Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.57.009034

Battle Against Drug Resistant Cancer Using Nanotechnology: Cellular and Molecular Mechanistic Pathways

Swapan Maity, Dipesh Kumar Dubey and Pralay Maiti*

School of Materials Science and Technology, Indian Institute of Technology (Banaras Hindu University), India

***Corresponding author:** Pralay Maiti, School of Materials Science and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi 221005, India

ARTICLE INFO

Received: July 08, 2024

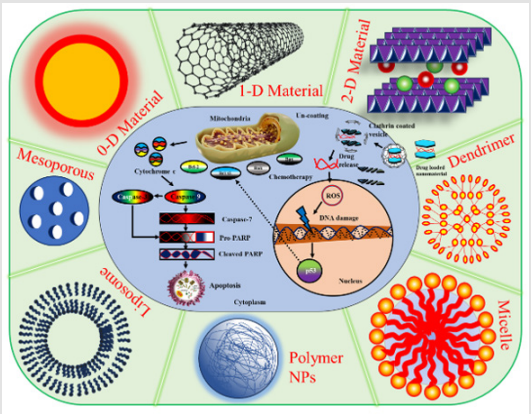
Published: July 17, 2024

Citation: Swapan Maity, Dipesh Kumar Dubey and Pralay Maiti. Battle Against Drug Resistant Cancer Using Nanotechnology:Cellular and Molecular Mechanistic Pathways. Biomed J Sci & Tech Res 57(4)-2024. BJSTR. MS.ID.009034.

ABSTRACT

Cancer, with its somber embrace, stands as one of the foremost reasons of mortality across the globe. Chemotherapy stands as the steadfast cornerstone in the battle against cancer. Yet, amidst its promise, a formidable obstacle casts its shadow, impeding the triumph of this therapeutic endeavor is its multidrug resistance. In the intricate realm of medical advancement, nanotechnology emerges as a luminary, its delicate intricacies and infinitesimal wonders offering profound promise in the fight against cancer. Against the backdrop of conventional pharmaceuticals, they unveil a unique advantage with greater precision and purpose. Enhanced stability and biocompatibility grace their essence, while an inherent ability to navigate the labyrinthine pathways of the body while enhances their efficacy. Moreover, in the chronicles of resistance and resilience, nanoparticle-based drug delivery systems emerge as champions, wielding their prowess against the scourge of drug resistance in cancer. Multi-drug resistance stems from various unrelated mechanisms, including overexpression of proteins, reduced drug uptake, altered drug targets, cell cycle checkpoint modifications, agent inactivation, compartmentalization, apoptosis inhibition, and abnormal sphingolipid metabolism. Nanoparticles targeting drug resistance mechanisms can enhance reversal of multidrug resistance. Additionally, as extra resistance mechanism emerges where nanoparticles are progressively utilized to target them. Researchers are exploring nanoparticles' role in immunotherapy, crucial in cancer treatment. This review examines nanoparticles' roles, including hybrid nanoparticles, in delivery of drug for immunotherapy, chemotherapy and targeted therapy, highlighting their targeting mechanisms and ability to reverse drug resistance along with cellular and molecular mechanism (Graphical Abstract).

Keywords: Nanotechnology; Drug Resistance; Cancer, Cellular Mechanism; Molecular Mechanism



Graphical Abstract: Nanotechnology induced therapeutic approaches for targeted drug delivery to overcome drug-resistance in cancer cells. Illustration of probable cancer drug resistance mechanistic way in the battle of cancer using various nanomaterials. Cancer cells resist drugs via multiple mechanisms like drug-loading, improved drug uptake, DNA damage and repair enhancement, apoptosis inhibition, chemotherapy, altered metabolism, target modification, epigenetic alternation, and gene magnification. These pathways suggest molecular mechanism pathways for the apoptotic cell death caused due to nano-formulation.

Introduction

In the delicate tapestry of human existence, cancer emerges as a somber refrain, the second leading cause of mortality, echoing across the globe as a socio-economic dilemma of profound magnitude [1]. Chemotherapy, surgery, radiation therapy, immunotherapy—all stand as important sentinels against the advance of this relentless foe, though their efficacy remains a realm of formidable challenge, where satisfaction is yet to be fully realized [2-4]. Chemotherapy, a widely used cancer treatment, indiscriminately kills speedily splitting cells, causing serious complicacy like bone marrow suppression, hair loss, and gastrointestinal reactions [5]. Efforts to develop drugs targeting tumor cells specifically have been a major focus of cancer research. While targeted therapy has advanced, significant adverse effects persist, alongside the challenge of drug resistance. Resistance to cancer drugs can occur in two ways: either limited to the specific drug used (single-agent resistance) or affecting many drugs with variable structures and functions (Multi Drug Resistance, MDR). This resistance poses a significant challenge for cancer therapy, undermining desired drug responses and complicating treatment regimens, thus becoming a clinician's nightmare [6]. Drug resistance is a critical issue in cancer treatment [7], alongside challenges like cytotoxic agent resistance and toxic chemotherapy [8]. New approaches targeting molecular aspects of cancer, such as RNA interference (RNAi), oncogenes and tumor suppressor genes, are being explored [9].

These treatments aim to inhibit cell proliferation, enhance immune responses, tailor medications, provide drugs to cancer cells, and minimize the complication of anticancer drugs. Chemotherapy resistance arises from the mechanisms like drug liberation, multi-drug resistance, apoptosis crushing, and altered drug metabolism, changes in epigenetic and targets drug, intensify DNA repair, and gene magnification [10]. In recent decades, nanotechnology has revolutionized medicine, particularly in the battle field of cancer. Nanoparticle mediated drug delivery networks offer precise targeting, reduced difficulties, and improved drug efficacy. These systems deliver chemotherapeutic agents and nucleic acids to tumor cells, enhancing both cytotoxic and gene therapy. Additionally, they encapsulate poorly soluble drugs, prolonging their circulation and accumulation in tumor tissues. This targeted approach protects normal cells, mitigating adverse effects. Examples include doxorubicin-loaded liposomes reducing cardiotoxicity [11] and nanoparticle albumin-bound paclitaxel exhibiting fewer side effects [12]. Nanoparticle drugs also find applications in immunotherapy and ablation treatment [13,14], potentially reversing the tumor immunosuppressive microenvironment [15]. Nanoparticles (NPs) offer advantages in combating anti-tumor multidrug resistance (MDR) by facilitating drug combination therapy and inhibiting specific mechanistic pathway of drug resistance like efflux transporters on cell membranes [16].

Recent studies indicate the potential of nanoparticle-based therapy in overcoming MDR across various cancers, including breast cancer [17], ovarian cancer [18], and prostate cancer [19]. The convergence of nanotechnology and medicine marks a promising frontier in cancer treatment, warranting further exploration through comprehensive research. In this review, we dissected cancer drug resistance mechanisms, examined treatment failures with traditional chemotherapy, and introduced novel strategies to combat resistance. We also discussed basic principles of nanovehicles systems in the cancer treatment, addressed present questionnaire, and outlined future research regulations.

Drug Resistance and its Classification

Drug resistance falls into two main heading: intrinsic and acquired. Intrinsic resistance is the innate capacity of cells to resist treatment with chemotherapeutic drugs, existing prior to their administration [20]. Intrinsic resistance arises from various mechanisms like genetic mutations within tumor cells, emergence of impenetrable society like cancer stem cells in diverse tumors along with mobilization of intrinsic detoxification tracks. Conversely, acquired resistance occurs following anti-cancer treatment. Acquired resistance in cancer can result from different cellular and molecular reactions like initiation of second proto-oncogene post-therapy leading to new mutations or altered expression; changes in drug targets; alterations in drug metabolism within the tumor; efflux of drugs via transmembrane transporters such as ATP binding cassette transporters; epigenomic modifications like acetylation, methylation, and altered microRNA levels affecting receptor pathways; and modifications in the tumor microenvironment (TME) post-treatment [20]. These mechanisms can act independently or simultaneously, promoting multidrug resistance in cancer.

Cellular Mechanistic Pathway for Drug Resistance

In general, cancer cells constantly adapt to survive, complicating the treatment procedure. Studying biochemical and genetic factors behind multidrug resistance (MDR) may enhance drug design, offering new treatments. Cellular mechanisms contributing to MDR vary, including following different factors, pivotal in drug resistance development [21-23]. Through the presentation of Figure 1, one witness the intricate interplay of pathways, where mutations and cellular signaling converge to fortify cancer cells against the onslaught of pharmaceutical assault. It is a testament to the ingenuity of nature, a reminder of the ceaseless struggle between life and its adversaries (Figure 1). Cancer cells resist drugs via multiple mechanisms like diminished drug uptake, improved drug removal, DNA repair enhancement, apoptosis inhibition, altered metabolism, target modification, epigenetic alternation, and gene magnification. These mechanisms can play alone or simultaneously, causing one or many drug resistances in cancer cells. (M- Methylation; dM- demethylation).

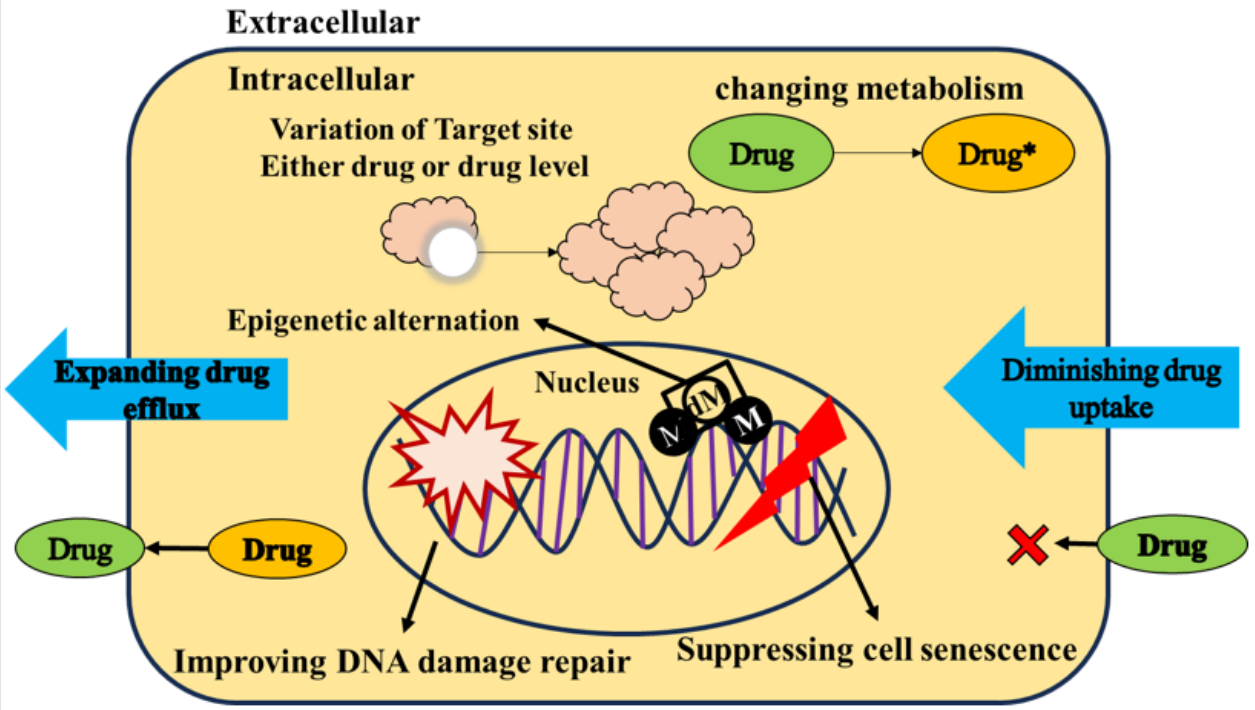


Figure 1: Illustration of probable cancer drug resistance mechanistic way in the battle of cancer. Cancer cells resist drugs via multiple mechanisms like diminished drug uptake, improved drug removal, DNA repair enhancement, apoptosis inhibition, altered metabolism, target modification, epigenetic alternation, and gene magnification. These mechanisms can play alone or simultaneously, causing one or many drug resistances in cancer cells. (M- Methylation; dM- demethylation).

