due to insufficient oxygen and nutrition supplies. As a result, an acidic environment is created when tumor cells employ glycolysis to get additional energy (Pelicano et al., 2006). Certain enzymes that are expressed and released by cancer cells include matrix metalloproteinases, which are involved in the mobility and survival of these cells (Deryugina et al., 2006).

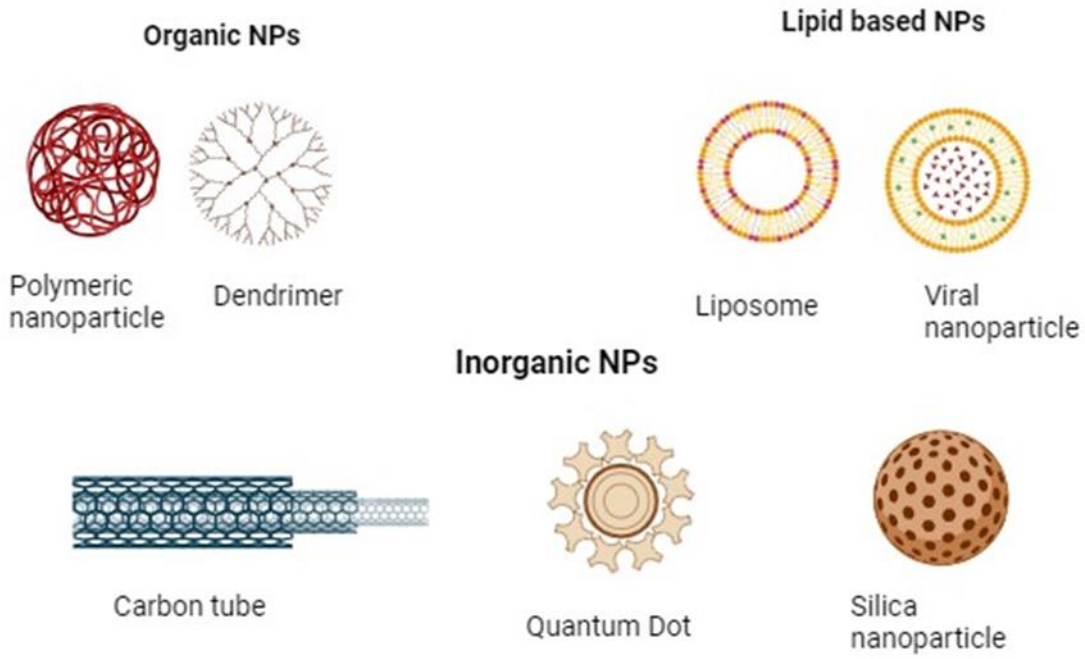

Fig 1: Types of NPs (Retrieved from Biorender).

Active Nanoparticle Targeting

There will inevitably be limitations to the selectivity of a drug administration strategy involving a two-conjugate or polymer medication combination it solely depends on the passive target techniques. One way to get around these restrictions is to add a targeted ligand or antibody to polymer-drug conjugates (Allen et al., 2002). An antibody and a medication were first tried to be directly conjugated. However, these early conjugates of antibodies and drugs have not demonstrated efficiency over a targeted delivery method for cancer treatment in clinical studies that have been carried out so far. This is due, in part, to the restricted quantity of molecules of drugs that may be incorporated into an antibody without compromising its ability to recognize immunological stimuli. Because a wide variety of liposomes and polymers have recently been discovered and introduced for use as drug delivery carriers, compared to previous antibody-drug conjugates, a bigger number of medications may be coupled with particular NPs without altering their targeting affinity. The ternary configuration of an antibody or ligand as the target moiety, an active chemotherapeutic drug as the carrier, and a polymer or lipid as the carrier is used by many recently identified targeted conjugates of drugs to take advantage of the wide range of transporters, targeting molecules, and medications available. Making ternary-structure NPs requires consideration of a few factors in order to produce more efficient delivery systems.

Expression of an Antigen or a Receptor

Antigens and receptors on the cell surface should ideally possess a number of characteristics that make them especially well-suited as targets unique to tumors. First, only tumor cells should exhibit them; normal cells should not express them. Secondly, on all targeted tumor cells, they need to express uniformly. Finally, antigens and receptors on the cell surface shouldn't leak into the bloodstream (Allen et al., 2002).

Targeted Conjugates Internalization

The ability of the intended conjugates to be internalized after adhering to the target cells is a crucial consideration when selecting the appropriate targeting ligand. Usually, internalization happens through endocytosis mediated by receptors. Using the foliate receptor as an example, an endosome is formed when the combination of the ligand and the receptor is encased in the invading plasma membrane after a foliate-targeted compound binds to the acid region on the cell surface. Target organelles get newly produced endosomes. When an endosome's pH level drops and enzymes are triggered, the drug exits the conjugation process. It reaches the cytoplasm if it possesses the necessary physical and chemical properties to cross the endosomal membrane. Depending on the substance, the target organelle will then trade the released medicines. As this is going on, the conjugate's released foliate receptor goes back to the cell surface and binds to fresh conjugates that target foliate to initiate a new round of transport (Leamon et al., 2004).

