WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 18, 1183-1205. Review Article ISSN 2277–7105

NANOREVOLUTION: TRANSFORMING CANCER THERAPY THROUGH NANOTECHNOLOGY

Pavankumar P. Wankhade[1]* Harshwardhan Prakash Mane[2], Rushikesh Balasaheb Patil[2], Anand Anil Jadhav[2] and Vedantika Ramesh Salunkhe[2]

[1]Assistant Professor, Department of Pharmacology, Dr D.Y. Patil College of Pharmacy, Akurdi, Pune, 411044 [M.S] India.

[2]Students, Final Year Bachelor of Pharmacy, Dr D.Y. Patil College of Pharmacy, Akurdi, Pune, 411044 [M.S] India.

Article Received on
02 August 2024,

Revised on 22 August 2024,
Accepted on 12 Sept. 2024

DOI: 10.20959/wjpr202418-33938

***Corresponding Author**
Pavankumar P. Wankhade
Assistant Professor, Department of Pharmacology, Dr D.Y. Patil College of Pharmacy, Akurdi, Pune, 411044 [M.S] India.

ABSTRACT

Nanotechnology has emerged as a promising avenue in cancer treatment, offering novel approaches to overcome the limitations of conventional therapies. This abstract provides an overview of recent advancements and future perspectives in the application of nanotechnology for cancer treatment. Nanoparticles, with their unique physicochemical properties, can be tailored to target tumors specifically, enhancing drug delivery while minimizing systemic toxicity. Moreover, nanotechnology enables the development of multifunctional platforms capable of simultaneous imaging, targeting, and therapy—paving the way for personalized medicine approaches. By incorporating targeting ligands, such as antibodies or peptides, nanoparticles can selectively home to cancer cells, enhancing therapeutic outcomes. Furthermore, nanotechnology plays a crucial role in overcoming drug resistance mechanisms through the delivery of combination therapies and targeted inhibition of specific pathways. Additionally, nanomaterial's can enhance the efficacy of radiation therapy and photodynamic therapy by augmenting the delivery of therapeutic agents and sensitizing tumor cells to treatment. The integration of theranostic platforms, combining therapy and diagnostics, holds promise for real-time monitoring of treatment response and individualized therapy adjustment. Furthermore, advancements in nanotechnology have facilitated the development of novel immunotherapeutic approaches, such as cancer vaccines and immune checkpoint

inhibitors, for more effective cancer treatment.

KEYWORDS: Cancer, Nanotechnology, Gene Therapy, Immunotherapy, Active and Passive Targeting, Drug Delivery.

1) INTRODUCTION

Cancer is a complex and diverse illness, responsible for over 9.5 million deaths annually, making it a leading cause of global morbidity and mortality, especially as populations age.[1] Consequently, research into new cancer treatments is urgently needed. Traditional treatments, such as radiation, chemotherapy, and surgery, often have significant side effects and limited efficacy.[2,3] However, advances in oncology are introducing more effective therapies, including immunotherapy, gene therapy, photothermal therapy (PTT), photodynamic therapy (PDT), chemotherapeutic dynamic therapies (CDT), sonodynamic therapy (SDT), and nanomaterial-based chemotherapy.[4,9] Among these, nanomaterial-based chemotherapy is particularly promising due to its high absorption, specificity, and low toxicity.[10]

Medical nanotechnology represents a frontier in cancer treatment. Nanomaterials, typically ranging from 1 to 100 nm in size, offer high biocompatibility, a large surface area-to-volume ratio, and unique fluorescent properties.[11,12] These attributes improve drug specificity and enhance the efficacy of targeted therapies while reducing toxicity.[10] Nanoparticles are more biodegradable than microparticles, making them a superior option for cancer treatment.[13] Tumor-induced angiogenesis creates immature vasculatures that restrict lymphatic outflow, allowing nanoparticles to penetrate tumors more effectively—a phenomenon known as the "enhanced permeability and retention effect" (EPR).[14,15]

The term "Nano" originates from the Greek word for dwarf, νὶνος. A nanometer is one billionth of a meter, about 1/80,000 the diameter of a human hair. In his 1959 lecture, "There's Plenty of Room at the Bottom," physicist and Nobel laureate Richard Feynman laid the groundwork for modern nanotechnology.[16] Nanotechnology encompasses the study and application of structures ranging from one to 100 nanometers, combining mechanical, electrical, chemical, material science, microelectronics, and biological screening. Over 300 products claiming to use nanotechnology are currently available.[17]

Dendrimers represent a novel class of nanometric-sized, controlled-structure polymers. They are fundamental components for synthesizing inorganic and organic nanostructures with

dimensions from 1 to 100 nm. Dendrimers can interact with metallic nanocrystals, nanotubes, and organic structures like DNA, or encapsulate various substances.[18]

1.1) How nanotechnology is better than convectional technique in cancer treatment

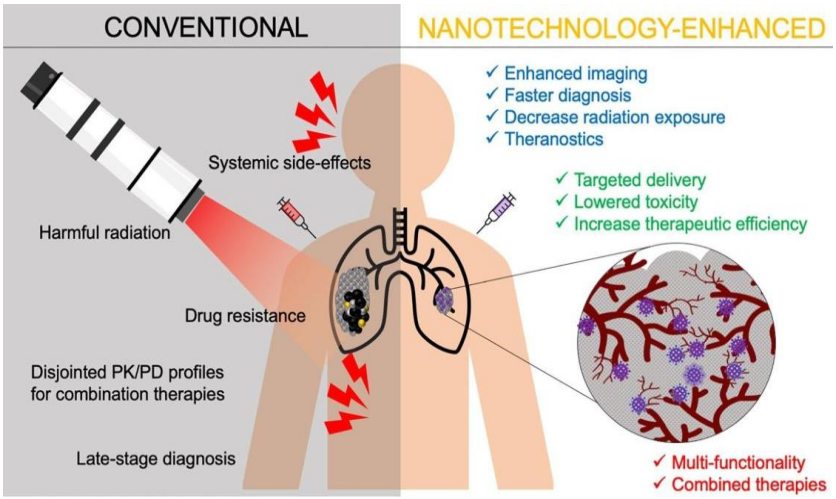


Fig. 1.

Nanotechnology offers several advantages over conventional techniques in cancer treatment, primarily due to its ability to target tumors more precisely while minimizing damage to healthy t tissues. Here's how nanotechnology can be superior to conventional methods.

1. Targeted Drug Delivery: Nanoparticles can be engineered to specifically target cancer cells, thereby reducing the systemic toxicity associated with conventional chemotherapy. These nanoparticles can carry drugs directly to the tumor site, increasing drug concentration in the cancerous tissue while sparing healthy cells.

2. Enhanced Penetration: Nanoparticles are small enough to penetrate deep into tumors, reaching areas that may be inaccessible to larger drug molecules. This improved penetration can enhance the effectiveness of chemotherapy and other treatments.

3. Multi-Functionality: Nanoparticles can be designed to have multiple functions, such as targeting, imaging, and drug delivery, in a single platform. This multi-functionality can lead to more comprehensive and personalized treatment strategies.

