A Reveiw : Nanocarriers For Precision Drug Targeting Are Revolutionising Cancer Therapy

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Running Title: ***Nanocarriers***

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Source of support: Nil

Conflict of interest: None declared

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Abstract

Nanoparticles are a significant drug delivery method that has been investigated extensively in the context of using nanotechnology to treat cancer. When compared to conventional approaches, the use of nanoparticles in medicine delivery offers a number of advantages, including as improved permeability and retention, accurate targeting, and enhanced stability and biocompatibility. Drug-carrier systems have had previously unheard-of success thanks to hybrid nanoparticles, which combine the benefits of multiple different nanoparticles. Drug resistance associated with cancer may be lessened with the use of nanoparticle-based drug delivery methods. A hypoxic environment, malfunctioning apoptotic pathways, or overexpression of efflux transporters can all lead to treatment-resistant cancer. The purpose of nanoparticle production is to target newly

discovered drug resistance mechanisms in tumors. This study looks at the delivery of medication using nanoparticles in immunotherapy, targeted therapy, and chemotherapy. Investigations are conducted into the targeting mechanism and how it affects drug resistance.

Keywords: *Nanoparticles, Drug Delivery, Chemotherapy, Hypoxia, Apototic, Immunotherapy.*

Introduction

Developing novel and cutting-edge cancer treatments is a significant global concern [1] . The word "cancer" describes a wide range of illnesses marked by invasiveness and abnormally fast cell division. Many efforts have been made in the last few years to pinpoint a range of cancer risk factors. Certain environmental factors, such radiation and pollution, have been closely connected to the genesis of particular cancers. A poor lifestyle, however, which includes stress, eating an unbalanced diet, smoking, drinking alcohol, and not getting enough exercise, has a significant impact on the estimate of cancer risk [2,3]. The therapeutic efficacy of various malignant tumours has grown dramatically as a result of the introduction of personalized medicine and the development of cancer therapy options. Chemotherapy is a well-known and widely utilised cancer treatment technique. Chemotherapy can have gastrointestinal adverse effects, inhibit bone marrow, and cause hair loss. Its principal objective is to indiscriminately destroy actively growing cells, both cancer and normal cells, even though it operates through a number of different paths [4]. Its applications range from tumour targeting to safer and more effective diagnosis and therapy. Research has demonstrated that the utilisation of nanoparticle-based drug delivery systems for the treatment of cancer has several benefits, including improved pharmacokinetics, precise targeting of tumour cells, minimal side effects, and decreased drug resistance [5,6] . One of the most promising areas of nanomedicine research is developing customised medication delivery systems for a range of illnesses, including cancer. Because of their rapid proliferation and resistance to current treatments, cancer cells are the focus of research on lipid-based drug delivery, which employs nanoparticles to encapsulate and transport drugs to specific cells or tissues [7].

The pathophysiology of the tumours is usually taken into consideration when choosing or producing the size and features of nanoparticles that are been used in drug delivery systems. Nanocarriers

mechanically target tumour cells in cancer therapy by acting as carriers for nanoparticles and influencing the positioning of the targeted substance following absorption. Following that, drugs are injected into tumors to kill the cells. The nanocarriers contain nucleic acids and traditional chemotherapeutic chemicals, suggesting that they could be used in both gene therapy and cytotoxic medicines [8] . Cancer therapy employs a wide range of nanoparticles. Nanoparticles can be used to deliver chemotherapy medications directly to cancer cells, increasing their efficacy and decreasing their side effects [9]. Furthermore, nanoparticles can enhance medical imaging techniques by enabling more accurate tumour tracking and localization. All things considered, nanoparticles hold a lot of promise for enhancing oncology and patient outcomes [10]. Consequently, it is key to fully explore features and affects the behaviour of nanoparticles before moving forward with investigations involving humans. Furthermore, the successful translation of nanoparticles into therapeutic applications will need the development of strategies to maximise their stability and reduce organ accumulation [11].

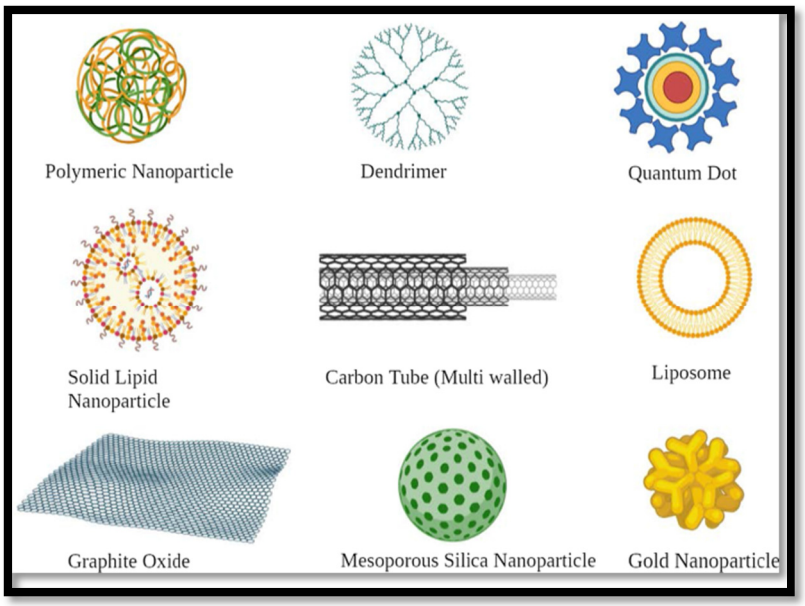

Figure 1. Various types of nanoparticles are used in cancer treatment. [7]

The most prevalent side effects are neuropathy, fatigue, gastrointestinal and skin disorders, bone marrow suppression, and hair loss. Anthracyclines with bleomycin can produce pulmonary toxicity and cardiotoxicity, among other side effects specific to the medication [12]. The use of hybrid nanoparticles has resulted in significant improvements in the field of NP-based medicine delivery systems. Hybrid nanoparticles, which combine the features of several nanoparticle types, increase the efficacy and endurance of any drug delivery system [13]. Furthermore, because NPs provide

platforms for the administration of drug combinations and hinder the activity of certain drug resistance mechanisms, such as cell membrane efflux transporters, they have demonstrated some benefits in terms of anti-tumor multidrug resistance (MDR) [14] .