REFERENCES

Allen, T. M. (2002). Ligand-targeted therapeutics in anticancer therapy. *Nature Reviews Cancer*, *2*(10), 750-763.

Alonso, M. J. (2004). Nanomedicines for overcoming biological barriers. *Biomedicine and Pharmacotherapy*, *58*(3), 168-172.

American Cancer Society. (2007). *Breast cancer facts and figures*. American Cancer Society.

Andronescu, E., and Grumezescu, A. M. (2017). *Nanostructures for drug delivery*. Elsevier.

Bagalkot, V., Zhang, L., Levy-Nissenbaum, E., Jon, S., Kantoff, P. W., Langer, R., and Farokhzad, O. C. (2007). Quantum dot–aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence resonance energy transfer. *Nano Letters*, *7*(10), 3065-3070.

Bangham, A. D. (1993). Liposomes: the Babraham connection. *Chemistry and Physics of Lipids*, *64*(1-3), 275-285.

Basoglu, H., Goncu, B., and Akbas, F. (2018). Magnetic nanoparticle-mediated gene therapy to induce Fas apoptosis pathway in breast cancer. *Cancer Gene Therapy*, *25*(5), 141-147.

Boisseau, P., and Loubaton, B. (2011). Nanomedicine, nanotechnology in medicine. *Comptes Rendus Physique*, *12*(7), 620-636.

Carmeliet, P., and Jain, R. K. (2000). Angiogenesis in cancer and other diseases. *Nature*, *407*(6801), 249-257.

Castaneda, R. T., Khurana, A., Khan, R., and Daldrup-Link, H. E. (2011). Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. *JoVE (Journal of Visualized Experiments)*, (57), e3482.

Deryugina, E. I., and Quigley, J. P. (2006). Matrix metalloproteinases and tumor metastasis. *Cancer and Metastasis Reviews*, *25*, 9-34.

Gavas, S., Quazi, S., and Karpiński, T. M. (2021). NPs for cancer therapy: current progress and challenges. *Nanoscale Research Letters*, *16*(1), 173.

Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., and O'Shaughnessy, J. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *Journal of Clinical Oncology*, *23*(31), 7794-7803.

Harris, J. M., Martin, N. E., and Modi, M. (2001). Pegylation: a novel process for modifying pharmacokinetics. *Clinical Pharmacokinetics*, *40*, 539-551.

Harris, J. M., Martin, N. E., and Modi, M. (2001). Pegylation: a novel process for modifying pharmacokinetics. *Clinical Pharmacokinetics*, *40*, 539-551.

Heister, E., Neves, V., Tîlmaciu, C., Lipert, K., Beltrán, V. S., Coley, H. M., and McFadden, J. (2009). Triple functionalisation of single-walled carbon nanotubes with doxorubicin, a monoclonal antibody, and a fluorescent marker for targeted cancer therapy. *Carbon*, *47*(9), 2152-2160.

Hobbs, S. K., Monsky, W. L., Yuan, F., Roberts, W. G., Griffith, L., Torchilin, V. P., and Jain, R. K. (1998). Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. *Proceedings of the National Academy of Sciences*, *95*(8), 4607-4612.

Hofheinz, R. D., Gnad-Vogt, S. U., Beyer, U., and Hochhaus, A. (2005). Liposomal encapsulated anti-cancer drugs. *Anti-cancer Drugs*, *16*(7), 691-707.

Jamieson, T., Bakhshi, R., Petrova, D., Pocock, R., Imani, M., and Seifalian, A. M. (2007). Biological applications of quantum dots. *Biomaterials*, *28*(31), 4717-4732.

Katragadda C, Choudhury P, Murthy P (2021) NPs as non-viral gene delivery vectors. [online] Ijper.org. http://www.ijper.org/article/259. Accessed 30 July 2021

KHOSRAVI, D. K., Mozafari, M. R., Rashidi, L., and Mohammadi, M. (2010). Calcium based non-viral gene delivery: an overview of methodology and applications.

Kim, K. Y. (2017). Nanotechnology platforms and physiological challenges for cancer therapeutics. *Nanomedicine in Cancer*, 1-19.

Kukowska-Latallo, J. F., Candido, K. A., Cao, Z., Nigavekar, S. S., Majoros, I. J., Thomas, T. P., and Baker Jr, J. R. (2005). Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. *Cancer Research*, *65*(12), 5317-5324.

Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., and Muller, R. N. (2008). Magnetic iron oxide NPs: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical Reviews*, *108*(6), 2064-2110.

Leamon, C. P., and Reddy, J. A. (2004). Folate-targeted chemotherapy. *Advanced Drug Delivery Reviews*, *56*(8), 1127-1141.

Li, C. (2002). Poly (L-glutamic acid)–anticancer drug conjugates. *Advanced Drug Delivery Reviews*, *54*(5), 695-713.