4. Reduced Side Effects: By targeting only cancer cells, nanotechnology can minimize damage to healthy tissues, reducing the side effects commonly associated with conventional chemotherapy, such as hair loss, nausea, and fatigue.

5. Improved Imaging: Nanoparticles can be engineered to act as contrast agents for imaging techniques such as MRI, CT scans, and PET scans. This allows for better visualization of tumors, aiding in diagnosis and treatment monitoring.

6. Theranostics: Nanotechnology enables the development of theranostic platforms, which combine therapy and diagnostics in a single system. This approach allows for real-time monitoring of treatment response and adjustment of therapy as needed.

7. Overcoming Drug Resistance: Nanoparticles can help overcome drug resistance mechanisms commonly encountered in cancer treatment by delivering multiple drugs simultaneously or by targeting specific pathways involved in drug resistance.

8. Local Therapy Enhancement: Nanotechnology can enhance the efficacy of local therapies such as radiation therapy and photodynamic therapy by improving the delivery of therapeutic agents to the tumor site.

2) Principles of nanotechnology

The application of nanotechnology to enhance therapies is no longer unique; in fact, as the advantages become more obvious, research on the subject has been steadily increasing.[19,20] The majority of currently licenced cancer nanomedicines are liposomal formulations and drug conjugates (protein, polymer, and/or antibody) that aim to leverage passive targeting and enhance the pharmacokinetics and pharmacodynamics (PK/PD) of the free medication. Nanomaterials for therapeutic and diagnostic applications, including imaging modalities are currently the subject of several clinical studies.[21,22] The increased permeation and retention (EPR) effect, which allows NPs to accumulate preferentially within the tumour vasculature, is the basis for passive targeting of tumours.[23] Leaky blood arteries that allow nanoparticles to enter and concentrate in the tumour tissue are a common feature of tumours.[24]

Nevertheless, passive targeting does not completely prevent drug action in healthy tissues or the negative effects that come with systemic distribution, thus the EPR effect is not a panacea.[25] Even in the absence of a disease, NPs must overcome physiological barriers to reach their target, which can be particularly difficult for cancer patients to overcome.[26] Stability and distribution capability can be compromised by protein and lipid adsorption, blood flow rate, coronas, and phagocytic cells.[27,30] Access to a tumour may also be restricted by extracellular matrix and interstitial pressure.[31,32] Variations in cancer types

can exacerbate these problems, necessitating formulation optimisation specific to each type.[33] Major cancer therapies' pharmacokinetic (PK) characteristics, solubility, bioavailability, and stability have all been significantly enhanced by first-generation nanomedicines.[34]

Nanomaterials can expand into new territories and incorporate highly specialised design and function as a result of the increasing accessibility of technology and information. This makes it possible for combination therapies, targeted delivery, triggered drug release, gene therapy, innovative immunotherapy techniques, radiation, and multimodal therapies to be included in the future generation of nanomedicine. Additionally, as scientific understanding clarifies the principles of cancer initiation and survival, nanotechnology will be a vital tool for enhancing bioimaging and diagnostics to prevent metastasis.

2.1) Tumor-specific target modification of smart nanoparticles categorized by aptamers

"Tumor-specific target modification of smart nanoparticles categorized by aptamers" refers to the use of aptamers, which are single-stranded DNA or RNA molecules selected for their high affinity and specificity to target molecules, to guide nanoparticles specifically to tumor sites. Smart nanoparticles are engineered to carry therapeutic agents or imaging agents and possess characteristics that allow them to respond to stimuli or target specific cells or tissues. By coupling aptamers to these nanoparticles, researchers can enhance their ability to specifically target tumors while minimizing off-target effects.

This approach offers several advantages, including precise tumor targeting, reduced systemic toxicity, and improved therapeutic efficacy. The review article would delve into the principles of aptamer selection, the design and engineering of smart nanoparticles, applications in cancer therapy such as drug delivery and imaging, synergistic approaches with other targeting moieties or therapeutic agents, and the current status of preclinical and clinical studies. Additionally, challenges and future directions in this field would be discussed, providing insights into the potential impact of aptamer-guided smart nanoparticles on cancer treatment.

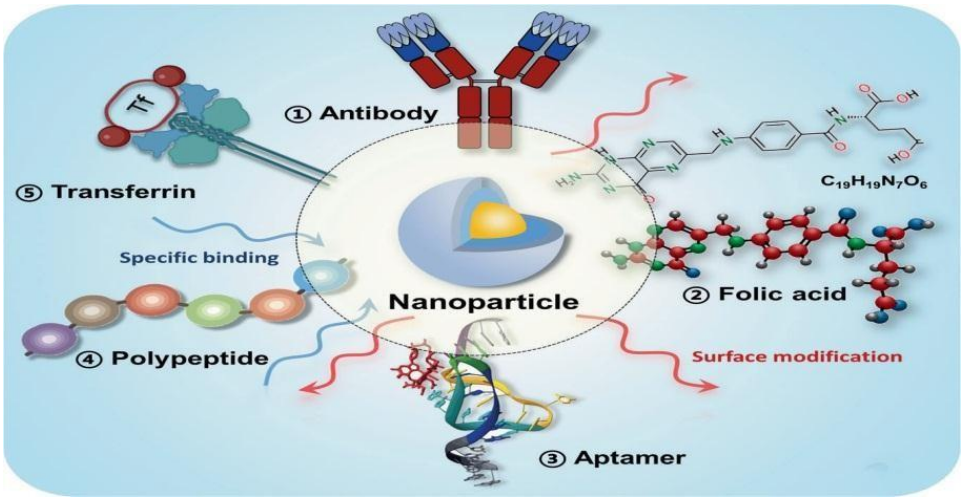


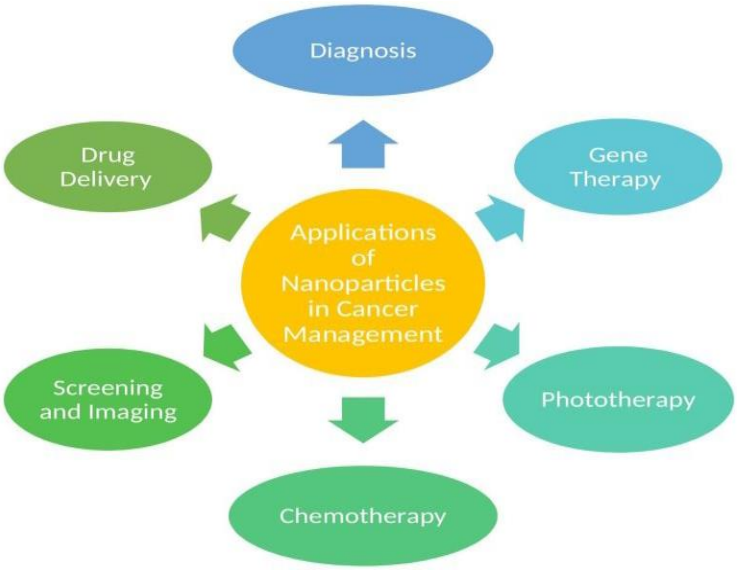
Fig. 2: Tumor-specific target modification of smart nanoparticles categorized by aptamer, antibody, peptide, folic acid and transferrin.