Microenvironment of Tumor: Growing evidence underscores the pivotal part of the tumor microenvironment in fostering drug resistance, a major contributor to cancer sinks along with the treatment ineffectiveness. This microenvironment comprises usual stromal cells (SC), extracellular matrix (ECM), and various solvable components like cytokines and growth agents. Communication between tumor cells, stromal cells, and the ECM, along with the influence of growth factors and cytokines, facilitate direct interactions ruling to drug resistance. This phenomenon, termed as environment-mediated drug resistance (EM-DR), encompasses cell adhesion-mediated drug resistance (CAM-DR) and soluble factor-mediated drug resistance (SM-DR), involving molecules like VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), SDF-1 (stromal cell-derived factor- 1), IL-6 (interleukin-6), NO (nitric oxide), IL-3(interleukin-3), G-CSF (granulocyte colony stimulating factor), M-CSF (macrophage colony stimulating factor), GM-CSF (granulocyte-macrophage colony stimulating factor), as well as TNF super family members BAFF (B cell-activating factor of the TNF family) and APRIL (a proliferation-inducing ligand) among others, orchestrated by tumor cell interactions [24-26].

Tumor Diverseness: Intra-tumor heterogeneity arises from various factors at the cellular level, leading to proteomic effects, diverse genetic, epigenetic and transcriptomic. Genotypic alters such as mutations, gene stretching, and chromosomal alternation contribute to this heterogeneity, alongside genomic instability. Epigenetic elements, including miRNA alterations along with transcriptomic / proteomic variations, also play a role, influenced by cell cycle phase, stochastic differences, or hierarchical operation as per the theory of the cancer stem cell [27-31]. Intrinsic elements like this drive tumor diverseness, while external ingredients like paracrine signaling interactions, pH and hypoxia further modulate gene products linked to drug resistance and prognosis [32,33].

Cancer Stem Cells Study: The population of cancer stem-cell have been found in various hematopoietic along with solid tumors and are believed to be the origin of these tumors. Chemotherapy, while affecting numerous tumor cells, often fails to target cancer stem cells for their capability to expel chemotherapy agents through mechanisms such as enhancing of ATP-binding cassette (ABC) drug transporters like ABCB1 and ABCG2. These stem cells possess characteristics akin to standard stem cells, including drug resistance, DNA repair capacity, resistance to apoptosis, and dormancy [34-36]. Their stability and ability to metastasize contribute to cancer recurrence. Recognizing and removing these cancer stem cells is crucial to overcoming drug resistance and preventing recurrence.

Cancer Associated Fibroblasts (CAF): Cancer-associated fibroblasts (CAFs) are pivotal in the tumor microenvironment (TME), contributing to tissue remodeling, matrix deposition, immune cell interactions, and extensive communication with cancer cells [37]. CAFs exhibit phenotypic and functional diversity influenced by their origin and stimuli. Besides their role in tumor progression, CAFs drive multidrug resistance (MDR) in anti-cancer therapy [38]. Materializing confirmation suggests that breast cancer-associated fibroblasts confer resistance to doxorubicin in triple-negative breast cancer cells (MDA-MB-231) through HMGB1-induced sustained autophagy. Understanding the various mechanisms employed by CAFs [39], including transporter proteins, to induce drug resistance necessitates further investigation to overcome chemotherapy resistance.

Oxidative Stress: Oxidative stress arises from an imbalance between oxygen radicals and antioxidants, often due to mitochondrial dysfunction. These radicals can induce DNA mutations, aiding tumor development, yet also trigger apoptosis, hindering tumor progression. Certain anticancer drugs generate ROS to combat tumors but can lead to resistance over time. Tumor cells develop survival mechanisms against ROS-induced apoptosis, fostering heterogeneity and drug resistance. Anticancer drugs reliant on ROS production for DNA damage may fail due to limited oxygen supply within cells, enabling cancer cell survival. Alternative pathways, such as cell senescence, also contribute to drug resistance. Understanding ROS and redox signaling in multidrug resistance remains a crucial area for further research in cancer treatment [40].

Cancer Metabolism: Metabolic reprogramming is a hallmark of cancer cells, adapting to their environment through elevated oxidative stress and altered energy production pathways. The "Warburg effect," identified by Otto Warburg, highlights the shift towards less efficient glycolysis over oxidative phosphorylation [41]. This reprogramming extends beyond glucose metabolism to include lipids and glutamine. Lactate, a byproduct of glycolysis, plays a significant role in cancer progression. Glycolytic enzyme, Pyruvate kinase isoform (2PKM2) is upregulated in many cancers, regulating glycolysis and inhibiting oxidative phosphorylation while influencing gene transcription and cell cycle progression. PKM2 also impacts programmed cell death and drug resistance, contributing to the challenge of overcoming drug resistance in cancer therapy [42]. Additional investigation is demanded to appreciate the interplay between cancer metabolism and chemotherapy resistance.

Inflammation: Inflammation, an innate immune response to injury or pathogens, drives tumor growth and development by activating inflammatory cells and releasing pro-inflammatory mediators [43]. This inflammatory microenvironment fosters cancer progression, including angiogenesis, evasion from cell death, and drug resistance [44,45]. Inflammation is recognized as the seventh hallmark of cancer [46]. Immune cell initiation along with pro-inflammatory cytokine liberation nurture drug resistance by altering cellular responses to chemotherapy [47,48]. Understanding the molecular mechanisms linking inflammation and cancer offers avenues to combat multidrug resistance.

Molecular Mechanistic Pathway for Cancer Drug Resistance

Cancer cells from a patient can vary significantly in genetic makeup due to factors like tissue of origin, oncogene activation, tumor suppressor activity, and gene expression related to mutator phenotypes. This leads to diverse drug-resistant gene profiles among cancers. Despite being clonally derived, tumors exhibit considerable heterogeneity, especially in drug resistance mechanisms. Notably, a primary mechanism for multidrug resistance (MDR) in cultured cancer cells is the expression of an energy-dependent drug efflux pump, P-gp, which functions as a multidrug transporter [49] (Figure 2).

Cancer Drug Efflux by the ATP Binding Cassette (ABC) Transporter Family: A key factor driving drug resistance in cancer is the overexpression of ABC transporter proteins, which expel various drugs across cell membranes via ATP hydrolysis [50]. These transporters reduce intracellular drug levels, hindering chemotherapy effectiveness [51]. Humans have 48 identified ABC transporters [52], many primarily expressed in tissues like the kidney, pancreas, liver, gastrointestinal tract, and certain blood vessels. Thirteen types of ABC transporters are linked to multidrug resistance in cancer, notably ABCB1 (P-glycoprotein/MDR1), ABCC1 (MRP1), and ABCG2 (BCRP) [53]. These transporters, essential for removing toxins, are exploited by cancer cells to resist drugs, with ATP playing a crucial role. Cancer cells with elevated ATP levels exhibit resistance, while ATP depletion enhances chemotherapy sensitivity. Extracellular ATP boosts ABC transporter expression, increasing drug efflux and promoting a resistant tumor microenvironment [54]. Macropinocytosis facilitates intracellular ATP elevation, contributing to multidrug resistance. Major drug-effluxing transporters [40] include the following points and shows in Figure 2.

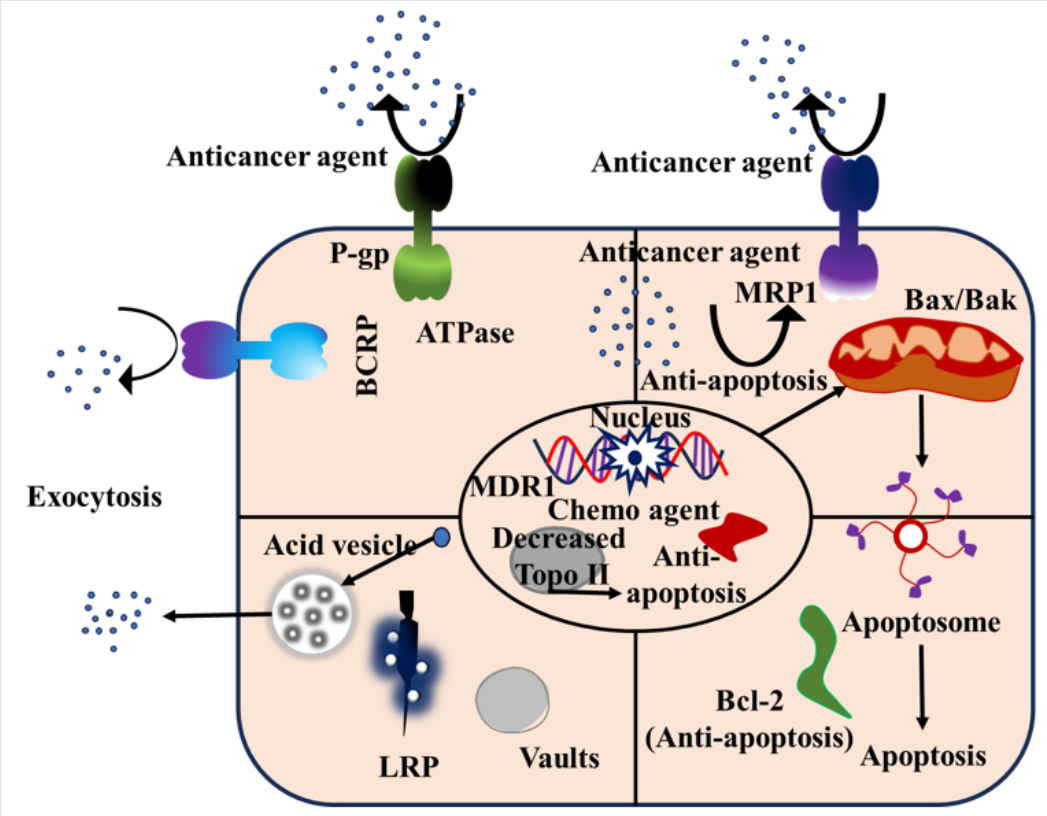


Figure 2: An illustrative introduction of mechanism of drug resistance into cancer cells involve several key players such as ABC transporter, LRP, Bcl-2, and Topo ll. The ATP-binding cassette (ABC) Transporter, an ATP-activated transporter, generally in chemotherapy, cells indicate ABC transporters to separate exotic particles such as xenobiotics, anticancer agents, etc. from the intracellular domain. P-glycoprotein (P-gp), multidrug-resistant protein 1 (MRP-1), and breast cancer resistance protein (BCRP) are mainly the principal projection of the ABC transporter family. Lung resistance protein (LRP) occupies in vaults (cytoplasmic) provide the exocytosis of exotic particles like drugs which are used in the battle of cancer. Research also investigated that the enhanced activity of bcl-2 (an anti-apoptotic factor acted upon by anticancer agents that activate in the normal apoptosis process), p53 loss-of-function of p53, and the downregulation of topoisomerase II (Topo-II) also contracts cell apoptosis to accelerate the resistance of cancer cells to anticancer drugs.

