Nanotechnology has emerged as a promising approach for the targeted delivery of therapeutic agents while improving their efficacy and safety. As a result, nanomaterial development for the selective targeting of cancers, with the possibility of treating off-target, detrimental sequelae caused by chemotherapy, is an important area of research. Breast and ovarian cancer are among the most common cancer types in women, and chemotherapy is an essential treatment modality for these diseases. However, chemotherapy-induced neurotoxicity, neuropathy, and cardiomyopathy are common side effects that can affect breast and ovarian cancer survivors quality of life. Therefore, there is an urgent need to develop effective prevention and treatment strategies for these adverse effects. Nanoparticles (NPs) have extreme potential for overcoming drug resistance, improving bioavailability, and naturally accumulating at the tumor site, through passive targeting (EPR). NPs can achieve active targeting to an intended therapeutic site with the use of antibody, peptide, aptamer, or other targeting moieties. [4] To mediate the adverse toxicity of chemotherapy, NPs targeting the brain or heart may be attractive for mitigating complications such as cardiomyopathy and neuropathy (Figure 1). [4] In this regard, NP-based treatments have shown potential for reducing the side effects of chemotherapeutics while improving drug efficacy. In this article, the latest nanotechnology approaches and their potential for the prevention and treatment of chemotherapy-induced neurotoxicity, neuropathy, and cardiomyopathy in breast and ovarian cancer survivors are discussed.

1. Introduction

Over the past several decades, nanotechnology has been increasingly applied to treat a variety of diseases due to its malleable physiochemical, biological, and nanoscale properties. There has been a great deal of research conducted on the biocompatibility and therapeutic efficacy of FDA-approved materials, particularly NPs made of lipids and polymers. [3] Although nanotechnology has received a surge of attention and is perceived as an attractive technology, there are still challenges in clinical translation, leading some to argue that it has not yet reached its true potential. Although these challenges have proven difficult, many promising nanomaterials have come into play for detection, diagnosis, and treatment of cancer. Cancer is a critical and complicated health problem that affects millions of lives. [2] Breast cancer and ovarian cancer are two of the most common types of cancer in women, making them critical targets for therapeutic interventions. [7b,c]

Although massive improvements in cancer treatment have led to many survivors, chemotherapeutics can have critical off-target side effects. In recent years, a tremendous amount of research in cancer pathology and nanoscience, technology, and industry (NSTI) has been conducted to provide nanomaterials geared towards cancer treatment and diagnosis. [3] NPs such as liposomes, dendrimers, lipid NPs, polymeric NPs, and inorganic NPs have been widely researched for controlled chemotherapeutic delivery and alleviation of nonspecific toxicity (Figure 1). [4] To mediate the adverse toxicity of chemotherapy, NPs targeting the brain or heart may be attractive for mitigating complications such as cardiomyopathy and neuropathy (Figure 1). In this regard, NP-based treatments have the potential to overcome drug resistance, improve bioavailability, maintain bioactivity, and enhance host immunity. [5] NPs can naturally accumulate at the tumor site, through passive targeting with the use of enhanced permeability and retention (EPR). NPs can also achieve active targeting to an intended therapeutic site with the use of antibody, peptide, aptamer, or...
small molecule surface functionalization. Along with specific delivery of chemotherapies to the tumor site, NPs can mitigate off-target adverse effects through the controlled release of therapeutics. Furthermore, some nanomaterials have been engineered to possess enzymatic activity, such as the ability to scavenge reactive oxygen species (ROS) and superoxide to prevent oxidative stress and cell death.\(^6\) Compared to free-chemotherapeutic delivery, NP-based targeted delivery and controlled release have the potential to help reduce toxicity in healthy cells, prevent drug degradation, prolong half-life, increase loading capacity, and improve solubility.\(^6\) In this review, we will discuss the mechanisms by which chemotherapeutics cause off-target effects at the cellular level, detail current treatment options, and explore emerging nanotechnology with the potential for preventive and enhanced treatment strategies for chemotherapy-induced diseases.

2. Diseases Resulting from Chemotherapy Treatment: Cardiomyopathy, Neuropathy, and Neurotoxicity

Breast cancer is one of the most pervasive and debilitating malignant forms of cancer, primarily affecting adult women and encompassing approximately 12% of all cancer cases worldwide.\(^2\) According to the National Cancer Institute’s Surveillance, Epidemiology, and End Result (SEER) program, in the United States alone, 12.9% of American-born women will develop cancer in their lifetime.\(^8\) Amongst women specifically, breast cancer constitutes 25% of all cancer diagnoses. Ovarian cancer is another major health problem for women worldwide and accounts for approximately 3% of all cancer diagnoses in women.\(^7\) Ovarian cancer is the fifth leading cause of cancer-related deaths in women due to late diagnosis.\(^9\) Ovarian cancer...
prognosis heavily depends on the tumor type. Despite significant advances in chemotherapeutic treatment strategies, managing breast and ovarian cancer remain a challenge, given their phenotypic heterogeneity and propensity for metastasis. The heterogeneous biological nature of these cancers makes them difficult to detect and treat effectively. Despite these limitations, improved diagnostics, a bench-to-bedside translational research strategy, and a move toward a personalized treatment approach have markedly improved cancer remission rates and treatment outcomes.

Several leading chemotherapies have been associated with extensive cardiotoxicity which results in heart failure (HF) in approximately 10% of cancer patients. In this context, HF can occur as a result of cardiotoxicity related to cancer treatment secondary to chemotherapy. Many cancer patients are older and frequently have various co-morbidities associated with aging, adding to the complexity of management. Cardiomyopathy, a resulting disease of chemotherapy-associated cardiotoxicity, may present itself as a consequence of treatment. Cardiomyopathy is characterized by the inability of the weakened heart muscles to effectively pump blood to the rest of the body, as it usually does. Although there are several types of cardiomyopathy, a common form of cardiomyopathy that can result from chemotherapy is known as dilated cardiomyopathy. Dilated cardiomyopathy is characterized by the dilation of the left ventricle in the heart, negatively affecting the ability to pump blood effectively throughout the body. Shortly after introducing chemotherapies such as anthracyclines in the 1960s, cardiac dysfunction was discovered to be an important dose-limiting side effect. Despite the dosing restrictions, incidences of anthracycline-induced cardiac dysfunction (ACD) have been found to be 6% for overt HF and up to 18% for subclinical cardiac dysfunction. Furthermore, the prognosis of ACD is poor, with associated cardiovascular mortality rates ranging from 9% to 24% at 5 and 10 years, respectively, and even up to 60% at 2 years in patients who have developed symptomatic HF.

Chemotherapy-induced peripheral neuropathy primarily affects the sensory system, especially sensory neurons of the basal root ganglia. The dorsal root ganglia is considered an easier target for chemotherapeutics due to its location outside of the blood-brain barrier (BBB) and in the peripheral nervous system. Sensory and mechanical neurons are critical for the function of the peripheral nervous system. Although there is some evidence of changes in motor neuron function in peripheral neuropathy, many critical changes are more localized within the function of the sensory neurons. Dorsal root ganglia has fluctuating ion channels and mitochondria damage, causing a malfunction of sensory neurons and glial cells. Nerve dysfunction involves several critical cell types, including sensory neurons, Schwann cells, macrophages, and fibroblasts. Schwann cells, a type of glial cell in the peripheral nervous system, which surrounds neurons and protects them through myelination, have a critical role in neuronal function and axon regeneration. Chemotherapeutic treatment leads to long-term cell malfunction, including oxidative stress, dysregulated Ca\(^{2+}\) signaling, inflammation, and axonal degeneration. The role of mitochondria in regulating energy production, supply, and cell death is critical for cell function. Chemotherapy-induced neuropathy is linked with increased swollen and vacuolated mitochondria in sensory neurons, leading to impaired ATP production and nitro-oxidative stress, which causes excessive ROS and reactive nitrogen species (RNS) release. Transient receptor potential (TRP) channels are critical to sensory neuron function. Multiple TRPs have been shown to play a role in oxidative stress and undergo changes in neuropathic pain. Calcium dysregulation in the peripheral nervous system is a critical problem in the mechanism of peripheral neuropathy onset. Oxidative stress and ROS formation lead to downstream effects on calcium homeostasis. Calcium dysregulation has been linked to the atrophy and loss of dorsal root ganglia as well as sensory neuron axonal degeneration causing activation of calpain, a ubiquitous calcium-sensitive protease. Sensory axon degeneration is a primary cause of neuropathy and is caused by dysregulation of the processes described above. Therefore, axonal regeneration is also a key target of interest for treating peripheral neuropathy.

3. Breast and Ovarian Cancer Treatment with Associated Pathology

In the majority of breast and ovarian cancer patients, chemotherapeutics are utilized to reduce tumor size. However, these treatments often cause off-target effects, including cardiomyopathy, neurotoxicity, and neuropathy, leading to a reduced quality of life. Therefore, awareness of the importance of improving chemotherapeutics to mitigate and treat off-target effects in cancer survivors is essential to improve health outcomes and quality of life. Chemotherapeutics include many critical classes for treating breast and ovarian cancer such as: alkylating agents, taxanes, vinca alkaloids, anthracyclines, folate antagonists, thalidomide and thalidomide-derivatives, fluoropyrimidines, and inhibitors. These chemotherapeutics use a variety of cellular mechanisms to induce toxicity in cancer cells.

3.1. Alkylating Agents

Chemotherapeutics such as cisplatin, cyclophosphamide, and carboplatin are crosslinking agents commonly used in the systemic treatment of germ cell tumors, including cancers of the ovaries, testes, lungs, cervical, esophageal, breast, brain, and solid tumors of the head and neck. Cisplatin belongs to a class of platinum drugs that alkylate DNA by forming platinum-DNA adducts, leading to DNA damage, G1/S arrest, and apoptosis. Cisplatin inhibits DNA synthesis by binding to mitochondrial and genomic DNA to stop further DNA replication and transcription. Specifically, it interacts with nucleophilic N7 sites of purine bases to cause intra-strand crosslinking to form DNA lesions inducing cytotoxicity in cells. The effects of cisplatin on mitochondrial DNA cause ROS formation and oxidative damage due to dysregulated metabolic pathways. Long-term and high-dose platinum-based chemotherapeutic delivery is associated with many adverse effects, including but not limited to neurotoxicity, cardiomyopathy, and neuropathy. Cisplatin has been reported to cause cardiovascular diseases (CVDs), such as myocardial infarction.
and angina, in some 7–32% of patients.[33] Furthermore, a long-term unfavorable cardiovascular risk profile associated with hypercholesterolemia, hypertriglyceridemia, hypertension, and insulin resistance was found in individuals treated with cisplatin 10 years later.[34] The underlying mechanism of cisplatin cardiotoxicity is mainly attributed to cardiomyocyte toxicity and ROS production, leading to inflammation and thrombus formation.[35] For cyclophosphamide, the mechanism of induced cardiotoxicity is better understood through its metabolism to acrolein. Acrolein causes cardiomyocyte inflammation, ROS production, and reduced endothelial nitric oxide synthase activity. Acrolein has been reported to induce caspase activation resulting in apoptosis in cardiomyocytes in addition to calcium overload, leading to HF.[36]

Cisplatin-induced peripheral neuropathy occurs in 92% of patients treated at a cumulative dose of 500–600 mg m⁻².[37] Platinum-induced neuropathy is linked to morphological changes and degeneration of dorsal root ganglion cell bodies through binding DNA, modulating cell metabolism, and disruption of axonal transport.[37,38] Platinum accumulation in dorsal root ganglia is 10 to 20 times higher than in other nerve cells due to the high number of transport proteins in the cells.[39] ROS formation in the dorsal root ganglia leads to dys- function, although the specific mechanism of taxane-induced neuropathy is not well understood.[40] Unlike platinum-based chemotherapeutics, paclitaxel does not directly affect mitochondria DNA rather causing downstream ROS production in the peripheral nervous system.[22a] Taxanes have recently been shown to cause changes in Ca²⁺ signaling and axonal transport.[53] TRPV4 has been implicated in inducing mechanical hypersensitivity in sensory neurons in vivo after paclitaxel treatment.[54] In a separate study, TRPV4 was shown to specifically act on the central nervous system to affect TRPMA-resistant mechanical allodynia.[23] Along with cardiomyopathy and neuropathy, paclitaxel use is associated with central and peripheral neurotoxicity. Paclitaxel-induced emotional distress and cognitive impairment have been described in the domains of working memory, executive function, processing speed, and verbal/visual memory.[35] The prevalence of acute chemotherapy-related cognitive impairment ranges from 17% to 75% and may last for up to 2 years following treatment, although some patients (17%–34%) exhibit persistent deficits for decades after treatment.[56]