2.2) Tumor-specific target modification of smart nanoparticles categorized by antibodies

"Tumor-specific target modification of smart nanoparticles categorized by antibodies" involves the modification of nanoparticles with antibodies for precise targeting of tumor cells. Antibodies are proteins produced by the immune system that can specifically bind to antigens present on the surface of tumor cells. By conjugating antibodies to nanoparticles, researchers aim to enhance their specificity for tumor cells while minimizing off-target effects.

This approach offers several advantages, including targeted delivery of therapeutic agents or imaging agents to tumor sites, improved efficacy of cancer treatment, and reduced systemic toxicity. The review article would likely cover the principles of antibody selection, nanoparticle design and engineering, applications in cancer therapy such as drug delivery and imaging, and the current status of preclinical and clinical studies. Additionally, challenges and future directions in this field would be discussed, providing insights into the potential impact of antibody-guided smart nanoparticles on cancer treatment.

3) Applications of nanotechnology



3.1) Nanotechnology-based Chemotherapy

Chemotherapy combined with nanotechnology is an effective technique to target malignant cells and solve various medication delivery-related issues. Target-based medication delivery is crucial for the successful outcomes of chemotherapy, but the drug's ability to treat the cancer must also be required. Furthermore, nanotechnology is essential to both processes. Some of the combinational studies of nanotechnologies with chemotherapies are listed below:

For cases of advanced melanoma skin cancer, chemotherapy has been employed with medications such dacarbazine, temozolo-mide, nitrosoureas, vinca alkaloids, taxanes, and cisplatin. 5-FU is a medication that is currently being used extensively to treat cancers, including basal cell carcinomas and actinic keratosis. Nevertheless, 5-FU's strong hydrophilicity restricts its capacity to penetrate tumour tissues via skin cancer.[35,37] Dacarbazine is an FDA-approved single-agent anticancer medication with a short half-life and low solubility. It is the recommended drug for use in chemotherapy for melanoma skin cancer.[38,39] Lipid nanoparticles containing this medication have been developed for topical administration in the treatment of melanoma skin cancer.[40] Liu et al. (2017) cleverly created a nanocarrier based on hol-low mesoporous silica nanoparticles encased with folic acid-grafted liposomes, leading to the development of more sophisticated nanoparticles. Using a chitosan-β-glycerophosphate gel, carboplatin, a second-generation platinum drug also suggested by the FDA for the treatment of melanoma, was loaded into poly (ε-caprolactone) NPs for intratumoral administration.[41]

Additionally, Su et al.,[42] (2017), who created paclitaxel-loaded copolymer NPs, assessed an anticancer effect in vitro and in a xenograft tumour model in vivo. Doxorubicin, an anticancer, was encapsulated in polymeric nanoparticles (NPs) and produced a pH-responsive amphiphilic polymer through self-assembly triggered by polyphosphazenes. Temozolomide, which was initially explored for the treatment of mesenchymal stem cells, was delivered using solid lipid nanoparticles.[43] A temozolomide-loaded polyamide-amine dendrimer in a PAMAM delivery system was investigated for in vitro targeting of human melanoma cells in studies by Jiang et al.,[44] (2017**).**

3.2) Nanotechnology-based cancer diagnosis

One of the most important phases in any diagnosing process is screening. The negative effects of the disease can be reduced with an early screening that is successful. A group of illnesses known as cancer are caused by aberrant cell proliferation, which eventually results in the formation of tumours. Secondary malignant growths form at a location distinct from the initial site of cancer origin throughout the metastatic process. This turns into one of the primary causes of delayed disease identification, and as a result, cancer either becomes incurable at a later stage or has a worse success rate when it comes to treatment.[45] Thus, a key factor in providing effective treatment and reducing the cancer death rate is screening and early diagnosis. The traditional approach to diagnosing cancer makes use of a variety of scanning techniques, which typically yield significant results once the tumor's significant growth level and the effects of metastasis have been examined.[46] Early cancer identification should therefore be given top attention. And we can make use of the special quality of nanoparticles for this purpose. Because of their small size, they are able to infiltrate cells and evaluate a variety of molecular and genetic functioning mechanisms, which will aid in the early detection of any functional problems and be achievable in both in vitro and in vivo settings.[47]

Nanoparticles are used to alter several imaging modalities for cancer detection. These particles can offer information at the molecular and subcellular levels, making them useful for following a variety of biological pathways. These cellular pathways' departure from their typical mechanism may aid in the identification of a number of early signs of cancer development as well as other disorders. Nanotechnology is used to manipulate well-established imaging techniques such as photoacoustic imaging, computed

tomography (CT) scans, and other biomarkers that may be further useful for cancer diagnosis. The CT scan is utilised to diagnose cancer in its early stages and aids in achieving sensitive results. The accuracy of these approaches is particularly noteworthy.[48] While small iodinated molecules, which are used as CT scan contrast agents, are good at absorbing X-rays, their micro-vascular and targeting capabilities have been somewhat hampered by their non-specific distribution and quick pharmacokinetics. As a result, non-invasive treatments are given greater weight in diagnosis and therapy because there is a lower risk of injury to normal bodily functions when using them.[49] In addition to having characteristics for optical imaging and the penetrability of ultrasonic imaging, the various photo imaging techniques are used because they are largely non-invasive and produce high contrast images for cancer diagnosis. According to Zhang et al. (2018), there is a significant anticancer use of gold nanoparticles with three functional components: folate, DNA to load doxorubicin (DOX), and gold nanoparticles with photoacoustic action that can be used in drug delivery platforms. These features of the nanoparticle are made possible by the use of gold nanoparticles, which are further detected by real-time photoacoustic flow cytometry, to improve photoacoustic imaging and identify the varied expression levels of distinct cancer cells. Along with threshold sensitivity, an assessment of these circulating cells labelled with gold nanoparticles is carried out.[50,51]

3.3) Nano-technology based drug delivery

Cancer drug delivery can be enhanced by nanotechnologies, primarily using nanoparticles. Nanoparticle-based delivery allows control over drug cytotoxicity through the nanoparticle's biodistribution profile rather than the drug's free form.[52,53] This system extends the half-lives of proteins and sensitive drugs and improves the solubility of hydrophobic medications, benefiting drug-based therapies.[54] Various scientific and technological factors indicate that drug delivery via nanoparticles is more efficient. Hydrogel nanoparticle-based drugs use exclusive hydrophobic polysaccharides for encapsulating proteins and/or antibodies. Nanogels are nanoparticulate hydrogels that can encapsulate magnetic material to form particles (~25 nm in diameter) with ligands attached in varying quantities.