Permeability Glycoprotein (P-gp)/MDR-1: P-glycoprotein (P-gp) is a large plasma membrane glycoprotein and the first discovered human ABC transporter encoded by the ABCB1 gene on chromosome 7. It consists of 1280 amino acids with a molecular weight of approximately 170 kDa [55], featuring transmembrane and nucleotide-binding domains. P-gp has a flexible drug binding cavity within its membrane-bound domain, allowing interaction with various substrates. ATP binding induces conformational changes, facilitating unidirectional transport [56] of lipophilic substrates out of cells. Its basal expression in tissues like liver, intestine, and blood-brain barrier protects against xenobiotics [57]. Overexpression of P-gp is common in multidrug-resistant cancer cells, diminishing intracellular drug accumulation and contributing to chemotherapy resistance. P-gp also influences drug bioavailability and effects, exhibiting broad substrate specificity and conferring cross-resistance against multiple drugs [58,59]. Cancer cells upregulate P-gp expression in response to cytotoxic agents, hypoxia, and altered cellular signaling, contributing to multidrug resistance [60]. P-gp may be expressed in nuclear and mitochondrial membranes, further facilitating drug efflux and resistance in cancer cells [61].

Multidrug resistance protein (MRPs/ABCC1): The Multidrug resistance protein (MRP1/ABCC1) is a large transporter protein involved in drug resistance, similar to P-glycoprotein (P-gp), belonging to the ABC transporter family. It consists of three transmembrane domains (TMD), two nucleotide-binding domains (NBD), and an additional N-terminal domain. MRP1 [62] is primarily expressed in tumor cells, where it pumps out toxic substances, including anticancer drugs, in an ATP-dependent manner [63]. Its main location is in the proximal tubules of the kidney, aiding in excretory functions. MRP1 is constitutively expressed in various tissues and barriers, with notably higher levels in many cancers like lung, pancreatic, prostate, brain, and breast cancer [64]. It plays a significant role in expelling anticancer agents and organic anion substrates, especially under hypoxic conditions. The expression of MRP1 in cancer cells is influenced by factors unique to cancer cells, often leading to multidrug resistance.

Breast Cancer Resistance Protein (BCRP/ABCG2): BCRP/ABCG2, a transporter protein, and functions to expel toxic substances extracellularly under normal conditions. It is composed of one transmembrane domain (TMD) and one nucleotide-binding domain (NBD), weighing approximately 72 kDa. Typically found in stem cells and epithelial apical membranes, it plays a role in drug disposition [65]. Also known as MXR, it has implicated in mitoxantrone efflux in carcinoma cells, contributing to drug resistance [66]. Upregulated BCRP expression in cancer cells further enhances drug resistance, affecting various anticancer drugs. BCRP is prevalent in breast cancer but also appears in leukemia and lung cancer [67,68], sometimes serving as a cancer stem cell marker. It efficiently transports chemotherapeutic drugs and tyrosine kinase inhibitors. Interactions of ABCB1, ABCC1, and ABCG2 with cancer-related genes were analyzed, confirming their involvement in cancer pathology.

Deactivation of Anticancer Drugs: The effectiveness of anticancer drugs relies on complex mechanisms involving interactions with proteins in vivo. Cancer cells can develop resistance by decreasing drug activity [69]. For instance, cytarabine (AraC) treatment for acute myeloid leukemia illustrates this phenomenon, where its phosphorylated form becomes lethal to cells [70]. Down-regulation or mutations in proteins implicated in this pathway reduce AraC's efficacy, leading to drug-resistant cancer cells [71]. Another example involves the glutathione S-transferase family (GST), comprising cytosolic, mitochondrial, and microsomal (MAPEG) proteins. GST enzymes play a crucial role in detoxifying drugs and inhibiting the MAPK pathway, thereby increasing drug resistance in cancer cells. Elevated GST expression enhances drug detoxification, reduces drug-induced damage, and promotes resistance to apoptosis [72].

Changing the Anticancer Drug Targets and Mutations: Genomic instability plays a crucial role in cancer initiation and progression, stemming from various mechanisms like DNA mutations, chromosomal abnormalities, telomere damage, and impaired DNA repair [73]. This instability fosters tumor growth and leads to tumor heterogeneity and drug resistance, affecting patient survival. Solid tumors and hematological malignancies commonly exhibit genomic instability, ranging from single nucleotide to chromosomal alterations [74]. These alterations can affect drug targets, reducing therapeutic efficacy and promoting resistance. For instance, mutations in genes like the estrogen receptor can cause resistance to anti-cancer drugs like tamoxifen in breast cancer [75], while mutations in tyrosine kinase proteins can lead to resistance in chronic myelogenous leukemia. Mutations in tumor suppressor gene p53 can impair apoptotic balance and promote drug resistance, such as resistance to cisplatin in non-small cell lung cancer [76]. Additionally, mutant p53 stabilization upon drug treatment contributes to resistance against drugs like gemcitabine in cancer therapy [77].

Intensifying the DNA Damage Repair: DNA repair mechanisms contribute significantly to drug resistance in cancer. Chemotherapeutic agents straightly or secondarily damage cancer cell DNA, prompting repair mechanistic path. For instance, platinum-based drugs like cisplatin induce DNA damage, triggering tumor cell apoptosis. Resistance emerges via DNA repair systems like nucleotide excision repair (NER) and homologous recombination repair (RRM). Inhibiting these repair systems enhances drug efficacy by sensitizing cancer cells [78]. Targeting DNA repair system defects, due to mutations or epigenetic changes, presents a therapeutic opportunity. Additionally, increased DNA repair and alkyl transferase activity confer resistance to alkylating agents like doxorubicin [79].

Evasion of Programmed Cell Death: Cell demise is moderated by three main occasions: necrosis, apoptosis, and autophagy, each differing in biological characteristics while facilitating cell death. Apoptosis involves internal and external pathways, with external pathway involving ligands, cell death receptors like FAS and TNF-R, and proteins such as caspases-3, -6, -7, and -8. This leads to proteolysis of actin and nuclear lamin proteins, culminating in apoptosis [80]. The internal pathway, occurring in mitochondria, involves anti-apoptotic proteins like Bcl2 and AKT, and pre-apoptotic proteins like Bax, Bak, and caspase-9. Up-regulation of anti-apoptotic genes and down-regulation of pre-apoptotic genes in tumor cells contribute to chemotherapy resistance [81]. Mutations in p53 gene can induce apoptosis in response to cell stress and DNA damage, but mutations may impair this process, reducing sensitivity to chemotherapy [82].

Epigenetic Changes: One key aspect of drug resistance in cancer therapy is epigenetic alterations, which occur through two main mechanisms: DNA methylation and histone modifications [83]. DNA methylation involves the addition of methyl groups to cytosine bases, particularly in CpG islands near gene promoters, but can occur elsewhere in the genome as well [84]. Histone modifications, such as acetylation and deacetylation, regulate chromatin structure and gene expression, shows in Figure 3. For instance, methylation often silences tumor suppressor genes while hypermethylation can activate oncogenes [85]. In cancer cells, demethylation of genes like MDR1 can lead to multi-drug resistance, reducing the effectiveness of chemotherapy [86] (Figure 3). Combining epigenetic and conventional chemotherapy can be effective against drug-resistant tumors and cancer cells.

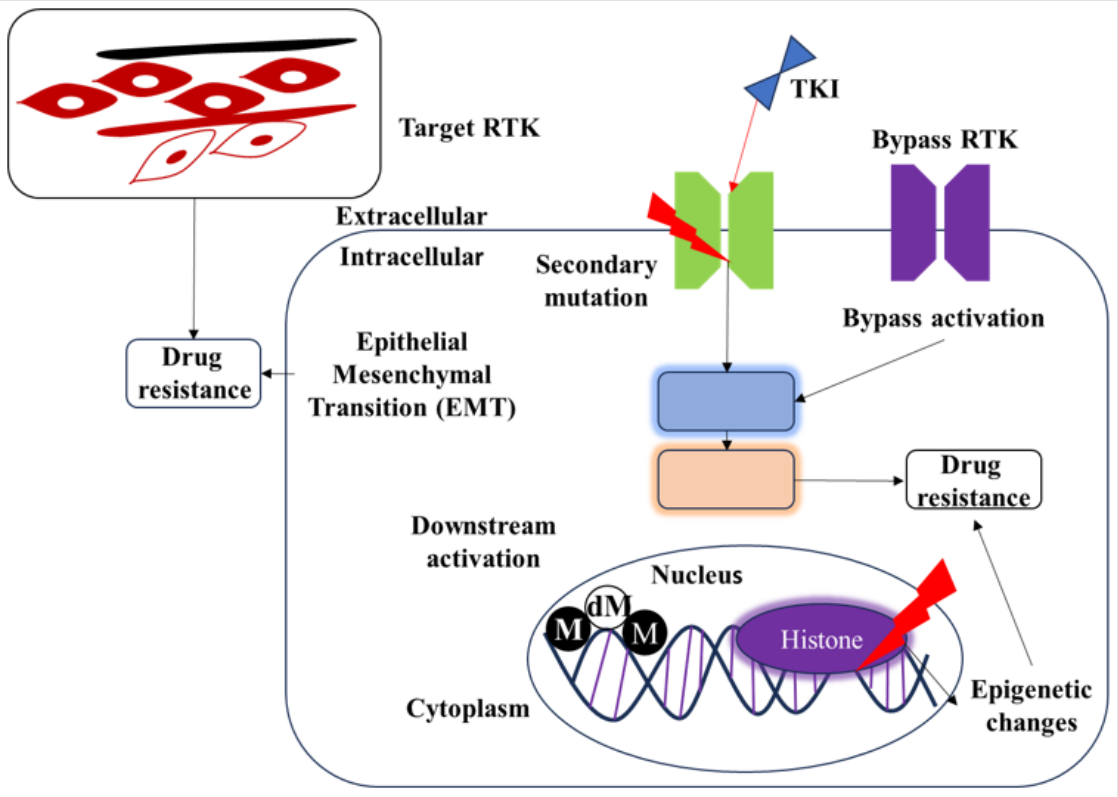


Figure 3: A schematic of drug resistance mechanistic path in cancer cells highlights two main types: pathway-dependent (black) and pathway-independent (red). Pathway-dependent mechanisms involve activation of target receptors (e.g., EGFR mutations), downstream component mutations (e.g., PIK3CA), or bypass activation leading to pathway amplification. Pathway-independent mechanisms mainly entail epigenetic changes, such as epithelial–mesenchymal transition (EMT) and alterations in the tumor microenvironment. These mechanisms act crucial roles in cancer treatment resistance.