3.3. Vinca Alkaloids

Vinca alkaloids are commonly used for breast cancer treatment. Specifically, vinorelbine is an extremely common chemotherapeutic for advanced breast cancer treatment.[57] Vinca alkaloids are another microtubule targeting agent and inhibit cell mitosis by promoting microtubule assembly to disrupt mitotic spindles in a similar manner to taxanes.[58] Furthermore, they are another chemotherapeutic class leading to short and long-term peripheral neuropathic pain. Because vinca alkaloids, like taxanes, break microtubules, there is defective axonal transport and cytoskel- eton damage in sensory neurons.[59] Disrupted calcium homeo- stasis and axonal degeneration are also downstream effects of vinca alkaloids.[60] These changes in normal cellular function and pathways within the dorsal root ganglia lead to degenerating sen- sory neurons and activated glial cells. These effects lead to short- and long-term peripheral neuropathy reported in many breast cancer patients treated with vinca alkaloids.
3.4. Anthracyclines

Anthracyclines have been used for years in a regimen with taxanes for treating both breast and ovarian cancer and are one of the most potent chemotherapeutics for treating these tumors. Unfortunately, they also have toxicity and major side effects associated with short- and long-term use.[61] Anthracyclines are thought to block interaction with topoisomerase-II which prevents fixing breaks in double-stranded DNA leading to inhibition of cell growth and division as well as inducing apoptosis.[62] Necrosis and apoptosis of cardiac myocytes and associated myocardial fibrosis play a role in the onset of cardiotoxicity caused by ACD. As a result, ACD caused by agents such as doxorubicin is thought to be irreversible. Cardiotoxicity resulting from ACD involves several processes, such as the peroxidation of lipids in the membranes of myocardial mitochondria after producing iron-dependent oxygen free radicals. The free radicals produced can also suppress the production of DNA, RNA, and subsequent protein synthesis, including important transcription factors that regulate cardiac-specific genes. As a result of this widespread dysfunction, adrenergic and adenylyl cyclase activity as well as calcium homeostasis are severely dysregulated. In the past, several studies have reported that cardiac dysfunction associated with anthracyclines is mediated by topoisomerase-2β (Top-2β) in cardiomyocytes, an enzyme tasked with solving topological problems in duplex DNA, such as supercoiling and knotting. More recently, other cell types—such as cardiac progenitor cells, cardiac fibroblasts, and endothelial cells—have additionally been identified as targets.[63] Ultimately, transcending multiple cell types, the principal mechanisms of ACD are oxidative stress, DNA damage, and cell death.

3.5. Folate Antagonists

Folate antagonists, such as methotrexate, have long been used to treat breast cancer due to their potent activity in preventing cell proliferation, specifically during the S phase of the cell cycle.[64] Methotrexate inhibits multiple enzymes, including dihydrofolate reductase, thymidylate synthase, and 5-aminomidazole-4-carboxamide ribonucleotide formyl transferase.[65] Methotrexate is a cell cycle-specific agent that disrupts folate acid metabolism and DNA synthesis by inhibiting the enzyme dihydrofolate reductase. Research conducted in a murine model injected with a breast cancer cell line (FM3A) revealed cognitive dysfunction and depression after methotrexate administration. In addition, methotrexate significantly increased the levels of several pro-inflammatory factors, such as COX2 and iNOS. Interestingly, it decreased the population of progenitor cells in the hippocampus, which could explain the cognitive impairment observed in these subjects inoculated with breast cancer cells.[66] Methotrexate has recently been found to increase depression-like behaviors in mice both 1 and 7 days after treatment, which was related to reduced neurogenesis and cell viability of the hippocampal region, in addition to increased cytotoxicity and apoptosis.[66a] Breast cancer studies show methotrexate-treated patients perform significantly worse in immediate and delayed verbal memory as well as exhibit slower speeds in functional execution than patients with no history of cancer.[67]

3.6. Thalidomide and Thalidomide Derivatives

While thalidomide and derivatives are less traditionally used for treating breast and ovarian cancer than the groups previously discussed, they still have a prevalence for solid tumor treatment and cause long-term off-target effects that are detrimental to the patients’ quality of life.[68] Thalidomide has been shown to bind to cereblon, an E3 ligase complex that can bind to proteins and tag them with ubiquitin for degradation by the proteasome.[69] Thalidomide binding to cereblon affects protein breakdown, causing protein overexpression in cancer cells and disorganizing mitochondrial activity and apoptotic pathways. Recently, low-dose thalidomide therapy for breast and ovarian cancer was evaluated in phase II clinical trials, which minimized long-term peripheral neuropathy induced by this chemotherapeutic treatment.[68b] Thalidomide-induced peripheral neuropathy varies widely depending on the treatment dosage and timeline.[68a] Thalidomide-induced peripheral neuropathy is seen at an incidence rate ranging from 11% to 75%, depending on these factors.[70] Thalidomide causes inhibition of important neurotrophic factors such as VEGF, bFGF, NF-kB, and TNF-α leading to down-stream dysregulation of neurotrophins, molecules important to neuronal proliferation and function.[71] Thalidomide has also been shown to interfere with angiogenesis by blocking endothelial cell migration by altering actin polymerization.[72] Many TRPs are linked to mitochondrial damage and the formation of ROS, two critical components of thalidomide and thalidomide derivative-induced peripheral neuropathy. TRPA1 malfunction has been associated with thalidomide-induced peripheral neuropathy. Thalidomide derivatives also have a prevalence for targeting the central nervous system to induce neuropathy through modulating TRPV4 channel activity.[23]

3.7. Fluoropyrimidines

Fluoropyrimidines are the second most common cause of chemotherapy-induced cardiotoxicity after anthracyclines.[73] 5-fluorouracil (5-FU) and its prodrug capecitabine is the most commonly used and acts as a cytostatic agent by intercalating into DNA or RNA to treat colorectal, breast, gastric, pancreatic, prostate, and bladder cancers.[74] Of patients treated with fluoropyrimidine, 1–18% experience cardiovascular toxicity.[75] Although the pathogenesis of fluoropyrimidine-induced cardiotoxicity has not been fully elucidated, several hypotheses have been proposed. Mostly, vasoconstriction, direct myocardial toxicity, endothelial dysfunction, and a hypercoagulable state result in thrombus and ultimate cardiac damage.[76] Coronary vasospasm and ischemia, which are frequently linked with cardiomyocyte mortality, are the most studied adverse cardiac events related to fluoropyrimidine therapy. Additionally, 5-FU has been reported to induce protein kinase C-mediated vasoconstriction in vascular smooth muscle cells and reduce the oxygen transport capacity of erythrocytes, inducing relative ischemia of the myocardium.[77] Ultimately, fluoropyrimidines, such as 5-FU, increase ROS production and induce cardiomyocyte apoptosis and autophagy.[79]
3.8. Inhibitors

Protein kinases are critical messengers in regulating various biological processes, which involve the transfer of a phosphate group from ATP to various substrates. Small molecule kinase inhibitors (SMKIs) are designed to primarily compete for the ATP binding pocket on such kinases, rendering them inactive and mitigating protein kinase-mediated disease progression. Small molecule tyrosine kinase inhibitors (TKIs) are among the most widely used SMKIs, paired with substantial side effects such as gastrointestinal toxicity, hepatotoxicity, and cardiovascular toxicity. TKIs block intracellular phosphorylation of tyrosine residues, leading to blocked intracellular signaling pathways in cancer cells. Unregulated TK activation has been shown to be a critical problem in treating breast and ovarian cancer. Therefore, many TKI's are approved and used in clinical trials to treat both breast and ovarian cancer. Common cardiotoxicity presentations include tachycardia, palpitation, prolonged QT interval, and reduced left ventricular ejection fraction (LVEF). Many TKIs have failed in clinical trials due to the accompanying cardiotoxic adverse effects. In an analysis of the wide range of small molecule TKIs, investigators found that 73% of treatments have reported toxicities ranging from arrhythmias, LVEF dysfunction, HF, and myocardial infarction. HER-2 is an oncogene closely associated with the progression of breast cancer and can be pathologically amplified for the development of personalized treatment for patients. The development of targeted therapies to inhibit HER-2 has greatly improved the prognosis of HER-2-positive breast cancer. HER-2 inhibitors, such as trastuzumab, which targets HER-2, have become one of the primary forms of treatment for patients with HER-2+ breast cancer in recent years. Trastuzumab acts on breast cancer cells by inhibiting HER-2 expression, leading to downstream effects on cancer cells. Lapatinib, a tyrosine kinase inhibitor used to treat HER-2+ breast cancer, targets both HER-1 and HER-2. Although HER-2 inhibition has improved the outcomes for patients with HER-2-positive breast cancer, they also display significant cardiotoxicities, such as an impaired left ventricular ejection fraction, arrhythmias, and heart failure. HER-2 inhibition in cardiomyocytes results in ROS production, mitochondrial function disruption, and pro-apoptotic signaling induction. Ultimately, 2–5% of breast cancer patients treated with trastuzumab experienced severe cardiotoxicity, 1–4% of which led to HF. Interestingly, when trastuzumab was administered alongside anthracyclines, HF incidence in patients increased to 28%, indicative of an enhanced combinatorial anthracycline-induced toxicity.

While these treatment methods often help extend the lives of women with cancer, therapeutic off-target effects are critical problems that must be studied (Figure 2 and Table 1). Treatments must be found for the millions of women who have survived cancer but have long-lasting severe health problems to overcome for the rest of their lives. Treatment strategies for breast cancer have been optimized to help prevent recurrence and bad patient outcomes. However, many long-term effects of these therapeutic regimens are detrimental to survivors' quality of life. Therefore, understanding the mechanisms related to chemotherapeutic-induced health problems in survivors that lead to a deterioration in the quality of life is critical to improving current cancer treatments and targeting diseases induced by chemotherapy with nanotechnology.

4. Nanotechnology Approaches for Enhanced Chemotherapy Delivery

Chemotherapy-induced cardiomyopathy, neuropathy, or neurotoxicity can originate from nonspecific toxicity induced by the administration of the various chemotherapeutic agents described previously. Each type of chemotherapy has a different pathological process; however, most of them end up causing similar macroscopic issues. For chemotherapy-induced cardiomyopathy (CIC), these include but are not limited to myocardial fibrosis, myocardial infarction, inflammation, thrombosis, and ischemia, which can all lead to HF. Many treatments for chemo-induced neuropathy and neurotoxicity result in neuronal damage, microglial inflammation, and dysfunctional intercellular signaling. Nanomaterials can efficiently target and deliver therapeutics in vivo. When handling the complication of chemo-induced adverse damage, an attractive approach for mitigation has been the design of nanotherapeutics for the efficient delivery of chemotherapeutic agents to the tumor site, while improving local bioavailability and tumor-killing efficacy.

4.1. Nanomaterial-Enhanced Chemotherapy Delivery for the Reduction of Chemo-Induced Cardiomyopathy

Improving the delivery efficiency of chemotherapies has remained a challenge in cancer treatment due to the non-specific nature of the currently available therapies. However, nanomaterials have provided the foundation for developing "smart" vehicles for active targeting of the tumor site (Figure 3). Although EPR-mediated passive targeting has been used in the past for nanomaterial localization in tumors, it is not nearly as effective as active delivery. Although cancer can be divided into a plethora of cancer sub-types, numerous cancers overexpress similar receptors that can be taken advantage of when designing such nano-based chemotherapeutics. In general, numerous studies involving active targeting of tumors using nanomaterials have been achieved using four separate targeting ligands: 1) folate-linked NPs, 2) transferrin-linked NPs, 3) hyaluronic acid-linked NPs, and 4) HER-2 antibody-labeled NPs.