Magnetic nanogels, with an iron oxide core (~10 nm diameter) coated with a polymer, can carry up to 1000 anticancer drug molecules and can be tracked via MRI as they accumulate

in tumors.[55,56] Systemic administration of chemotherapeutic drugs causes significant toxicity, which nanotechniques address by encapsulating and targeting chemotherapy specifically to cancer cells in 400 nm nanocells. These nanocells can be further optimized by adjusting charge, hydrophobicity, and solubility. Effective targeting of nanocells requires a bio-specific antibody receptor on the malignant cell membrane, enabling endocytosis for intracellular drug release or breakdown.[57] Various nano-systems can be employed for tumor-targeted drug delivery, with structural and analytical features of specific nanoparticles preprogrammed for extracellular and intracellular administration.

3.4) Nanotechnology-based gene therapy

Nanotechnology leverages DNA's amphipathic properties to unlock new potentials. For instance, single-stranded DNA (ssDNA) can solubilize hydrophobic nanoparticles like carbon nanotubes (cNTs), making them suitable for biological use. Gene therapy introduces specific exogenous genes into tumor cells to create a tumoricidal effect. DNA's shape and self-assembly abilities make it an excellent scaffold for nanoparticle arrangement in biochips and biosensors, and DNA sequences can process information in biochemical assays.[58] Viral vectors have traditionally been used to transfer genes to targeted cells, but they present challenges such as toxicity, immune responses, gene control, targeting issues, and the risk of viral reactivation. Non-viral gene transfer methods are preferred to address these challenges. Common non-viral vectors include liposome-mediated cationic polymers, polymers, dendrimers, cell-penetrating peptides, and gold nanoparticles. The physical properties of nanoparticles, such as size, shape, charge density, and colloidal stability, are crucial in determining their effectiveness as non-viral gene delivery vehicles.[59]

In gene therapy studies[60] (2009), Jere et al. successfully used a biodegradable nano-polymeric carrier loaded with Akt1 small interference-RNA, silencing the Akt1 protein and reducing cancer cell survival, proliferation, malignancy, and metastasis. Similarly, p53 gene therapy nanoparticles led to sustained p53 protein production in target cells, a recognized method in cancer gene therapy. While a single dose only temporarily inhibits cell growth, direct intratumoral injection is typically required for nanoparticles. However, intravascular administration is possible if the particles are modified to avoid reticuloendothelial system trapping. Another approach uses poly (D, L-lactide-co-glycolide) nanoparticles loaded with wild type (wt) p53 DNA, showing delayed intracellular DNA release and persistent antiproliferative effects in a breast cancer cell line. The study suggests that wt-p53 DNA-

loaded nanoparticles could be useful in treating p53 gene-related cancers, including breast cancer.[61,62]

3.5) Nanotechnology-based phototherapy

The process of phototherapy involves converting light energy into heat or chemical energy, which in turn triggers a chemical reaction and produces a variety of therapeutic effects on the body. In order to eradicate cancerous cells, patients are given photoreactive chemicals, then light is delivered to the affected area to start a photoreaction that produces Reactive Oxygen Species (ROS). Numerous combined effects of phototherapy were evaluated, including favourable tumour ablation and less intrusive treatment, making it a more practical method of treating cancer. The two types of phototherapies are thermal stress inducing photothermal therapy and oxidative stress inducing photodynamic therapy.[63]

3.6) Nanomaterials for Cancer Immunotherapy

Nanomaterials have the potential to significantly increase the effectiveness of cancer immunotherapy. Cancer vaccines and TME modulation are the two components of cancer immunotherapy. While TME modification seeks to increase the capacity of cytotoxic T cells to kill cancer cells, cancer vaccines are designed to deliver cancer antigen to DCs and foster a strong effector T-cell response.[64,65] Furthermore, some cells have the ability to absorb nanomaterials laden with targeted ligands.[66] It's interesting to note that a recent study found that a D-enantiomeric supermolecule nanoparticle was created, shown p53-dependent antiproliferative activity, and improved antitumor immunity.[67] Nanomaterials will help deliver tumour antigens, and because of their unique properties, they can also modify the immune response, which will be beneficial for immunotherapy.[68,69] Notably, the PC7A nanoparticles triggered the pathway that stimulates interferon genes, which provides a strong response in anti- tumor immunotherapy.[70]

4) Targeted Delivery of Therapeutic Nanoparticles

4.1) Passive targeting

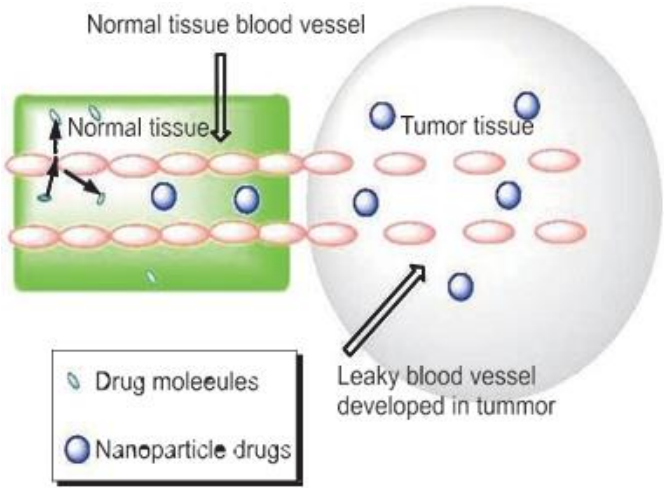


Fig. 5: Schematic diagram of nanoparticle accumulation in tumor tissue through EPR effect. Normal tissue vasculatures are lined by tight endothelial cells, thereby preventing nanoparticle drugs from escaping, whereas tumor tissue vasculatures are leaky and hyperpermeable allowing preferential accumulation of nanoparticles in the tumor interstitial space (passive targeting).

Passive targeting is utilized by clinically proven nanoparticles to ensure targeted delivery of medications to tumors. Nanoparticles exploit their inherent size and the unique characteristics of tumor vasculature.[71,74] Tumors, in need of more oxygen and nutrients, release cytokines and signaling molecules that attract new blood vessels through angiogenesis. Unlike normal tissues, angiogenic blood vessels in tumors have gaps between endothelial cells up to 800 nm wide.[75,76] These gaps, along with impaired vascular architecture and poor lymphatic drainage, allow nanoparticles to selectively accumulate in the tumor interstitium.[77,78] Factors like nanoparticle size, surface properties, circulation half-life, and degree of tumor angiogenesis influence accumulation in tumor tissues.[79] The ideal size range for accumulation is between 10-100 nm. For example, smaller polymeric micelles (20 nm) accumulate in tumors more rapidly than larger liposomes (100 nm).[80,81] Proper surface properties and extended circulation times enhance tumor uptake. Unaltered phospholipid surfaces on liposomes can attract plasma proteins, leading to rapid clearance by the mononuclear phagocytic system (MPS), hindering drug delivery to tumors. This issue is addressed by surface-modified (stealth) liposomes, which have significantly extended blood circulation times.[82,83] Other nanoparticles, such as IT-101[86], Xyotax[85], and Abraxane[84], also exhibit lower clearance rates.