Lim, J., Kostiainen, M., Maly, J., Da Costa, V. C., Annunziata, O., Pavan, G. M., and Simanek, E. E. (2013). Synthesis of large dendrimers with the dimensions of small viruses. *Journal of the American Chemical Society*, *135*(12), 4660-4663.

Maeda, H. (2001). The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. *Advan Enzyme Regul*, *41*, 1898-207.

Markman, M. (2006). Pegylated liposomal doxorubicin in the treatment of cancers of the breast and ovary. *Expert Opinion on Pharmacotherapy*, *7*(11), 1469-1474.

Maurya, A., Singh, A. K., Mishra, G., Kumari, K., Rai, A., Sharma, B., and Awasthi, R. (2019). Strategic use of nanotechnology in drug targeting and its consequences on human health: A focused review. *Interventional Medicine and Applied*

Science, *11*(1), 38-54.

Moghimi, S. M., and Szebeni, J. (2003). Stealth liposomes and long circulating NPs: critical issues in pharmacokinetics, opsonization and protein-binding properties. *Progress in Lipid Research*, *42*(6), 463-478.

Moghimi, S. M., Hunter, A. C., and Murray, J. C. (2001). Long-circulating and target-specific NPs: theory to practice. *Pharmacological Reviews*, *53*(2), 283-318.

Mozafari, M. R., Reed, C. J., and Rostron, C. (2007). Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *62*(3), 205-209.

Ou, L., Song, B., Liang, H., Liu, J., Feng, X., Deng, B., and Shao, L. (2016). Toxicity of graphene-family NPs: a general review of the origins and mechanisms. *Particle and Fibre Toxicology*, *13*, 1-24.

Palazzolo, S., Bayda, S., Hadla, M., Caligiuri, I., Corona, G., Toffoli, G., and Rizzolio, F. (2018). The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric NPs, micelles, liposomes and exosomes. *Current Medicinal Chemistry*, *25*(34), 4224-4268.

Pelicano, H., Martin, D. S., Xu, R. A., and Huang, P. (2006). Glycolysis inhibition for anticancer treatment. *Oncogene*, *25*(34), 4633-4646.

Rawat, M., Singh, D., Saraf, S. A. S. S., and Saraf, S. (2006). Nanocarriers: promising vehicle for bioactive drugs. *Biological and Pharmaceutical Bulletin*, *29*(9), 1790-1798.

Roco, M. C., Williams, R. S., and Alivisatos, P. (Eds.). (2000). *Nanotechnology research directions: IWGN workshop report: vision for nanotechnology in the next decade*. Springer Science and Business Media.

Ross, J. S., Schenkein, D. P., Pietrusko, R., Rolfe, M., Linette, G. P., Stec, J., and Hortobagyi, G. N. (2004). Targeted therapies for cancer 2004. *American Journal of Clinical Pathology*, *122*(4), 598-609.

Shin, W. K., Cho, J., Kannan, A. G., Lee, Y. S., and Kim, D. W. (2016). Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO2 NPs for lithium-ion polymer batteries. *Scientific Reports*, *6*(1), 26332.

Sievers, E. L., and Senter, P. D. (2013). Antibody-drug conjugates in cancer therapy. *Annual Review of Medicine*, *64*, 15-29.

Stewart, B. W., and Kleihues, P. (Eds.). (2003). *World cancer report* (Vol. 57). Lyon: IARC press.

Swaminathan, S., Pastero, L., Serpe, L., Trotta, F., Vavia, P., Aquilano, D., and Cavalli, R. (2010). Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. *European Journal of Pharmaceutics and Biopharmaceutics*, *74*(2), 193-201.

Tabata, Y., Murakami, Y., and Ikada, Y. (1997). Photodynamic effect of polyethylene glycol–modified fullerene on tumor. *Japanese Journal of Cancer Research*, *88*(11), 1108-1116.

Tiwari, J. N., Tiwari, R. N., and Kim, K. S. (2012). Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. *Progress in Materials Science*, *57*(4), 724-803.

Torchilin, V. P. (2005). Recent advances with liposomes as pharmaceutical carriers. *Nature reviews Drug Discovery*, *4*(2), 145-160.

Wang, X., Yang, L., Chen, Z., and Shin, D. M. (2008). Application of nanotechnology in cancer therapy and imaging. *CA: a Cancer Journal for Clinicians*, *58*(2), 97-110.

Wisse, E., Braet, F., Luo, D., De Zanger, R., Jans, D., Crabbe, E., and Vermoesen, A. N. (1996). Structure and function of sinusoidal lining cells in the liver. *Toxicologic Pathology*, *24*(1), 100-111.

Wu, J., Liu, Q., and Lee, R. J. (2006). A folate receptor-targeted liposomal formulation for paclitaxel. *International Journal of Pharmaceutics*, *316*(1-2), 148-153.

Yih, T. C., and Al-Fandi, M. (2006). Engineered NPs as precise drug delivery systems. *Journal of Cellular Biochemistry*, *97*(6), 1184-1190.