Nanoparticle-based therapy has the potential to overcome multi-resistant resistance in a variety of cancer types, including breast cancer, ovarian cancer, and prostate cancer [15,16,17]. Nanotechnology in medicine has opened a new era of cancer treatment, and more research should be performed at the intersection of these two areas (Figure 2). This paper describes the potential for future research, highlights current problems, and underlines the underlying ideas of using the nanocarrier system in cancer therapy [14].

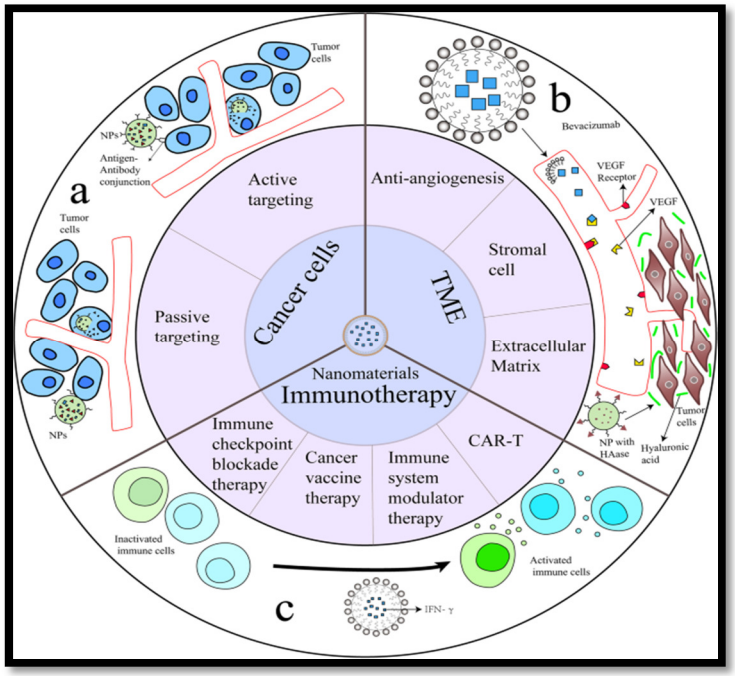

Figure 2. Nanomaterials for Cancer Treatment: Present Developments and Future Prospects.

Nanoparticles Based Drug Delivery System

Drugs given to cancer cells cause minimum harm to healthy tissues, and drug delivery systems based on nanoparticles have showed promise in improving cancer treatments [18]. Researchers are working to develop techniques for combating medication resistance and improving the performance of these systems. Combination therapies use nanoparticle-based technologies to deliver several medications simultaneously, addressing numerous drug resistance pathways and reasons [19]. When medications are delivered to the correct areas and perform as

intended, nanoparticles actively bypass drug-resistant systems found in cancer cells. Nanoparticles can be used to safely distribute medications by decreasing side effects and providing drugs in a controlled manner. Current research efforts are aimed at improving the selectivity of nanoparticle-based systems in order to target cancer cells while protecting healthy organs. This has huge potential to develop more powerful and customised cancer treatments in the future [20]. Moreover, the complex interplay that exists between nanoparticles and cancer cells may cause unanticipated toxicities or side effects that could endanger healthy organs and tissues. Understanding the types of cancer cells can also be responsible for the treatments based on nanoparticles is crucial [21]. Certain characteristics of cancer cells may make them more resistant to nanoparticle therapy. Furthermore, it is necessary to carefully assess the potential of off-target effects and unanticipated outcomes before widely applying nanoparticle-based therapeutics in clinical settings. It is also important to consider how malignant cells are exposed to nanoparticles [22].

Structure of Nanoparticles

The effectiveness of immunotherapy depend upon the dimension, figure, and exterior characteristics of nanoparticles since these factors affect how they interact with immune cells and deliver therapeutic chemicals (Figure 1) [23] . Over time, patient safety and the reduction of adverse effects depend on stability and biocompatibility. Biodegradable polymers such as PLGA and chitosan have the ability to safely and accurately release therapeutic drugs, enabling tailored administration to specific immune cells or malignant locations [24]. Scientists have developed PLGA-based nanoparticles containing anti-cancer drugs that specifically target tumour cells, decreasing side effects and minimising injury to healthy cells. These nanoparticles enable for the regulated, gradual release of medication, which leads to shorter dosing intervals and more persistent therapeutic advantages [25]. Unexpected organs may become accumulated with nanoparticles, leading to toxicity and undesirable consequences. Scaffolds based on chitosan might not break down as predicted, which could lead to insufficient tissue regeneration or protracted foreign body reactions. Researchers are looking on ways to make chitosan-based scaffolds more biocompatible and degradable. Surface alterations, such as the addition of growth hormones or bioactive substances, can improve tissue regeneration and cell adhesion [26] .

Synthesis of Nanoparticles

The NPs differ in size, shape, and form. To do this, a range of synthesis techniques are applied. Top-down and bottom-up techniques are the two main groups into which these strategies

can be separated. These methods can be separated into different subclasses according to how they operate and react (Figure 3).

Bottom up Approach

Bottom up approach technique which is often to referred as the constructive method which involves formation of material from atoms to clusters or nanoparticles from simpler compounds [27].

Top Down Approach

Top down approach referred to as the destructive process because it produces nanoparticles (NPs) with a low bulk content. Nanoparticles form when a bigger molecule disintegrates or breaks down into smaller bits. It covers techniques such as thermal breakdown, chemical etching, mechanical milling, sputtering, laser ablation, electroexplosion, and mechanical milling 28. It is surprising to discover that modifying the synthesis parameters and reaction conditions can alter the morphological properties of nanoparticles (NPs), including size, shape, and charge. Furthermore, the development procedure regulates the chemical properties of the NPs. As a result, knowing the growth process is critical for synthesising the requisite NPs [29] .