Tumor vascularization impacts nanoparticle accumulation; poorly vascularized, small pre-angiogenic, and large necrotic tumors generally show poor accumulation. Nanoparticles improve pharmacokinetics, pharmacodynamics, efficacy, and reduce toxicity when used as drug delivery systems.[80] For instance, Abraxane (ABI-007), an albumin-bound paclitaxel nanoparticle approved for metastatic breast cancer treatment, showed higher efficacy than free paclitaxel in a phase III trial.[87] The Abraxane group had significantly lower grade 4 neutropenia even at higher doses. Pharmacokinetic studies revealed that Abraxane had a larger volume of distribution and paclitaxel clearance compared to free paclitaxel: Distribution was 663.8 L/m2 for Abraxane vs. 433.4 L/m2 for paclitaxel (p=0.04), and clearance was 13 L/h/m2 for Abraxane vs. 14.76 L/h/m2 for paclitaxel (p=0.048).[84] Similarly, NK105, a micellar nanoparticle form of paclitaxel, demonstrated enhanced pharmacokinetics, pharmacodynamics, efficacy, and reduced toxicity in preclinical studies and a phase I trial compared to free paclitaxel.[88,89]

In an animal model, the area under the curve (AUC) for NK105 in tumors was 25 times higher than for free paclitaxel, and the plasma AUC was 90 times higher.[88] In patients, the plasma AUC for NK105 at 180 mg/m2 was 30 times higher than that of traditional paclitaxel.[89] Due to increased drug accumulation in the tumor, NK105 showed significantly stronger antitumor activity in an HT-29 human colorectal cancer cell line xenograft compared to free paclitaxel.[88] The phase I trial found NK105 to be effective and well-tolerated in pancreatic cancer patients.[90] These differences in pharmacokinetics may explain the enhanced drug accumulation observed with nanoparticles compared to free drugs. Other nanoparticles like Doxil, a PEG-liposome loaded with doxorubicin (DOX)[91], SP1049C, a pluronic micelle loaded with DOX[80], NK911, a PEG-Asp micelle loaded with DOX[92], and Xyotax, a polyglutamic acid nanoparticle carrying paclitaxel[85], also demonstrated improved pharmacokinetics compared to free drugs.

4.2) Active targeting

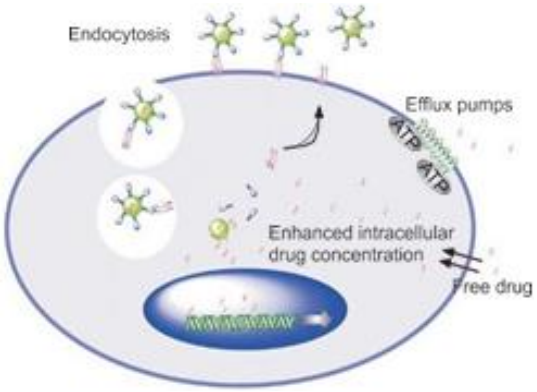


Fig. 6: Internalization of nanoparticles via receptor-mediated endocytosis. Tumor-specific ligands/antibodies on the nanoparticles bind to cell through an endosome-dependent mechanism. Drug- loaded nanoparticles bypass the drug efflux pump not being recognized when the drug enters cells, leading to high intracellular concentration.

To enhance targeted delivery to tumors, nanoparticles listed in Table 1 leverage the EPR effect and tumor microenvironment. However, non-targeted nanoparticles face limitations. For example, inadequate lymphatic drainage can cause drug outflow due to increased osmotic pressure in the interstitium, leading to drug redistribution in some cancer areas, despite helping drugs enrich in the tumor interstitium.[93] Most anticancer drugs require internalization into tumor cells to be effective, so accumulation in the tumor microenvironment alone might not guarantee therapeutic success. A promising approach to address these limitations is to add a targeting moiety to the nanoparticle surface. This moiety is expected to bind to a tumor-associated antigen or receptor, enhancing nanoparticle delivery to the intracellular drug action site and improving therapeutic outcomes. Recent preclinical studies show that targeted nanoparticles offer superior anticancer activity compared to non-targeted ones.[94,97] They achieve higher intracellular drug delivery and significantly improved antitumor efficacy, though they may not always increase tumor drug accumulation compared to non-targeted nanoparticles.[94,96] The primary role of targeting ligands is to boost cellular absorption into cancer cells while minimizing uptake in healthy cells. Despite the promise of tailored nanoparticles in treating tumors, the field is still developing.

Most targeted nanoparticles are not yet in clinical use, resulting in limited clinical data. A few targeted nanoparticles are currently under investigation, including MCC-465, an immunoliposome encapsulating doxorubicin (Dox). This liposome features PEG and the F(ab')2 fragment of the GAH monoclonal antibody, which targets a cell surface protein found

in various cancer cells.[98] Phase I trials show that MCC-465 has different pharmacokinetics compared to free Dox but is similar to human Doxil (non-targeted liposome-encapsulated Dox). Unlike Doxil, MCC-465 did not cause severe skin toxicities such as palmar-plantar erythrodysesthesia (PPE) or mucositis.[98] Other examples of targeted therapeutic nanoparticles include SGT-53, a liposome containing a plasmid for the tumor suppressor p53[100], MBP-426, which encapsulates the cytotoxic platinum-based drug oxaliplatin[99], and CALAA-01, a polymer-siRNA conjugate.[101,102] All these nanoparticles target the transferrin receptor, which is overexpressed in various cancer types.[103]

5) RESULTS AND DISCUSSION

Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs, and have shown a bright future as a new generation of cancer therapeutics. Furthermore, the development of multifunctional nanoparticles may eventually render nanoparticles able to detect and kill cancer cells simultaneously. Although there are certain critical questions and many challenges remaining for the clinical development of nanoparticles, as more clinical data are available, further understanding in nanotechnology will certainly lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy, and safety.

6) CONCLUSION

In conclusion, nanotechnology offers unprecedented opportunities to revolutionize cancer treatment by providing precise, effective, and personalized therapeutic strategies. Continued interdisciplinary collaboration and translational research efforts are essential to harness the full potential of nanotechnology in combating cancer and improving patient outcomes.