Folic acid (FA) is a member of the vitamin B family and plays a key role in DNA synthesis and cell proliferation. The folic acid receptor (FR) is a tumor marker that binds firmly to a folate substrate. FRs have been observed to be overexpressed on cell surfaces of various solid tumors, including kidney, ovary, lung, bladder, breast, pancreas, and colon. Studies using FA-modified NPs have successfully targeted FRs for subsequent internalization into the cell via receptor-mediated endocytosis. In 2020, Jang et al. developed a "smart" tumor-targeting NP system for the selective delivery of doxorubicin. It has been demonstrated that glycol-modified chitosan NPs can be hydrophobically modified with 4-nitrobenzyl chlorofor-
effects, a solution of doxorubicin and the modified chitosan self-assembled into a core-shell polymeric NP consisting of a FA decorated exterior, chitosan frame, and 4-nitrobenzyl chloroformate interior loaded with doxorubicin. Under hypoxic conditions, 4-nitrobenzyl chloroformate cleaves itself from the chitosan backbone, disrupting the NP structure and releasing doxorubicin. The nanotherapeutic showed improved in vivo cancer-targeting ability in mice compared to controls without FA labeling. Additionally, in vitro drug release profiles revealed that NPs rapidly release doxorubicin under hypoxia conditions compared to normoxia conditions. Finally, NPs showed a selective release profile of doxorubicin in vivo, reducing off-target toxicities from anthracyclines elsewhere in the body.

Transferrin (Tf) is a serum glycoprotein that primarily mediates iron uptake by cells. Typically, transferrin binds to the transferrin receptor (TfR), facilitating iron transport into the cell from the blood, before being internalized through receptor-mediated endocytosis. The TfR is an attractive receptor for cancer and tumor targeting due to its 100-fold expression levels on cancer cells in comparison to normal cells. In 2021, Yu et al. aimed to improve the delivery and mitigate the off-target side effects of docetaxel in breast cancer by incorporating it into a transferrin-docetaxel-loaded pegylated-albumin NP (TF-PEG-DANP). In general, the growth inhibitory effects and the ability of unmodified DANPs or PEG-DANPS to induce apoptosis in 4T1 mouse mammary cancer were compared to treatment with TF-PEG-DANPS using MTT and flow cytometry. Subsequently, these experiments were expanded in vivo to IV treatment of 4T1 tumors for the same conditions, but with the addition of combined ultrasound (US). In vivo TF-PEG-DANPS were more efficient in inhibiting tumor growth compared to the competing conditions. Using Tf to target the 4T1 tumors significantly enhanced the specificity and subsequently mitigated off-target effects normally associated with docetaxel treatment. Lastly, incorporating US-facilitated drug release once the treatment had localized with the tumor microenvironment, however, was unnecessary for docetaxel release and was used to provide a more “burst-like” release profile.

Hyaluronic acid (HA) is a natural polysaccharide polymer with associated biocompatible and biodegradable properties, also known to contribute to the composition of the extracellular matrix (ECM). Additionally, HA has been reported to specifically bind to CD44, a cell-surface glycoprotein that is overexpressed on tumor cell surfaces, primarily those of pancreatic, lung, and breast cancers. Therefore, designing anticaner drug delivery systems targeting CD44 receptors utilizing HA has become an attractive route. In 2022, Mansoori-Kermani et al. designed an epirubicin (Epi)-loaded niosomal (Nio) NP...
Table 1. Summary of commonly used chemotherapeutic drugs in the clinical treatment of breast and ovarian cancer. (ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; SCLC, small cell lung cancer, NSCLC, non-small cell lung cancer; TLS, tumor lysis syndrome).

<table>
<thead>
<tr>
<th>Generic name (FDA label ID)</th>
<th>FDA-approved use (first approval time)</th>
<th>Common off-label clinical use</th>
<th>Mechanism of Action</th>
<th>Major long-term side effects</th>
</tr>
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<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
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<tr>
<td>Cisplatin</td>
<td>Advanced ovarian cancer, testicular cancer, bladder carcinoma (1978)</td>
<td>Gastrointestinal malignancies, cervical and endometrial carcinoma, gestational trophoblastic neoplasia, triple-negative breast cancer, lung cancer; metastatic, advanced, and refractory cancers</td>
<td>DNA intrastrand and interstrand crosslinking, inhibiting DNA synthesis and function</td>
<td>Nephrototoxicity, peripheral neuropathy, myelosuppression, ototoxicity, ocular toxicity, secondary malignancies, embryo-fetal toxicity</td>
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<tr>
<td>Carboplatin</td>
<td>Advanced ovarian carcinoma, NSCLC, SCLC (1989)</td>
<td>Head and neck cancer, brain cancer, neuroblastoma, triple-negative breast cancer.</td>
<td>DNA intrastrand and interstrand crosslinking, inhibiting DNA synthesis and function</td>
<td>Myelosuppressive effect (leukopenia, neutropenia, and thrombocytopenia), anemia, loss of vision</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Colorectal (2002)</td>
<td>Metastatic breast cancer, gastric cancer, pancreatic cancer, esophagus cancer</td>
<td>DNA intrastrand and interstrand crosslinking, inhibiting DNA synthesis and function</td>
<td>Peripheral sensory neuropathy, myelosuppression, posterior reversible encephalopathy syndrome, pulmonary toxicity, hepatotoxicity, QT interval prolongation, rhabdomyolysis, embryo-fetal toxicity</td>
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<td><strong>Taxanes</strong></td>
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<td>Paclitaxel</td>
<td>Ovarian carcinoma, metastatic breast cancer, pancreatic cancer, NSCLC, AIDS-related Kaposi sarcoma (1998)</td>
<td>Gastroesophageal cancer, endometrial cancer, cervical cancer, prostate cancer, head and neck cancer, sarcoma, leukemia, lymphoma</td>
<td>Stabilizes β-tubulin polymerization to promote microtubule assembly to disrupt mitotic spindles and inhibit the cell cycle</td>
<td>Sensory neuropathy, sepsis, pneumonitis</td>
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<td>Docetaxel</td>
<td>Breast cancer, NSCLC, prostate cancer, head and neck squamous cell carcinomas, gastric cancer (1996)</td>
<td>Ovarian cancer</td>
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<td><strong>Anthracyclines</strong></td>
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<tr>
<td>Doxorubicin</td>
<td>Metastatic breast cancer, lymphoma, neuroblastoma, soft tissue sarcoma, Wilms’ tumor, bone sarcomas, AML, ALL, ovarian cancer, bladder cancer, thyroid cancer, gastric cancer, bronchogenic cancer (1974)</td>
<td>Advanced renal cell carcinoma, multiple myeloma, advanced endometrial carcinoma, uterine sarcoma, metastatic hepatocellular cancer, thymomas, thymic malignancies, Waldenstrom macroglobulinemia</td>
<td>Intercalates DNA and disrupts topoisomerase-II-mediated DNA repair, generates free radicals that damage cellular membrane, DNA, and proteins</td>
<td>Cardiomyopathy, secondary AML, MDS, extravasation and tissue necrosis, hepatotoxicity, TLS, severe myelosuppression, radiation-induced toxicity, cardiac arrhythmias, embryofetal toxicity</td>
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<tr>
<td>Daunorubicin</td>
<td>AML (2017)</td>
<td>Acute lymphocytic anemia, metastatic breast cancer</td>
<td>Damages DNA by intercalating between base pairs, resulting in uncoiling of the helix and inhibiting DNA synthesis and RNA synthesis</td>
<td>Serious or fatal hemorrhagic events with associated prolonged thrombocytopenia, cardiotoxicity, local tissue necrosis, embryo-fetal toxicity</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Patients with evidence of axillary node tumor involvement following resection of primary breast cancer (1999)</td>
<td>Bladder cancer</td>
<td>Forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, inhibits DNA, RNA, and protein synthesis; triggers DNA cleavage by topoisomerase II, resulting in a cytotoxic activity</td>
<td>Cardiac toxicity: myocardial damage including acute left ventricular failure, secondary malignancies: secondary AML, MDS, extravasation and tissue necrosis, severe myelosuppression</td>
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Table 1. Continued.

<table>
<thead>
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<td><strong>Thalidomide</strong></td>
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<tr>
<td>Thalidomide (#4752812)</td>
<td>Multiple myeloma, erythema nodosum leprosum (1998)</td>
<td>Graft-versus-host disease, Langerhans cell histiocytosis, Kaposi sarcoma, Jessner lymphocytic infiltrate, lupus erythematosus</td>
<td>Inhibits the production of IL-6; binds to cerelion, disrupts protein degradation, and dysregulates mitochondrial function in cancer cells; activates apoptotic pathways through caspase 8-mediated cell death</td>
<td>Ischemic heart disease (including myocardial infarction), stroke, peripheral neuropathy, neutropenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, TLS, venous thromboembolism, embryo-fetal toxicity</td>
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<tr>
<td><strong>Vinca alkaloids</strong></td>
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<tr>
<td>Vinorelbine (#4551177)</td>
<td>Locally advanced or metastatic NSCLC (1994)</td>
<td>Metastatic breast cancer, rhabdomyosarcoma</td>
<td>Disrupts the normal function of microtubules and thereby stopping cell division.</td>
<td>Severe myelosuppression, hepatic toxicity, severe bowel obstruction, neurologic toxicity, pulmonary toxicity, respiratory failure, embryo-fetal toxicity</td>
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<td><strong>Folate antagonists</strong></td>
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<tr>
<td>Methotrexate (#4770153)</td>
<td>Breast cancer, gestational trophoblastic disease, head and neck cancer, lung cancer, non-Hodgkin lymphoma, osteosarcoma, ALL, rheumatoid arthritis, and plaque psoriasis</td>
<td>Scleroderma, sarcoma, alopecia areata, atopic dermatitis, psoriatic arthritis, systemic lupus erythematosus.</td>
<td>Inhibits multiple enzymes including dihydrofolate reductase, thymidylate synthase, and 5-aminomimidazole-4-carboxamide ribonucleotide formyl transferase</td>
<td>Hepatotoxicity, fibrosis, cirrhosis, pulmonary damage, unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, gastrointestinal toxicity, embryo-fetal toxicity, severe central nervous toxicity or metabolic acidosis, secondary malignancies, infertility</td>
</tr>
</tbody>
</table>

FDA-approved administration methods for each generic drug are indicated in the table: \( ^{a} \) Intravenous injection; \( ^{b} \) oral administration.

Coated with HA, engineered for targeting breast cancer cells (Figure 4). Niosomes are a class of vesicle-like NPs composed of non-ionic surfactants, in contrast to liposomes. By nature, niosomes have an EPR effect for passive tumor targeting, in addition to high bioavailability, enhanced stability, and greater entrapment efficiency (EE). In this study, the Epi-Nio-HA NPs could target and deliver epirubicin to breast cancer cell lines both in vitro and in vivo with efficiency to achieve excellent therapeutic effects. Cellular uptake was shown to be CD44-mediated, indicative of breast cancer-cell-specific targeting. Furthermore, in vivo results displayed safe and efficient suppression of tumor growth in mice, associated with the selectivity of NP localization at the tumor site.\(^{[100]}\)

To investigate the potential of combining the targeting affinity of trastuzumab for HER-2 with the stability, enhanced localization, and loading ability of NPs, in 2022, Xu et al. developed trastuzumab functionalized pullulan-doxorubicin NPs (Tz-P-Dox). Pullulan, a nonionic natural polysaccharide, was decorated with doxorubicin to produce P-Dox, at which point hydrophobic effects drove the NP self-assembly. Once formed, the investigators functionalized the surface of the NP with Tz residues, providing the ability and affinity to target HER-2+ breast cancer. Compared to P-Dox and Tz-P-Dox, the latter was significantly more effective at internalizing in HER-2+ breast cancer cells in vitro, validating the targeting capacity of Tz. Additionally, higher cytotoxicity was observed from doxorubicin.
in HER-2+ cells in contrast to HER-2- cells, supporting the cell-specific targeting ability of the nanotherapeutic. \[102\]

### 4.2. Nanomaterial-Enhanced Chemotherapy Delivery for the Reduction of Chemo-Induced Neuropathy

Currently, there are limited options for treating chemotherapy-induced neuropathy, so nanomaterial-based approaches have gained increasing interest due to the current limitations. Most research has focused on current ways to improve chemotherapy treatments, as it is the first line of defense against chemotherapy-induced peripheral neuropathy. The main targets of chemotherapy-induced peripheral neuropathy include neuronal protection and regeneration, glial cell polarization, and ROS scavenging. By utilizing nanomaterials in conjunction with current chemotherapy treatments, cases of peripheral neuropathy induced by adverse chemotherapeutic damage can be mitigated.