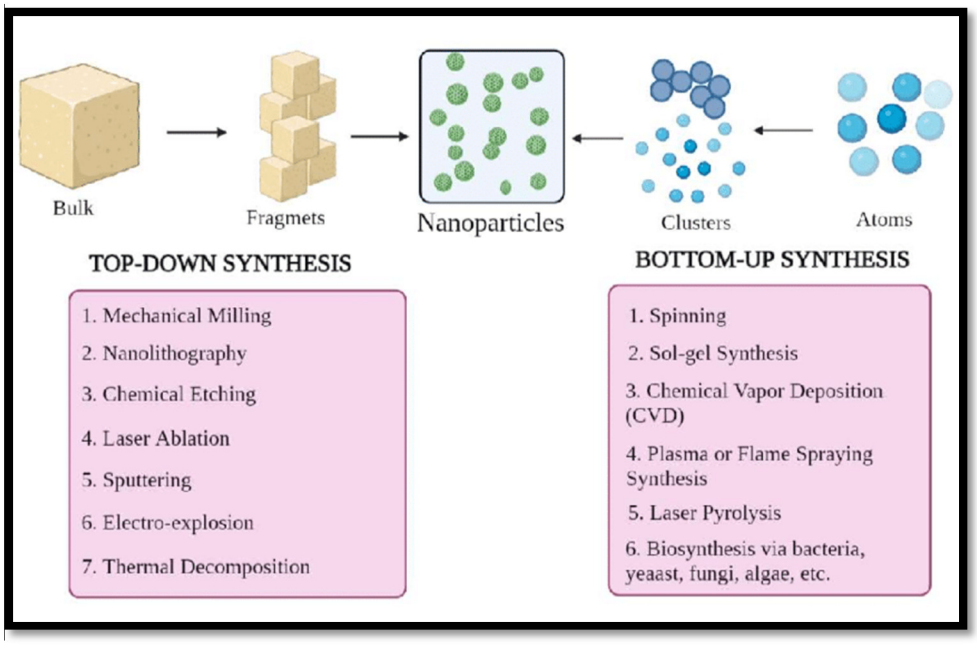

Figure 3. Categorization of Nanoparticles synthesis of top-down and bottom-up approaches.

Mechanism of Targeting

The capacity of nanocarriers to target cancer cells is important for pharmaceutical administration because it improves therapeutic efficacy while protecting healthy cells from injury. Numerous studies have been conducted on the targeting design of nanoparticle-based therapeutics. To successfully address difficulties related to cancer targeting and the creation of nano-carrier systems, it is required to first understand tumor biology and the interaction between nano-carriers and tumour cells. A nanoparticle's diameter usually ranges from 10 to 100 nm. To understand the interactions and exchanges between NP carriers, cancer cells, and tumour biology, the targeting mechanisms must be identified. The two main types of targeting approaches are passive targeting and active targeting. Gene therapy can modify cancer cells to generate proteins that make them more sensitive to chemotherapy or radiation [30] (Figure 4).

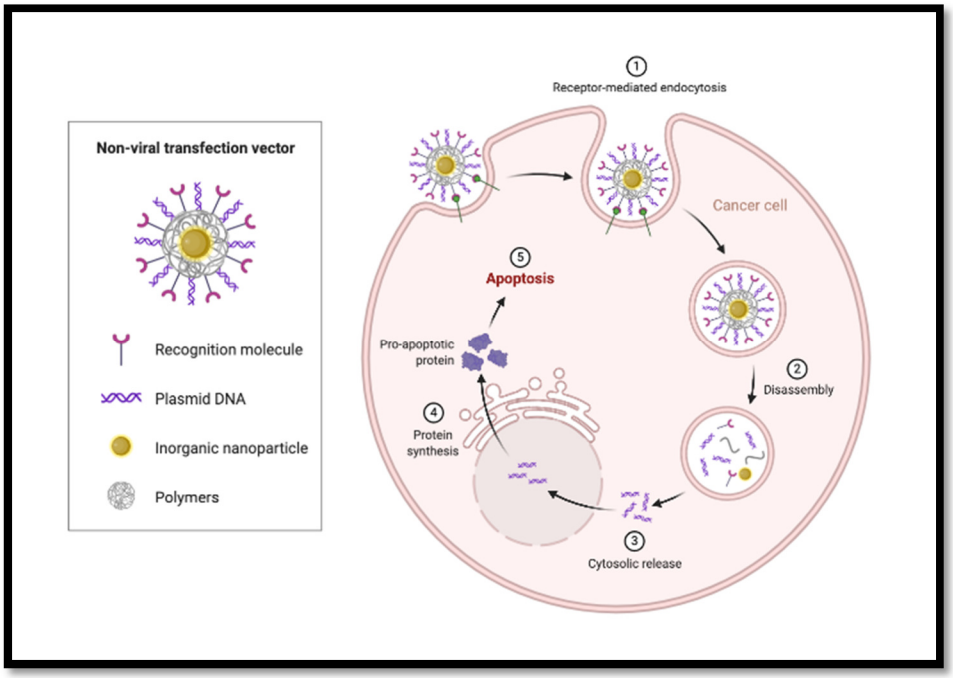

Figure 4. Cancer gene therapy produced by a nanosystem.

Passive Targeting

Passive targeting makes use of the distinctions between normal tissue and tumors. Passive targeting cannot function until drug transport to the target site is completed in order to produce therapeutic effects. Large perforations in the arterial wall decrease the tumour arteries' permselectivity in comparison to healthy vessels, and cancer cells grow, causing revascularization [31]. Macromolecular constructs like nanoparticles (NPs) can seep out of blood arteries and accumulate in cancerous tissue when angiogenesis runs too fast or goes wrong.

Cancer patients retain more nanoparticles, which can be transported into tumour cells due to impaired lymphatic outflow. Passive aiming requires the EPR effect (Figure 5) [30,32]. Because smaller Nanoparticles penetrate more easily and are less likely to leak into normal vasculature, they can affect the EPR effect [33,34]. However, significant drawbacks includes non-specific drug delivery system, non-specific EPR action and varying blood vascular permeability among tumour types [35].