Despite significant progress, challenges remain in the clinical translation of nanotechnology-based cancer therapies, including scalability, regulatory hurdles, and long-term safety concerns. However, ongoing research efforts aimed at optimizing nanoparticle design, improving targeting strategies, and addressing biocompatibility issues hold promise for the continued advancement of nanotechnology in cancer treatment.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin., 2021; 71: 209–49. doi:

10.3322/caac.21660

2. Perez-Herrero E, Fernandez-Medarde A. Advanced Targeted Therapies in Cancer: Drug Nanocarriers, the Future of Chemotherapy. Eur J Pharm Biopharm, 2015; 93: 52–79. doi: 10.1016/j.ejpb.2015.03.018
3. Baumann M, Krause M, Hill R. Exploring the Role of Cancer Stem Cells in Radioresistance. Nat Rev Cancer, 2008; 8: 545–54. doi: 10.1038/ nrc2419
4. Zou L, Wang H, He B, Zeng L, Tan T, Cao H, et al. Current Approaches of Photothermal Therapy in Treating Cancer Metastasis With Nanotherapeutics. Theranostics, 2016; 6: 762–72. doi: 10.7150/thno.14988
5. Fan W, Huang P, Chen X. Overcoming the Achilles' Heel of Photodynamic Therapy. Chem Soc Rev, 2016; 45: 6488–519. doi: 10.1039/C6CS00616G
6. Hu Q, Sun W, Wang C, Gu Z. Recent Advances of Cocktail Chemotherapy by Combination Drug Delivery Systems. Adv Drug Delivery Rev., 2016; 98: 19–34. doi: 10.1016/j.addr.2015.10.022
7. Ribas A, Wolchok JD. Cancer Immunotherapy Using Checkpoint Blockade. Science, 2018; 359: 1350–5. doi: 10.1126/science.aar4060
8. Hartshorn CM, Bradbury MS, Lanza GM, Nel AE, Rao J, Wang AZ, et al. Nanotechnology Strategies To Advance Outcomes in Clinical Cancer Care. ACS Nano, 2018; 12: 24–43. doi: 10.1021/acsnano.7b05108
9. Chen Q, Li N, Wang X, Yang Y, Xiang Y, Long X, et al. Mitochondria- Targeting Chemodynamic Therapy Nanodrugs for Cancer Treatment. Front Pharmacol., 2022; 13: 847048. doi: 10.3389/fphar.2022.847048
10. Xu JJ, Zhao WW, Song S, Fan C, Chen HY. Functional Nanoprobes for Ultrasensitive Detection of Biomolecules: An Update. Chem Soc Rev., 2014; 43: 1601–11. doi: 10.1039/C3CS60277J
11. Song Y, Li X, Wang L, Rojanasakul Y, Castranova V, Li H, et al. Nanomaterials in Humans: Identification, Characteristics, and Potential Damage. Toxicol Pathol., 2011; 39: 841–9. doi: 10.1177/0192623311413787\
12. Zhao CY, Cheng R, Yang Z, Tian ZM. Nanotechnology for Cancer Therapy Based on Chemotherapy. Molecules, 2018; 23: 1–29. doi: 10.3390/ molecules23040826
13. Obireddy SR, Lai WF. Preparation and Characterization of 2-Hydroxyethyl Starch Microparticles for Co- Delivery of Multiple Bioactive Agents. Drug Delivery, 2021; 28: 1562–8. doi: 10.1080/10717544.2021.1955043
14. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor Vascular Permeability and the

EPR Effect in Macromolecular Therapeutics: A Review. J Control Release, 2000; 65: 271–84. doi: 10.1016/S0168-3659(99) 00248-5

15. Zhao T, Wu W, Sui L, Huang Q, Nan Y, Liu J, et al. Reactive Oxygen Species- Based Nanomaterials for the Treatment of Myocardial Ischemia Reperfusion Injuries. Bioact Mater, 2022; 7: 47–72. doi: 10.1016/j.bioactmat.2021.06.006
16. AD Maynard; RJ Aitken; T Butz; V Colvin; K Donaldson; G. Oberdörster; MA Philbert; J Ryan; A Seaton; V Stone; SS Tinkle; L Tran, NJ Walker; DB Warheit. Nature, 2006; 444: 267-269.
17. The Nanotechnology Consumer Products Inventory (Woodrow Wilson International Center for Scholars, Washington DC, 2006. Published online at http://www.nanotechproject.org/consumerproducts.
18. DA Tomalia; Aldrichimica Acta., 2004; 37(2): 39-57.
19. J. Shi, P.W. Kantoff, R. Wooster, O.C. Farokhzad, Nat. Rev. Cancer, 2017; 17: 20.
20. A.Wicki, D. Witzigmann, V. Balasubramanian, J. Huwyler, J. Control. Release, 2015; 200: 138.
21. S. Tran, P.-J. DeGiovanni, B. Piel, P. Rai, Clin. Transl. Med., 2017; 6: 1.
22. E. Beltrán-Gracia, A. López-Camacho, I. Higuera-Ciapara, J.B. Velázquez- Fernández, A.A. Vallejo-Cardona, Cancer Nanotechnol., 2019; 10: 11.
23. V. Torchilin, Adv. Drug Del. Rev., 2011; 63: 131.
24. M. Izci, C. Maksoudian, B.B. Manshian, S.J. Soenen, Chem. Rev., 2021; 121: 1746.
25. J. Fang, W. Islam, H. Maeda, Adv. Drug Del. Rev., 2020; 157: 142.
26. H. Kang, S. Rho, W.R. Stiles, S. Hu, Y. Baek, D.W. Hwang, S. Kashiwagi, M.S. Kim, H.S. Choi, Adv. Healthc. Mater., 2020; 9: 1901223.
27. C.D. Walkey, J.B. Olsen, H. Guo, A. Emili, W.C. Chan, J. Am. Chem. Soc., 2012; 134: 2139.
28. G. Fullstone, J. Wood, M. Holcombe, G. Battaglia, Sci. Rep., 2015; 5: 1.
29. Y.Y. Chen, A.M. Syed, P. MacMillan, J.V. Rocheleau, W.C. Chan, Adv. Mater., 2020; 32: 1906274.
30. H.H. Gustafson, D. Holt-Casper, D.W. Grainger, H. Ghandehari, Nano Today, 2015; 10: 487.
31. C.T. Curley, B.P. Mead, K. Negron, N. Kim, W.J. Garrison, G.W. Miller, K.M. Kingsmore, E.A. Thim, J. Song, J.M. Munson, Sci. Adv., 2020; 6: eaay1344.
32. M. Bartneck, H.A. Keul, G. Zwadlo-Klarwasser, J. Groll, Nano Lett., 2010; 10: 59.
33. J.Y. Yhee, S. Jeon, H.Y. Yoon, M.K. Shim, H. Ko, J. Min, J.H. Na, H. Chang.