Several new approaches have been tested in vitro and in vivo mice models to improve the targeting ability of chemotherapeutics to reduce off-target effects. Reducing the likelihood of neuropathy onset is the most promising strategy for neuropathy treatment as the only current treatment is changing the cancer treatment protocol. \[103\] Recently, NP albumin-bound paclitaxel made by Green et al. \[104\] has been investigated in a phase II clinical trial and shown to reduce chemotherapy-induced peripheral neuropathy as the patients treated with the NP had low scores when assessed for peripheral neuropathy induced by the paclitaxel-bound albumin NP. \[105\] Approximately 41% of patients experienced sensory peripheral neuropathy and 13.85% of patients experienced motor peripheral neuropathy, an improvement over reported numbers of patients with peripheral neuropathy onset from paclitaxel delivery alone. \[106\] Nanomaterials have been used to deliver chemotherapeutics to cancer cells through antibody and peptide targeting, and the properties of nanomaterials, such as photothermal therapy, have been studied for their ability to kill cancer cells more efficiently with minimal off-target effects than traditional methods of treating them. These nanomaterials also often have intrinsic properties, allowing for simultaneous imaging or multifunctional therapeutics. Wu et al. developed a FRET-based two-photon mesoporous silica NP (MTP-MSNs) loaded with...
Figure 4. a) Niosomes were loaded with epirubicin and coated with a hyaluronic acid for active targeting of breast cancer tumor. b) Characterization of the niosomes by TEM shows the size is around 100 nm. c) There are sustained drug delivery peaks after 72 hrs. d) Cytotoxicity reported via IC_{50} values over 72 hrs. e,f) The nanoparticle is efficacious in cancer cell death and reducing tumor volume. Reproduced under the terms of the CC-BY license.[101] Copyright 2022, Elsevier.
doxorubicin and capped with aptamers targeting the cancer cells (Figure 5A).[107] The FRET signal could be adjusted by varying the ratio of three dyes doped into the NP, and the particles had extended release of doxorubicin over approximately 20 hours (Figure 5B,C). Overall, this FRET-based doxorubicin-loaded NP allows for fluorescent imaging simultaneously with targeted chemotherapy to create a targeted imaging and therapeutic platform for enhancing chemotherapy treatment.

A growing number of chemotherapeutic agents are being targeted by stimuli-responsive NPs, which could improve their targeting efficiency and reduce the off-target effects. Hu et al. developed metal-organic-framework (MOF) based polymer hybrid nanocomposites that were used for coencapsulation and selective delivery of cisplatin and doxorubicin to the cancer microenvironment. The nanocomposite was pH-responsive and released therapeutics in the tumor environment with minimal off-target effects due to the negligible change in mice weight during in vivo tests.[108] In 2019, Yang et al. developed PEG-phenylhydrazone-dilaurate micelles loaded with paclitaxel for release under acidic conditions, specific to the tumor microenvironment. There was a significant increase in the accumulation and cytotoxicity of cancer cells upon delivery of the pH-responsive micelles compared to that of the regular micelles. This increased targeting of cancer cells indicates another promising strategy for using NPs to reduce off-target effects of chemotherapeutics. Guan et al. developed a BSA-based NP loaded with paclitaxel and the Pgp inhibitor cyclosporin A that released the therapeutics upon laser irradiation and produced ROS for a multifunctional light-responsive particle.[109] This NP had promising efficacy in treating breast cancer in an in vitro and in vivo mouse model without inducing systemic toxicity in mice showing its potential for preventing paclitaxel-induced peripheral neuropathy. A final type of stimuli-responsive NP-based system for the targeted delivery of chemotherapeutics to cancer cells involves ROS-responsive NPs. In 2022, Hu et al. developed a self-assembled anti-PD-L1 peptide block polymer micelle surrounding paclitaxel for simultaneous immunotherapy and chemotherapy under high ROS conditions. PD-L1 blockade therapy is an important type of immunotherapy that has shown extreme promise in treating many cancer types, including breast and ovarian cancer.[110] Polymer NPs have also been employed for the ROS-responsive release of chemotherapeutics by connecting paclitaxel and cucurbitacin B, a molecule shown to cause ROS generation and help improve paclitaxel efficacy intracellularly, to dextran through a thioet (TK) bond.[111] Paclitaxel-TK-dextran and cucurbitacin B-TK-dextran self-assembled into micelles, and under high ROS conditions, the TK bond was cleaved for release of paclitaxel and cucurbitacin B (Table 2).
Mitigating Chemo-Induced Cardiomyopathy

5. Current Treatments, Preventative Measures, and Relevant Pathological Mechanisms Associated for the Reduction of Chemotherapy-Induced Damage

5.1. Current Treatments and Preventative Measures for Mitigating Chemo-Induced Cardiomyopathy

In general, early identification and management of the risk of cardiovascular side effects contribute to the prevention and mitigation of cardiotoxicity in chemotherapy. The main patient-related risk factors of most significant concern include diabetes mellitus, hypertension, dyslipidemia, smoking, increased body weight, a previous history of CVD, left ventricle dysfunction, heart failure, and coronary artery disease. Furthermore, overall survival in cancer patients who developed CVD was poor, accounting for 60% at 8 years, relative to 81% in cancer survivors without CVD. This highlights the need for cardio prevention and treatment in individuals at the highest risk for CVD.

Preventive measures are typically used to mitigate most cases of CIC, but treatments can also alleviate the condition. Initially, a thorough cardiovascular assessment is necessary before, during, and after therapeutic administration to prevent...
and detect cardiovascular toxicity. This assessment includes the LVEF, widely used to measure heart pumping efficiency, and is used to classify HF types. Biomarkers, specifically serum cardiac biomarkers, have been associated with a higher cardiovascular risk and have been used to identify subclinical cardiac damage. Troponin has been considered a predictor of left ventricle dysfunction in cancer patients receiving chemotherapy, particularly agents such as anthracyclines. An established strong predictor of imminent cardiovascular dysfunction has been proven to be increased troponin I (cTnI) levels in patients receiving high-dose chemotherapy. In a study of 78 breast cancer patients undergoing doxorubicin and trastuzumab therapy, an early elevation in cTnI and myeloperoxidase (MPO) levels were observed, indicative of cardiotoxic risk. In this study, cTnI was associated with cardiac dysfunction with HF, and MPO presented itself as a biomarker of induced cardiotoxicity. Over the past two decades, the approved and most established strategies for managing and preventing CIC in HF with left ventricle dysfunction have been using beta-blockers, renin-angiotensin inhibitors, statins, dexrazoxane, and physical exercise.

5.1. Beta Blockers

In the case of CIC, beta-blockers (BBs) have been shown to increase pro-survival signaling through the EGFR pathway and mitigate free radicals. Of the many beta-blockers used in several studies over the past few years, nebivolol and carvedilol have been reported to be the most efficient to this date. Carvedilol, in particular, is a nonselective BB that suppresses lipid peroxidation, decreases free radicals, and prevents mitochondrial dysfunction. Furthermore, lower troponin-I levels and lower incidence of diastolic dysfunction were observed in patients using carvedilol twice a day compared to controls. On the other hand, Nebivolol has vasodilatory and antioxidant properties attributed to increased nitrous oxide, decreasing ROS in the microenvironment, and protection against LVEF compared with controls.

5.1.2. Renin-Angiotensin Inhibitors

Another commonly used cardioprotective drug for CIC is renin-angiotensin inhibitors, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors and ARBs are used to treat hypertension and facilitate cardiac remodeling by neurohormonal blocking. Their action attenuates oxidative stress and myocardial fibrosis, improving intracellular calcium handling, cardiomyocyte metabolism, and mitochondrial function. Enalapril is an ACE inhibitor used daily as a protective strategy in chemotherapy patients. Cardinale et al. demonstrated that starting treatment with daily enalapril reduced the increase in troponin levels and had fewer cardiotoxic incidents than the control group. In a recent study,Valsartan, an ARB agent, was additionally indicated to have cardioprotective effects. At a low dose of 80 mg per day, inhibition of LVDd dilation, BNP elevation, and QT interval prolongation was observed in 40 patients undergoing chemotherapy.

5.1.3. Statins

As anthracyclines are the most commonly prescribed chemotherapeutic agents, they have also been reported to cause the highest percentage of adverse effects and complications among patients with CIC. Statins are small molecules that act by inhibiting the enzyme HMG CoA reductase, ultimately reducing cholesterol synthesis and exhibiting pleiotropic properties by decreasing oxidative stress and inflammation. Additionally, statins have been reported to improve endothelial function and nitric oxide delivery. The cardioprotective effect of statins has highlighted their use to mitigate ACD. In a study of 67 women with newly diagnosed breast cancer, statins and anthracyclines were coadministered, and they had a lower risk of HF compared to 134 women not treated with statins. Furthermore, statins were also shown to prevent a decrease in LVEF after chemotherapy with anthracyclines compared to the placebo.

5.1.4. Dexrazoxane

Of all the drugs listed to ameliorate ACD, dexrazoxane is the only one FDA-approved. Specifically, dexrazoxane has been approved for children and adolescents treated with high doses of anthracyclines. The primary action of dexrazoxane is to reduce ROS formation by preventing anthracycline–iron complex formation. This way, dexrazoxane binds to iron before entering the cardiomyocytes, preventing free radical formation and cardiac damage. Additionally, dexrazoxane prevents anthracyclines from binding to Top-2β, the main source of cardiomyocyte death in ACD. The effectiveness of dexrazoxane in reducing ACD in patients with cancer has been supported for over 30 years.

5.1.5. Exercise

Although a nonpharmaceutical cardioprotective strategy, exercise has been studied over the years. Exercise generally decreases ROS formation, improves endothelial health, and decreases intracellular anthracycline levels. Furthermore, exercise increases heart tolerance against cardiotoxic agents and subsequently improves functional to subclinical to clinical parameters. During chemotherapy, patients tend to gain approximately 3 kg in weight over treatment. As a result, functional capacity is compromised, as indicated by peak VO2 during cardiopulmonary exercise tests. Although exercise does not directly circumvent cardiotoxicity induced by chemotherapy, it has been shown to improve the overall function of the cardiovascular system and decrease the risk of HF.