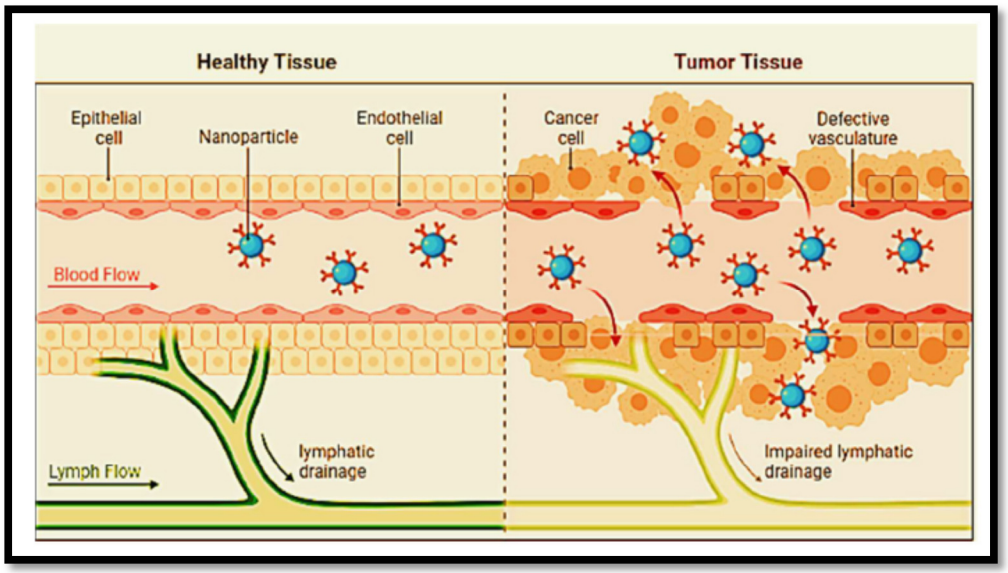

Figure 5. Passive Targeting of Nanoparticles.

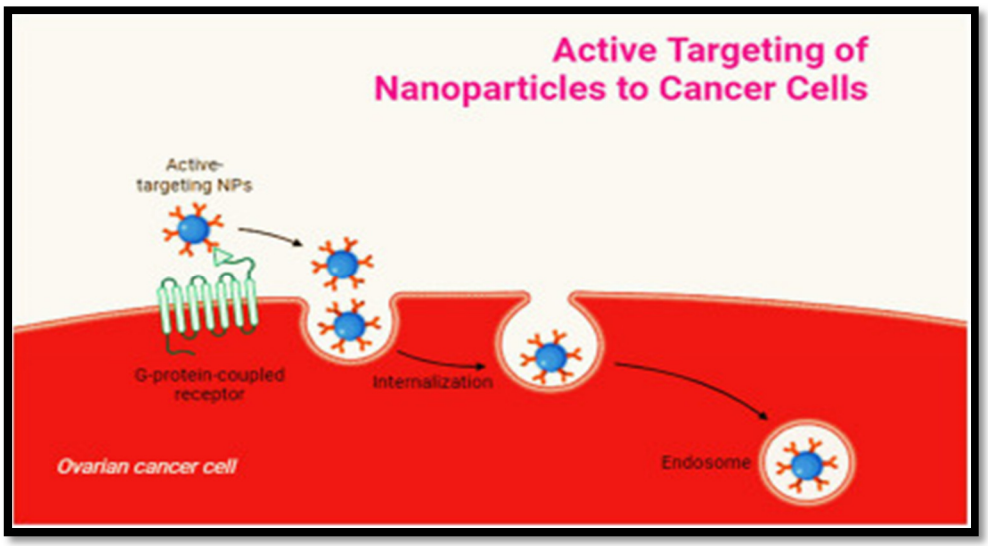

Figure 6. Active Targeting of Nanoparticles.

Active Targeting

Ligands or chemicals like as transferrin and folate are required for active targeting because they bind to specific receptors expressed on target cells or subcellular domains [36] . Active targeting depends on target substrate receptors detecting ligands and also known as ligand-mediated targeting [37]. Common ligands include things like proteins, peptides, antibodies, nucleic acids, carbohydrates, and tiny particles [38]. The receptors that are most commonly researched are EGFR, glycoproteins, transferrin, and folate. Ligand-target contact results in membrane infolding and NP internalisation by receptor-mediated endocytosis.Active targeting involves a number of mechanisms. The primary target of nucleic acids is cancer cells. The penetration of cells is enhanced by this technique. Transferrin is one receptor that has been studied in depth. This serum glycoprotein helps to transfer iron into cells. While these receptors are expressed less in healthy cells, they are overexpressed in most cancer cells, particularly solid tumours. It is possible to modify NPs with ligands to selectively target transferrin (Figure 6) [30,39].

Nanoparticles' function in cancer immunotherapy

Immunotherapy has revolutionised the way that cancer is treated and having the potential to be employed in immunotherapy as well as the administration of chemotherapy. Immunotherapy for cancer tries to boost the immune system's ability to fight the disease. NP-associated immunotherapy employs artificial antigen-presenting cells to target the immunosuppressed tumor microenvironment [4,40,41]. Adjuvants, such as NPs, can improve DC maturation and APC antigen presentation, hence activating cytotoxic T cells' anti-tumor activity [4, 42, 43]. TAAs can be delivered into DCs utilizing liposomes, gold NPs, PLGA NPs, micelles, and dendrimers, improving the immune response against cancer cells [44]. PEG treatment is commonly applied to nanoparticles to decrease their interactions with the reticuloendothelial system [41].

Nanoparticles' Function in DNA Technology

Numerous uses for DNA-based nanostructures have been developed, such as drug administration, Pb-activated DNAzyme-based lead sensing, nucleic acid detection, morphological organisation of inorganic and organic molecules, and molecular transporters. Numerous applications for DNA-based nanostructures have been developed, including drug delivery, molecular transporters, lead sensing by Pb-activated DNAzyme, nucleic acid detection, and the organization of organic and inorganic molecules into distinct morphologies, as shown in Table 1. Nanotechnology has transformed the domains of cancer detection, treatment, and management.

Nanoparticles (NPs) can boost the intracellular concentration of medication while causing no danger to healthy tissue through active or passive targeting. The sensitivity of targeted nanoparticles to pH or temperature can be adjusted to control medicine release. The pH-sensitive drug delivery device can be used to provide medication to the acidic TME. Temperature-sensitive nanoparticles (NPs) release medication at the target site when magnetic fields or ultrasonic vibrations create a change in temperature. Nanoparticles' (NPs) size, shape, molecular mass, and surface chemistry are all crucial for targeted medication delivery.