34. H. Han, J.-H. Kim, M. Suh, H. Lee, J.H. Park, K. Kim, I.C. Kwon, J. Control. Release, 2017; 267: 223.
35. R. van der Meel, E. Sulheim, Y. Shi, F. Kiessling, W.J. Mulder, T. Lammers, Nat. Nanotechnol., 2019; 14: 1007.
36. Li J, Wang Y, Liang R, An X, Wang K, et al. Recent advances in tar- geted nanoparticles drug delivery to melanoma. Nanomedicine: Nanotechnology, Biology and Medicine, 2015; 11: 769-794.
37. Haque T, Rahman KM, Thurston DE, Hadgraft J, Lane ME. Topical therapies for skin cancer and actinic keratosis. European Journal of Pharmaceutical Sciences, 2015; 77: 279-289.
38. Wang MZ, Niu J, Ma HJ, Dad HA, Shao HT, et al. Transdermal siRNA delivery by pH-switchable micelles with targeting effect suppress skin melanoma progression. Journal of Controlled Re- lease, 2020; 322: 95-107.
39. Tarhini AA, Agarwala SS. Cutaneous melanoma: Available ther- apy for metastatic disease. Dermatologic therapy, 2006; 19: 19-25.
40. Liu Q, Xu N, Liu L, Li J, Zhang Y, et al. Dacarbazine-loaded hol- low mesoporous silica nanoparticles grafted with folic acid for enhancing antimetastatic melanoma response. ACS applied ma- terials & interfaces, 2017; 9: 21673-21687.
41. Hafeez A, Kazmi I. Dacarbazine nanoparticle topical delivery sys- tem for the treatment of melanoma. Scientific Reports, 2017; 7: 1.
42. Bragta P, Sidhu RK, Jyoti K, Baldi A, Jain UK, et al. Intratumoral administration of carboplatin bearing poly (ε-caprolactone) nanoparticles amalgamated with in situ gel tendered augment- ed drug delivery, cytotoxicity, and apoptosis in melanoma tu- mor. Colloids and surfaces B: Biointerfaces, 2018; 166: 339-348.
43. Su Y, Hu J, Huang Z, Huang Y, Peng B, et al. Paclitaxel-loaded star- shaped copolymer nanoparticles for enhanced malignant mela- noma chemotherapy against multidrug resistance. Drug design, development and therapy, 2017; 11: 659.
44. Clemente N, Ferrara B, Gigliotti CL, Boggio E, Capucchio MT, et al. Solid lipid nanoparticles carrying temozolomide for melano- ma treatment. Preliminary in vitro and in vivo studies. Interna- tional journal of molecular sciences, 2018; 19: 255.
45. Jiang G, Li R, Tang J, Ma Y, Hou X, et al. Formulation of temo- zolomide-loaded nanoparticles and their targeting potential to melanoma cells. Oncology reports, 2017; 37: 995-1001.
46. Jin JO, Kim G, Hwang J, Han KH, Kwak M, et al. Nucleic acid nano- technology for

cancer treatment. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 2020; 188377.

47. do Nascimento T, Tavares M, Monteiro MS, Santos-Oliveira R, Todeschini AR, et al. Trends in Nanotechnology for in vivo Can- cer Diagnosis: Products and Patents. Current Pharmaceutical Design., 2020; 26: 2167-2181.
48. Stephen BJ, Suchanti S, Mishra R, Singh A. Cancer Nanotechnol- ogy in Medicine: A Promising Approach for Cancer Detection and Diagnosis. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2020; 37: 375-405.
49. Faintuch BL, Faintuch S. Nanotheranostics in oncology and drug development for imaging and therapy. InPrecision Medicine for Investigators, Practitioners and Providers. Academic Press., 2020: 453-458.
50. Caracciolo G, Vali H, Moore A, Mahmoudi M. Challenges in mo- lecular diagnostic research in cancer nanotechnology. Nano To- day, 2019; 27: 6-10.
51. Zhang Y, Xiao J, Sun Y, Wang L, Dong X, et al. Flexible nanohy- brid microelectrode based on carbon fiber wrapped by gold nanoparticles decorated nitrogen doped carbon nanotube ar- rays: In situ electrochemical detection in live cancer cells. Bio- sensors and Bioelectronics, 2018; 100: 453-461.
52. Beik J, Khademi S, Attaran N, Sarkar S, Shakeri-Zadeh A, et al. A nanotechnology-based strategy to increase the efficiency of cancer diagnosis and therapy: Folate-conjugated gold nanopar- ticles. Current Medicinal Chemistry, 2017; 24: 4399-4416.
53. MacDiarmid JA, Mugridge NB, Weiss JC, Phillips L, Burn AL, et al. Bacterially derived 400 nm particles for encapsulation and cancer cell targeting of chemotherapeutics. Cancer cell, 2007; 11: 431-445.
54. Elias DR, Poloukhtine A, Popik V, Tsourkas A. Effect of ligand density, receptor density, and nanoparticle size on cell targeting. Nanomedicine Nanotechnology, Biol Med., 2013; 9: 194-201.
55. Dang Y, Guan J. Nanoparticle-based drug delivery systems for cancer therapy. Smart Mater Med., 2020; 1: 10-19.
56. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev., 2001; 47: 65-81.
57. Zhang Y, Sun C, Kohler N, Zhang M. Self-assembled coatings on individual monodisperse magnetite nanoparticles for efficient intracellular uptake. Biomed Microdevices, 2004; 6: 33-40.
58. Larina IV, Evers BM, Ashitkov TV, Bartels C, Larin KV, et al. En- hancement of drug

delivery in tumors by using interaction of nanoparticles with ultrasound radiation. Technology in cancer research & treatment, 2005; 4: 217-226.

59. Roma-Rodrigues C, Rivas-García L, Baptista PV, Fernandes AR. Gene Therapy in Cancer Treatment: Why Go Nano?. Pharmaceu- tics., 2020; 12: 233.
60. Malekshah OM, Chen X, Nomani A, Sarkar S, Hatefi A. Enzyme/ prodrug systems for cancer gene therapy. Current pharmacol- ogy reports, 2016; 2: 299-308.
61. Jere D, Jiang HL, Kim YK, Arote R, Choi YJ, et al. Chitosan-graft- polyethylenimine for Akt1 siRNA delivery to lung cancer cells. International journal of pharmaceutics, 2009; 378: 194-200.
62. Prabha S, Sharma B, Labhasetwar V. Inhibition of tumor angio- genesis and growth by nanoparticle-mediated p53 gene therapy in mice. Cancer gene therapy, 2012; 19: 530-537.
63. Sukumar UK, Rajendran JC, Gambhir SS, Massoud TF, Paulmuru- gan R. SP94-Targeted Triblock Copolymer Nanoparticle Delivers Thymidine Kinase-p53-Nitroreductase Triple Therapeutic Gene and Restores Anticancer Function against Hepatocellular Car- cinoma in Vivo. ACS Applied Materials & Interfaces, 2020; 12: 11307-11319.
64. Li Y, Li X, Zhou F, Doughty A, Hoover AR, et al. Nanotechnology- based photoimmunological therapies for cancer. Cancer letters, 2019; 442: 429-438.
65. Melero I, Gaudernack G, Gerritsen W, Huber C, Parmiani G, Scholl S, et al. Therapeutic Vaccines for Cancer: An Overview of Clinical Trials. Nat Rev Clin Oncol., 2014; 11: 509–24. doi: 10.1038/nrclinonc.2014.111
66. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 Pathway Blockade for Cancer Therapy: Mechanisms, Response Biomarkers, and Combinations. Sci Transl Med., 2016; 8: 328rv324. doi: 10.1126/scitranslmed.aad7118
67. Sykes EA, Dai Q, Sarsons CD, Chen J, Rocheleau JV, Hwang DM, et al. Tailoring Nanoparticle Designs to Target Cancer Based on Tumor Pathophysiology. Proc Natl Acad Sci U.S.A., 2016; 113: E1142–1151. doi: 10.1073/pnas.1521265113
68. Yan J, Yao Y, Yan S, Gao R, Lu W, He W. Chiral Protein Supraparticles for Tumor Suppression and Synergistic Immunotherapy: An Enabling Strategy for Bioactive Supramolecular Chirality Construction. Nano Lett., 2020; 20: 5844–52. doi: 10.1021/acs.nanolett.0c01757
69. Bolhassani A, Safaiyan S, Rafati S. Improvement of Different Vaccine Delivery Systems for Cancer Therapy. Mol Cancer, 2011; 10: 3. doi: 10.1186/1476-4598-10-3
70. Smith MJ, Brown JM, Zamboni WC, Walker NJ. From Immunotoxicity to Nanotherapy:

The Effects of Nanomaterials on the Immune System. Toxicol Sci, 2014; 138: 249–55. doi: 10.1093/toxsci/kfu005

71. Luo M, Wang H, Wang Z, Cai H, Lu Z, Li Y, et al. A STING-Activating Nanovaccine for Cancer Immunotherapy. Nat Nanotechnol, 2017; 12: 648–54. doi: 10.1038/nnano.2017.52
72. Gao X, Cui Y, Levenson RM, Chung LW, Nie S. In vivo cancer targeting and imaging with semiconductor quantum dots. Nat Biotechnol, 2004; 22: 969-76.
73. Jain TK, Morales MA, Sahoo SK, Leslie-Pelecky DL, Labhasetwar V. Iron oxide nanoparticles for sustained delivery of anticancer agents. Mol Pharm., 2005; 2: 194-205.
74. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene, 2006; 25: 4633-46.
75. Deryugina EI, Quigley JP. Matrix metalloproteinases and tumor metastasis. Cancer Metastasis Rev., 2006; 25: 9-34.
76. Edens HA, Levi BP, Jaye DL, Walsh S, Reaves TA, Turner JR, et al. Neutrophil transepithelial migration: evidence for sequential, contact-dependent signaling events and enhanced paracellular permeability independent of transjunctional migration. J Immunol., 2002; 169: 476-86.
77. Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin., 2008; 58: 97-110.
78. Jain RK. Transport of molecules across tumor vasculature. Cancer Metastasis Rev., 1987; 6: 559-93.
79. Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev., 2004; 56: 1649-59.
80. Cuenca AG, Jiang H, Hochwald SN, Delano M, Cance WG, Grobmyer SR. Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer., 2006; 107: 459-66.
81. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science, 2004; 303: 1818-22.
82. Sutton D, Nasongkla N, Blanco E, Gao J. Functionalized micellar systems for cancer targeted drug delivery. Pharm Res., 2007; 24: 1029-46.
83. Weissig V, Whiteman KR, Torchilin VP. Accumulation of protein-loaded long-circulating micelles and liposomes in subcutaneous Lewis lung carcinoma in mice. Pharm Res., 1998; 15: 1552-6.
84. Papahadjopoulos D, Gabizon A. Liposomes designed to avoid the reticuloendothelial system. Prog Clin Biol Res., 1990; 343: 85-93.

85. Wagner V, Dullaart A, Bock AK, Zweck A. The emerging nanomedicine landscape. Nat Biotechnol., 2006; 24: 1211-7.
86. Sparreboom A, Scripture CD, Trieu V, Williams PJ, De T, Yang A, et al. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). Clin Cancer Res., 2005; 11: 4136-43.
87. Boddy AV, Plummer ER, Todd R, Sludden J, Griffin M, Robson L, et al. A phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-weekly and 2-weekly schedules. Clin Cancer Res., 2005; 11: 7834-40.
88. Schluep T, Cheng J, Khin KT, Davis ME. Pharmacokinetics and biodistribution of the camptothecin-polymer conjugate IT-101 in rats and tumor-bearing mice. Cancer Chemother Pharmacol., 2006; 57: 654-62.
89. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil- based paclitaxel in women with breast cancer. J Clin Oncol., 2005; 23: 7794-803.
90. Kato K, Hamaguchi T, Yasui H, Okusaka T, Ueno H, Ikeda M, et al. Phase I study of NK105, a paclitaxel- incorporating micellar nanoparticle in patients with advanced cancer. Proc Am Soc Clin Oncol., 2006; 24: 83S (abstract 2018).
91. Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M, Ueno H, et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. Br J Cancer, 2007; 97: 170-6.
92. Charrois GJ, Allen TM. Drug release rate influences the pharmacokinetics, biodistribution, therapeutic activity, and toxicity of pegylated liposomal doxorubicin formulations in murine breast cancer. Biochim Biophys Acta., 2004; 1663: 167-77.
93. Matsumura Y, Hamaguchi T, Ura T, Muro K, Yamada Y, Shimada Y, et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. Br J Cancer, 2004; 91: 1775-81.
94. Stohrer M, Boucher Y, Stangassinger M, Jain RK. Oncotic pressure in solid tumors is elevated. Cancer Res., 2000; 60: 4251-5.
95. Kirpotin DB, Drummond DC, Shao Y, Shalaby MR, Hong K, Nielsen UB, et al. Antibody targeting of long- circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. Cancer Res., 2006; 66: 6732-40.
96. Bartlett DW, Su H, Hildebrandt IJ, Weber WA, Davis ME. Impact of tumor-specific

targeting on the biodistribution and efficacy of siRNA nanoparticles measured by multimodality in vivo imaging. Proc Natl Acad Sci U S A., 2007; 104: 15549-54.

97. Farokhzad OC, Cheng J, Teply BA, Sherifi I, Jon S, Kantoff PW, et al. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. Proc Natl Acad Sci U S A., 2006; 103: 6315-20.
98. Gu F, Zhang L, Teply BA, Mann N, Wang A, Radovic-Moreno AF, et al. Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. Proc Natl Acad Sci U S A., 2008; 105: 2586-91.
99. Matsumura Y, Gotoh M, Muro K, Yamada Y, Shirao K, Shimada Y, et al. Phase I and pharmacokinetic study of MCC-465, a doxorubicin (DXR) encapsulated in PEG immunoliposome, in patients with metastatic stomach cancer. Ann Oncol., 2004; 15: 517-25.
100. MedBiopharm Co. L. Safety study of MBP-426 (liposomal oxaliplatin suspension for injection) to treat advanced or metastatic solid tumors. ClinivalTrials.gov web site 2008. [online] http;//www.clinicaltrials.gove/ct/show/NCT00355888/
101. SynerGene Therapeutics I. safety study of infusion of SGT-53 tp treat solid tumors. ClinicalTrials.govwebsite2008[online],http://www.clincaltrials.gov/ct2/show/NCT00470613/
102. Calando-Pharmaceuticals. Safety study of CALAA-01 to treat solid tumor cancers. ClinicalTrials.gov web site, 2008. [online], http://www.clincaltrials.gov/ct/show/NCT00689065
103. Gatter KC, Brown G, Trowbridge IS, Woolston RE, Mason DY. Transferrin receptors in human tissues: their distribution and possible clinical relevance. J Clin Pathol., 1983; 36: 539-45.