5.2. Current Treatments for Mitigating Chemo-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy primarily affects the sensory system, especially sensory neurons of the basal root ganglia. The dorsal root ganglia is considered an easier target for chemotherapeutic drugs because ganglion neurons...
are located outside the BBB and in the peripheral nervous system. Sensory and mechanical neurons are critical for the function of the peripheral nervous system. Although there is some evidence of changes in motor neurons in peripheral neuropathy, many changes are more localized within the function of the sensory neurons. Dorsal root ganglia have fluctuating ion channels and mitochondria damage, causing a malfunction of sensory neurons and glial cells. Schwann cells, a type of glial cell in the peripheral nervous system, which surrounds neurons and protects them through myelination, have a critical role in neuronal function and axon regeneration. Nerve dysfunction involves several critical cell types, including sensory neurons, Schwann cells, macrophages, and fibroblasts. Overall, many of the same changes occur in the peripheral nervous system with the treatment of different chemotherapeutics leading to long-term cell malfunction, including oxidative stress, dysregulated Ca\(^{2+}\) signaling, inflammation, and axonal degeneration. The role of mitochondria in regulating energy production, supply, and cell death is critical for cell function. Chemotherapy-induced neuropathy is linked with increased swollen and vacuolated mitochondria in sensory neurons, leading to impaired ATP production and nitro-oxidative stress, meaning the ratio ROS to RNS levels fluctuates, which leads to excessive ROS and RNS release. TRP channels are critical to the function of sensory neurons. Multiple TRPs have been indicated to play a role in oxidative stress and undergo changes in neuropathic pain. Calcium dysregulation in the peripheral nervous system is a critical problem in the mechanism of peripheral neuropathy onset. Oxidative stress and ROS formation lead to downstream effects on calcium homeostasis. Calcium dysregulation has been linked to the atrophy and loss of dorsal root ganglia and sensory neuron axonal degeneration due to calcium dysregulation causing calpain activation. Sensory axon degeneration is a primary cause of neuropathy and happens due to the dysregulation of the processes described above. Therefore, axonal regeneration is a key target of interest for treating peripheral neuropathy.

Historically, therapeutic targets to treat peripheral pain have not been well defined, so medications that do not target the underlying cause have been common. Opioids have traditionally been used to treat cancer-induced peripheral neuropathy, but the benefits are often negligible and vary on a patient-by-patient basis. Due to the addicting effects of opioids, their use has diminished over the last 20 years as researchers investigate alternatives that target the mechanisms of peripheral-induced neuropathy. Therefore, creating therapeutics to better target peripheral pain is a topic of great interest. While certain cellular processes, such as oxidative stress, dysregulated calcium levels, and axonal degeneration, contribute to malfunctioning neurons and dorsal root ganglia, which are key components of peripheral neuropathy, the molecular basis for chemotherapy-induced neuropathy remains unknown, as previously stated. Few clinically available treatments alleviate neuropathy in cancer survivors. When a cancer patient has symptoms of peripheral neuropathy after chemotherapy treatment, the method to deter these symptoms is to adjust the chemotherapy dose and the combination of medications. Sometimes peripheral neuropathy will depend on high doses of chemotherapy for a short or long-term period.

Some recently studied neuropathy targets include deoxidants, antioxidants, neurotrophic growth factors, and electrolyte and ion modifiers. However, none of these have led to clinically approved treatments. Neurotrophic growth factors are proteins that are critical for neuronal function and survival. Neurotrophic growth factors signal the cells to bind with protein kinase receptors of the Trk family. Preclinically, antioxidants such as vitamin E have been tested as natural antioxidants to reduce chemotherapy-induced peripheral neuropathy, but the results were inconclusive. In the past few years, calmodinafidipir has also been tested in phase II clinical trials and showed promising results, but increased the percentage of patients with chemotherapy-induced peripheral neuropathy during a 2021 phase III clinical trial. Deoxidants have also all failed during clinical trials. Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)) inhibitor, improved cisplatin-induced peripheral neuropathy in mice by raising superoxide dismutase (SOD) and catalase levels, enzymes that eliminate ROS. Due to the role of inflammation in chemotherapy-induced peripheral neuropathy, Piotrowska et al. tested maraviroc, a CCR5 antagonist, and showed its role in regulating microglia polarization in vitro. Maraviroc delivery in vivo correlated with downregulated phosphorylated p38 MAPK, ERK1/2 and NF-kB proteins in the spinal cord and upregulated STAT3 in the basal root ganglia. Maraviroc represents one of the many promising approaches currently in the initial phases of research to treat chemotherapy-induced peripheral neuropathy. P2X\(_7\) is a receptor on satellite glial cells in the dorsal root ganglia and is involved in nerve signaling pathways. Liu et al. tested P2X\(_7\) siRNA for treating diabetes-induced peripheral neuropathy in the dorsal root ganglia and showed its ability to reduce peripheral-induced neuropathy in rats. Treatments alike for diabetes-induced peripheral neuropathy have promise for the treatment of chemotherapy-induced peripheral neuropathy due to the similarities in cell types and mechanisms those cells undergo in the peripheral nervous system. In general, many new approaches are being studied to improve chemotherapy-induced peripheral neuropathy. There are currently no approved treatments for chemotherapy-induced peripheral neuropathy, so there is a great need and interest in developing new therapeutics targeting peripheral neuropathy.

5.3. Pathology of the Chemobrain and Associated Mechanisms as Targets for Treatment

Although improved survival has been achieved as a result of chemotherapy advances, cognitive function and emotional valence are also often impaired, a condition known as cancer-related cognitive impairments (CRCI). In addition to sequelae resulting from the malignancy itself, chemotherapy and/or radiotherapy result in CRCI in a subset of breast and ovarian cancer patients. Although greater than 50% of breast cancer patients report cognitive dysfunctions following chemotherapy, persistent long-term measurable dysfunctions are attributed to 15–25% of breast cancer survivors. CRCI is highly correlated with neurotoxicity in cancer survivors. Although breast cancer patients report cognitive dysfunctions prior to chemotherapy, these reports result from multiple converging factors.
including high levels of stress from cancer diagnosis, peripheral pro-inflammatory sequelae caused by tumor malignancy, and the response of the immune system. Consequently, chemotherapy exacerbates dysfunctional cognitive symptomatology in cancer survivors by detrimentally affecting multiple brain regions that control memory and attentional processing, such as the hippocampus and the pre-frontal cortex (PFC). In support, preclinical studies by our group, and others, have found that chemotherapy impairs hippocampal and cortical neurobiological processes known to control memory and attentional processes such as adult-born neuron generation (i.e., neurogenesis) and synaptic plasticity. In this section, pathological hallmarks of CICI will be discussed in the context of developing therapeutic approaches for management and attenuation.

5.3.1. Neuroinflammation

Neuroinflammation is a pathological hallmark of neurological, neuropsychiatric, and neurodegenerative disorders that are associated with cognitive declines as well as emotional impairments. In addition to those neurological conditions, increasing evidence suggests that neuroinflammation is one of the most prominent mechanisms contributing to CICI. For example, clinical evidence shows that increased cytokine levels, such as interleukin-6 (IL-6) or IL-8, are observed in patients with breast cancers receiving doxorubicin and methotrexate. Another study in breast cancer patients treated with cyclophosphamide in combination with doxorubicin or docetaxel found that the incidence of IL-1ß and IL-6 elevations were significantly associated with poor processing speed, in addition to self-perceived lapses in memory, concentration, and mental acuity. Once across the BBB, peripheral cytokines such as IL-1, IL-6, and TNF-α can activate local inflammatory responses (e.g., microglia), leading to neuroinflammation and cognitive impairment. In support, attentional and processing speed deficits were associated with higher levels of the pro-inflammatory cytokine IL-6 and soluble TNF receptors (sTNFR1 and sTNFR2), while conversely, anti-inflammatory IL-4 and IL-10 were detected with cognitive impairments as well as emotional declines. The hippocampus is one of few brain regions where newborn neurons are continuously generated from neural stem cells throughout life in a process called adult hippocampal neurogenesis, which is thought to be essential for maintaining proper learning and memory function, as well as emotional regulation. Notably, adult hippocampal neurogenesis is the most frequently investigated neural mechanism found to be affected by standard chemotherapy treatment. In comparison to cancer cells, neural stem cells/progenitors are pathologically vulnerable to chemotherapeutic drugs in vitro.

Growing in vivo evidence also shows a variety of chemotherapeutics, including cisplatin and paclitaxel, impair neural progenitors and neuronal maturation of newborn neurons in adult mouse hippocampus. Similarly, methotrexate treatment has resulted in decreased hippocampal neurogenesis in combination with the induction of depressive-like behavior in breast cancer mouse models, while 5-fluorouracil chemotherapy similarly decreased DCX expression with increased microglial density and elevations in proinflammatory cytokines in the cortex and hippocampus. More recently, multiple studies have reported that cisplatin drastically suppressed the dendrite outgrowth of newborn neurons. Most importantly, demonstrated the critical causative role of adult neurogenesis mediating CICI. Another additional mechanism of chemobrain is chemotherapies’ deleterious effects on synaptic integrity, which is a hallmark of cognitive function. For example, cisplatin has been demonstrated to decrease mitochondrial synaptic integrity, which is routinely associated with cognitive deficits in mouse models of chemobrain. Similar decrements in synaptic densities have been elucidated in preclinical studies of paclitaxel, while functional deficits in synaptic LTP by cyclophosphamide have also been recently elucidated.

5.3.3. Mitochondria Defects and Oxidative Stress

Mitochondrial dysfunction and oxidative stress are two of the main mechanisms mediating CICI. Several studies demonstrate that doxorubicin facilitates ROS production and mitochondrial membrane depolarization in neurons. Other studies also show that doxorubicin increases mitochondrial outer membrane permeabilization (MOMP) and Bax/Bcl-2 ratio, resulting in mitochondrial degeneration and neuronal defect. In addition to doxorubicin, cisplatin causes DNA damage and forms adducts with mitochondrial DNA (mtDNA), while inhibiting mtDNA replication and mitochondrial gene transcription. Cisplatin is also known to cause neuronal DNA damage, an increase in mitochondrial ROS production, a decrease in ATP synthesis, and a loss of mitochondrial membrane potential, all of which are hallmarks of oxidative DNA damage leading to mitochondrial functional abnormalities. In addition, the ultrastructural analysis demonstrated that cisplatin causes loss of cristae membrane integrity and matrix swelling in human excitatory human cortical neurons derived from hiPSCs. Furthermore, cisplatin-induced mitochondrial DNA damage and degradation, impaired respiratory activity, reduced dendritic branching and spine density, increased oxidative stress, and activated caspase-9 were observed in cultured hippocampal neurons and neuronal stem cells. These results suggest that increased mitochondrial oxidative stress and functional defects play a key role in chemotherapy-induced neurotoxicity.
5.3.4. Genetic Predispositions

The central nervous system (CNS) comprises the brain and spinal cord, with neurons and their connections detrimentally affected by chemotherapeutic agents, leading to pathological changes such as reduced brain connectivity (Figure 6).\(^{158a,b}\) It is possible that genetic predisposition may play a predictive role in long-term cognitive decline in cancer patients. For example, the apolipoprotein E4 (APOE4) gene, a risk factor for Alzheimer’s disease (AD), may be associated with cancer-related cognitive decline. Previous studies have reported that cancer survivors, particularly those with the allele e4 of the apolipoprotein E (APOEe4), have an increased risk for more significant cognitive impairment compared with patients with other APOE alleles.\(^{156}\) Furthermore, patients with alleles associated with dysfunctional DNA-repair mechanisms may be at increased risk for CICI. DNA damage and accompanying increased oxidative stress, including ROS generation and mitochondrial dysfunction, has also been proposed as another potential mechanism of CICI.\(^{156a}\) In addition, breast, lymphoma, and testicular cancer survivors, who carried the e4 allele of the APOE gene, revealed a decrease in the visual memory and spatial ability domains as well as scored lower in psychomotor functioning after chemotherapy.\(^{175}\) Previous studies of breast cancer survivors associated a decreased hippocampal volume to the APOE e4 allele, consistent with attenuated memory functioning.\(^{155c,174,176}\)

6. Nanotechnology Approaches for Treating Chemotherapy-Induced Damage

Nanomaterial-based therapeutics have shown extreme promise for the treatment of a variety of diseases. Nano-based treatments have been able to target cancer cells for the mitigation of chemotherapy-induced cardiomyopathy, neuropathy, and neurotoxicity. Additionally, nanomaterials can provide an effective means of treatment for these diseases after chemotherapy. Designing a nanotherapeutic to provide cardioprotection and regenerative capabilities in damaged cardiac tissue, during or after CIC, improves overall function and mitigates the risk of...
HF. Many studies have shown promise in nanomaterials for the treatment of CVDs, many of which can arise from CIC. In this way, the potential of these studies in treating CIC can be examined based on the efficacy of the treatment for the respective CVD. The main targets of chemotherapy-induced peripheral neuropathy include neuronal protection and regeneration, glial cell polarization, and ROS scavenging. Nanomaterials have been used to address these critical problems for various diseases and injuries, such as spinal cord injury, ischemic stroke, and diabetes-induced peripheral neuropathy. Thus, there is great potential for nanomaterials, which have been shown to target these mechanistic changes in other critical medical issues, to be applied to the treatment of chemotherapy-induced peripheral neuropathy, as these nanomaterials have been proven to target these changes in other similar medical issues. NP-based medicine has shown to be a promising solution for attenuating chemo-induced cardiomyopathy, neuropathy, and neurotoxicity, which has sparked great interest for its use in treating a multitude of maladies that result from chemotherapy.