Table 1: List of FDA-approved nanomedicines for cancer treatment. [45-47]

Tradename	Material	Drug	Company	Indication	Years Approved
Doxil	Liposome PEG	Doxorubin	Jansen	MBC, Metastic, Ovarian cancer	1995
Eligard	PLGA	Leoprolide Acetate	Tolmar	Prostate Cancer	2002
Abraxane	Albumin	Paclitaxel	Celgene	Mestastic breast Cancer	2005
Genexol PM	mPEG-PLA	Paclitaxel	Samyang Corporation	Mestastic breast Cancer	2007
Onlvyde	Liposome	Irinotecan	Merrimack	Pancreatic Cancer	2015

Moreover, NPs can be made to specifically target certain moieties. Conventional chemotherapy and radiation therapy have limited efficacy and unfavorable side effects due to their uneven distribution and cytotoxic properties. Careful dosing is necessary to successfully eliminate cancer cells while causing the least amount of damage. To reach its objective, the medication must pass through a number of defences. Drug metabolism is a very complex process. The medication must cross the kidney, RES, BBB,

and TME in a physiological state. The RES, or macrophage system, is composed of blood monocytes, macrophages, and other immune cells [48] .

Mechanism of Nanoparticles in drug resistance

Despite advances, drug resistance remains a significant challenge in cancer treatment. When many cancer treatments fail due to multidrug resistance, the illness advances and the outlook is bleak. Tumour treatment resistance is caused by a number of cellular and physiological factors, including overexpression of ATP binding cassette (ABC) transporters (such as the efflux transporter), dysfunctional apoptotic machinery, interstitial fluid pressure, and an acidic and hypoxic tumour environment. It has been demonstrated that employing nanotechnology to deliver drugs for the treatment of cancer can significantly overcome drug resistance [49] (Table 2).

Targeting Efflux Transporter

One class of ABC transporter that is known to contribute to drug resistance is the efflux transporter. Drugs are removed from cells by efflux transporters, which results in treatment failure. A well-researched efflux transporter called P-glycoprotein is over expressed in several cancers that are opposed to to drug [50]. Numerous studies demonstrate that chemotherapeutic-loaded nanoparticles (NPs) can evade efflux transporters, facilitating the more effective entry of anticancer medications into the body. Drugs can be released from cells in a perinuclear site, away from membranes and efflux pumps, thanks to endocytosis [51]. More control over drug release is possible with the pharmaceutical delivery technique based on nanoparticles. Low pH and redox have been used as medicine release triggers in NPs in a number of investigations [52,53]. Drug-resistant tumours is a combination therapy which can be modulated by polymers and nanoparticles through MDR pathway. NP-based combination therapy reduces drug resistance and increases the efficacy of cells by mixing it with many drugs in a single carrier to overcome pharmacokinetic discrepancies across medications [54] . According to a study, miRNA-495 and doxorubicin combined in a silica nanoparticle coated with a cancer cell membrane efficiently overcame drug resistance in cancer therapy. The researcher has discovered that in cancer cells resistant to many drugs, miRNA-495 down regulated the expression of P-glycoprotein [55]. In addition, it was found that medication delivery was able to overcome multidrug resistance in P-gp-expressing cancer cells by targeting the receptors in nanoparticles [56].

Targeting Apotolic Pathway

Cancer cells can avoid apoptosis and enhance their survival rate due to malfunctioning apoptotic machinery, which leads to treatment resistance in the illness [57]. Failures in the apoptotic mechanism cause cancer cells to multiply and develop a greater resistance to treatment, hence increasing drug resistance [58]. "Deregulation of Bcl-2" and "nuclear factor kappa B (NF-κB)" turn on the defective apoptotic pathway[59,60]. Bcl-2, a frequently studied anti-apoptotic protein, is extensively expressed in many malignancies and plays a major role in treatment resistance and it may be a target for reversing medication resistance [60]. These anti-apoptotic proteins may be the primary targets for overcoming medication resistance due to their substantial investigation. One method of overcoming MDR is to use NPs in the traditional codelivery of "Bcl-2 siRNA and chemotherapeutics" [59,61].

In addition, NF-kB inhibitors such as curcumin [62,63] and pyrrolidine dithiocarbamate (PDTC) [64], have been employed in NP-based combination therapy. Pro-apoptotic molecules can be triggered in addition to reducing anti-apoptotic molecules to offset drug resistance brought on by the apoptotic process. For instance, the chemotherapeutic medication Paclitaxel combined with Ceramide increases the therapeutic efficacy of several forms of tumours that are resistant to treatment [65,66]. However, ceramide has been shown in a recent study to control alternative pre-mRNA splicing, which in turn brings back the expression of the tumour suppressor protein p53 in its wild-type form. Nanoparticles provide a more efficient way to deliver ceramide to cancer cells that have p53 missense mutations [67]. Since p53 is essential for apoptosis, restoring the function of p53 or other tumour suppressors is considered a feasible approach to overcoming medicine resistance in cancer. As a consequence, considerable study has been conducted on p53 gene therapy delivered via nanoparticles. It has been documented that cationic solid lipid NPs and PLGA can transfect the p53 gene in lung[68] and breast cancer cells [69]. Another study also showed that folic acid-conjugated planetary ball-milled nanoparticles (NPs) containing docetaxel and resveratrol were efficient in treating multidrug-resistant prostate cancer [70,71].

Targeting Hypoxia

Another element that goes back to MDR [59,72] and fuels multidrug resistance is hypoxia [73]. Because the cancer is growing quickly and some blood vessels are malfunctioning, some tumour cells are hypoxic. Usually, chemotherapy drugs are unable to reach the hypoxic area of the cancer.

Tumour aggressiveness and heterogeneity both rise in hypoxia. Additionally, there is evidence that hypoxia stimulates the synthesis of efflux proteins [72]. Taking aim at or inhibiting the HIF-1α gene can aid in overcoming drug resistance. Nanoparticles carrying HIF-1α siRNA can reduce hypoxic medication resistance [73]. t has been proven that specific cancer cells overexpress hypoxia-inducible factor 1a (HIF-1a), a vital component in the process [74]. Another therapeutic technique for overcoming medication resistance is targeting HIF-1a [75,76]. Indirect inhibition of HIF-1α signalling is an effective substitute for direct targeting. Obstructing this route reduces HIF-1α expression, making MDR cells more susceptible to cancer therapy [77]. Liposomes and PLGA-PEG nanoparticles, whether PEGylated or not, can be efficiently employed. Furthermore, "heat shock protein 90 (HSP90)" reduces HSP90, which is important for HIF-1 transcriptional activity and restricts the quantity of HIF-1α generated [76–77]. The HSP-90 inhibitor in "17AAG loaded NPs" significantly improved MDR in the treatment of bladder cancer [70,78]. The use of NPs in the treatment of hypoxia has been extensively researched. Silencing the HIF-1a gene can help to prevent hypoxia. Numerous studies have indicated that HiF-1a siRNA-based nanosystems are successful at reducing treatment resistance in cancer patients [76,79]. HIF-1a expression can be decreased by inhibiting the PI3K/Akt/mTOR pathway, increasing the susceptibility of MDR cells to cancer therapies [80]. Moreover, HIF-1 transcriptional activity requires heat shock protein 90 (HSP90), and HSP90 reduction can lower HIF-1a synthesis.The HSP90 inhibitor in 17AAG-loaded NPs has been demonstrated to significantly improve bladder cancer treatment [78,81].