Nanoparticles (NPS) in Cancer Treatment

Nanoparticles (NPs) applied in medical diagnostic must have particular sizes, shapes, and surface characteristics, which significantly affect nano-drug delivery efficiency and therapeutic efficacy [87]. NPs ranging from 10 to 100 nm in diameter are preferred for cancer therapy due to their ability to effectively deliver drugs and exploit the enhanced permeability and retention (EPR) effect. Smaller particles risk leakage from normal vasculature or kidney filtration [88], while larger particles face phagocyte clearance [89]. Surface modifications, like coating with hydrophilic materials such as polyethylene glycol (PEG), reduce opsonization, enhancing circulation time and tumor penetration [90]. These tailored characteristics determine NPs' therapeutic impact in cancer management. Figure 4 illustrates different NP types for cancer therapy, with subsequent text detailing their advantages in tumor treatment (Figure 4).

Inorganic Nanoparticles: In recent years, inorganic nanocarrier have been extensively studied for therapeutic along with imaging applications due to their numerous supremacies, including large surface area, high drug loading capacity, improved bioavailability, reduced toxic side effects, sustained drug release, and compatibility with most organic solvents, unlike polymer-based nanoparticles. Quantum dots, carbon nanotubes, layered double hydroxides, mesoporous silica, and magnetic nanoparticles, presented in Figure 5, are commonly utilized in cancer treatment. Quantum dots particularly excel as imaging probes, offering potent capabilities for long-term, multiplexed, and quantitative imaging and diagnostics [91-93]. Zero-dimensional fluorescent nanoparticles, like quantum dots (QDs) sized between 1–10 nm, are highly promising for targeted drug delivery, intracellular monitoring, resistance to photobleaching, and multicolor imaging. However, challenges such as hydrophobicity and aggregation hinder their biological applications. Coating QDs with polar species or ligand shells enhances water solubility and bioactivity. Multifunctional QDs, embedded with imaging agents and hydrophobic drugs, and carrying hydrophilic therapeutic agents and targeting biomolecules, show promise for cancer targeting and therapy. Recently, polymer-coated QDs have emerged as potential vehicles for cancer diagnosis and image-guided chemotherapy [94]. AuNPs, extensively researched inorganic NPs, particularly mixed monolayer-protected clusters with a gold core, show promise in drug delivery.

DOI: 10.26717/BJSTR.2024.57.009034

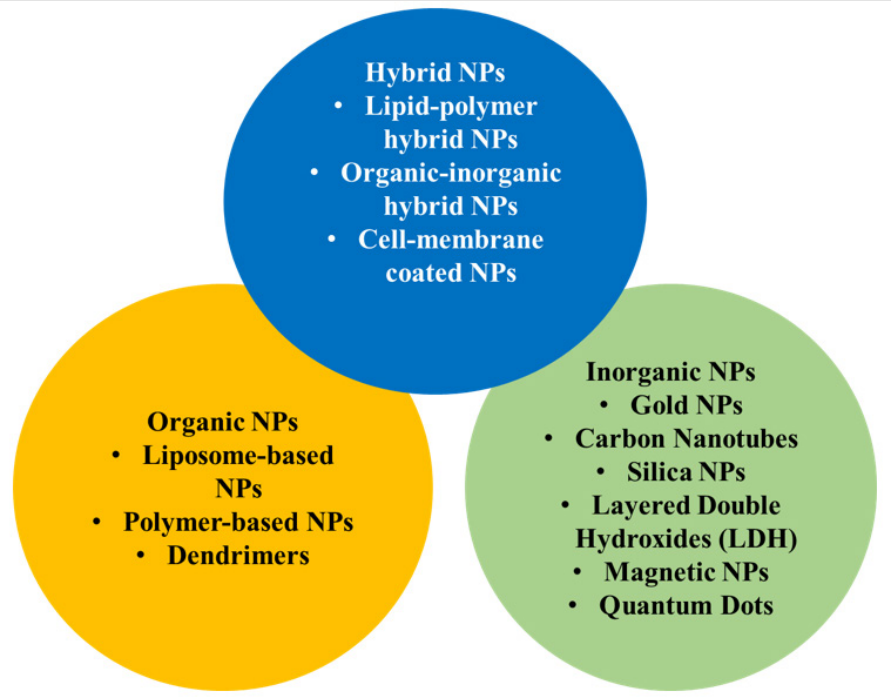


Figure 4: Nanoparticles (NPs) for cancer therapy encompass various types including organic, inorganic, and hybrid NPs.

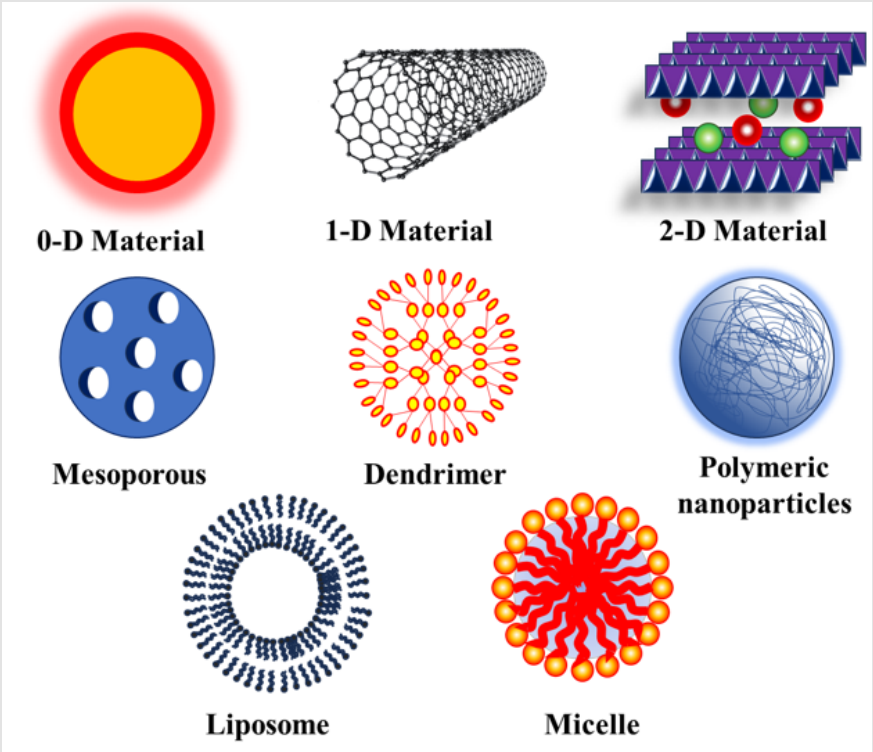


Figure 5: Different types of nanocarriers for using the nanotechnology-based cancer drug resistance mechanism.

Their inert, non-toxic gold core, along with surface functionalization, enhances drug accumulation in tumors and overcomes drug resistance. Additionally, AuNPs are explored for multimodal cancer treatment, including gene therapy, photothermal therapy, and immunotherapy [95]. Carbon nanotubes (CNTs) are synthetic one-dimensional nanomaterials composed of rolled sheets of graphene rings made from sp2 hybridized carbon atoms, forming hollow tubes. They are utilized for near-infrared photothermal ablation therapy, elevating tumor temperature upon light exposure. Water-soluble, functionalized CNTs are explored for gene and drug delivery due to their ability to cross biological barriers efficiently without toxicity. Chemotherapeutic drugs are often linked to CNTs through surface functional groups or polymer coatings via cleavable bonds. In antitumor immunotherapy, CNTs serve as antigen-presenting carriers, enhancing the immunogenicity of tumor-based peptides/antigens to stimulate a humoral immune response within tumors [96,97]. Mesoporous silica nanoparticle carriers, known as SNPs, excel in drug delivery due to their large internal pore volume, which maximizes drug encapsulation. Their supramolecular components act as caps, facilitating drug capture and release. SNPs offer superior pharmacokinetics, treatment efficacy, and stability, making them prime candidates for drug delivery vehicles. Additionally, porous silicon NPs exhibit promising potential in immunotherapy by promoting antigen cross-presentation, lymphocyte polarization, and interferon-γ secretion [98].

Magnetic nanoparticles (MNPs) for drug delivery typically consist of metal or metal oxide nanoparticles. To enhance stability and biocompatibility, MNPs are often coated with organic materials like polymers and fatty acids. They exhibit promising effectiveness in chemotherapy and gene therapy for cancer treatment. Additionally, MNPs enable magnetic hyperthermia, allowing for tumor thermal ablation, presenting an alternative cancer treatment option [99]. Among inorganic nanocarriers, 2D layered double hydroxides (LDHs) are gaining attention due to their biocompatibility, anion exchange capability, high drug loading efficacy, pH-responsive release, and ease of preparation. LDHs, composed of divalent and trivalent metal ions, can carry anions between layers, facilitating drug loading and release. They protect drugs, allow functionalization for targeting, and possess high surface area and stability for various applications [94,100] (Figure 5).

Organic Nanomaterials: In general, the nanoparticles of polymer are solid, biocompatible, colloidal, and often biodegradable systems with nanoscale dimensions. They are simple soft materials for nanomedicine, easily modifiable for desired properties such as drug loading efficacy and biodistribution. Made from synthetic (e.g., PLA, PLGA, PCL) [101-103], or natural polymers (e.g., gelatin, chitosan, cyclodextrin) [104-109], they enable controlled drug delivery via various mechanisms. Synthetic polymers offer sustained release benefits over natural ones. Widely investigated for drug delivery, FDA-approved examples include PLA and PLGA. Strategies like drug conjugation and careful manipulation of parameters allow fine-tuning of drug release for effective cancer treatment [94]. Organic NPs, like liposomes, widely explored for decades. Liposomes consist of an outer lipid layer and a drug-containing core. They mimic living cells and enhance therapeutic drug delivery. Liposomes, evolving through generations, are crucial in cancer therapy, delivering drugs like doxorubicin and paclitaxel [110] with higher efficiency. They reduce cardiotoxicity, offer drug combination options, and combat drug resistance. Many liposome-based drugs now in clinical use for cancer treatment.

Hybrid Nanoparticles: Combining organic and inorganic nanoparticles (NPs) enhances drug delivery effectiveness and reduces resistance. Lipid-polymer hybrid NPs are promising for treating various cancers. They encapsulate both hydrophilic and hydrophobic drugs efficiently. Liposome-silica hybrids (LSH) effectively deliver drugs to kill cancer cells. Advanced nano-in-micro platforms improve drug delivery and enhance cell death in resistant cancers. Hybrid NPs like CNTs and chitosan increase anticancer activity while reducing toxicity. Metal multilayer half-shells and PLGA hybrids can target drug delivery and hyperthermia for tumor cell destruction. Hybridizing natural biomaterials with organic or inorganic NPs, like cell membrane coating nanotechnology, enhances NP biological characteristics. Coatings from leukocytes, red blood cells, platelets, cancer cells, and bacteria have shown promise. For example, leukocyte-derived cell membrane coating on nanoporous silicon particles prevents phagocyte clearance, increasing circulation time and tumor accumulation. Cancer cell membrane-cloaked mesoporous silica NPs improve stability and targeting. Dual-membrane coatings, such as erythrocyte-platelet hybrids, enhance stability and circulation life. Multistage NP delivery systems, like protease degradation of 100-nm gelatin NPs to release 10-nm quantum dot NPs, enable deep tumor penetration [111].

