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Review

Strategies, Challenges, and Prospects of Nanoparticles in Gynecological Malignancies

Yingfeng Zhang and Jing Tian*

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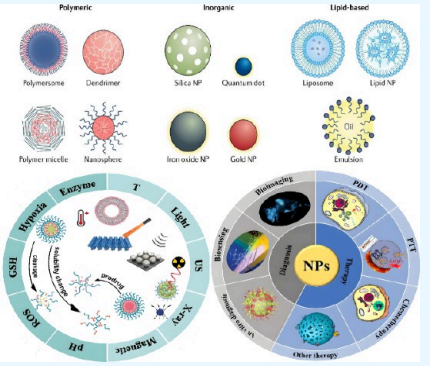
ABSTRACT: Gynecologic cancers are a significant health issue for women globally. Early detection and successful treatment of these tumors are crucial for the survival of female patients. Conventional therapies are often ineffective and harsh, particularly in advanced stages, necessitating the exploration of new therapy options. Nanotechnology offers a novel approach to biomedicine. A novel biosensor utilizing bionanotechnology can be employed for early tumor identification and therapy due to the distinctive physical and chemical characteristics of nanoparticles. Nanoparticles have been rapidly applied in the field of gynecologic malignancies, leading to significant advancements in recent years. This study highlights the significance of nanoparticles in treating gynecological cancers. It focuses on using nanoparticles for precise diagnosis and continuous monitoring of the disease, innovative imaging, and analytic methods, as well as multifunctional drug delivery systems and targeted therapies. This review examines several nanocarrier systems, such as dendrimers, liposomes, nanocapsules, and nanomicelles, for gynecological malignancies. The review also examines the enhanced therapeutic potential and targeted delivery of ligand-functionalized nanoformulations for gynecological cancers compared to nonfunctionalized anoformulations. In conclusion, the text also discusses the constraints and future exploration prospects of nanoparticles in chemotherapeutics. Nanotechnology will offer precise methods for diagnosing and treating gynecological cancers.



1. INTRODUCTION

Women's health worldwide is significantly impacted by gynecologic malignancies. They are a collection of malignant tumors that impact the reproductive tissues and organs in women, such as the ovaries, uterus, cervix, vagina, vulva, and endometrium (Figure 1B).[1] Cervical cancer, ovarian cancer, and endometrial cancer can contribute to more than 10% of all female cancer-related deaths.[2] Early detection and prompt treatment of gynecologic cancers in women can prevent the spread of cancer cells and greatly improve the 5-year survival rate of female patients.[3] Regrettably, numerous women diagnosed with gynecologic cancers are in advanced stages as a result of inadequate screening methods and vague symptoms.[4] In the field of cancer therapy, utilizing traditional methods like surgery, chemotherapy, hormonal therapy, radiation therapy, immunotherapy, and adjuvant therapy can enhance the prognosis and quality of survival.[5] However, challenges such as cancer recurrence, inadequate treatment monitoring, limited therapeutic effectiveness, severe toxicity, and resistance to multiple drugs persist.[6] Hence, the advancement of sophisticated diagnostic and therapeutic technology remains a distant objective within the area.

In recent decades, there has been a notable advancement in the creation, manipulation, and analysis of nanoparticles for cancer treatment and diagnostics. Nanomedicine involves utilizing nanoparticles and macromolecules that are typically between 10 and 200 nm in size to create distinctive and intricate interactions with biological systems.[8] Nanocarrier examples comprise self-assembled polymers, liposomes, micelles, dendrimers, hydrogels, magnetic nanoparticles, quantum dots, carbon-based nanoparticles such as carbon nanotubes and buckyballs, and oxide- or metal-based nanoparticles such as silica, colloidal gold, and titanium dioxide. Nanotechnology aims to improve the techniques used for treatment, diagnosis, or a combination of both (theranostics) in various diseases, including gynecological cancers.[9] Nanoparticles have several benefits, including targeted delivery of hydrophobic compounds, stabilization of the delivery carrier, reduced systemic toxicity of antineoplastic drugs, and improved biodistribution and pharmacokinetics of API.[7] Nanoparticles for imaging or diagnosis consist of contrasting agents such as magnetic, iron oxide, and gold nanoparticles, as well as fluorescent agents like quantum dots. These agents can contain targeting moieties.[10] Certain nanoparticles, including

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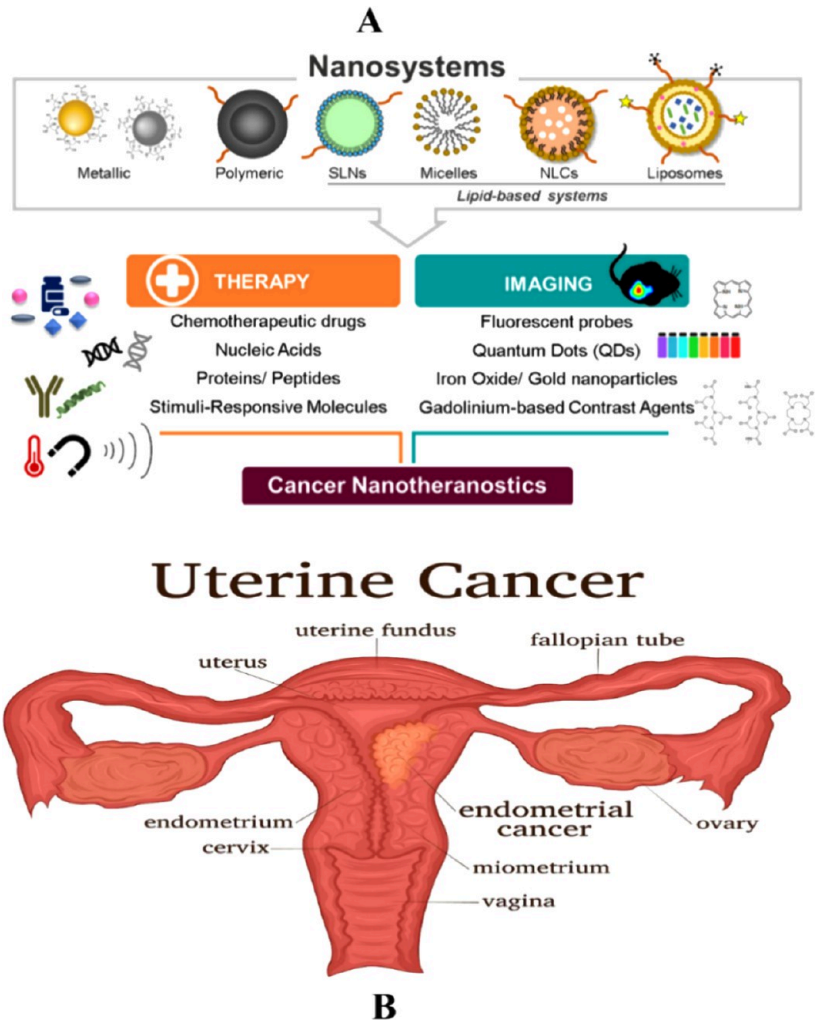

Figure 1. A. Nanotheranostics: polymeric, metallic, and lipid-based nanosystems for cancer management. Reprinted in part with permission from [Silva, C.O.; Pinho, J.O.; Lopes, J.M.; Almeida, A.J.; Gaspar, M.M.; Reis, C. Current Trends in Cancer Nanotheranostics: Metallic, Polymeric, and Lipid-Based Systems. Pharmaceutics **2019**, *11*(1), 22].[389] B. Schematic figure to describe the location of different types of gynecological cancer in the female reproductive system.

carbon nanotubes, gold nanoparticles, and magnetic nanoparticles, possess intrinsic optical features that can be used to deliver tremendous energy to cells for destruction and function as nanotheranostics. Various nanoparticles have been effectively utilized in different applications of nanomedicine.[11,12] For example, electrochemical biosensors combine the high sensitivity of the sensors with the specificity of biomolecule recognition strategies. Combining CRISPR-Cas with electrochemical techniques and advanced 2D materials has excellent potential in nucleic-acid-related diagnostics.[13] However, their transition to medical oncology is still insufficient. Engineered nanoparticles have advanced applications such as gene delivery and site-specific targeted medication delivery systems and serve as agents in magnetic resonance imaging to improve diagnostic capabilities or create new imaging techniques. Nanoparticles have unique characteristics, including quantum effects, a high surface-to-volume ratio, and the capacity to transport therapeutically active chemicals to specific sites because of their nanoscale dimensions.[10]

This study covers different types of nanoparticles used in gynecological malignancies, focusing on their applications in targeted sensing, imaging, drug delivery, and therapy. This text provides a detailed overview of the benefits and possible challenges associated with using nanomedicines for theranostics in gynecologic malignancies. The obstacles and future prospects in the development of this discipline are also addressed in relation to their actual clinical application. This review is expected to generate more interest in the use of nanoparticles in gynecologic cancers and promote further clinical research to progress this promising field.

2. DIAGNOSIS AND TREATMENT OF GYNECOLOGICAL MALIGNANCIES

Gynecologic cancer, which includes endometrial cancer (EC), cervical cancer (CC), and ovarian cancer (OC), is a leading cause of cancer-related mortality and a major challenge to women's health. The prognosis for those with advanced and recurrent disease is poor, with a low 5-year survival rate. The treatments for gynecologic cancer are limited. Malignant tumors are becoming increasingly diverse and can be treated with surgery, radiotherapy, chemotherapy, and immunotherapy.[14,15] Studies have recognized the importance of comprehensive and multidisciplinary strategies for the radical treatment of tumors (Table 1).