Conclusion and Future Prospective

Nanotechnology has revolutionised the treatment of cancer. Nanoparticles (NPs), both organic and inorganic, are frequently used in therapeutic cancer treatment. Nanoparticle-based drug delivery techniques surpass standard therapies in terms of biocompatibility, stability, pharmacokinetics, and tumor targeting. They also reduce systemic toxicity and overcome pharmaceutical resistance. Owing to these advantages, medications based on nanoparticles have applications in targeted therapy, heat stroke, radiation, chemotherapy, and gene therapy. Nanocarrier delivery methods improve combination therapy by addressing drug resistance mechanisms such as hypoxia in the cancer microenvironment, faulty apoptotic pathways, and overexpression of the efflux transporter. The greater attractiveness of hybrid nanoparticles can be attributed to their improved distribution capabilities. More research on the biological traits of particular tumours will provide more accurate research guidelines for these medications. Further

research is needed to create hybrid nanoparticles that specifically target cancer cells utilising targeting moieties and are more suitable for cancer treatment. The immune system and nanoparticles have complex relationships [82]. The immune system's response to nanoparticles is influenced by their size, shape, composition, and surface. Although synthetic APCs and nanovaccines are more successful than conventional immunotherapy, there is still a lack of clinical utility with them. Further research is needed to ensure the safety and tolerability of these innovative techniques. The production of nanoparticles containing immunomodulatory elements may increase the immunotherapy vaccinations' efficacy.

Acknowledgments

Authors are thankful to Shri. Yogendraji Gode, President, IBSS's Dr. Rajendra Gode Institute of Pharmacy, Amravati and Dr. Rajendra Gode College of Pharmacy, Amravati for providing necessary facility to undertake this work.

Disclosure of conflict of interest

The author declares no conflict of interest.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. Nat Commun. 2018;9(1):3490.
3. Quazi S. Telomerase gene therapy: a remission towards cancer. Preprints. 2021. doi: 10.20944/preprints202110.0407.v1.
4. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nat Rev Immunol. 2008;8:59-73.
5. Dadwal A, Baldi A, Kumar Narang R. Nanoparticles as carriers for drug delivery in cancer. Artif Cells Nanomed Biotechnol. 2018;46:295-305.
6. Palazzolo S, Bayda S, Hadla M, Caligiuri I, Corona G, Toffoli G, et al. The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric nanoparticles, micelles, liposomes and exosomes. Curr Med Chem. 2018;25:4224-4268.

7. Zhang S, Langer R. Enteric elastomer enables safe gastric retention and extended oral drug delivery for improved medication adherence. Nanomedicine. 2018;14:621-624.
8. Chen Y, Gao DY, Huang L. In vivo delivery of miRNAs for cancer therapy: challenges and strategies. Adv Drug Deliv Rev. 2015;81:128-141.
9. Badea I. New strategies in melanoma therapy: can nanoparticles overcome chemoresistance. Nanomedicine (NY). 2017;12:1623-1626.
10. Wang C, Chen C. Light-activated mesoporous nanocarriers to overcome drug resistance of cancer cells. Nanomedicine. 2016;12:519-529.
11. Piret G, Prinz CN. Could the use of nanowire structures overcome some of the current limitations of brain electrode implants. Nanomedicine (NY). 2016;11:745-747.
12. Chan H-K, Ismail S. Side effects of chemotherapy among cancer patients in a Malaysian general hospital: experiences, perceptions and informational needs from clinical pharmacists. Asian Pac J Cancer Prev. 2014;15:5305-5309.
13. Mottaghitalab F, Farokhi M, Fatahi Y, Atyabi F, Dinarvand R. New insights into designing hybrid nanoparticles for lung cancer: diagnosis and treatment. J Control Release. 2019;295:250-267.
14. Li W, Zhang H, Assaraf YG, Zhao K, Xu X, Xie J, et al. Overcoming ABC transporter-mediated multidrug resistance: molecular mechanisms and novel therapeutic drug strategies. Drug Resist Updat. 2016;27:14-29.
15. Alimoradi H, Greish K, Barzegar-Fallah A, Alshaibani L, Pittalà V. Nitric oxide-releasing nanoparticles improve doxorubicin anticancer activity. Int J Nanomed. 2018;13:7771-7787.
16. Wang H, Agarwal P, Zhao G, Ji G, Jewell CM, Fisher JP, et al. Overcoming ovarian cancer drug resistance with a cold responsive nanomaterial. ACS Cent Sci. 2018;4:567-581.
17. Zhang J, Wang L, You X, Xian T, Wu J, Pang J. Nanoparticle therapy for prostate cancer: overview and perspectives. Curr Top Med Chem. 2019;19:57-73.
18. Viswanadh MK, Muthu MS. Targeted bioadhesive nanomedicine: an effective approach for synergistic drug delivery to cancers. Nanomedicine (NY). 2018;13:1401-1403.
19. Vyas K, Rathod M, Patel MM. Insight on nano drug delivery systems with targeted therapy in treatment of oral cancer. Nanomedicine. 2023;49:102662.