Mechanistic Pathways of Targeting

Targeting cancer cells specifically is crucial for nano-carriers in drug delivery, enhancing efficacy while safeguarding normal cells. Extensive studies focus on NP-based drug targeting design. Understanding tumor biology and nano-carrier interaction is essential. Targeting mechanisms include passive and active targeting reflects in Figure 6 (Figure 6). Active targeting in cancer therapy involves ligands on nanoparticles (NPs) interacting with overexpressed molecules on cancer cells, distinguishing them from healthy cells. This interaction induces receptor-mediated endocytosis, enabling targeted drug delivery, especially for macromolecular drugs such as proteins along with siRNAs. Attacking moieties incorporate monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates, binding to receptors like transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR). Passive targeting exploits tumor characteristics for drug delivery. Cancer cell proliferation induces leaky vasculature, allowing nanocarriers to accumulate in tumors via the EPR effect. Tumor microenvironment, including acidic pH, enhances drug release. Limitations include non-specific distribution and variability in EPR effect and vessel permeability across tumors.

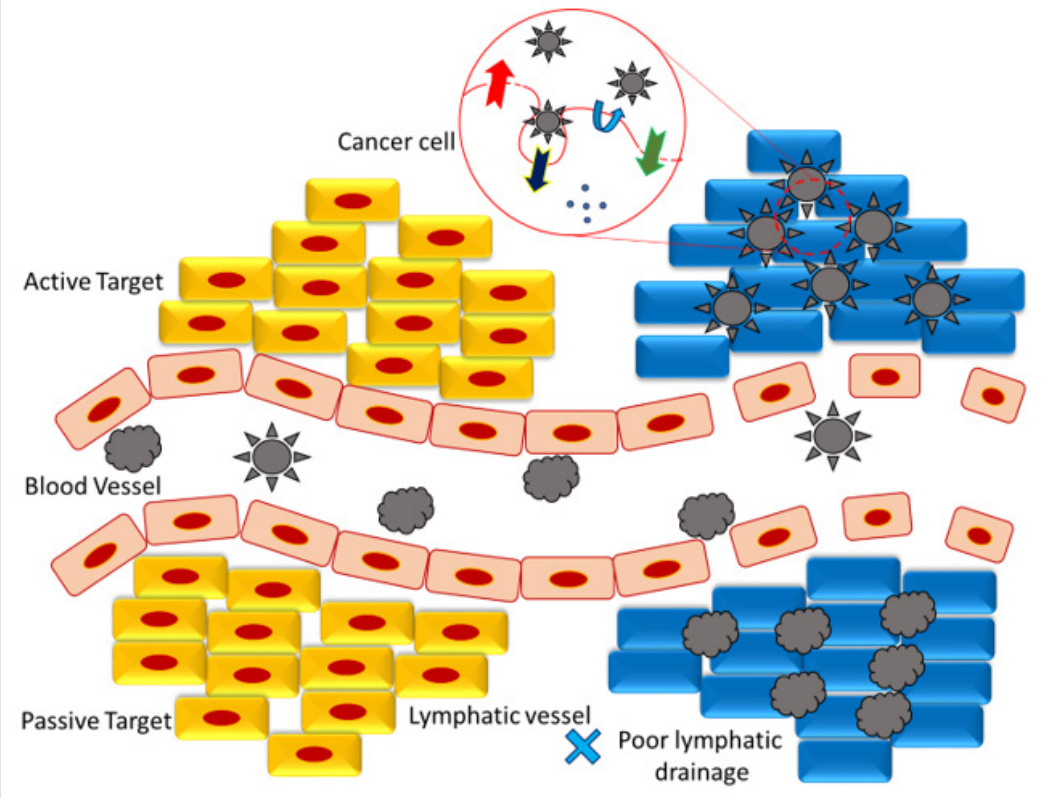


Figure 6: Passive and active targeting of nanoparticles (NPs) to cancer cells enhances therapy efficacy while minimizing systemic toxicity. Passive targeting utilizes the enhanced permeability and retention (EPR) effect, leveraging increased vascular permeability and weakened lymphatic drainage. Active targeting involves ligand-receptor interactions, with receptors on cancer cells including transferrin, folate, glycoproteins, and EGFR [111].

Attacking to Endothelium

Some nanoparticles (NPs) target angiogenesis instead of cancer cells directly. VEGF and VEGFR interaction are crucial in vascularization [112]. Liposomes targeting VEGFR-2 and VEGFR-3 simultaneously enhance efficacy [113]. Integrins, especially avb3, facilitate tumor cell migration. Cationic NPs with $\alpha v\beta 3$ ligands show promising gene delivery. $\alpha v\beta 3$ integrin is linked to VEGFR-2 signaling, enhancing anti-VEGFR treatment effectiveness. VCAM-1 is expressed in tumor endothelium, aiding NP drug delivery. VCAM-1 targeted NPs demonstrate high efficiency in breast cancer models. MMP in the tumor microenvironment aids in extracellular matrix remodeling and neovascularization [114].

Mechanisms of Nanomaterials to Overcome the Drug Resistance

Drug resistance remains a significant hurdle in cancer treatment despite advances in therapy methods. Multidrug resistance undermines various treatments, fueling cancer progression and dismal prognoses. Mechanisms include ABC transporter overexpression, faulty apoptotic pathways, and hostile tumor microenvironments.

Nanoparticles Attacking Hypoxic Tumor Microenvironment: Hypoxia contributes to multidrug resistance in cancer by inducing tumor cells into a drug-resistant state and increasing tumor heterogeneity. Targeting hypoxiainducible factor 1 α (HIF-1 α), NPs containing HIF-1 α siRNA, and inhibitors of heat shock protein 90 (HSP90) show promise in overcoming drug resistance [111]. Researchers recently proposed a new nano-chemotherapy approach involving a liposome nanodrug holding glucose oxidase (GOx), tirapazamine (TPZ), and platinum (IV) prodrug. This innovative strategy aims to maximize drug utilization and exacerbate intracellular hypoxia in cisplatin-resistant tumor cells, thereby fully activating TPZ's therapeutic effects. Activated TPZ effectively suppresses the expression of the XPF protein, which promotes DNA repair in tumor cells, resulting in synergistically enhanced antitumor therapy when combined with platinum drugs [115]. The schematic presentation is in Figure 7.

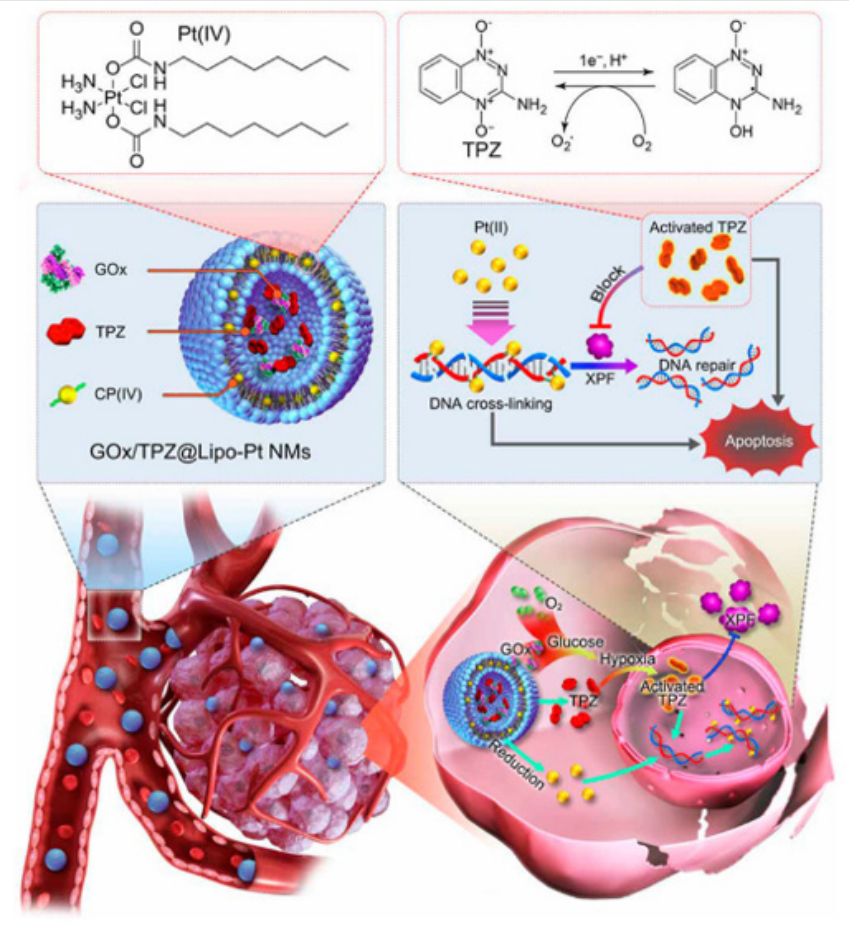


Figure 7: Diagrammatic presentation of the GOx/TPZ@Lipo-Pt nanomaterial along with hypoxia-induced reversal of cisplatin resistance. Replicate with permission [115]. Copyright 2021, American Chemical Society.

Advantage of Nanocarriers to Overcome the Cancer Drug Pump Efflux: The development of nanotechnology has led to the discovery of numerous new nanostructures, with gold nanoparticles (AuNPs) standing out due to their principal optical characteristics and surface plasmon resonance effect. Attaching polyethylene glycol (PEG) to AuNPs enhances stability and circulation time of chemotherapy drugs. Modifying AuNPs' shape to nanorods shifts the surface plasmon band (SPR), enabling near-infrared (NIR) absorption for deeper tissue penetration. AuNPs, including gold nanorods, show promise in circumventing drug resistance, exemplified by Vishwakarma et al. on sorafenib-gold nanoconjugates (SF-GNP) reversing drug resistance in liver cancer cells. Additionally, nitric oxide (NO)-stimulated nanosystems combat multidrug resistance by inhibiting ABC transporters. Nitric oxide (NO) reverses cancer cell drug resistance by reducing P-glycoprotein (P-gp) expression, aiding treatment of doxorubicin (Dox)-resistant cancer cells. Wang et al. developed a sophisticated nano system, ADLAu@CuS YSNPs, releasing NO and doxorubicin (Dox) sequentially, offering a potential avenue for drug-resistant cancer therapy [116]. This system involved embedding an NO-responsive lipid in a liposome's bilayer structure, encapsulating l-arginine/Dox-loaded gold@copper sulfide yolk-shell nanoparticles (ADAu@CuS YSNPs) to generate ADLAu@CuS YSNPs. Under 808 nm laser irradiation, the process generated reactive oxygen species (ROS) that converted l-Arg into NO, progressively destabilizing the liposome and eventually releasing Dox. This sequential release significantly inhibited P-gp expression, enhancing Dox accumulation in Dox-resistant MCF-7/ADR cells and demonstrating promise for MDR cancer therapy. In the eloquence of Figure 8, we find not just a representation, but a narrative-a story of perseverance, of resilience, and ultimately, of triumph over adversity.