2.1. Ovarian Cancer. OC is a type of malignant tumor in the female reproductive system that has a high incidence and

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Table 1. Characteristics of Different Gynecological Malignancies

Cancer type	Risk factor(s)	Local symptoms/signs	Local/locoregional diagnostic methods	Transfer route	Staggered	Treatments	Prognosis	Surveillance recommendations
Ovarian cancer	Fertility factors, ovulation year	Pelvic nodularity/mass	Primary tumor characterization •Subjective assessment by expert sonographers (level III) or the use of IOTA ultrasound-based diagnostic models •Pelvic MRI as second-line imaging For pelvic and abdominal staging •Ultrasound or CECT abdomen/pelvis or WB-DWI/MRI •FDG-PET-CT as problem solving tool Image-guided core needle biopsy •Ultrasound-guided biopsy •CT-guided biopsy as an option at poorly assessable sites	Disseminated metastases, direct infiltration, lymphatic metastases, hematogenous metastases	FIGO surgical pathology staging (2014)[391]	Surgery, chemotherapy	Epithelial cancers have the worst prognosis	Follow-up every 3 months after the first year of treatment; every 4−6 months after year 2; annually after year 5
Cervical cancer	Sexual behavior, menstruation, and childbirth, HPV	Vaginal bleeding	Local (locoregional) staging •Pelvic MRI or ultrasound*	Haematogenous metastasis, lymphatic metastasis, direct spread	International Federation of Gynaecology and Obstetrics (FIGO2018)[392]	Surgery, chemotherapy, radiotherapy	Poor prognosis for those with lymph node metastases	Review every 3−6 months for 2 years after treatment; every 6 months for 3−5 years; annually starting in year 6
Endometrial cancer	Estrogen, obesity, hypertension, diabetes	Vaginal bleeding	Abnormal uterine bleeding •Pelvic ultrasound •Pelvic MRI as second-line imaging Local (locoregional) staging •Pelvic MRI or ultrasound*	Haematogenous metastasis, lymphatic metastasis, direct spread	FIGO surgical pathology staging (2009)[393]	Surgery, radiotherapy, medication	Depending on the malignancy of the tumor and the extent of the lesion	Follow-up every 3 months for 2−3 years after surgery; every 6 months after 3 years and annually after 5 years
Uterine sarcoma	Uterine smooth muscle retention, etc.	Irregular vaginal bleeding with abdominal pain	Vaginal ultrasound, MRI, diagnostic curettage	Haematogenous dissemination, direct spread, lymphatic metastasis	Surgical pathology staging (FIGO, 2009)[393]	Combination of surgical treatment, radiotherapy, and chemotherapy	High recurrence rate and poor prognosis	Postoperative follow-up every 2 to 3 months until 3 years after surgery, and every 3 to 4 months or half a year after 3 years
Vaginal cancer	Uterus, HPV	Irregular vaginal bleeding	Local (locoregional) staging •Pelvic MRI or ultrasound*	Direct spread, lymphatic spread	FIGO surgical pathology staging[393]	Radiotherapy, surgical treatment, combined with chemotherapy	Related to tumor stage, differentiation, etc.	Follow-up every 3−6 months for 2 years, every 6−12 months for 3−5 years and annually after 5 years after treatment
Vulvar cancer	HPV, sclerosing moss of the vulva, differentiated squamous intraepithelial neoplasia of the vulva	Vulvar itching, vulvar swellings and nodules with pain	Local staging (≥T2 tumor or if the finding is equivocal) •Pelvic MRI or ultrasound* Inguinofemoral lymph nodes (>T1 a) •Percutaneous ultrasound ± node biopsy •Pelvic MRI is an option	Direct infiltration, lymphatic metastasis, hematological dissemination	International Federation of Gynaecology and Obstetrics Surgical Pathology Staging (FIGO 2009)[394]	Surgery, radiotherapy, chemotherapy, or targeted therapy	Related to staging, lymph node metastasis is closest	Follow-up every 3−6 months for 2 years, every 6−12 months for 3−5 years and annually after 5 years after treatment

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Table 1. continued

Cancer type	Risk factor(s)	Local symptoms/signs	Local/locoregional diagnostic methods	Transfer route	Staggered	Treatments	Prognosis	Surveillance recommendations
Choriocarcinoma	Vitellogenic pregnancy, miscarriage, ectopic pregnancy	Vaginal bleeding, incomplete uterine regeneration	Serum hCG measurement, ultrasonography, imaging	Hematogenous dissemination	Anatomical staging of trophoblastic tumors (FIGO, 2000)[395]	Chemotherapy, surgery	Related to diagnostic techniques and chemotherapy	First 3 months after discharge, then every 6 months up to 3 years, then annually up to 5 years

death rate. Currently, there is an inadequate screening method for the treatment of ovarian cancer. The average age of onset for all stages and subtypes combined is 63 years, with the epithelial type being the most prevalent and deadliest.[16] Around 75% of ovarian cancer patients are first identified with intrabdominal illness, and less than 40% of stage 3 patients survive for 5 years.[17] Many patients experience a recurrence of ovarian cancer metastases, mostly in the peritoneum, and intraperitoneal administration is linked to significant damage. Surgery and platinum-based chemotherapy are the primary treatments for advanced ovarian cancer. Over the past few decades, intraperitoneal chemotherapy has been shown to increase the effectiveness of cytotoxic treatment and decrease the occurrence of ascites in advanced ovarian cancer by improving the tumor's exposure to anticancer drugs.[18] Platinum-based medicines (oxaliplatin, cisplatin, carboplatin), paclitaxel, and mitomycin are commonly used for intraperitoneal infusion in both clinical and experimental settings.[19] Various specific medications, such as Bevacizumab and Olaparib, are now being used in the ongoing treatment of ovarian cancer.[20] Current evidence indicates that ovarian cancer cells have a high level of resistance to traditional chemotherapeutic treatments, leading to challenges in treatment effectiveness and recurrence.[21] Key issues in ovarian cancer involve precise and quick diagnosis and characterization of the disease, optimizing tumor removal during cytoreductive surgery and efficiently tracking disease recurrence after treatment. Furthermore, the insufficient efficacy of screening programs and early identification of ovarian cancer highlight the requirement for innovative techniques and technology for the disease.

2.2. Cervical Cancer. Uterine cervical cancer is the second most prevalent cancer in women globally and has a high death rate, particularly in underdeveloped nations.[22] CC remains a significant medical problem, despite early advancements in identification and therapy. Persistent infection of the cervix with "high-risk" genotypes of human papillomavirus (HPV) is a common cause of precancerous cervical lesions. Untreated persistent infection can lead to aggressive cervical cancer.[23] Additional variables, including immunosuppression, parity, smoking, and oral contraceptive use, can also play a role in promoting cervical cancer.[24] Three primary approaches for treating tumors include surgical treatments, radiotherapy, and chemotherapy. These methods can be utilized for curative, palliative, or preventive reasons, either alone or in combination.[25] The surgical procedure varies significantly among patients based on factors such as age, size, illness stage, and the patient's reaction to postsurgical care. Cisplatin is the most effective conventional chemotherapy medication for treating cervical cancer and is typically the preferred option in treatment protocols. Cisplatin induces cancer cell death and inhibits its activity by binding to and cross-linking with tumor DNA. Nevertheless, this medication has limitations when adverse effects, including neutropenia, thrombocytopenia, neurotoxicity, nephrotoxicity, or hematological toxicity, arise, and new treatment approaches like VEGF-targeted therapy and immunotherapy have demonstrated restricted efficacy. Currently, it is customary to use a combination of chemotherapeutic agents to increase the intended impact and reduce the toxicity. Radiotherapy fights the disease by using ionizing radiation, which can be challenging to control in order to minimize damage to nearby healthy tissue cells, depending on the specific characteristics of the cancer and the patient. Novel

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strategies are required to aggressively treat cervical cancer in order to reduce side effects, toxicity, and frequency of medication administration, overcome multidrug resistance (MDR), and improve survival rates.[26]

2.3. Endometrial Carcinoma. EC is a type of malignant tumor that develops in the endometrium and is associated with significant morbidity and mortality. It ranks as the third most deadly disease among prevalent gynecologic malignancies, posing a serious threat to global health.[27] EC is one of the two major malignancies that does not follow the general pattern of decreasing incidence and mortality rates. Survival rates are currently lower than they were in the 1970s.[28] EC is categorized into two main categories according to clinicopathological characteristics. Type I endometrial cancer is highly specialized, is usually identified in its early stages, accounts for 80% of all occurrences, and is linked to a positive outlook.[29] Conversely, poorly differentiated type II endometrial cancer consists predominantly of uterine serous carcinoma (USC) and indicates a grim prognosis.[29] While the majority of women with endometrial cancer are detected at an early stage and can be cured with surgery alone, around 25% will have an advanced stage or recurrent illness and will need further therapy. Advanced endometrial malignancies progress to a metastatic stage where surgery is no longer the optimal treatment.[30] Chemotherapy is the primary treatment, utilizing cisplatin, carboplatin, doxorubicin, and taxane either individually or in combination. Hormone treatments such as megestrol are also used for Type I estrogen-responsive tumors.[31] New therapeutic techniques are urgently needed to address the limited effectiveness of conventional chemotherapy and radiation in treating EC. Targeted cancer therapy has promise for reducing nonspecific toxicity and enhancing therapeutic efficacy compared with traditional chemotherapy.