20. Benoit DS, Koo H. Targeted, triggered drug delivery to tumor and biofilm microenvironments. Nanomedicine (NY). 2016;11:873-879.
21. Lin M, Teng L, Wang Y, Zhang J, Sun X. Curcumin-guided nanotherapy: a lipid-based nanomedicine for targeted drug delivery in breast cancer therapy. Drug Deliv. 2016;23:1420-1425.
22. Koppers-Lalic D, Hogenboom MM, Middeldorp JM, Pegtel DM. Virus-modified exosomes for targeted RNA delivery; A new approach in nanomedicine. Adv Drug Deliv Rev. 2013;65:348-356.
23. Trigueros S. Nanoscale metal particles as nanocarriers in targeted drug delivery system. J Nano Res. 2016;4:1-9.
24. Jaiswal P, Gidwani B, Vyas A. Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed Biotechnol. 2014;44:27-40.
25. Li Y, Deng G, Hu X, Li C, Wang X, Zhu Q, et al. Recent advances in mesoporous silica nanoparticle-based targeted drug-delivery systems for cancer therapy. Nanomedicine (NY). 2022;17:1253-1279.
26. Juneja R, Roy I. Iron oxide-doped niosomes as drug carriers for magnetically targeted drug delivery. Int J Nanomed. 2018;13:7-9.
27. Yang Q, Jones S, Parker C, Zamboni W, Bear J, Lai S. Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation.
28. Shafey A. Green synthesis of metal and metal oxide nanoparticles from plant leaf extracts and their applications: a review. Green Process Synth. 2020;9(1):304-339.
29. Lassalle V, Ferreira M. PLA nano- and microparticles for drug delivery: an overview of the methods of preparation. Macromol Biosci. 2007;7:767-783.
30. Omidi Y, Barar J. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. Bioimpacts. 2014;4(2):55-67.
31. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000;407:249-257.
32. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul. 2001;41:189-207.

33. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4:145-160.
34. Carita AC, Eloy JO, Chorilli M, Lee RJ, Leonardi GR. Recent advances and perspectives in liposomes for cutaneous drug delivery. Curr Med Chem. 2018;25:606-635.
35. Jain RK. Barriers to drug delivery in solid tumors. Sci Am. 1994;271:58-65.
36. Mukwaya G, Forssen EA, Schmidt P, Ross M. DaunoXome® (Liposomal Daunorubicin) for first-line treatment of advanced, HIVrelated Kaposi's Sarcoma. In: Woodle MC, Storm G, eds. Long circulating liposomes: old drugs, new therapeutics. Berlin, Heidelberg: Springer; 1998.
37. Peer D, et al. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751-760.
38. Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv Drug Deliv Rev. 2008;60(15):1615-1626.
39. Saha RN, Vasanthakumar S, Bende G, Snehalatha M. Nanoparticulate drug delivery systems for cancer chemotherapy. Mol Membr Biol. 2010;27(7):215-231.
40. Zhang F, Correia A, Mäkilä E, Li W, Salonen J, Hirvonen JJ, et al. Receptor-mediated surface charge inversion platform based on porous silicon nanoparticles for efficient cancer cell recognition and combination therapy. ACS Appl Mater Interfaces. 2017;9:10034-10046.
41. Paulis LE, Mandal S, Kreutz M, Figdor CG. Dendritic cell-based nanovaccines for cancer immunotherapy. Curr Opin Immunol. 2013;25:389-395.
Shao K, Singha S, Clemente-Casares X, Tsai S, Yang Y, Santamaria P. Nanoparticle-based immunotherapy for cancer. ACS Nano. 2015;9:16-30.
42. Yang R, Xu J, Xu L, Sun X, Chen Q, Zhao Y, et al. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. ACS Nano. 2018;12:5121-5129.
43. Guo Y, Wang D, Song Q, Wu T, Zhuang X, Bao Y, et al. Erythrocyte Membrane-Enveloped Polymeric Nanoparticles as Nanovaccine for Induction of Antitumor Immunity against Melanoma. ACS Nano. 2015;9:6918-6933.
44. Kato RB, Roy B, De Oliveira FS, Ferraz EP, De Oliveira PT, Kemper AG, Hassan MQ, Rosa AL, Beloti MM. Nanotopography directs mesenchymal stem cells to osteoblast

lineage through regulation of microRNASMAD-BMP-2 circuit. J Cell Physiol. 2014;229(11):1690-1696.

45. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res. 2016;33(10):2373-2387.
46. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. P & T. 2017;42(12):742-755.
47. Rezvantalab S, Drude NI, Moraveji MK, Guvener N, Koons EK, Shi Y, Kiessling F. PLGA-based nanoparticles in cancer treatment. Front Pharmacol. 2018;9:1260.
48. Litman T, Brangi M, Hudson E, Fetsch P, Abati A, Ross DD, et al. The multidrug-resistant phenotype associated with overexpression of the new ABC half-transporter. MXR (ABCG2). J Cell Sci. 2000;113(Pt 11):2011-2021.
49. Allen JD, Brinkhuis RF, van Deemter L, Wijnholds J, Schinkel AH. Extensive contribution of the multidrug transporters P-glycoprotein and Mrp1 to basal drug resistance. Cancer Res. 2000;60:5761-5766.
50. Murakami M, Cabral H, Matsumoto Y, Wu S, Kano MR, Yamori T, et al. Improving drug potency and efficacy by nanocarrier-mediated subcellular targeting. Sci Transl Med. 2011;3:64ra62.
51. Kundu M, Sadhukhan P, Ghosh N, Chatterjee S, Manna P, Das J, et al. pH-responsive and targeted delivery of curcumin via phenylboronic acid-functionalized ZnO nanoparticles for breast cancer therapy. J Adv Res. 2019;18:161-172.
52. Qin L, Wu L, Jiang S, Yang D, He H, Zhang F, et al. Multifunctional micelle delivery system for overcoming multidrug resistance of doxorubicin. J Drug Target. 2018;26:289-295.
53. Susa M, Iyer AK, Ryu K, Hornicek FJ, Mankin H, Amiji MM, et al. Doxorubicin loaded Polymeric Nanoparticulate Delivery System to overcome drug resistance in osteosarcoma. BMC Cancer. 2009;9:399.
54. He J, Gong C, Qin J, Li M, Huang S. Cancer Cell Membrane Decorated Silica Nanoparticle Loaded with miR495 and Doxorubicin to Overcome Drug Resistance for Effective Lung Cancer Therapy. Nanoscale Res Lett. 2019;14:339.