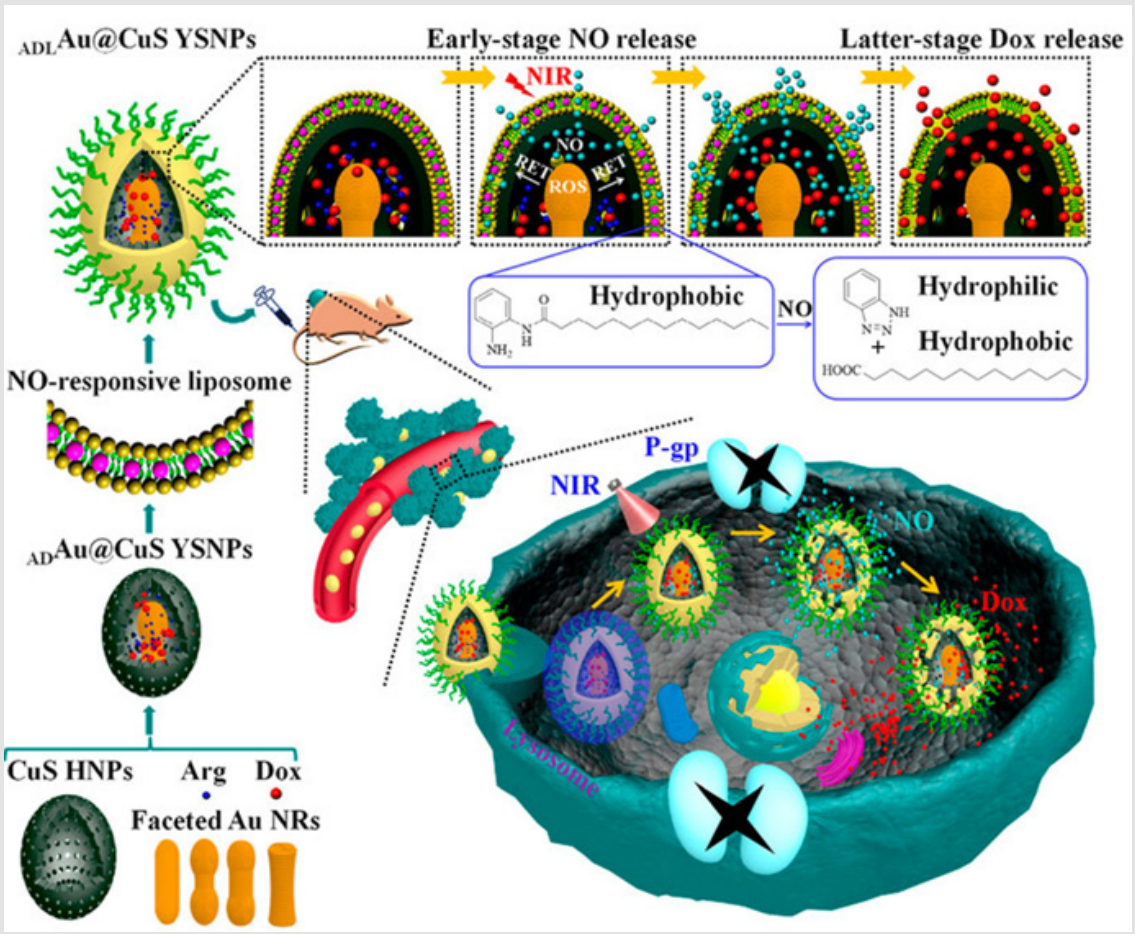


Figure 8: Presentation of the NO and Dox programmable released ADLAu@CuS YSNPs in MDR cancer therapy. Reproduced with permission [116].

Functions of Co-Delivery Nano-Formulations for Targeting Drug Resistance Mechanism: The co-delivery system of chemo-pharmaceutical agents and siRNA is a potent nano-therapeutic approach for targeting tumor cells. By targeting drug-resistant associated genes like MDR1, STC2, K-Ras, and Bcl2, it effectively overcomes drug resistance in various cancers. Zhang et al. developed a pH-sensitive nanocarrier, DOX + siRNA/ePL, which demonstrated enhanced cellular uptake, endosomal escape, and significant inhibition of proliferation, apoptosis induction, and downregulation of P-gp expression in vivo, making it a promising solution for drug-resistant breast cancer treatment [117] and is presented in Figure 9. Antitumor drugs with siRNA can overcome this resistance. A pH-sensitive and targetable drug delivery system was developed to co-deliver MDR1-siRNA and DOX. This carrier, EphA10 antibody-conjugated pH-sensitive doxorubicin (DOX), MDR1-siRNA lipoplexes (DOX + siRNA/ePL), showed stability and favorable properties. It increased cellular uptake, downregulated P-gp, and enhanced cytotoxicity in breast cancer cells (MCF-7/ADR). Colocalization studies confirmed pH-responsive endosomal escape. In vivo, DOX + siRNA/ePL prolonged circulation, accumulated in tumors via receptor-mediated endocytosis, and demonstrated antitumor effects. This system holds promise for overcoming MDR.

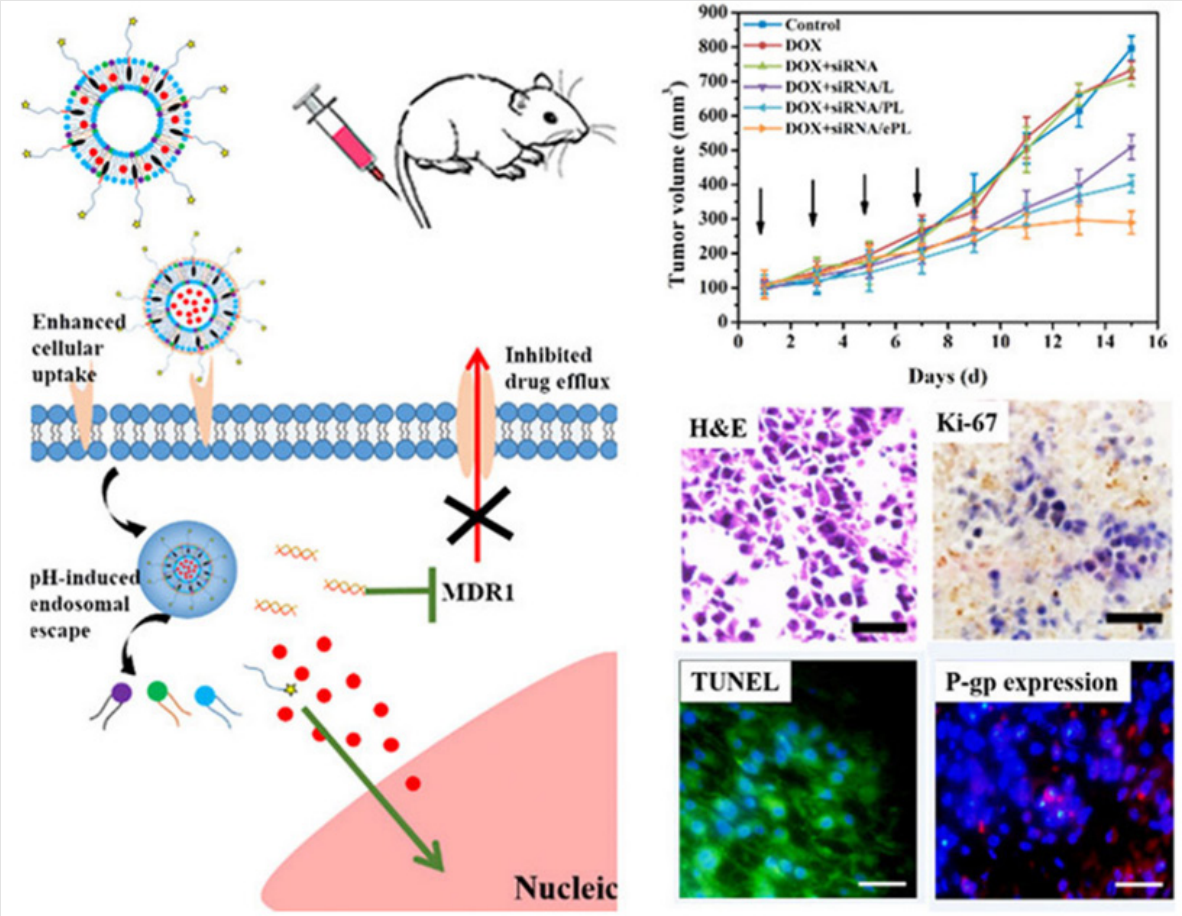


Figure 9: Schematic presentation of multifunctional DOX + siRNA/ePL lipoplexes to overcome MDR effect. Reproduced with permission [117].

Function of Nanoparticles in Cancer Immunotherapy to Overcome Drug Resistance: The rise of immunotherapy marks a new era in cancer treatment, where nanoparticles (NPs) serve crucial roles in both chemotherapy delivery and immunotherapy applications. Cancer immunotherapy primarily activates the anti-tumor immune response, with NP-associated methods including nanovaccines, artificial antigen-presenting cells (aAPCs), and targeting the immunosuppressive tumor microenvironment (TME). Nanovaccines deliver tumor-associated antigens (TAAs) and adjuvants to antigen-presenting cells (APCs), enhancing immune responses against tumors. Various NPs such as liposomes, gold NPs, PLGA NPs, micelles, and dendrimers aid in cytoplasmic delivery of TAAs into APCs, bolstering immune responses. Inorganic NPs and polymers like mesoporous silica and acetylated dextran (AcDEX) act as adjuvants, stimulating immune responses. Artificial APCs directly activate T cells, while targeting the immunosuppressive TME involves combating tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). NPs are often PEG-modified to minimize interactions with the reticuloendothelial system. Combining chemotherapy with immunotherapy shows promise, with studies demonstrating enhanced immune responses and tumor cell death while minimizing toxicity in immune cells. Alternative strategies include co-delivery of chemotherapeutics along with monoclonal antibodies using porous silicon NPs, effectively stimulating immune responses against cancer cells [111].

Conclusion and Future Perspectives

High lifetime cancer probabilities for men (45%) and women (38%) contribute to 1 in 4 deaths in are alarming. Despite extensive knowledge, cancer continues to outpace our understanding. Development has been shaped in uncovering cellular and molecular mechanisms of progression, metastasis, and invasion, offering potential avenues for nanodrug therapy when conventional treatments fail. However, drug resistance persists as a significant challenge even after initial positive responses [118]. Nanotechnology transforms cancer treatment by enhancing drug delivery, targeting, and reducing toxicity. Nanoparticle-based therapies, spanning chemotherapy to gene therapy, offer improved outcomes and resistance reversal, marking a

new era in cancer care. Increasing research has highlighted the efficacy of hybrid NPs in drug delivery, prompting greater interest. Further exploration of cancer biology will refine drug development. Designing hybrid NPs for precise cancer therapy and enhancing targeting mechanisms warrant attention. Nanoparticles interactions with the immune system are intricate, influenced by size, shape, composition, and surface properties. While nano vaccines and artificial APCs show promise, their clinical efficacy requires enhancement, and safety concerns persist. Loaded with immunomodulatory factors, NPs could enhance vaccine effectiveness for immunotherapy. Understanding the tumor microenvironment and nanoparticle-tumor immunity crosstalk is crucial for optimizing drug design and utilization.

Acknowledgements

The University Grants Commission (UGC), New Delhi, India, provided funding for the author's (SM) fellowship is highly acknowledged. The research support grant of Tata Innovation Fellowship (sanction no. BT/HRD/35/01/02/2020) is also acknowledged. The research support grants of SERB (sanction no. IPAj2020/000025 and CRG/2022/004287) are also acknowledged.

Author Contributions

This study's conception and critical analysis were provided by Swapan Maity, Dipesh Kumar Dubey and Prof. Pralay Maiti.