2.4. Other Gynecological Malignancies. Choriocarcinoma is a fast-growing and vascular cancer that can occur in the placenta, testes, or ovaries. It usually develops after a hydatidiform mole, miscarriage, or full-term delivery.[32] Choriocarcinoma may occur during ectopic pregnancy, particularly in women of childbearing age.[33] Personalised chemotherapy based on the prognosis score of each patient is efficacious for treating prenatal choriocarcinoma.[34] Standard chemotherapy for prenatal choriocarcinoma consists of methotrexate for low-risk cases and the EMACO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) for intermediate or high-risk cases.[34] Chemotherapy is greatly hindered in clinical settings due to its severe adverse effects. Nongestational choriocarcinoma is resistant to single-agent treatment and has a poorer prognosis than gestational choriocarcinoma.[35] Hence, it is essential to create new approaches to eradicate choriocarcinoma.

Vulvar carcinoma is an uncommon and fast-growing cancer that affects the female reproductive system. Elderly ladies are primarily affected, with the average age of diagnosis falling between 55 and 60 years. It is typical for cancer to spread to the lymph nodes in the groyne region. Pelvic node involvement is common, particularly in individuals with pathologically positive inguinal nodes. The management of individuals with these tumors should be personalized based on the underlying tumor and the condition of the groyne lymph nodes. Treatment for early stage disease often involves surgery with the possibility of concurrent chemoradiotherapy based on patient characteristics. Chemoradiation is the primary treatment for advanced-stage diseases, particularly in cases where extensive radical operations and exenteration are needed to ensure sufficient surgical margins.

Primary vaginal cancer is an uncommon malignant tumor, accounting for 1−2% of all gynecological cancers.[36] The cancer is clinically staged, and most patients are treated with primary radiation therapy. Surgical intervention is reserved for early stage disease localized to the vaginal mucosa and paravaginal tissue (Stages I−II). Well-defined lesions in the upper vagina at Stage I can be treated with radical vaginectomy, together with lymphadenectomy. Lesions in the lower part of the vagina may necessitate surgical removal of the vagina and vulva and examination of the lymph nodes in the groin. If the surgical margins and lymph nodes are free of cancer cells, then additional treatment is unnecessary. Adjuvant radiotherapy is typically recommended for patients who have undergone incomplete resection, has near or positive surgical margins, or shows pathologically implicated lymph nodes.

Uterine sarcomas are uncommon tumors that develop in the uterus. This rare type of cancer is believed to make up around 3% of all uterine tumors and about 1% of malignancies in the female genital tract.[37] Uterine sarcomas arise from the endometrial stroma or myometrium. Sarcomas are typically aggressive and have a worse prognosis compared to other types of uterine tumors.[37] The World Health Organisation categorizes these tumors into four groups: endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade ESS (HG-ESS), and undifferentiated uterine arcoma.[38] Endometrial stromal neoplasms might present with a uterine tumor, abnormal uterine bleeding, and pelvic pain. The diagnosis is usually confirmed following a hysterectomy or myomectomy planned for benign leiomyomas. Differentiating between these diagnoses necessitates surgical investigation and pathological analysis of the removed specimen. Total hysterectomy is the recommended treatment for patients with localized leiomyosarcoma confined to the uterus after surgery.[39] Optimal cytoreduction, aiming for no complete residual disease, is linked to improved overall survival when the disease spreads outside the uterus, in contrast to cases where residual disease remains after surgery.[40]

2.5. Challenge of Cancer Diagnosis and Therapy. *2.5.1. Diagnosis.* The prompt identification and prompt intervention of gynecologic malignancies in women have been shown to effectively impede the metastasis of cancerous cells and substantially enhance the 5-year survival rate of female individuals.[41] Regrettably, a significant number of female patients diagnosed with gynecologic cancers are in the middle or advanced stages as a result of inadequate screening methods and nonspecific symptoms.[4] As cancer grows and spreads, tumor cells go through more genetic and phenotypic changes. This makes them resistant to many common cytotoxic treatments and helps them come up with ways to avoid being found by the immune system. The inherent characteristics of individual tumors, their interactions with the adjacent stroma, and the specific pressure generated by anticancer treatments determine the magnitude and rate of these alterations. The clinical diagnosis of a tumor mass[42] often necessitates the identification of a cluster consisting of 10^9 cells with a diameter of approximately 10 mm.[43] The majority of these tumors do not exhibit any symptoms, and detection of these small tumors would necessitate the use of whole-body imaging techniques, which is both impractical and economically unfeasible. A clinical diagnosis typically reveals that approximately 75% of the doubling cell proliferation process

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has already occurred in a tumor. Most of the time, this means that the types of cancer that have been found already show many differences in how they look and behave. This makes treatment harder because some cells can spread to other parts of the body and are resistant to many drugs.

For example, diagnostic techniques for ovarian cancer include cancer antigen 125 (CA-125) serum levels, transvaginal ultrasonography, and imaging modalities like CT or MRI. The high levels of CA-125 in the advanced stages of the disease lead to its widespread use.[44] However, relying solely on CA-125 levels is often insufficient for identifying ovarian cancer without additional techniques. Challenges include limited sensitivity in detecting stage 1 disease and reduced specificity due to elevated CA-125 levels in malignancies and benign diseases.[45] Imaging approaches like CT and MRI have demonstrated greater reliability in diagnosing the initial recurrence of ovarian cancer, with overall survival and progression-free survival surpassing CA-125.[46] Transvaginal ultrasonography is used to determine the source of suspected pelvic masses.[47]

2.5.2. Therapy. Within the realm of cancer therapy, the utilization of conventional surgical procedures, chemotherapy, and radiation has demonstrated the potential to enhance prognosis and improve the quality of survival.[5] However, numerous challenges persist, including the recurrence of neoplasms, inadequate monitoring of treatment, limited therapeutic responses, intolerable cytotoxicity, and the emergence of multiple drug resistances.[6] Traditional drug delivery systems for chemotherapeutic agents encounter obstacles during the transportation of medications to the cancerous tumor. The pharmacochemical characteristics of the drug, including its surface makeup, particle size, and particle charges, play a significant role in the transportation of the drug to its intended site of action.[48] Further challenges arise from the pathophysiological heterogeneity of tumors, which restricts the uniform distribution of drugs throughout the entire tumor mass. The acidic milieu within tumors leads to the degradation of acid-sensitive medicines.

The physician determines the sequence of cytoreductive surgery and chemotherapy in the current treatment for ovarian cancer.[49] The initial chemotherapy treatment for advanced ovarian cancer is typically carboplatin and paclitaxel,[50] with the duration between tumor removal and chemotherapy commencing determining overall survival.[51] However, over 70% of patients experience recurrence,[44] and second-line surgery is less common due to the potential existence of distant metastases and micrometastases that cannot be effectively managed through further surgery.[52] Drug resistance, caused by changes in cancer cell responsiveness to chemotherapeutic agents, poses a significant obstacle to the treatment of recurrent cancer, with over 70% of patients experiencing recurrence within two years of initial treatment.[53]

Cancer therapies have detrimental effects on an individual's biological, psychological, and emotional well-being, hence impacting their overall quality of life. Sexuality, a significant facet of human existence, is also negatively impacted by this phenomenon, with sexual dysfunctions observed in a substantial proportion ranging from 40% to 100% of individuals affected.[54] Vaginal sensitivity, poor orgasm capability, decreased vaginal suppleness, and dyspareunia are frequently reported by women undergoing radiotherapy. A study revealed that 40% of women who engage in sexual activity experienced sexual difficulties due to dyspareunia (painful intercourse) and 50% experienced a shorter vagina. Additionally, there was a drop in the frequency of sexual intercourse.[55] Research has demonstrated a decline in sexual desire as a result of their cancer diagnosis and treatment.[56] In a study conducted by Tewari KS (2017), it was observed that while most individuals engaged in sexual activity half of them expressed only limited satisfaction with this activity.[57]

Advancements in cancer treatment, additional treatments, and the subsequent clinical results have led to a growing number of women with distinct health and psychological requirements.[58] The aforementioned demands encompass the management of adverse consequences arising from cancer surgery, chemotherapy, and radiation therapy.[59] Peripheral floor disorders (PFDs), such as urine incontinence and pelvic organ prolapse, are commonly observed within this demographic and have a detrimental impact on the overall well-being of women.[60]

The forthcoming task will involve precisely diagnosing sufferers and subsequently devising clinical trials for these RGTs. International trials led by investigators with the assistance of the pharmaceutical business have the potential to advance the existing body of knowledge. We posit that the resolution of the aforementioned challenges has the potential to yield significant outcomes. These outcomes include: (1) the progression of the current state-of-the-art in the domain of RGT; (2) the creation of novel diagnostic techniques that are less invasive or noninvasive, thereby facilitating earlier detection and enhancing the efficacy of RGT treatment; (3) a rise in the utilization of nanotechnology for both diagnostic and therapeutic purposes; and (4) the establishment of prospective databases incorporating biobanking.