55. Bai F, Wang C, Lu Q, Zhao M, Ban FQ, Yu DH, et al. Nanoparticle-mediated drug delivery to tumor neovasculature to combat P-gpexpressing multidrug resistant cancer. Biomaterials. 2013;34:6163-6174.
56. Viktorsson K, Lewensohn R, Zhivotovsky B. Apoptotic pathways and therapy resistance in human malignancies. Adv Cancer Res. 2005;94:143-196.
57. Soma CE, Dubernet C, Bentolila D, Benita S, Couvreur P. Reversion of multidrug resistance by co-encapsulation of doxorubicin and cyclosporin A in polyalkylcyanoacrylate nanoparticles. Biomaterials. 2000;21(1):1-7.
58. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res. 2016;33(10):2373-2387.
59. Choi KY, Correa S, Min J, Li J, Roy S, Laccetti KH, et al. Binary Targeting of siRNA to Hematologic Cancer Cells In Vivo using Layer-by-Layer Nanoparticles. Adv Funct Mater. 2019;29:1900018.
60. Chen AM, Zhang M, Wei D, Stueber D, Taratula O, Minko T, et al. Co-delivery of doxorubicin and Bcl-2 siRNA by mesoporous silica nanoparticles enhances the efficacy of chemotherapy in multidrug-resistant cancer cells. Small. 2009;5:2673-2677.
61. Misra R, Sahoo SK. Coformulation of doxorubicin and curcumin in poly(D,L-lactide-co-glycolide) nanoparticles suppresses the development of multidrug resistance in K562 cells. Mol Pharm. 2011;8:852-866.
62. Zhao MD, Li JQ, Chen FY, Dong W, Wen LJ, Fei WD, et al. Co-Delivery of Curcumin and Paclitaxel by “Core-Shell” targeting amphiphilic copolymer to reverse resistance in the treatment of ovarian cancer. Int J Nanomed. 2019;14:9453-9467.
63. Fan L, Li F, Zhang H, Wang Y, Cheng C, Li X, et al. Co-delivery of PDTC and doxorubicin by multifunctional micellar nanoparticles to achieve active targeted drug delivery and overcome multidrug resistance. Biomaterials. 2010;31:5634-5642.
64. Devalapally H, Duan Z, Seiden MV, Amiji MM. Paclitaxel and ceramide co-administration in biodegradable polymeric nanoparticulate delivery system to overcome drug resistance in ovarian cancer. Int J Cancer. 2007;121:1830-1838.

65. Vlerken LE, Duan Z, Little SR, Seiden MV, Amiji MM. Augmentation of therapeutic efficacy in drug-resistant tumor models using ceramide coadministration in temporal-controlled polymer-blend nanoparticle delivery systems. AAPS J. 2010;12:171-180.
66. Khiste SK, Liu Z, Roy KR, Uddin MB, Hosain SB, Gu X, et al. Ceramide-rubusoside nanomicelles, a potential therapeutic approach to target cancers carrying p53 missense mutations. Mol Cancer Ther. 2020;19:564-574.
67. Choi SH, Jin SE, Lee MK, Lim SJ, Park JS, Kim BG, et al. Novel cationic solid lipid nanoparticles enhanced p53 gene transfer to lung cancer cells. Eur J Pharm Biopharm. 2008;68:545-554.
68. Prabha S, Labhasetwar V. Nanoparticle-mediated wild-type p53 gene delivery results in sustained antiproliferative activity in breast cancer cells. Mol Pharm. 2004;1:211-219.
69. Zhao Y, Huan ML, Liu M, Cheng Y, Sun Y, Cui H, et al. Doxorubicin and resveratrol co-delivery nanoparticle to overcome doxorubicin resistance. Sci Rep. 2016;6:35267.
70. Singh SK, Lillard JW Jr, Singh R. Reversal of drug resistance by planetary ball milled (PBM) nanoparticle loaded with resveratrol and docetaxel in prostate cancer. Cancer Lett. 2018;427:49-62.
71. Xiao Q, Zhu X, Yuan Y, Yin L, He W. A drug-delivering-drug strategy for combined treatment of metastatic breast cancer. Nanomedicine. 2018;14:2678-2688.
72. Jing X, Yang F, Shao C, Wei K, Xie M, Shen H, et al. Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Mol Cancer. 2019;18:157.
73. Vadde R, Vemula S, Jinka R, Merchant N, Bramhachari PV, Nagaraju GP. Role of hypoxia-inducible factors (HIF) in the maintenance of stemness and malignancy of colorectal cancer. Crit Rev Oncol Hematol. 2017;113:22-27.
74. Rey S, Schito L, Wouters BG, Eliasof S, Kerbel RS. Targeting Hypoxia-inducible factors for antiangiogenic cancer therapy. Trends Cancer. 2017;3:529-541.
75. Hajizadeh F, Moghadaszadeh Ardebili S, Baghi Moornani M, Masjedi A, Atyabi F, Kiani M, et al. Silencing of HIF-1α/CD73 axis by siRNA-loaded TAT-chitosan-spion nanoparticles robustly blocks cancer cell progression. Eur J Pharmacol. 2020;882:173235.
76. Zhang J, Zhang Q, Lou Y, Fu Q, Chen Q, Wei T, et al. Hypoxia-inducible factor-1α/interleukin-1β signaling enhances hepatoma epithelial-mesenchymal transition through

macrophages in a hypoxic-inflammatory microenvironment. Hepatology. 2018;67(5):1872-1889.

77. Semenza GL. Evaluation of HIF-1 inhibitors as anticancer agents. Drug Discov Today. 2007;12(19-20):853-859.
78. Luan X, Guan YY, Liu HJ, Lu Q, Zhao M, Sun D, et al. A tumor vascular-targeted interlocking trimodal nanosystem that induces and exploits hypoxia. Adv Sci. 2018;5:1800034.
79. Zhang J, Zhang Q, Lou Y, Fu Q, Chen Q, Wei T, et al. Hypoxia-inducible factor-1a/interleukin-1b signaling enhances hepatoma epithelialmesenchymal transition through macrophages in a hypoxic-inflammatory microenvironment. Hepatology. 2018;67:1872-1889.
80. Long Q, Lin TY, Huang Y, Li X, Ma AH, Zhang H, et al. Image-guided photo-therapeutic nanoporphyrin synergized HSP90 inhibitor in patient-derived xenograft bladder cancer model. Nanomedicine. 2018;14:789-798.
81. Najafi-Hajivar S, Zakeri-Milani P, Mohammadi H, Niazi M, Soleymani-Goloujeh M, Baradaran B, et al. Overview on experimental models of interactions between nanoparticles and the immune system. Biomed Pharmacother. 2016;83:1365-1378.