Competing Interests

The authors claim to have no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA: A Cancer Journal for Clinicians 68(1): 7-30.
2. Beheshti M (2018) Different strategies to overcome multidrug resistance in cancer Research review. International Pharmacy Acta 31(8): 1397-1407.
3. Batrakova EV, Kabanov AV (2008) Pluronic block copolymers: evolution of drug delivery concept from inert nanocarriers to biological response modifiers. Journal of Controlled Release 130(2): 98-106.
4. Maeda H, Khatami M (2018) Analyses of repeated failures in cancer therapy for solid tumors: poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs. Clinical and translational medicine 7(1): 11.
5. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G (2008) Immunological aspects of cancer chemotherapy. Nature reviews immunology 8(1): 59-73.
6. Gottesman MM, Lavi O, Hall MD, Gillet JP (2016) Toward a better understanding of the complexity of cancer drug resistance. Annual review of pharmacology and toxicology 56: 85-102.
7. LS Goodman, MM Wintrobe (1946) Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. Journal of the American Medical Association 132: 126-132.
8. Barinaga M (1997) From bench top to bedside. Science 278(5340): 1036-1039.
9. Nabholtz JM, Slamon D (2001) New adjuvant strategies for breast cancer: meeting the challenge of integrating chemotherapy and trastuzumab (Herceptin). In Seminars in oncology 28(1): 1-12.
10. Kreitman RJ (2006) Immunotoxins for targeted cancer therapy. The AAPS journal 8(3).
11. OBrien ME, Wigler N, Inbar MCBCSG, Rosso R, Grischke E, et al. (2004). Reduced cardiotoxicity and comparable efficacy in a phase IIItrial of pegylated liposomal doxorubicin HCl (CAELYX™/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Annals of oncology 15(3): 440-449.
12. Cortes J, Saura C (2010) Nanoparticle albumin-bound (nab™)-paclitaxel: improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer. European Journal of Cancer Supplements 8(1): 1-10.
13. Riley RS, Day ES (2017) Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. Wiley Interdisciplinary Reviews Nanomedicine and Nanobiotechnology 9(4): 10.
14. Yoon HY, Selvan ST, Yang Y, Kim MJ, Yi DK, et al. (2018). Engineering nanoparticle strategies for effective cancer immunotherapy. Biomaterials 178: 597-607.
15. Zang X, Zhao X, Hu H, Qiao M, Deng Y, et al. (2017) Nanoparticles for tumor immunotherapy. European Journal of Pharmaceutics and Biopharmaceutics 115: 243-256.
16. Li W, Zhang H, Assaraf YG, Zhao K, Xu X, et al. (2016) Overcoming ABC transporter-mediated multidrug resistance: Molecular mechanisms and novel therapeutic drug strategies. Drug Resistance Updates 27: 14-29.
17. Alimoradi H, Greish K, Barzegar-Fallah A, Alshaibani L, Pittalà V, et al. (2018) Nitric oxide-releasing nanoparticles improve doxorubicin anticancer activity. International journal of nanomedicine (13): 7771-7787.
18. Wang H, Agarwal P, Zhao G, Ji G, Jewell CM, et al. (2018) Overcoming ovarian cancer drug resistance with a cold responsive nanomaterial. ACS central science 4(5): 567-581.
19. Zhang J, Wang L, You X, Xian T, Wu J, et al. (2019) Nanoparticle therapy for prostate cancer: overview and perspectives. Current Topics in Medicinal Chemistry 19(1): 57-73.
20. Gottesman MM (2002) Mechanisms of cancer drug resistance. Annual review of medicine 53(1): 615-627.
21. Sampath D, Cortes J, Estrov Z, Du M, Shi Z, et al. (2006) Pharmacodynamics of cytarabine alone and in combination with 7-hydroxystaurosporine (UCN-01) in AML blasts *in vitro* and during a clinical trial. Blood 107(6): 2517-2524.
22. Xue M, Cheng J, Zhao J, Zhang S, Jian J, et al. (2019) Outcomes of 219 chronic myeloid leukaemia patients with additional chromosomal abnormalities and/or tyrosine kinase domain mutations. International journal of laboratory hematology 41(1): 94-101.
23. Yeldag G, Rice A, del Río Hernández A (2018) Chemoresistance and the self-maintaining tumor microenvironment. Cancers 10(12): 471.
24. Li ZW, Dalton WS (2006) Tumor microenvironment and drug resistance in hematologic malignancies. Blood reviews 20(6): 333-342.
25. Dalton WS (2003) The tumor microenvironment: focus on myeloma. Cancer treatment reviews 29(S1): 11-19.
26. Hazlehurst LA, Landowski TH, Dalton WS (2003) Role of the tumor microenvironment in mediating de novo resistance to drugs and physiological mediators of cell death. Oncogene 22(47): 7396-7402.
27. Benner SE, Wahl GM, Von Hoff DD (1991) Double minute chromosomes and homogeneously staining regions in tumors taken directly from pa-

tients versus in human tumor cell lines. Anti-cancer drugs 2(1): 11-26.

28. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, et al. (2013) Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 155(6): 1309-1322.
29. Gupta PB, Fillmore CM, Jiang G, Shapira SD, Tao K, et al. (2011) Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. Cell 146(4): 633-644.
30. Kreso A, OBrien CA, Van Galen P, Gan OI, Notta F, et al. (2013) Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. Science 339(6119): 543-548.
31. Nathanson DA, Gini B, Mottahedeh J, Visnyei K, Koga T, et al. (2014) Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA. Science 343(6166): 72-76.
32. Gatenby RA, Gillies RJ, Brown JS (2010) The evolutionary dynamics of cancer prevention. Nature Reviews Cancer 10(8): 526-527.
33. Junttila MR, De Sauvage FJ (2013) Influence of tumour micro-environment heterogeneity on therapeutic response. Nature 501(7467): 346-354.
34. Pal B, Bayat Mokhtari R, Li H, Bhuyan R, Talukdar J, et al. (2016) Stem cell altruism may serve as a novel drug resistance mechanism in oral cancer. Cancer Research 76(S14): 251-251.
35. Settleman J (2016) Bet on drug resistance. Nature 529(7586): 289-290.
36. Dean M, Fojo T, Bates S (2005) Tumour stem cells and drug resistance. Nature Reviews Cancer 5(4): 275-284.
37. Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, et al. (2020). A framework for advancing our understanding of cancer-associated fibroblasts. Nature Reviews Cancer 20(3): 174-186.
38. Liu T, Han C, Wang S, Fang P, Ma Z, et al. (2019) Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. Journal of hematology & oncology 12(1): 86.
39. Ma Y, Wang Y, Xu Z, Fallon JK, Liu F, et al. (2017) Extreme low dose of 5-fluorouracil reverses MDR in cancer by sensitizing cancer associated fibroblasts and down-regulating P-gp. PLOS one 12(6): e0180023.
40. Vaidya FU, Sufiyan Chhipa A, Mishra V, Gupta VK, Rawat SG, et al. (2022) Molecular and cellular paradigms of multidrug resistance in cancer. Cancer reports 5(12): e1291.
41. Sreedhar A, Zhao Y (2018) Dysregulated metabolic enzymes and metabolic reprogramming in cancer cells. Biomedical reports 8(1): 3-10.
42. Amin S, Yang P, Li Z (2019) Pyruvate kinase M2: a multifarious enzyme in non-canonical localization to promote cancer progression. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1871(2): 331-341.
43. Lu H, Ouyang W, Huang C (2006) Inflammation, a key event in cancer development. Molecular cancer research 4(4): 221-233.
44. Kobayashi H, Lin PC (2009) Angiogenesis links chronic inflammation with cancer. Methods Mol Biol 511: 185-191.
45. Liu J, Charles Lin P, P Zhou B (2015) Inflammation fuels tumor progress and metastasis. Current pharmaceutical design 21(21): 3032-3040.
46. Farooque A, Afrin F, Adhikari JS, Dwarakanath BS (2009) Protection of normal cells and tissues during radio-and chemosensitization of tumors by 2-deoxy-D-glucose. Journal of Cancer Research and Therapeutics 5(S1): S32-S35.
47. Niiya M, Niiya K, Kiguchi T, Shibakura M, Asaumi N, et al. (2003) Induction of TNF-α, uPA, IL-8 and MCP-1 by doxorubicin in human lung carcinoma cells. Cancer chemotherapy and pharmacology 52: 391-398.
48. De Larco JE, Wuertz BR, Manivel JC, Furcht LT (2001) Progression and enhancement of metastatic potential after exposure of tumor cells to chemotherapeutic agents. Cancer Research 61(7): 2857-2861.
49. Bin Emran T, Shahriar A, Mahmud A, Rahman T, Abir M, et al. (2022) Multidrug resistance in cancer: Understanding molecular mechanisms, immunoprevention and therapeutic approaches. Frontiers in Oncology 12: 891652.
50. Kathawala RJ, Gupta P, Ashby Jr CR, Chen ZS (2015) The modulation of ABC transporter-mediated multidrug resistance in cancer: a review of the past decade. Drug resistance updates 18: 1-17.
51. Wilkens S (2015) Structure and mechanism of ABC transporters. F1000prime reports 7.
52. Dean M, Hamon Y, Chimini G (2001) The human ATP-binding cassette (ABC) transporter superfamily. Journal of lipid research 42(7): 1007-1017.
53. Xue X, Liang XJ (2012) Overcoming drug efflux-based multidrug resistance in cancer with nanotechnology. Chinese journal of cancer 31(2): 100-109.
54. Yin Y, Li W, Deng M, Zhang P, Shen Q, et al. (2014) Extracellular high mobility group box chromosomal protein 1 promotes drug resistance by increasing the expression of P glycoprotein expression in gastric adenocarcinoma cells. Molecular medicine reports 9(4): 1439-1443.
55. Ambudkar SV, Dey S, Hrycyna CA, Ramachandra M, Pastan I, et al. (1999) Biochemical, cellular, and pharmacological aspects of the multidrug transporter. Annual review of pharmacology and toxicology 39(1): 361-398.
56. Ward AB, Szewczyk P, Grimard V, Lee CW, Martinez L, et al. (2013) Structures of P-glycoprotein reveal its conformational flexibility and an epitope on the nucleotide-binding domain. Proceedings of the National Academy of Sciences 110(33): 13386-13391.
57. Cascorbi I (2011) P-glycoprotein: tissue distribution, substrates, and functional consequences of genetic variations. Drug transporters (201): 261-283.
58. Sui H, Fan ZZ, Li Q (2012) Signal transduction pathways and transcriptional mechanisms of ABCB1/Pgp-mediated multiple drug resistance in human cancer cells. Journal of International Medical Research 40(2): 426-435.
59. Szakács G, Paterson JK, Ludwig JA, Booth Genthe C, Gottesman MM, et al. (2006) Targeting multidrug resistance in cancer. Nature reviews Drug discovery 5(3): 219-234.
60. Callaghan R, Luk F, Bebawy M (2014) Inhibition of the multidrug resistance P-glycoprotein: time for a change of strategy? Drug Metabolism and Disposition 42(4): 623-631.
61. Zhang J, Zhou F, Wu X, Zhang X, Chen Y, et al. (2012). Cellular pharmacokinetic mechanisms of adriamycin resistance and its modulation by 20 (S)-ginsenoside Rh2 in MCF-7/Adr cells. British journal of pharmacology 165(1): 120-134.
62. Kruh GD, Belinsky MG (2003) The MRP family of drug efflux pumps. Oncogene 22(47): 7537-7552.
63. Stavrovskaya AA (2000) Cellular mechanisms of multidrug resistance of tumor cells. Biochemistry c/c of Biokhimiia 65(1): 95-106.
64. Lu JF, Pokharel D, Bebawy M (2015) MRP1 and its role in anticancer drug resistance. Drug metabolism reviews 47(4): 406-419.
65. Staud F, Pavek P (2005) Breast cancer resistance protein (BCRP/ABCG2). The international journal of biochemistry & cell biology 37(4): 720-725.
66. McIntosh K, Balch C, Tiwari AK (2016) Tackling multidrug resistance mediated by efflux transporters in tumor-initiating cells. Expert opinion on drug metabolism & toxicology 12(6): 633-644.