3. BIOLOGICAL CHARACTERIZATION AND CONSTRUCTION OF NANOPARTICLES FOR MALIGNANT TUMORS

Current diagnostic and therapeutic methods for gynecological malignancies do not offer early and accurate diagnosis or complete relief from the malignancy. Specific treatments, along with an accurate diagnosis, can aid in making prompt clinical decisions and perhaps save lives.[61] Nanotechnology offers a dependable platform for both imaging and treating tumors.[62] Nanotechnology can address the limitations of traditional methods by enabling precise medication delivery to the tumor site,[63] continuous release of pharmaceuticals, prolonged circulation in the bloodstream,[64] and targeting certain biomarkers[65] at different stages. In recent years, different nanoparticles such as carbon nanotubes (CNTs), quantum dots (QDs), mesoporous silica NPs (MSNPs), superparamagnetic iron oxide nanoparticles (SPIONs), gold nanoparticles (GNPs), and silver nanoparticles (Ag-NPs) have been extensively researched for their potential in precise drug delivery and imaging in cancer treatment (Figure 1A).

3.1. Biological Properties of Nanoparticles. The solubility criterion heavily influences the determination of medication disposal and bioavailability. Nanotechnology has been widely used to improve the solubility of medications that are not well soluble in water.[66] Nanoparticles possess distinct colloidal properties, including diminutive particle sizes, elevated specific surface area, and specialized surface characteristics. These attributes enable the effective dissolution and delivery of low solubility medicines in oncotherapeutic combinations via the intravenous route.[67] A wide range of

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nanoparticles have been utilized for the purpose of delivering diverse oncotherapeutic agents.

The issue of inadequate tumor penetration is exacerbated by the presence of densely packed tumor stroma and elevated tumor interstitial pressure. Nanoparticles possess unique physicochemical and biointeractive properties that provide them with specific benefits in overcoming barriers associated with permeability. The delivery of polar therapies, such as antisense oligonucleotides, nucleic acids, plasmid DNA, and siRNA, to their subcellular targets poses challenges due to their limited ability to penetrate tumors. The administration of polar and poorly permeable medicines is facilitated by nanoparticles due to their small size and high permeability across biological membranes. Nanoparticles can help deliver a treatment that is either weakly or fairly permeable in combination.

Nanoparticles have the potential to address the challenges associated with sequential and spatiotemporal drug release through the implementation of a meticulously regulated drug release pattern. Specially engineered trigger-activated systems can achieve highly targeted medication release in the desired sequence, specifically for tumors.

Several factors can contribute to the pharmacokinetic parameters of nanoformulations including circulation half-life, distribution kinetics, and clearance. These factors include, among other things, the route of administration, size, shape, drug release kinetics, surface modulation, and composition. Therefore, the effectiveness of nanoformulations is mostly influenced by these characteristics, making it impractical to make generalizations across all nanoformulations. Pharmacokinetic modeling based on physiological principles can significantly contribute to the prediction and optimization of the absorption, distribution, metabolism, and excretion (ADME) of the nanoformulations that have been created.[68] Nanocarrier-based drug delivery systems, when combined with bioenhancers such as P-gp inhibitors, can achieve targeted drug delivery, high metabolic stability, improved bioavailability through reduced elimination, and a longer duration of action. These advantages can be further explored for dose reduction of cytotoxic agents.[69,70]

Nanoparticles possess the ability to alter the kinetics of drug release, hence potentially facilitating the regulation of the drug's pharmacokinetic profile by mitigating the occurrence of sudden elevations in serum concentrations that exceed toxicity thresholds.

3.2. Construction of Nanoparticles. Cancer drugs can be loaded onto nanoparticles through entrapment, adsorption, or covalent binding.[71] The appropriate transportation device should have biocompatibility, reduced particle size, a high drug-loading rate, and efficient drug encapsulation and entrapment. Factors like drug solubility, drug−polymer interaction, and final functional groups are crucial.[72] Encapsulation can occur during nanoparticle formulation or after nanoparticle formation. High encapsulation efficiency occurs when encapsulation is done close to the isoelectric point, avoiding the impact of the formulation on the drug's functions.[73]

There are several methods for the preparation of nanoparticles. Liposomes are created by drying lipids in organic solvents, distributing them in an aqueous solution, and purifying them.[74] Sonication is the most common method for creating multilamellar vesicles, using probe or bath sonication in a controlled atmosphere.[75] The solvent dispersion method dissolves lipids in an organic solvent, forming an organic phase that is slowly introduced into a hot aqueous solution. Liposomes can be formed by fully evaporating the organic phase.[76] The freeze−thaw approach involves cycles of quick freezing and delayed thawing, separating components, and thawing to form unilamellar vesicles.[77] The extrusion process passes the liposome suspension through a membrane filter with a specific pore size using an extruder. Factors such as applied pressure, number of cycles, and pore size influence the mean diameter and size distribution of the liposomes formed.[78]

Polymeric nanoparticles can be created from pre-existing polymers or directly polymerized monomers. They are produced as aqueous colloidal suspensions. Preformed polymers can be processed using various methods, while polymerization techniques like microemulsion, nanoemulsion, surfactant-free emulsion, and interfacial polymerization can be used.[79] Alternative approaches such as supercritical fluid technology, ultrasonic, spray drying, and membrane reactor methods are also effective but uncommon. Supercritical fluid synthesis is gaining interest due to its purity and environmental friendliness.

Nanoemulsions can be created using two primary methods: high-energy emulsification, which involves stirring, ultrasonic emulsification, high-pressure homogenization, and microfluidization, and low-energy emulsification,[80] which involves phase inversion temperature, emulsion inversion point, and spontaneous emulsification. High-pressure homogenization uses a high-pressure homogenizer to create nanoemulsions with smaller particle sizes.[81] Microfluidization uses a microfluidizer to generate small particles 150−170 nm in size.[82] There are three steps to spontaneous emulsification: making an organic solution with oil and surfactants, adding the organic phase to the water phase, and then drying out the organic phase to make the nanoemulsion.[83]

Nanocrystals can be created by using top-down or bottom-up techniques. Top-down methods use high mechanical energy to create nanocrystals from large crystals, often used for insoluble medications for oral administration.[84] High-pressure homogenization breaks down large crystals into smaller particles, with particle size control achieved by adjusting valve pressure and spacing.[85] Media milling grinds big drug crystals using solid particles like yttrium-stabilized zirconia, cerium, polystyrene resin-coated beads, and stainless steel.[84]

The preparation of dendrimers primarily involves two processes known as divergent and convergent procedures. The divergent method involves initiating the synthesis process by incorporating the dendrimer's core, followed by the gradual addition of arms to achieve the desired 3-dimensional structure. On the other hand, the convergent method entails initially preparing the arms and subsequently attaching them to the core to produce the desired final structure.[88,89]

Stöber's method, established in 1968, is a widely used technique for synthesizing solid silica nanoparticles. It involves mixing silicates with ammonia, water, and ethanol to produce the desired nanoparticles. Nanoparticle size can be influenced by solvent concentration and silica additions.[86] The reverse microemulsion process creates spherical micelles by introducing a surfactant into a stable organic solvent. Silica nanoparticles are generated at micelle contacts.[87] The chemical vapor deposition process, also known as high-temperature flame decomposition, prepares precursors for nucleation.[90]

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Table 2. Summary of the Selective Examples of Each Application of Nanoparticles

	Nanoparticle	Application	Cancer type	Reference
Liposomes	EGFR-LPDS	Gene drug delivery	Choriocarcinoma	101
	SCS-modified liposomes	Drug delivery	Sarcoma	102
Solid lipid nanoparticles (SLNs)	NLC-verteporfin	Treating	Breast and ovarian cancer	109
	FA-CIS-NLC	Enhancing its anticancer efficacy	Cervical cancer	111
Nanostructured lipid carriers (NLCs)	CXCR4 and loaded with the near-infrared dye IRues	Impede tumor growth	Pan-cancer	114
	LHRH-liganded PTX-NLCs	siRNA resistance	Pan-cancer	115
Nanoemulsions	Imiquimod in nanoemulsion	Treatment	Cervical cancer	121
Nanocrystals	NC@PDA-NH2	Tumor inhibition	Cervicovaginal cancer	128
Natural polymer-based nanoparticle	Antigen-loaded DCs	Antitumor responses	Pan-cancer	396
	Gal-BSA-Cur nanoparticles	Treating	Hepatocellular carcinoma (HCC)	397
	DP hydrogels	Controlled release of antibiotics	No	398
	HCPT	Treatment	Cervical cancer	154
Synthetic polymer-based nanoparticle	Polymeric nanoparticle made of methoxy poly(ethylene glycol) and poly(L-lactic acid)	Anticancer	Ovarian cancer	160
	PEG−PGA−PLeu	Reduced CAC and higher DLC	No	161
Micelles	SAHA	Treating	Endometrial cancer	399
Dendrimers	Ce6	Treatment	Cervical cancer	178
	MT-PAMAM	Inducing cell death	Uterine sarcoma	179
Metallic nanoparticles	CuONPs@CS	Antitumor immune responses	Cervical cancer	187
	NMOFs	Treatment	Ovarian cancer	188
Carbon nanoparticles	MEC	Treating	Ovarian cancer	194
	SWCNT and MWCNT	Treatment	Cervical cancer	196
Silica nanoparticles (SiNPs)	nanoPMOs	Anticancer effects	Prostate cancer	400
	DIMSN/F	Treatment	Cervical cancer	200
	MSN-Hydrazone-Dox	Resistant cancer	Uterine sarcoma	201
	Fe3O4@AuNPs	Anticancer	Cervical cancer	211
Quantum dots	FA-Se@DOX	Anticancer effects	Cervical carcinoma	220

4. CHARACTERISTICS OF NANOPARTICLE PLATFORMS AND THEIR APPLICATIONS IN GYNECOLOGICAL MALIGNANCIES

Nanotechnology has emerged as a vast field for biomedical applications. Various nanoparticles, such as polymeric nanoparticles, micelles, dendrimers, solid lipid nanoparticles, quantum dots, and magnetic nanoparticles, possess substantial physical and chemical properties due to their nanosized effect. In recent years, significant progress has been made in the application of different nanoparticles in various gynecologic cancers, including ovarian, cervical, and endometrial cancers (Table 2).