6.1. Nanomaterial-Induced Cardioprotection and Regeneration

Many strategies to provide a cardioprotective or regenerative effect using nanomaterials in CVD have been employed. In light of these strategies, many different therapies have been used to repair or regenerate heart tissue. These include: 1) direct reprogramming of resident cardiac fibroblasts into contractile cells, 2) endogenous cardiomyocyte proliferation induction via the Hippo signaling pathway, and 3) nanozyme ROS scavenging for the attenuation of oxidative stress in cardiomyocytes and surrounding tissue. By each of these mechanisms, nanomedicine has been utilized to improve therapies aimed at restoring function and alleviating damage to the heart as a result of CVD.

In 2019, Yang et al. developed an in vivo miRNA delivery system for restoring infarcted myocardium. In the study, investigators used polymeric NPs to carry miRNA for localized delivery within a shear-thinning injectable hydrogel. The miRNA utilized, miR-199a-3p, promotes cardiovascular regeneration by stimulating the proliferation of mouse/rat cardiomyocytes. The nanotherapeutic was able to trigger the proliferation of resident cardiac fibroblasts into contractile cells, while promoting angiogenesis in hypoxic conditions, and inducing significantly lower cytotoxicity compared to Lipofectamine. Additionally, in myocardial infarction rats (MI-rats), one injected dose of the nanotherapeutic lead to significantly improved cardiac functions in MI-rats: reduced scar size from 20% to 10%, increased ejection fraction from 45% to 64%, and doubled capillary density in the border zone compared to the control group at 4 weeks.

A further investigation in 2018 adopted a similar strategy for tackling myocardial infarction by implementing dendrimers to administer miRNA molecules. In general, myocardial infarction progresses rapidly and is fatal, requiring effective intervention within 24 hours. Certain miRNAs have been reported to play a key role in the progression of the disease through post-transcriptional regulation. In particular, upregulation of miR-1 has been heavily associated with cardiomyocyte apoptosis following inhibition of anti-apoptotic protein expressions such as PKCe and Bcl-2. To this end, Xue and co-workers utilized anti-miR-1 antisense oligonucleotide (AMO-1), a miR-1 inhibitor, to treat myocardial infarction. The nanotherapeutic was composed of dendrigraft poly-L-lysine (DGL), a highly branched, cationic dendrimer-like 3D molecular structure. This dendrimer was PEGylated with an AT1 targeting peptide, interacting with the AT1 receptor highly expressed on cardiomyocytes 24 hrs after myocardial infarction. Last, the AMO-1 was loaded into the cationic cavities of the dendrimer for high-capacity loading and protection from degradation during circulation. After IV injection in mice, in vivo imaging demonstrated that nanotherapeutic accumulated quickly in the myocardial infarction heart during the desired early period, significantly outperforming the control group without AT1 targeting. Upon a single IV injection, a pronounced in vivo anti-apoptotic effect was observed. Furthermore, apoptotic cell death in the infarct border zone was significantly decreased, and the myocardial infarct size was reduced by 64.1% in comparison to that in the control group, displaying a high potential for early myocardial infarction treatment.

In general, many chemotherapies exacerbate cardiotoxicity through ROS production in cardiomyocytes, often leading to mitochondrial dysfunction, oxidative stress, and cell death. As such, the development of nanomaterials to remove excessive mitochondrial super oxide (O_2^•−) has become an effective treatment strategy. In 2021, Zhang et al. designed a biomimetic artificial hybrid nanozyme for efficient mitochondrial targeting and recovery of heart function in a cardiac ischemia-reperfusion animal model (Figure 7). The nanozymes consisted of a ferritin-heavy-chain-based protein (Ftn) as the enzyme scaffold and a MnO2 metal NP core as the active center of the enzyme. The artificial cascade nanozyme possessed SOD-like and CAT-like activities, with efficient mitochondrial targeting provided by triphenyl phosphonium (TPP) moieties on the surface. Overall, the artificial nanozyme was capable of i) overcoming the intracellular lysosomal barrier to escape into the cytoplasm and allow accumulation at mitochondria, ii) avoiding secondary damage resulting from highly cytotoxic OH• generation during O2•− elimination, iii) preferential accumulation and targeting to ischemic tissues after systemic delivery according to the heightened expression of Ftn receptor in ischemic tissues, and iv) rapid and deep penetration into cardiac tissues when locally administered in combination with adhesive hydrogel cardiac patches.

Lastly, in 2019 Zhang et al. designed a combinatorial approach to alleviate ischemic myocardial infarction in rats using magnetic NPs for the controlled and guided delivery of endothelial progenitor cells (EPC) into the infarct area of the heart. EPCs have been commonly studied and used to treat ischemic diseases due to their mobilization, homing,
and angiogenic effects. In general, low retention of EPCs in the infarct area has been suggested to be responsible for the poor clinical efficacy of EPC therapy for myocardial infarction. Recently, the use of nanomaterials to modify and manipulate the properties of cells has been of great importance and impact in the field. Since then, magnetic fields have been used to label and manipulate cells using superparamagnetic iron oxide NPs (SPIONs). Zhang and co-workers combined the technologies described to evaluate whether magnetized EPCs could increase the aggregation of EPCs in an ischemic area, subsequently enhancing therapeutic efficacy. SPIONs were synthesized and coated with silicon oxide (SiO₂), before being incubated in primary isolated EPCs for labeling. Once labeled, magnetized EPCs were transplanted into a female rat model.

Figure 7. Nanomaterials for cardio protection and regeneration following chemotherapy-induced damage. a) Zhang et al. developed a MnO₂ fenozyme to target mitochondrial oxidative injury following infarction. The MnO₂ fenozyme shows high ROS scavenging ability to b) scavenge superoxide radicals and c) hydrogen peroxide. MnO₂ is also essential for the material, as d) the superoxide elimination rate is higher than iron oxide. e) Embedding the platform in a hyaluronic acid hydrogel releases the nanoparticle over 24 h. The nanoparticle is then absorbed into f,g) the cardiac muscle and is retained for h) 3 days. Reproduced under the terms of the CC-BY license.[184] Copyright 2021, Wiley-VCH.
of myocardial infarction via tail vein injection on day 7. After 4 weeks of treatment, magnetically guided transplantation of EPCs improved cardiac function, decreased infarction size, and reduced myocardial apoptosis in rats. Furthermore, compared to the control, increased microvascular density and increased expression of pro-angiogenic factors were observed under treatment conditions.\[^{183}\]

6.2. Nanomaterial-Induced Peripheral Neuroprotection

Along with improving the only clinically approved treatment for peripheral neuropathy and changing the chemotherapy treatment regimen, many researchers are studying NPs that scavenge ROS, regenerate axons, target inflammation in microglia and other glial cell types, and selectively deliver therapeutics of interest, all of which have the potential for treating chemotherapy-induced neurotoxicity based on the disease pathology and cellular changes undergone.

In nature, natural enzymes exhibit prominent catalytic activities as indispensable biocatalysts with high substrate selectivity for mediating in vivo biochemical reactions. Unfortunately, many enzymes are globular proteins that are easily denatured under severe physiological conditions. In recent years, the development of artificial nanomolecules to overcome the limitations associated with natural enzymes has been largely successful, attributed to various unique nanomaterials. Certain nanomaterials have been shown to have intrinsic catalytic properties for scavenging ROS in cells, such as cerium oxide (CeO\(\text{2}\)), manganese dioxide (MnO\(\text{2}\)), and Prussian blue (PB).\[^{186}\] These nanomaterials can be synthesized to form different nanostructures, such as sheets, particles, cubes, and films. In general, nanomolecules of this type have been discovered to possess enzyme-like properties, such as peroxidase (POD)-, catalase (CAT)-, oxidase (OXD)-, superoxide dismutase (SOD)-, and glutathione peroxidase (GPx)-like activities.\[^{187}\] Many of these processes involve the metabolism of various ROS that can cause oxidative stress, resulting in a quantity of diseases.\[^{188}\] Furthermore, each of these mechanisms of endogenous enzymatic function is efficiently replicated using nanomaterials, but with the advantages of high stability, low cost, and chemical functionality for cell targeting or drug delivery.\[^{189}\] The synergetic and novel properties of nanomolecules have led to their use in biosensing, environmental treatment, disease diagnosis and treatment, antibacterial agents, and cytoprotection against biomolecules.\[^{190}\] Abdelhamid et al. demonstrated CeO\(\text{2}\) NPs have protective effects on oxiplatin- and cisplatin-induced peripheral neuropathy through SOD-, POD-, and Cat-like activities, leading to a reduction in activated astrocytes and degenerating neurons.\[^{191}\] The effect of MnO\(\text{2}\) nanomolecules on neuropathic pain, synthesized using a hydrothermal method, has also been shown using an in vivo rat model due to their SOD- and CAT-like activity.\[^{192}\] Overall, these nanomolecules are extremely promising for the treatment of diseases.

Due to the role of macrophages in the peripheral nervous system and the link between inflammation and chemotherapy-induced peripheral neuropathy, nanomaterials with intrinsic properties to reduce the effects of inflammation in macrophages and other glial cells are an important area of study for peripheral nerve regeneration. Polarizing macrophages to a proinflammatory state has promising effects in the treatment of cancer, but inducing a proinflammatory phenotype in the peripheral nervous system is one of the main cellular changes undergone and a key component of peripheral neuropathy. Mesoporous hollow iron oxide NPs under an alternating magnetic field were shown to induce macrophage polarization by Guo et al.\[^{193}\] Macrophage polarization also had downstream effects on neuronal proliferation and vasculature formation in vitro. CeO\(\text{2}\) NPs have been shown to polarize macrophages and have enzyme-like properties for ROS scavenging.\[^{194}\] The CeO\(\text{2}\) NPs indicated significant downregulation of pro-inflammatory markers and upregulation of anti-inflammatory markers in an in vivo rat model of spinal cord injury. While this NP was used to target a different disease, it showed promise for macrophage polarization and had potential to be applied to treat chemotherapy-induced peripheral neuropathy. Berberine-capped gold nanoclusters have also been shown to polarize macrophages and microglia from M1 to M2 after spinal cord injury.\[^{195}\] Specifically, the gold nanoclusters led to the downregulation of pro-inflammatory cytokines linked to M1 macrophage polarization, including IL-1\(\beta\), IL-6, TNF-\(\alpha\), Cleaved Caspase-3, and Bax. Polarizing macrophages and microglia after spinal cord injury also inhibited neuronal apoptosis and could have similar protective effects on sensory neurons after chemotherapy-induced peripheral neuropathy. Overall, there are many methods for NP-based delivery depending on the therapeutic choice and target of interest.