67. Mao Q, Unadkat J D (2015) Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport—an update. The AAPS journal 17(1): 65-82.

68. Horsey AJ, Cox MH, Sarwat S, Kerr ID (2016) The multidrug transporter ABCG2: still more questions than answers. Biochemical Society Transactions 44(3): 824-830.

69. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, et al. (2001) Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. New England Journal of Medicine 344(14): 1038-1042.

70. Zahreddine H, Borden K (2013) Mechanisms and insights into drug resistance in cancer. Frontiers in pharmacology 4: 28.

71. Michael M, Doherty MM (2005) Tumoral drug metabolism: overview and its implications for cancer therapy. Journal of Clinical Oncology 23(1): 205-229.

72. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B, et al. (2017). The different mechanisms of cancer drug resistance: a brief review. Advanced pharmaceutical bulletin 7(3): 339-348.

73. Ferguson LR, Chen H, Collins AR, Connell M, Damia G, et al. (2015) Genomic instability in human cancer: Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition. In Seminars in cancer biology 35.

74. McGranahan N, Burrell RA, Endesfelder D, Novelli MR, Swanton C, et al. (2012) Cancer chromosomal instability: therapeutic and diagnostic challenges: 'Exploring aneuploidy: the significance of chromosomal imbalance review series. EMBO reports 13(6): 528-538.

75. Luqmani YA (2005) Mechanisms of drug resistance in cancer chemotherapy. Medical principles and practice 14(S1): 35-48.

76. Tung MC, Lin PL, Wang YC, He TY, Lee MC, et al. (2015) Mutant p53 confers chemoresistance in non-small cell lung cancer by upregulating Nrf2. Oncotarget 6(39): 41692-41705.

77. Fiorini C, Cordani M, Padroni C, Blandin G, Di Agostino S, et al. (2015). Mutant p53 stimulates chemoresistance of pancreatic adenocarcinoma cells to gemcitabine. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research 1853(1): 89-100.

78. De Pagter MS, Kloosterman WP (2015) The diverse effects of complex chromosome rearrangements and chromothripsis in cancer development. Chromosomal Instability in Cancer Cells 200: 165-193.

79. Beach LR, Palmiter RD (1981) Amplification of the metallothionein-I gene in cadmium-resistant mouse cells. Proceedings of the National Academy of Sciences 78(4): 2110-2114.

80. Lothstein L, Hsu SI, Horwitz SB, Greenberger LM (1989) Alternate overexpression of two phosphoglycoprotein genes is associated with changes in multidrug resistance in a J774. 2 cell line. Journal of Biological Chemistry 264(27): 16054-16058.

81. Higgins CF (1992) ABC transporters: from microorganisms to man. Annual review of cell biology 8(1): 67-113.

82. De Vree JML, Jacquemin E, Sturm E, Cresteil D, Bosma PJ, et al. (1998) Mutations in the MDR 3 gene cause progressive familial intrahepatic cholestasis. Proceedings of the National Academy of Sciences 95(1); 282-287.

83. García Pérez J, López Abente G, Gómez Barroso D, Morales Piga A, Romaguera EP, et al. (2015) Childhood leukemia and residential proximity to industrial and urban sites. Environmental research 140: 542-553.

84. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, et al. (2015) Childhood acute lymphoblastic leukemia: progress through collaboration. Journal of Clinical Oncology 33(27): 2938-2948.

85. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. Nature Reviews Cancer 13(10): 714-726.

86. Wojtuszkiewicz A, Assaraf YG, Hoekstra M, Jansen G, Peters GJ, et al. (2015) The relevance of aberrant FPGS splicing for *ex vivo* MTX resistance and clinical outcome in childhood acute lymphoblastic leukemia. Cancer Research 75(S15): 4437-4437.

87. Bahrami B, Hojjat Farsangi M, Mohammadi H, Anvari E, Ghalamfarsa G, et al. (2017) Nanoparticles and targeted drug delivery in cancer therapy. Immunology letters 190: 64-83.

88. Venturoli D, Rippe B (2005) Ficoll and dextran vs. globular proteins as probes for testing glomerular permselectivity: effects of molecular size, shape, charge, and deformability. American Journal of Physiology-Renal Physiology 288(4): F605-F613.

89. Decuzzi P, Pasqualini R, Arap W, Ferrari M (2009) Intravascular delivery of particulate systems: does geometry really matter?. Pharmaceutical research 26(1): 235-243.

90. Yang Q, Jones SW, Parker CL, Zamboni WC, Bear JE, et al. (2014) Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation. Molecular pharmaceutics 11(4): 1250-1258.

91. Bharali DJ, Lucey DW, Jayakumar H, Pudavar HE, Prasad PN (2005) Folate-receptor-mediated delivery of InP quantum dots for bioimaging using confocal and two-photon microscopy. Journal of the American Chemical Society 127(32): 11364-11371.

92. Zrazhevskiy P, Sena M, Gao X (2010) Designing multifunctional quantum dots for bioimaging, detection, and drug delivery. Chemical Society Reviews 39(11): 4326-4354.

93. Kairdolf BA, Smith AM, Stokes TH, Wang MD, Young AN, et al. (2013) Semiconductor quantum dots for bioimaging and biodiagnostic applications. Annual review of analytical chemistry 6(1): 143-162.

94. Senapati S, Mahanta AK, Kumar S, Maiti P (2018) Controlled drug delivery vehicles for cancer treatment and their performance. Signal transduction and targeted therapy 16(3): 7.

95. Riley RS, Day ES (2017) Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology 9(4): 10.

96. Fadel TR, Fahmy TM (2014) Immunotherapy applications of carbon nanotubes: from design to safe applications. Trends in biotechnology 32(4): 198-209.

97. Villa CH, Dao T, Ahearn I, Fehrenbacher N, Casey E, et al. (2011) Single-walled carbon nanotubes deliver peptide antigen into dendritic cells and enhance IgG responses to tumor-associated antigens. ACS nano 5(7): 5300-5311.

98. Fontana F, Shahbazi MA, Liu D, Zhang H, Mäkilä E, et al. (2017) Multistaged nanovaccines based on porous silicon@ acetalated dextran@ cancer cell membrane for cancer immunotherapy. Adv Mater 29(7).

99. Legge CJ, Colley HE, Lawson MA, Rawlings AE (2019) Targeted magnetic nanoparticle hyperthermia for the treatment of oral cancer. Journal of Oral Pathology & Medicine 48(9): 803-809.

100. Senapati S, Shukla R, Tripathi YB, Mahanta AK, Rana D, et al. (2018). Engineered cellular uptake and controlled drug delivery using two-dimensional nanoparticle and polymer for cancer treatment. Molecular Pharmaceutics 15(2): 679-694.

101. Singh AP, Prakash O, Kumar S, Shukla A, Maiti P, et al. (2022) Poly (lactic acid-co-glycolic acid) as sustained drug delivery vehicle for melanoma therapy. Materials Today Communications 31: 103661.

102. Singh AP, Biswas A, Shukla A, Maiti P (2019) Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal transduction and targeted therapy 4(33).

103. Kumar S, Singh AP, Senapati S, Maiti P (2019) Controlling drug delivery using nanosheet-embedded electrospun fibers for efficient tumor treatment. ACS Applied Bio Materials 2(2): 884-894.

104. Shukla A, Singh AP, Maiti P (2021) Injectable hydrogels of newly designed brush biopolymers as sustained drug-delivery vehicle for melanoma treatment. Signal Transduction and Targeted Therapy 6(1): 63.

105. Shukla A, Singh AP, Dubey T, Hemalatha S, Maiti P, et al. (2019) Third generation cyclodextrin graft with polyurethane embedded in hydrogel for a sustained drug release: complete shrinkage of melanoma. ACS Applied Bio Materials 2(4): 1762-1771.

106. Shukla A, Singh AP, Ray B, Aswal V, Kar AG, et al. (2019) Efficacy of polyurethane graft on cyclodextrin to control drug release for tumor treatment. Journal of colloid and interface science 534: 215-227.

107. Mahanta AK, Maiti P (2019) Injectable hydrogel through hydrophobic grafting on chitosan for controlled drug delivery. ACS Applied Bio Materials 2(12): 5415-5426.

108. Mahanta AK, Senapati S, Paliwal P, Krishnamurthy S, Hemalatha S, et al. (2018) Nanoparticle-induced controlled drug delivery using chitosan-based hydrogel and scaffold: application to bone regeneration. Molecular pharmaceutics 16(1): 327-338.

109. Kumar MA, Vikas M, Nitesh S, Debabrata D, Sudip M, et al. (2015) Polyurethane-Grafted Chitosan as New Biomaterials for Controlled Drug Delivery. Research gate 48(8).

110. Han B, Yang Y, Chen J, Tang H, Sun Y, et al. (2020) Preparation, characterization, and pharmacokinetic study of a novel long-acting targeted paclitaxel liposome with antitumor activity. International journal of nanomedicine 15: 553-571.

111. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, et al. (2020) Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Frontiers in molecular biosciences 7: 193.

112. Apte RS, Chen DS, Ferrara N (2019) VEGF in signaling and disease: beyond discovery and development. Cell 176(6): 1248-1264.

113. Orleth A, Mamot C, Rochlitz C, Ritschard R, Alitalo K, et al. (2016) Simultaneous targeting of VEGF-receptors 2 and 3 with immunoliposomes enhances therapeutic efficacy. Journal of drug targeting 24(1): 80-89.

114. Li NG, Shi ZH, Tang YP, Duan JA (2009) Selective matrix metalloproteinase inhibitors for cancer. Current medicinal chemistry 16(29): 3805-3827.

115. Chen J, Wang X, Yuan Y, Chen H, Zhang L, et al. (2021) Exploiting the acquired vulnerability of cisplatin-resistant tumors with a hypoxia-amplifying DNA repair–inhibiting (HYDRI) nanomedicine. Science Advances 7(13): eabc5267.

116. Wang L, Chang Y, Feng Y, Li X, Cheng Y, et al. (2019) Nitric oxide stimulated programmable drug release of nanosystem for multidrug resistance cancer therapy. Nano Letters 19(10): 6800-6811.

117. Zhang J, Du Z, Pan S, Shi M, Li J, et al. (2018) Overcoming multidrug resistance by codelivery of MDR1-targeting siRNA and doxorubicin using EphA10-mediated pH-sensitive lipoplexes: *in vitro* and *in vivo* evaluation. ACS applied materials & interfaces 10(25): 21590-21600.

118. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY (2013) Nanomedicine therapeutic approaches to overcome cancer drug resistance. Advanced drug delivery reviews 65(13-14): 1866-1879.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.57.009034

Pralay Maiti. Biomed J Sci & Tech Res