4.1. Lipid-Based Nanoparticles. Lipid nanoparticles are often created from phospholipids, triglycerides, or cholesterol. They improve medication solubility, encapsulation, and transport, thereby increasing the absorption of chemotherapy. In addition to lipid nanoparticles, other organic nanoparticles include liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).[91] Lipid-based nanoparticles offer numerous benefits in drug delivery systems, including in vivo durability, high drug loading efficiency, biocompatibility, elimination of organic solvents, and adjustable drug release modes during manufacture.[92] They are proficient in transporting nucleic acids and cytotoxic medicines and have been utilized in diverse areas like biopharmaceuticals and food safety.[93]

4.1.1. Liposomes. Liposomes are small, spherical vesicles derived from naturally occurring, nontoxic phospholipids. The liposomes have a diameter ranging from 400 nm to 2.5 mm. Liposomes are synthetic membranes that have bilayer structures that resemble those of biological membranes. Amphoteric molecules like phospholipids and spingolipids form closed vesicles with bilayer structures when dispersed in the aqueous phase.[94] Their hydrophobic tails cluster together to escape the aqueous phase, while the hydrophilic heads are exposed to it. Liposomes can encapsulate lipophilic, water-soluble, and amphoteric compounds. Liposomes have several advantages, including biocompatibility, biodegradability, low toxicity, and the capacity to contain both hydrophilic and hydrophobic molecules due to their innate biodegradability. Liposomal formulations are the most extensively researched and effective lipid-based nanosystems currently in biomedical use or undergoing clinical studies.[95] In addition to transporting various chemotherapeutic compounds, nanoparticles have been studied for their potential to deliver a wide range of diagnostic agents, such as 64Cu,[96] QDs,[97] gadolinium (Gd)-based contrast agents,[95] and fluorescent probes.[98] Considering all of these considerations, liposomes are a very promising theranostic tool with a wide range of therapeutic uses in cancer treatment.

Hybrid systems combining liposomes and chitosan particles have been utilized to address these shortcomings. The mucoadhesive nanocarrier was specifically developed to provide an advantage in the treatment of cervical cancer, as shown in the experiments. Research has demonstrated that the liposome−chitosan nanocarrier system enhances the permeability of curcumin, making it a more effective formulation for

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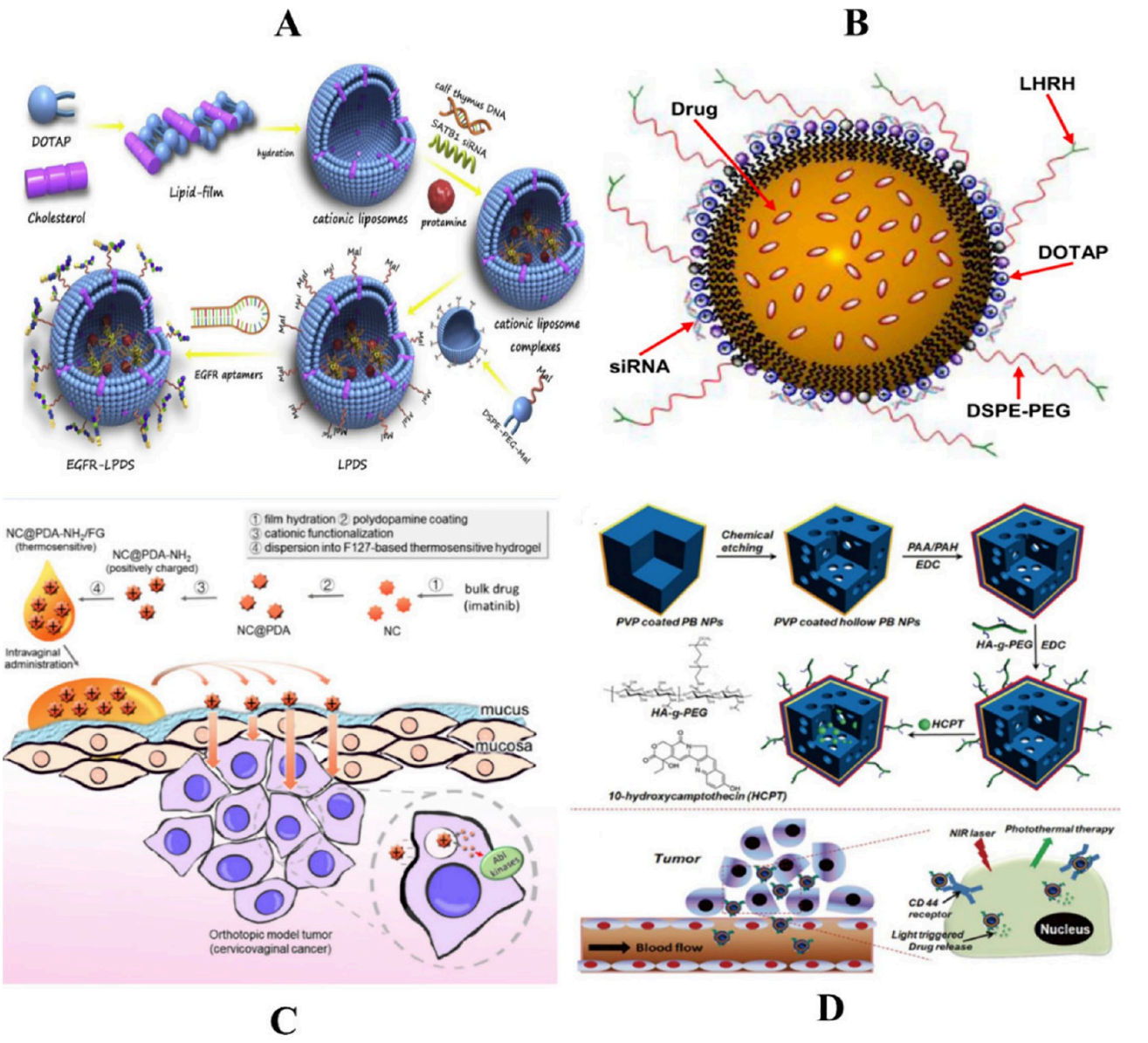

Figure 2. A. EGFR aptamer-conjugated liposome−polycation−DNA complex for targeted delivery of SATB1 small interfering RNA to choriocarcinoma cells. Reprinted in part with permission from [Dong, J.; Cao, Y.; Shen, H.; Ma, Q.; Mao, S.; Li, S.; Sun J. EGFR aptamer-conjugated liposome-polycation−DNA complex for targeted delivery of SATB1 small interfering RNA to choriocarcinoma cells. *Biomed Pharmacother.* **2018**, *107*, 849−859].[101] B. A schematic representation of NLC-based drug delivery system for pulmonary codelivery of an anticancer drug, siRNA, and targeting peptide. Reprinted in part with permission from [Taratula, O.; Kuzmov, A.; Shah, M.; Garbuzenko, O. B.; Minko, T. Nanostructured lipid carriers as multifunctional nanomedicine platform for pulmonary codelivery of anticancer drugs and siRNA. *J. Control Release* **2013**, *171* (3), 349−57].[115] C. Illustration of the preparation and in vivo fate of amino-group-functionalized polydopamine (PDA)-coated imatinib NC dispersed in F127 (FG) hydrogel (NC@PDA-NH2/FG) in the orthotopic mouse cervicovaginal cancer model after intravaginal administration. Reprinted in part with permission from [Ci, L.Q.; Huang, Z.G.; Lv, F.M.; Wang, J.; Feng, L. L.; Sun, F.; Cao, S. J.; Liu, Z. P.; Liu, Y.; Wei, G.; Lu, W.Y. Enhanced Delivery of Imatinib into Vaginal Mucosa via a New Positively Charged Nanocrystal-Loaded in Situ Hydrogel Formulation for Treatment of Cervical Cancer. *Pharmaceutics* **2019** *11* (1), 15].[128] D. Engineering procedure and functional description of hyaluronic acid grafting polyethylene glycol modified hollow Prussian blue nanoparticle loading 10-hydroxycamptothecin for tumor-targeted thermochemotherapy. Reprinted in part with permission from [Jing, L.; Shao, S.; Wang, Y.; Yang, Y.; Yue, X.; Dai, Z. Hyaluronic Acid Modified Hollow Prussian Blue Nanoparticle Loading 10-hydroxycamptothecin for Targeting Thermochemotherapy of Cancer. *Theranostics* **2016**, 6 (1), 40−53].[154]

vaginal administration compared with traditional methods. This system, specifically phospholipid−chitosan hybrid nanoliposomes, facilitates drug delivery for treating cervical cancer by promoting cell entry.[99]