A variety of polymer, lipid, and other types of nanomaterials show promise for small molecule and biologic delivery due to their biodegradable, targeting, and stimuli-responsive properties, depending on their formulation and design.\[^{196}\] The targeted delivery of molecules such as antioxidants, deoxidants, and neurotrophic growth factors to cells related to nerve regeneration in the peripheral nervous system is another promising avenue for the treatment of chemotherapy-induced peripheral neuropathy. Despite these advancements, nanomaterials with these intrinsic properties have recently become the main avenue of research. Selective delivery of therapeutics to the peripheral nervous system to treat chemotherapy-induced peripheral neuropathy is critical, as there are different mechanistic targets for cancer and chemotherapy-induced peripheral neuropathy. Patients who need treatment for peripheral neuropathy due to chemotherapy will still undergo cancer treatment in many cases. Zeng et al. developed a self-assembling cyclodextrin NP to encapsulate and deliver the antioxidant enzymes superoxide dismutase and catalase.\[^{197}\] The cyclodextrin NP showed synergistic effects between the enzymes for scavenging ROS, reducing the release of pro-inflammatory cytokines, and protecting cells from oxidative damage. While morphine can help the symptoms of neuropathic pain, it has been shown to negatively interact to prevent the activity of antioxidant enzymes such as CAT and SOD. To help prevent morphine-related off-target effects, Kuthati et al. made mesoporous polydopamine NPs loaded with morphine for treating neuropathic pain in an in vivo rat model (Figure 8).\[^{198}\] In 2022, Tran et al. developed fexofenadine encapsulated PLGA NPs for prolonged pain relief in an in vivo rat model of neuropathic pain.\[^{199}\] The fexofenadine encapsulated NPs could inhibit...
microglia activation, which plays a similar role to macrophages in inducing inflammatory processes, and led to similar protective effects on preventing peripheral neuropathy as macrophage polarization by the intrinsic properties of nanomaterials.

As axonal degeneration in sensory neurons is a major factor in chemotherapy-induced peripheral neuropathy, NPs showing neuroprotective effects on sensory neurons and causing axonal growth are a potential treatment method for chemotherapy-induced peripheral neuropathy. A common way to provide neuronal protection and development is with the development of neurotrophic growth factors. Ziv-Polat et al. showed the feasibility of using iron oxide NPs for extending the half-life and delivering neurotrophic growth factors to cause neuronal regeneration and development in the dorsal root ganglia. Specifically, the stability of BDNF, GDNF, and FGF-2 was increased by conjugation with iron oxide NPs and led to

Figure 8. a) Morphine-loaded mesoporous polydopamine nanoparticles for neuropathic pain are b) approximately 100 nm, and c) scavenge ROS. d) The nanoparticles show sustained delivery of morphine, which downregulates proinflammatory cytokines e) TNF-α, and f) NF-κB. Reproduced under the terms of the open access CC-BY license. Copyright 2021, MDPI.
enhanced nerve regeneration in the peripheral nervous system. Lopes et al. used thiolated tri-methyl chitosan for the encapsulation and delivery of BDNF DNA selectively to neurons in the peripheral nervous system for nerve regeneration.[201] Lipid-based formulations are another promising method of therapeutic delivery due to their capability to encapsulate hydrophobic and hydrophilic drugs. Recently, Kuo et al. designed a cationic solid lipid NP to deliver nerve growth factor for enhanced neuronal differentiation of iPSCs.[202] There is still major room for improvement in the treatment of chemotherapy-induced peripheral neuropathy through the further elucidation of chemotherapeutic mechanism of action on the peripheral nervous system and research into targeting these mechanistic changes with the creation of new targeted therapeutic platforms. Overall, targeted ROS, glial cell polarization towards an anti-inflammatory state, sensory and motor neuronal regeneration, and small molecule and biologic delivery with nanomaterials, represent promising approaches for treating chemotherapy-induced peripheral neuropathy.

6.3. Nanoparticle Delivery and Chemotherapy-Related Cognitive Impairment

NP-mediated cancer medicine is a promising translational approach that can foster a new age of personalized breast cancer treatment. Consequently, whether NP-based medicine can ameliorate cancer-related cognitive impairments, while maintaining chemotherapeutic efficacy in breast cancer, is a research topic that requires exploration. Solid lipid NPs and nanostructured lipid carriers can package and deliver molecules of varied physicochemical characteristics, such as lipophilic and/or hydrophilic molecules, in combination with biologics that include monoclonal antibodies, peptide fragments, siRNA, miRNA, and others.[203] Not surprisingly, invasive (intrathecal, interstitial microchip/implants) and non-invasive (intranasal, intravenous) delivery strategies have been recently implemented in preclinical studies of neurodegenerative conditions such as Alzheimer’s disease, Parkinson’s disease (PD), as well as neurological conditions such as pain, schizophrenia, and neuroAIDS.[204] Recent advances in brain cancer research and neurological disease have been made by developing strategies that overcome the neurovascular unit’s nested endothelial cell tight junction proteins (e.g., occludins, claudins, JAMs), basement membrane pericytes, astroglial endfeet, and active efflux proteins (e.g., p-glycoproteins, multi-drug resistance associated proteins) that prevent easy BBB penetration.[204a,205] Therefore, in a manner reminiscent of the work by Panagi and co-workers, a TGF-β inhibitor was combined with PEGylated liposomal doxorubicin/doxil to improve antitumor efficacy.[115] Hence, it is conceivable that future chemotherapeutics can be combined with neuroprotective agents conveniently packaged in NPs, delivered intranally or systemically, to prevent chemobrain.

Importantly, NP-mediated delivery has been recently reported to improve cognitive dysfunction and neurotoxicity in a tumor-bearing rat model of C6-glioblastoma.[206] In this study, Li and co-workers utilized metallic NPs that form graphite–graphene conjugates possessing inherent antiviral properties (termed AVNPs) to reduce tumor-associated inflammatory markers (NF-κB, IL-1β, IL-6, TNF-α), resulting in decreased brain tumor size. AVNP administration improved tumor-induced memory deficits while mitigating declines in hippocampal long-term potentiation and hippocampal dendrite spine densities. Additionally, treatment resulted in recovered impaired expression of the presynaptic marker synaptophysin and the postsynaptic marker PSD95.[206] Based on these findings, it would be interesting if AVNPs could be utilized with chemotherapies to determine if they can confer similar neuroprotective properties against breast cancer-related chemobrain. Cyclophosphamide is a frontline alkylating chemotherapy used in various malignancies, including breast cancer, and has been demonstrated to result in chemobrain.[207] Recently, oral administration via a nano-engineered lipid carrier system of the compound Nerolidol, a bioactive sesquiterpene with antioxidant and anticancer properties, was effective in reducing cyclophosphamide-induced spatial memory deficits, prevented elevations in anxiety, and attenuated depressive-like behavior (Figure 9).[100] Notably, nano-lipid packaged Nerolidol also attenuated cyclophosphamide-induced elevations in IL-1β, IL-6, TNF-α. It is important to mention that the formulation of nano-lipid packaged Nerolidol was designed to overcome the low solubility of Nerolidol, low bioavailability, fast first-pass hepatic metabolism, and general ineffectiveness in preventing cyclophosphamide-induced chemobrain. Similarly, curcumin has been hypothesized to have antioxidant, anti-inflammatory, and anticancer properties, although it also has low solubility, low bioavailability, rapid metabolism, and clearance. However, a recent study of nano-encapsulated curcumin packaged in polyethylene glycol-polylactide (PEG-PLA) di-block polymer micelles prevented doxorubicin-potentiated increases in rat cortical and hippocampal nitric oxide and malondialdehyde oxidative stress biomarkers.[208] Doxorubicin-induced chemobrain was also attenuated by CeO₂ NPs in a comprehensive set of studies that showed that treatment prevented spatial memory dysfunction while decreasing neuroinflammation, astrogliosis, NLRP3 inflammasome activation, and mitochondrial dysfunction, potentially via a Sirtuin-1 mediated mechanism.[209] This is interesting since our own group has found that cisplatin-induced memory dysfunction and neurogenesis impairments may be regulated through a NAD+ metabolic alterations in SIRT-2 expression.[43d]

Interestingly, it is possible that nanotechnology treatment strategies can attenuate CRCI like that recently implemented for preclinical models of Parkinson’s disease and Alzheimer’s disease.[210] PD is a disease characterized by degeneration of the striatal neurons that results in dysfunction of motor movement, emotive deficits (depression and anxiety), cognitive deficits, and eventual dementia. For example, nanoeumulsions, composed of oil phase vitamin-E:sesfol (1:1), Tween-80 (surfactant), Transcul P (co-surfactant), and naringenin, delivering the antioxidant resveratrol resulted in increased brain uptake in conjunction with increased antioxidant generation and improved behavior performance in 6-OHDA PD rodent models.[106,107] Using a similar 6-OHDA PD rodent model, poly(lactic-co-glycolic acid; PLGA) nanoparticles and titanium dioxide (TiO₂) nanowires have also been used to deliver neurotrophic growth factors and cerebrolysin, respectively, resulting in cellular and behavioral neuroprotection in this neurodegenerative model.[211] Similarly,
in a MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) PD mouse model, nanomicelles formulated with a combination of poly(ethylene glycol) and polyoxyethanyl-α-tocopherol sebacate to package the mitochondrial antioxidant coenzyme Q$_{10}$ (CoQ$_{10}$), was systemically delivered and showed efficacy in preventing nigrostriatal neuronal degeneration, recruiting neuroprotective astroglia, and improving motor function.\textsuperscript{[212]} Formulations of CoQ$_{10}$ encapsulated in Ubisol-Q$_{10}$, an amphiphilic self-emulsifying polyoxyethanyl-α-tocopherol sebacate (vitamin E), have also been used in AD mouse models to reduce amyloid burden and improve cognition.\textsuperscript{[213]} Reductions in amyloid burden, a molecular target of AD pathology, as

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**Figure 9.** a) Nerolidol docks to NLRP3 to attenuate inflammation and reduce neurotoxicity. b) Nerolidol formulated lipid nanoparticles elevate SOD activity. The nanoparticle downregulates c) pro-inflammatory cytokines TNF-α, d) IL-6, and e) IL-1β while upregulating IL-10. The nanoparticle is efficacious in cancer cell death and reducing tumor volume. Reproduced under the terms of the CC-BY license.\textsuperscript{[100]} Copyright 2020, Elsevier.
Table 3. Nanotechnology for treating chemotherapy-induced neurotoxicity, neuropathy, and cardiomyopathy (PFBT, poly(9,9-dioctylfluorene-alt-benzothia-diazole); PLGA, poly(lactic-co-glycolic acid); GDNF, glial cell line-derived neurotrophic factor; VEGF, vascular endothelial growth factor; LHRH, luteinizing hormone-releasing hormone).