PEGylation is performed to prevent liposomes from being eliminated by the phagocytic system and to enhance their circulation. Paclitaxel-loaded PEGylated liposome nanoformulations were created and tested in both laboratory and animal models of ovarian cancer to inhibit cancer cell growth. Treatment with a manufactured nanosystem significantly decreased the aggressiveness of the ovarian cancer cells. In ovarian cancer cells, increased expression of caspase 3/9 and ERK led to the induction of apoptosis.[100]

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Jinhua Dong and colleagues developed EGFR-LPDS, a gene drug delivery system that enhances the transport and effectiveness of SATB1 siRNA against choriocarcinoma cells. The system consists of an epidermal growth factor receptor aptamer-conjugated liposome−polycation−DNA complex loaded with SATB1 siRNA. The system selectively targets choriocarcinoma cells, reducing SATB1 expression, growth inhibition, and apoptosis in EGFR-overexpressing cells. In mice, it effectively suppressed SATB1 expression and showed superior therapeutic results compared with other treatments. The study provides the first evidence of SATB1 siRNA's therapeutic effectiveness in choriocarcinoma (Figure 2A).[101]

Sara Zalba and her team have developed a drug delivery method using nanotechnology and modifying tumor cell membranes. They used short-chain sphingolipids (SCSs) to make the membranes permeable to amphiphilic medicines such as doxorubicin (Dxr). In vitro experiments found that the liposomal composition of SCSs overcomes cell resistance with a more significant impact on resistant cells. They tested the liposomes in a sarcoma xenograft model to assess the drug accumulation, pharmacokinetics, and effectiveness. The findings showed that SCS-modified liposomes greatly increased the amount of Dxr that gathered in Dxr-resistant cells, making Dxr just as effective in those cells as it was in sensitive cells. However, the drug-resistant tumor model showed increased effectiveness, while sensitive tumors showed no advantage.[102]

4.1.2. Solid Lipid Nanoparticles (SLNs). SLNs were introduced as a type of colloidal drug carrier in the early 1990s.[103] They have been extensively utilized in clinical medicine for drug delivery purposes.[104] At the nanometric scale, SLNs represent the initial iteration of solid lipid matrix systems. These systems have demonstrated favorable tolerance in in vivo settings due to their composition as aqueous colloidal dispersions, whereby the solid matrix consists of biodegradable lipids.[105] Several solid lipids, including alba wax, carnauba wax, saturated glycerol esters, palmitic palmitate, stearic acid, beeswax PEG-8, cetyl palmitate, and glyceryl dibehenate, have been identified.[106] The utilization of nanoparticles offers several benefits, including enhanced drug solubility, reduced dosage requirements, improved stability attributed to the lipid matrix's capacity to safeguard chemically unstable compounds, modulation of drug release, facilitation of binding and internalization within tumor cells, and active targeting to enhance the distribution of SLNs within tumor vasculature and MDR cells.[107] These methods are limited by their low drug loading capacity and the premature drug ejection during storage.

The size and volume of NPs determine their ability to encapsulate pharmaceuticals on their surface. Modifying the surface of NPs with targeting ligands enhances the selectivity of the target and facilitates the release of the drug into tumor cells. Therefore, these specific forms of nanoparticles can be highly suitable for specifically targeting cancer tumors in order to enhance their retention within the tumor region.[108] Another benefit is that the small size of these nanoparticles allows for drug protection and facilitates administration through parenteral (e.g., intravenous) and oral routes. However, contact with gastrointestinal fluids has been a significant issue due to the particle size, which increases the surface area for enzymatic degradation. This, in turn, affects the stability of the drug.

Lee et al. developed a nanoformulation of paclitaxel for use in treating breast and ovarian cancer cells. They created sterically stabilized SLN-based nanoparticles, similar to commercially available paclitaxel formulations. These nanoparticles have the potential to serve as an innovative delivery technique for parenteral administration. A photosensitizer called verteporfin was incorporated into nanostructured lipid carriers for osteoclast therapy. The successful uptake of both unbound and lipid-nanocarrier-loaded vereporfin significantly reduced tumor cell survival following laser light exposure. The lipid nanoparticles have an extended circulation and facilitate tumor uptake. Five out of eight mice experienced mortality after the administration of a 2 mg/kg dosage of free verteporfin. However, intravenous administration of 8 mg/kg of NLC-verteporfin showed a notable inhibitory effect on tumor growth without any apparent toxicological consequences.[110]

Lee et al. created paclitaxel-encapsulated, sterically stabilized SLNs for treating MCF-7 breast and OVCAR-3 human ovarian cancer cell lines.[110]

Zhang and colleagues utilized folic acid (FA)-modified, cisplatin-loaded NLCs in HeLa cells and mouse cervical cancer models for chemotherapy. The study demonstrated the carriers' effectiveness in targeting drug release in tumor cells with high expression of FA receptors. Furthermore, targeting FA-CIS-NLC transfers CIS to cancer cells, enhancing its anticancer efficacy.[111]

4.1.3. Nanostructured Lipid Carriers (NLCs). NLCs are lipid nanoparticles made up of a combination of solid and liquid lipids, characterized by an amorphous form resembling a "natural welsh stone wall" with significant vacuum areas.[112] NLCs are the second generation of SLNs, consisting of a blend of several lipids, specifically a solid lipid matrix combined with a liquid lipid component. NLCs have a higher drug loading capacity compared to SLNs due to variations in drug solubility between solid and liquid lipids. Enhancing the quality of liquid fat can boost drug solubility and enhance the efficiency of lipid carriers' encapsulation.[113] NLCs exhibit reduced risk of gelation and drug leakage, as well as the ability to extend drug half-lives, boost the EPR effect, and thereby enhance the therapeutic efficacy of antitumor medications.

Liu and his team planned to create nanoliposomes targeted at CXCR4 and loaded with near-infrared dye IRues. The authors effectively created a basic, reliable, and versatile nanosystem that can impede tumor growth and inhibit the formation of metastasis. Considering these findings, scientists suggest that this lipid-based nanosystem has promise for clinical applications.[114]

Taratula et al. created a formulation with two siRNAs, one targeting MRP1 mRNA and the other targeting Bcl-2 mRNA, to combat tumor resistance. The study found that administering siRNA and LHRH-liganded PTX-NLCs simultaneously increased cytotoxicity by 120 times, compared to a 16-fold increase in LHRH-liganded PTX-NLCs.[115] This happened because the siRNA makes Bcl-2 and MRP1 proteins stop working at the same time when PTX was given (Figure 2B).

4.1.4. Nanoemulsions. Nanoemulsions consist of oil, water, emulsifier, and coemulsifier in certain ratios, with particle sizes ranging from 10 to 100 nm in diameter.[80] Nanoemulsions are extensively researched as a drug carrier for lipophilic chemotherapeutics because of their biodegradability, simple manufacturing, and ability to control drug release.[116] Nanoemulsions can prevent medication inactivation in the gastrointestinal system and enhance drug solubility, leading to better dispersion and absorption of pharmaceuticals, ultimately

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improving drug bioavailability. Nanoemulsions exhibit good biocompatibility by utilizing excipients that are universally recognized as safe, resulting in high entrapment effectiveness of hydrophobic components. This leads to enhanced physicochemical stability, increased bioavailability, and higher efficacy and safety.

Although nanoemulsions offer numerous benefits, their spreadability is hindered by their low viscosity, leading to inadequate retention of the formulation on the skin.[117] The clinical applications of nanoemulsions are hindered by this limitation.[118] The resolution of this matter has been achieved through the integration of a gelling agent into the nanoemulsion, resulting in the formation of a nanoemulgel.[119] Gels are prepared in a colloidal particle system using large amounts of aqueous or hydroalcoholic bases. The composition of nanoemulgel involves the integration of a nanoemulsion within a hydrogel matrix, resulting in a mitigation of the thermodynamic instability exhibited by the emulsion. The enhanced thermodynamic stability can be attributed to the decreased mobility of the nonaqueous phase resulting from the heightened uniformity of the external surrounding medium. The nanoemulgel formulation exhibits enhanced retention time and thermodynamic stability, facilitating regulated drug release over a specific duration. This characteristic renders it a suitable dosage form for topical administration, particularly advantageous for medicines with a limited half-life.[120]

Luiza Abrahão Frank et al. found that imiquimod in the nanoemulsion form is more effective in treating cervical cancer compared to its nonencapsulated form. Permeability experiments and in vitro investigations showed that a small amount of encapsulated imiquimod penetrated the vaginal mucosa, and a higher proportion of cells died after treatment with a low concentration (3.0 μmol L^{-1}) of the formulation. The unique formulation introduced a mode of cell death that combined autophagy and apoptosis, confirming its potential as a viable option for cervical cancer treatment.[121]

4.1.5. Nanocrystals. Nanocrystals are solid particles exhibiting crystal characteristics.[122] Nanocrystals have distinct characteristics, including a high surface-area-to-volume ratio, consistent dissolution rates, improved structural stability, and efficient drug-loading capacity. This is because nanocrystals are composed solely of the drug or payload, removing the need for a carrier and leading to effective therapeutic levels at low doses.[123] The size, shape, and surface characteristics of nanocrystals significantly affect their dispersal within an organism. Nanocrystals' size, stability, solubility, and bioavailability can be influenced by the pH of the surrounding media, contaminants generated during production, and crystallinity.[98] Because crystalline particles have stable and consistent physical features, it is expected that they will improve the pharmacokinetics and biodistribution of anticancer medicines.[124]

Nanocrystals were employed to augment the oral bioavailability of medicines with limited solubility. Currently, while studies on the use of drug nanocrystals in cancer treatment are still in the preclinical animal stage, there is significant interest in using nanocrystal formulations for the intravenous administration of anticancer medicines.[125] Intravenous nanocrystals have the ability to be passively carried to organs with a high concentration of mononuclear phagocytic system cells, such as the liver, spleen, and lungs, as a result of their quick absorption by macrophages.[126] The distribution of nanocrystals in vivo is significantly influenced by factors, such as particle size, shape, and surface modification. The pH of the dispersed medium, contaminants generated during manufacture, and crystallinity frequently influence the size, stability, solubility, and bioavailability of nanocrystals.[127]

The study made Imatinib nanocrystals (NC@PDA-NH2) with amino groups. These had spherical shapes, were all the same size at the nanoscale level, and had a large number of drugs in them. These nanocrystals worked well with mucin and were better than unaltered nanocrystals at absorbing cells, stopping their growth, and starting apoptosis in cells related to cervicovaginal cancer. They distributed them in a Pluronic F127-based thermosensitive in situ hydrogel for efficient intravaginal delivery. NC@PDA-NH2 had better tumor inhibition, smaller tumor size, longer median survival time, more apoptosis inside the tumor, and less damage to the mucosa (Figure 2C).[128]

4.1.6. Nanocapsules. Nanocapsules are tiny vesicles with a central chamber that can hold pharmaceuticals. Furthermore, an external polymeric shell surrounds the inner core, aiding in the attachment of different targeted ligands and moieties during surface functionalization.[129] Its protective coating properties, such as delayed medication release, pyrophoric, and readily oxidized characteristics, have attracted significant interest. Nanocapsules were produced using diverse processes, with nanodeposition and interfacial polymerization being the preferred approaches for their synthesis. Nanocapsules were utilized for precise drug delivery aimed at treating ovarian cancer due to their exceptional and consistent repeatability. Moreover, the precise and improved administration of drugs through nanocapsules offers new possibilities for developing advanced drug delivery systems for treating ovarian cancer.[130]

4.2. Polymeric Nanoparticles (PNPs). Polymeric nanoparticles are colloidal systems. They are organic polymer compound structures that exist as nanospheres (solid spheres) or nanocapsules (hollow spheres with an empty space in the middle).[131] PNPs are nanoparticles ranging in size from 1 to 100 nm,[132] with benefits such as protection from enzymatic degradation, controlled release, and great penetrating ability.[133] Polymeric nanoparticles can be used to load molecules such as antibodies, DNA, and RNA, allowing for precise interactions with targets like cancer cells.[134,135] Nevertheless, there are drawbacks such as degradation (e.g., enzymatic) and expensive manufacturing costs.[136]

4.2.1. Natural Polymer-Based Nanoparticles. Natural polymer-based nanoparticles have been extensively studied in dual drug delivery systems.[137] Some natural polymers with positively charged surfaces are excellent for delivering medicines and genes at the same time. Biopolymers are effective substitutes for transporting chemotherapeutic medicines and nucleic acids, including liposoluble medications and pDNA.[138]

Hyaluronic acid is an organic polymer made up of 2000−25,000 pairs of sugar molecules. Glucuronic acid and acetylglucosamine are the fundamental sugar units, and various molecular weights can be chosen based on requirements.[114] Hyaluronic acid can be highly ionized due to the presence of carboxyl groups in typical physiological pH circumstances, resulting in negative charge properties (anionic characteristics) at the specified pH. Hyaluronic acid's chemical composition includes carboxyl, hydroxy, and acetamido groups that can be utilized for structural modifications with other substances.

Chitosan is a cationic natural polysaccharide obtained from the deacetylation process of chitin, a compound commonly

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present in the cell walls of fungi and the shells of anthropods.[139] Chitosan is soluble in acid because of its amino groups, which have a strong propensity to accept protons under low pH conditions. This property allows it to exhibit preferred pH-responsive behavior in acidic subcellular organelles like endosomes and lysosomes. Chitosan and its oligomers have been shown to interact with negatively charged substances like tripolyphosphate (TPP) to create different nanosystems with varying particle sizes and zeta potentials.[140] Chitosan is highly valued in the field of nanomedicine due to its ability to create various nanosystems with diverse functions as well as its exceptional biocompatibility, lack of toxicity, and ability to adhere to mucus, which enhances drug absorption and availability.[141] Chitosan-based nanomedicines are known for their high biodegradability, superior biocompatibility, bioactivity, and polycationicity,[142] making them useful nanoparticles for drug delivery applications.[143] Saeed Daneshmandi's study provided evidence that mRNA/chitosan nanoparticles efficiently transport mRNA genes to dendritic cells (DCs) and induce the overexpression of CD40 and ICOSL in DCs. Furthermore, when these DCs were exposed to total tumor mRNA, they elicited robust antitumor responses. The participation of the CD40 molecule enhanced the effectiveness of these functions by stimulating lymphocytes in direct interactions between the DCs and T cells. While increasing the expression of both CD40 and ICOSL molecules on antigen-loaded DCs enhances the proliferation of T cells and their release of cytokines throughout the body, it is worth noting that using mRNA/chitosan nanocomplexes to specifically target DCs can generate even more powerful and effective antitumor responses.[144]

Albumin, a predominant plasma protein produced in the liver, serves as a carrier for delivering anticancer drugs to specific targets, enhancing their ability to kill tumors. This role is significant in the realm of protein-based nanoparticles.[145] Bovine serum albumin (BSA) is a globular protein without sugars made up of 583 amino acids arranged in a single chain, with a molecular weight of around 69 kDa. BSA is commonly used in the production of nanomedicine because of its widespread availability, affordability, ease of purification, and stability.[146] BSA NPs are effective protein carriers for drug administration. They have been demonstrated to be safe, nonreactive to the immune system, cost-effective, compatible with living tissues, and readily broken down in the body and can dissolve in water.[147] Camptothecin (CPT) and curcumin (CCM) are modified with 2-acetylphenylboronic acid (2-APBA) and then mixed with BSA to create nanoparticles with high loading efficiency and colloidal stability by iminoborate production. Simultaneously, its pharmacokinetics have been greatly enhanced. Nanoparticles efficiently deliver medications within the targeted tumor microenvironment.[148] There are around 650,000 protein−protein interactions (PPIs) in the human proteome, which do not offer potential treatment targets for different disorders.

Yike Huang's study successfully developed a drug-loaded delivery carrier using targeted NPs. The carrier is nontoxic and biocompatible and has a high drug loading (DL) capacity for delivering anticancer medications specifically to hepatocellular carcinoma (HCC) cells. The Gal-BSA-Cur nanoparticles exhibited a significant releasing effect and demonstrated favorable bioavailability in vitro. It has been demonstrated that GalBSA-Cur NPs, which include galactose, are more effectively taken up by HepG2 cells (ASGPR+ cells) compared with BSA-Cur NPs that do not have galactose molecules. This work confirmed that Gal-BSA-Cur NPs were able to enter HepG2 cells through the ASGPR receptor present on the cell surface. The absorption of Cur into HepG2 cells decreased when galactose was used as a pretreatment, namely, in the case of Gal-BSA-Cur NPs. Furthermore, the impact of GalBSA-Cur NPs was assessed, revealing their ability to suppress the growth of HepG2 cells, induce cellular death, and prevent cell migration. The impact of Gal-BSA-Cur NPs on HepG2 cells was linked to the deactivation of the NF-κB-p65 protein levels. The results confirm that Gal-BSACur NPs have the potential to be a more efficient targeted medication for HepG2 cells. This demonstrates the mechanism of ASGPR receptor-mediated endocytosis. The Cur-loaded Gal-BSA NPs have the potential to serve as a unique therapeutic platform for treating HCC by specifically targeting hepatocytes.[149]

Alginate is a linear polymer found in the cell walls of marine brown algae. Alginate is biocompatible, biodegradable, and bioadhesive to mucosal surfaces due to its chemical structure and physicochemical properties.[150] Moreover, the adaptable nature of alginate's structure permits alterations that enable the addition of precise targeting and functional components to enhance the mechanical properties, gelation, and cell compatibility of alginate-based nanomedicines.[151] Alginate-based materials have been extensively researched for their use in the biological field. Recent research has used alginate to create functional nanoparticles for treating cancer disorders through immune therapy.