<table>
<thead>
<tr>
<th>NP</th>
<th>Size</th>
<th>Surface functionality</th>
<th>Therapeutic</th>
<th>Pathological condition</th>
<th>Experimental model</th>
<th>NP functions</th>
<th>Refs.</th>
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<tr>
<td>DSPE-PEG polymeric NPs</td>
<td>≈110 nm</td>
<td>Cell-penetrating peptide, PFBT</td>
<td>miR-199a-3p</td>
<td>Myocardial infarction</td>
<td>hESC-CMs, hESC-ECs, MI-RNU rats</td>
<td>Protect miRNA from premature degradation, facilitate cellular uptake, and enhance localization</td>
<td>[179]</td>
</tr>
<tr>
<td>DGL dendrimer</td>
<td>≈200 nm</td>
<td>PEG, AT1 targeting peptide</td>
<td>AMO-1</td>
<td>Myocardial infarction</td>
<td>H9C2, SD neonatal rats origin primary myocardial cells, C57BL/6 mice</td>
<td>Quick targeting and accumulating in the MI heart, protecting from degradation during circulation</td>
<td>[183]</td>
</tr>
<tr>
<td>SPIONs</td>
<td>60 nm</td>
<td>Silica layer</td>
<td>EPCs</td>
<td>Ischemic myocardial infarction</td>
<td>SD rats origin primary EPC, MI-MD rats</td>
<td>Controlled and guided delivery of EPCs</td>
<td>[185]</td>
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<tr>
<td>Cerium oxide NPs</td>
<td>&lt;25 nm</td>
<td>Cisplatin and oxaliplatin</td>
<td>Nephrotoxicity</td>
<td>Male albino rats</td>
<td></td>
<td>Anti-inflammatory and antioxidant properties, Scavenge ROS</td>
<td>[191]</td>
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<td>Manganese oxide NPs</td>
<td>10–300 nm</td>
<td></td>
<td>Neuropathic Pain</td>
<td>BMDMs, Cns-1 neural cells, BALB/c mice, male Wistar rats</td>
<td></td>
<td>Antioxidant activity, Scavenge ROS</td>
<td>[192]</td>
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<tr>
<td>Mesoporous FeO₄</td>
<td>180–200 nm</td>
<td></td>
<td>Nerve regeneration</td>
<td>RAW 264.7, NE-4C, HUVECs</td>
<td></td>
<td>Inducing macrophage polarization via alternating magnetic field</td>
<td>[193]</td>
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<tr>
<td>Cerium oxide NPs</td>
<td>6.8 ± 0.5 nm</td>
<td></td>
<td>Chronic neuropathic pain</td>
<td>RAW 264.7, adult female Wistar rats spinal cord injury model</td>
<td></td>
<td>ROS scavenging, inhibiting macrophage activation and modulating macrophage polarization</td>
<td>[194]</td>
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<tr>
<td>Gold nanoclusters</td>
<td>121.982±20.913 nm</td>
<td></td>
<td>Berberine</td>
<td>Spinal cord injury</td>
<td>RAW 264.7, VSC 4.1, Sprague Dawley female rats</td>
<td>Inhibit the activation of M1 phenotype macrophages and neuronal apoptosis</td>
<td>[195]</td>
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<td>Cyclodextrin</td>
<td>136 nm</td>
<td>Superoxide dismutase and catalese</td>
<td>Inflammatory disease</td>
<td>RAW264.7 cells, colitis mice model</td>
<td></td>
<td>Encapsulate therapeutic proteins for effective oral delivery</td>
<td>[197]</td>
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<tr>
<td>PLGA NPs</td>
<td>260.3 ± 63.35 nm</td>
<td></td>
<td>Fexofenadine</td>
<td>Neuraphotic pain</td>
<td>Microglial BV2 cell line, lumbar 5 spinal nerve ligated rats</td>
<td>Crossing the BBB, increasing drug efficiency, prolonged drug release</td>
<td>[199]</td>
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<td>Iron oxide NPs</td>
<td>10–15 nm</td>
<td>Gelatin, dextran</td>
<td>Neural growth factors (JNF, GDNF, FGF-2)</td>
<td>Peripheral nerve regeneration</td>
<td>Organotypic dorsal root ganglion from rat fetuses</td>
<td>Prolong growth factors' activity and bioavailability</td>
<td>[200]</td>
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<td>Thiolated trimethyl chitosan NPs</td>
<td>90–240 nm</td>
<td>HC fragment</td>
<td>BDNF plasmid</td>
<td>Peripheral nerve injury</td>
<td>Primary embryonic rat dorsal root ganglion neurons, female BALB/c mice</td>
<td>Therapeutic encapsulation and targeted gene delivery</td>
<td>[219]</td>
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<td>Cationic solid lipid NPs</td>
<td>90–240 nm</td>
<td>Heparin</td>
<td>Nerve growth factor</td>
<td>Neuronal differentiation</td>
<td>iPSCs</td>
<td>Prolong the half-life of NGF, maintain NGF activity</td>
<td>[202]</td>
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<td>W-Ag-Cu AVNP2</td>
<td>10–30 nm</td>
<td>Graphite-graphene</td>
<td>C6 glioma</td>
<td>C6 glioma cells, male Sprague-Dawley rats</td>
<td></td>
<td>Reduce toxicity, alleviate inflammation, and protect against cognitive impairments</td>
<td>[206]</td>
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<td>Lipid NPs</td>
<td>154.177 ± 2.860 nm</td>
<td></td>
<td>Nerolidol</td>
<td>Neuroinflammation</td>
<td>Male Swiss albino mice</td>
<td>Overcome Nerolidol's low solubility, low bioavailability, fast metabolism, and general ineffectiveness</td>
<td>[100]</td>
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Table 3. Continued.

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<td>MnO2/Fe3O4 NPs</td>
<td>6.5 nm</td>
<td>Ferritin, triphenylphosphonium, Cy5</td>
<td>Cardiac ischemia-reperfusion injury</td>
<td>IR C57BL/6 mice</td>
<td>Mitochondrial targeting, scavenging excessive mitochondrial superoxide</td>
<td>[214]</td>
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<td>TiO2 nanowire</td>
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<td>Cerebrosolin</td>
<td>Neuroprotective effect</td>
<td>Sprague-Dawley rats</td>
<td>Penetrate the CNS and reach widespread areas to increase drug delivery within CNS</td>
<td>[211a]</td>
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<td>PLGA nanosphere</td>
<td>221–267 nm</td>
<td>Neurotrophic factors</td>
<td>Parkinson’s Disease</td>
<td>Parkinsonized Sprague-Dawley rats</td>
<td>Increase delivery efficiency</td>
<td>[219]</td>
<td></td>
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<tr>
<td>PLGA nanosphere</td>
<td>221–267 nm</td>
<td>VEGF, GDNF</td>
<td>Neurodegenerative process in Parkinson’s disease</td>
<td>PC-12 cells, male albino Sprague Dawley rats</td>
<td>Continuous and simultaneous drug release, enhanced dosages efficiency</td>
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<td>Gold NPs</td>
<td>5 nm</td>
<td>Bucladesine</td>
<td>Alzheimer’s disease</td>
<td>Hippocampal pyramidal cells, male Wistar rat</td>
<td>Relieving memory impairment and neural damage</td>
<td>[214]</td>
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well as spatial memory improvements have been facilitated by citrate stabilized gold NPs (AuNPs). Notably, FDA-approved drugs to treat AD, such as galantamine, rivastigmine, and memantine, have been nanodelivered in preclinical models that show promise in restoring cognitive deficits. For example, galantamine formulations have been delivered in solid-lipid NPs and thiolated chitosan constructs with efficacy in improving cognition. At the same time, rivastigmine and memantine have been nanodelivered in preclinical models that possess preclinical and, in time, clinical efficacy to combat chemobrain. 

In particular, these approaches could be combined with pharmacological candidates recently demonstrated to be neuroprotective in preclinical studies of chemobrain. These include the NAD+ boosting nicotine mononucleotide (NMN), the FDA-approved cognitive enhancer A2 adenosine receptor (A2A) antagonist istradefylline, the A3 receptor (A3A) antagonist MRSS980, and the cardiovascular disease treatment atorvastatin. Importantly, NMN, istradefylline, and atorvastatin mitigated cisplatin and trastuzumab-induced chemo brain, while maintaining efficacious breast tumor eradication. Similarly, neuroprotective compounds can protect against methotrexate chemotherapy-induced demyelination, such as the TrkB partial agonist LM22A-4, or attenuate cisplatin-induced mitochondrial dysfunction. For example, NMN or the indirect p53 inhibitor pifithrin-μ may be reformulated for NP-mediated delivery to alleviate cisplatin-induced neurotoxicity. Achieving this is feasible in the near future, for example, with cisplatin or methotrexate among other chemotherapies. Recent breast cancer studies have formulated cisplatin nanodelivery via luteinizing-hormone releasing-targeted polysaccharide NPs in vivo, L-lysine conjugated gold-NPs carrying cisplatin in vitro, and a pH-sensitive chitosan-modified nanomicelle carrier in MCF-7 breast cancer cell lines. Additionally, methotrexate nanodelivery has also been applied to breast cancer in vivo and in vitro preclinical models through dextran–curcumin conjugates, ultrafine gold–NPs, and mesoporous silica NPs conjugated to chitosan. Taken together, by combining existing compounds that ameliorate chemotherapy-induced cognitive dysfunction with advanced NP delivery methods, we can enhance the efficacy of neuroprotective compounds without losing antitumor efficacy, thus improving the quality of life of breast and ovarian cancer survivors (Table 3).

7. Conclusion and Future Perspectives

The critical short- and long-term detrimental side effects of cancer treatment greatly diminish the quality of life for breast and ovarian cancer patients and survivors. Therefore, new approaches to prevent and treat chemotherapy-induced off-target mechanistic changes have become a critical research avenue. One of the most promising emerging approaches for selective targeting of chemotherapeutics and reducing off-target effects is nanomaterial-based delivery. As described in this review, nanomaterials have a wide range of capabilities due to their malleable physical and chemical properties. Nanomaterials have the potential to revolutionize cancer treatment and improve the quality of life for cancer survivors. Advancements in nanomaterial design, synthesis, and application are leading to many promising directions for improving cancer treatment efficacy, decreasing off-target effects, and treating diseases induced by chemotherapy. This review examines the current state of nanotechnology-based approaches to investigate chemotherapy-induced neurotoxicity, neuropathy, and cardiomyopathy in breast and ovarian cancer survivors. A multitude of mechanisms can be linked to chemotherapy-induced diseases that decrease the quality of life for cancer patients and survivors. The thoughtful design of nanotechnology can be utilized to treat these diseases effectively. Specifically, nanomaterials have been applied for mitigating oxidative stress, cell reprogramming, cardiomyocyte proliferation, neuronal protection and regeneration, macrophage and microglia polarization, and as a small molecule and biologic delivery system. Although
promising progress has been made in the field of nanotechnology for treating the adverse effects of chemotherapies, there are no approved nanotechnology-based clinical treatments for these diseases.

Overall, nanotechnology-based approaches are extremely promising due to their potential to alleviate the side effects caused by chemotherapy. However, further research into these problems will help elucidate new nanomaterials for treating these diseases and direct nanomaterials approved for other applications toward these critical problems. Most research has focused on current ways to improve chemotherapy treatments, as this is the first line of defense against critical chemotherapy-induced side effects. Therefore, further study is urgently required to determine better ways to utilize nanomaterials for treatment of these diseases and lessen the off-target effects of chemotherapy to enhance the lives of women who have survived breast and ovarian cancer.

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Conflict of Interest
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cardiomyopathy, nanotechnology and nanomedicine, neuropathy, neurotoxicity, ovarian and breast cancer

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Callan D. McLoughlin is a Ph.D. candidate in the lab of Dr. Ki-Bum Lee within the chemistry and chemical biology program at Rutgers University. Callan received his B.A. degree from Marist College, studying biochemistry, and during his Ph.D. has since focused on designing and synthesizing novel nanomaterials that provide interesting therapeutic benefits in several inflammatory diseases. Specifically, he is interested in designing nanomaterials that facilitate the reprogramming and conversion of innate immune cells from a pro-inflammatory to an anti-inflammatory phenotype in diseases such as diabetes and sepsis.
Alfredo Oliveros is a Bosarge Family Foundation-Waun Ki-Hong Scholar and senior postdoctoral fellow in the Regenerative Neurobiology lab of Dr. Mi-Hyeon Jang at Rutgers University. Dr. Oliveros completed his Ph.D. apprenticeship at the Mayo Clinic College of Medicine. Currently, he investigates the detrimental effects that chemotherapy exerts on learning, memory, and hippocampal neurogenesis, while concomitantly searching for novel molecular therapeutic targets to treat chemotherapy-related cognitive impairments, colloquially known as “chemobrain.” His research efforts have been funded by the American Association for Cancer Research and the Cancer Institute of New Jersey Pediatric Cancer and Blood Disorders Pilot Program.

Mi-Hyeon Jang’s lab focuses on investigating neurobiological mechanisms that can promote neuronal regeneration for improving brain function in the context of chemotherapy-induced cognitive sequelae (also known as chemobrain). Ultimately, we hope to develop new regenerative therapeutic strategies to ameliorate chemobrain and thus improve quality of life for cancer survivors.

KiBum Lee is a distinguished professor of chemistry and chemical biology at Rutgers University, where he has been a faculty member since 2008. His group’s primary research interest is developing and integrating nanotechnologies to modulate signaling pathways in stem cells towards specific cell lineages or control their behavior. To address the challenges associated with conventional stem/cancer cell biology, his research program at Rutgers University focuses on developing novel nanotechnology and chemical biology methods. These methods include nanoparticle-based drug/gene delivery, molecular imaging, nanobioscaffolds, biosensing, and microfluidics for investigating and modulating complex signaling pathways during certain stem/cancer cell behaviors.