Dextran is a polysaccharide that contains α-1,6-glycosidic bonds in its chain. It is water-soluble, highly biocompatible, and biodegradable and exhibits low toxicity and non-immunogenicity. Modifying dextran by altering the hydroxyl groups in the backbone chain can enable interactions with specific receptors and therapeutic agents, while maintaining biocompatibility. This makes it a promising option for delivering therapeutic drugs at a nanoscale for effective disease treatment.[152] There is a strong demand for efficient approaches to treat bacterial infections due to the emergence of multidrug-resistant strains resulting from the overuse of antibiotics. Polysaccharide hydrogel-based drug delivery systems, which have a naturally large surface area and are biocompatible, offer a potential approach for the efficient administration of antibiotics. In Zhang's study, they introduced a very efficient technique for creating large-pore polysaccharide hydrogels made of dextran (DP) and polydopamine (PDA). These hydrogels are designed to release antibiotics in a regulated manner. The physicochemical characteristics of the resulting DP hydrogels were thoroughly assessed by assessing their ability to swell, their viscoelastic properties, their shape, their ability to absorb substances, and their thermal stability. We were able to manipulate these characteristics by adjusting the concentration of PDA in the initial gel solution. The minimal cytotoxicity of DP hydrogels was proven by conducting a coculture experiment with mouse fibroblast cells. Additionally, the drug-loaded DP hydrogels were assessed for their antibacterial characteristics in both in vitro and in vivo settings, demonstrating effective antibacterial activity and promoting healing. We believe that the suggested approach to facilitate and optimize polysaccharide hydrogels could result in a greater availability of hydrogel dressings by selecting appropriate carriers for the controlled release of antibiotics.[153]

Prussian blue nanoparticles (PB NPs) were created to serve as carriers and photothermal agents in the development of

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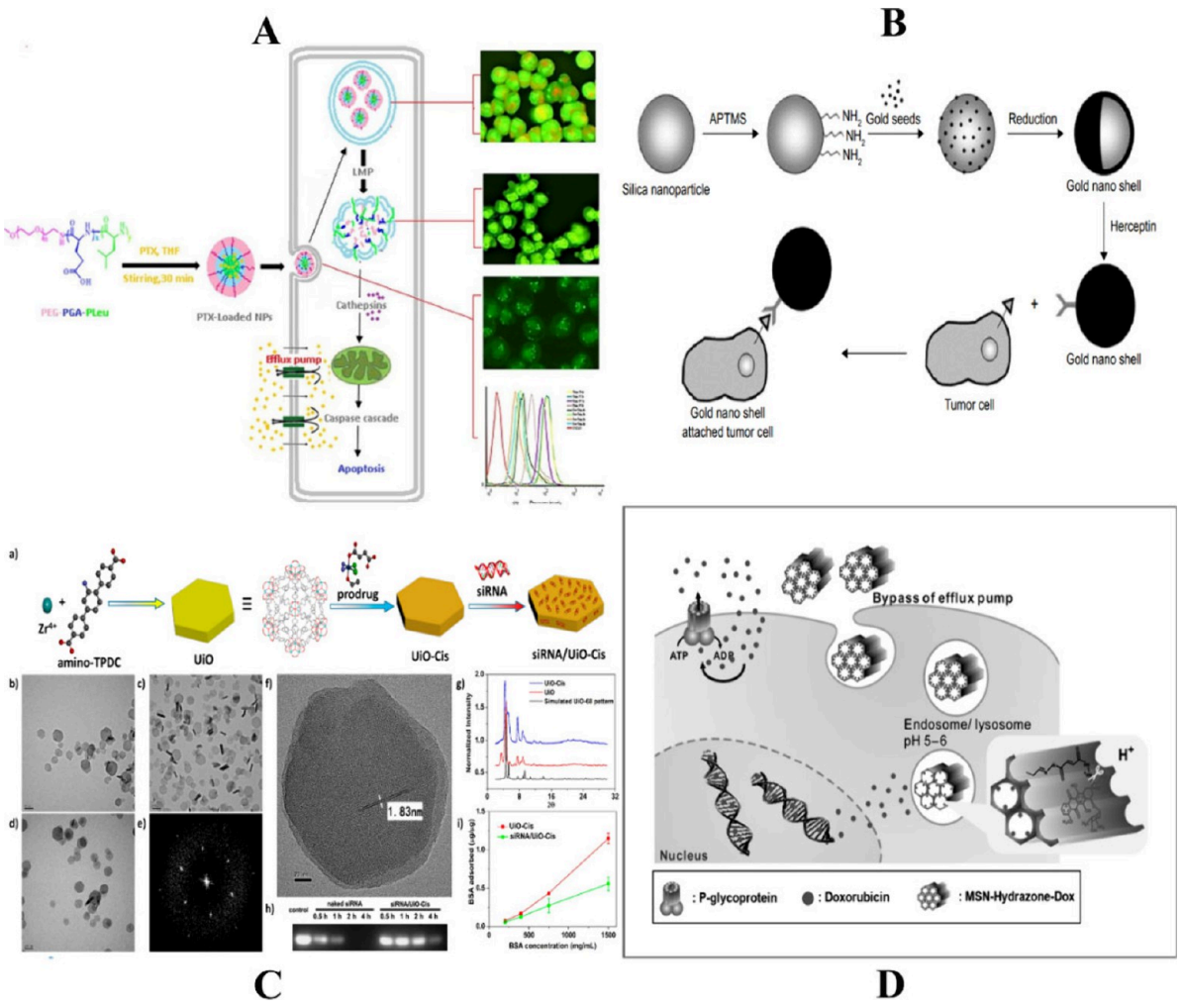

Figure 3. A. Reversing multidrug tumor resistance to Paclitaxel by well-defined pH-sensitive amphiphilic polypeptide block copolymers via induction of lysosomal membrane permeabilization. Reprinted in part with permission from [Mostoufi, H.; Yousefi, G.; Tamaddon, A. M.; Firuzi, O. Reversing multidrug tumor resistance to Paclitaxel by well-defined pH-sensitive amphiphilic polypeptide block copolymers via induction of lysosomal membrane permeabilization. *Colloids Surf B Biointerfaces* **2019**, *174*, 17−27].[161] B. Conceptual scheme of SGNS for tumor-specific targeting. Reprinted in part with permission from [De Matteis, V.; Cascione, M.; Toma, C. C.; Rinaldi, R. Engineered Gold Nanoshells Killing Tumor Cells: New Perspectives. *Curr. Pharm. Des.* **2019**, *25* (13), 1477−1489].[187] C. Preparation and characterization of siRNA/UiO-Cis. Reprinted in part with permission from [He, C.; Lu, K.; Liu, D.; Lin, W. Nanoscale metal−organic frameworks for the codelivery of cisplatin and pooled siRNAs to enhance therapeutic efficacy in drug-resistant ovarian cancer cells. *J. Am. Chem. Soc.* **2014**, *136* (14), 5181−4].[188] D. Schematic diagram of pH-sensitive MSN drug delivery system to MES-SA/Dx5 human uterine sarcoma cancer cells for enhanced chemotherapy efficacy. Reprinted in part with permission from [Huang, I. P.; Sun, S. P.; Cheng, S. H.; Lee, C. H.; Wu, C. Y.; Yang, C. S.; Lo, L. W.; Lai, Y. K. Enhanced chemotherapy of cancer using pH-sensitive mesoporous silica nanoparticles to antagonize P-glycoprotein-mediated drug resistance. *Mol Cancer Ther.* **2011**, *10* (5), 761−9].[201]

versatile nanoconjugates. HA-*g*-PEG was utilized as a capping agent and CD44 receptor targeting agent, while 10-hydroxycamptothecin (HCPT) was incorporated as an oncotherapeutic. HCPT is an alkaloid extracted from *Camptotheca acuminata* Decne that has shown notable effectiveness against cervical cancer. The HCPT-loaded nanoparticles were stable, biocompatible, and nontoxic when examined histologically and successfully targeted HeLa cells that overexpress CD44. The nanoparticles exhibited significant photothermal activity and light-triggered release of HCPT. The NPs generated in this study were shown to effectively decrease tumor size in HeLa xerograft nude mice by a combined chemo- and photothermal therapy approach, as demonstrated in in vivo experiments. The treatment resulted in minimum overall toxicity (Figure 2D).[154]

Chun-Jui Lin et al. have developed a dual-responsive nanoparticle from hyaluronic acid for drug delivery that is sensitive to both redox and pH. The nanoparticles, which act as ligands for overexpressed receptors in cancer cells, promote selective endocytosis without harming normal tissue. The nanoparticles exhibit synergistic release when activated by intracellular reductive agents and have a low pH in endosomes. The nanoparticles are tracked in real-time in living organisms using near-infrared fluorescence imaging using a noninvasive in vivo imaging system (IVIS).[155]

4.2.2. Synthetic Polymer-Based Nanoparticle. Synthetic polymers such as PLGA, PEI, and PAMAM, among others, are a synthetic polymer known for their biodegradable and biocompatible qualities. It is licensed by the FDA and has demonstrated potential as an effective drug delivery material.[156] Under acidic circumstances, PLGA breaks down into

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lactic acid and glycolic acid monomers.[157] The tricarboxylic acid cycle can metabolize these monomer units to prevent tissue toxicity from carrier buildup.[158] PLGA nanoparticles are internalized through endocytosis and then gradually release the enclosed drug within cells, leading to prolonged pharmacological effects. PEG has been approved by the U.S. Food and Drug Administration for human use. The most frequently used hydrophilic component in polymer micelles has a molecular weight ranging from 500 to 20 000 Da. Modifying the surface of PEG-based nanoparticles can decrease their interaction with plasma proteins and their nonspecific absorption by the reticuloendothelial system, thereby extending their circulation duration.[159]

Ming Shao and colleagues discovered that chloroquine (CQ) as a chemosensitizer significantly improved ovarian cancer's anticancer effects by raising the pH of lysosomes in tumor cells. To enhance pharmacokinetics and prevent systemic toxicity, CQ and chemotherapeutic drugs were enclosed within polymeric nanoparticles made of methoxy poly(ethylene glycol) and poly(L-lactic acid). Simultaneous delivery of CQ and chemotherapeutic drugs via nanoparticles improved anticancer effects compared to intravenous injections.[160]

Hybrid diblock copolymers of poly(L-glutamic acid-*b*-L-leucine) (PGA−PLeu), methoxy poly(ethylene glycol)-*b*-poly(L-leucine) (PEG−PLeu), methoxy poly(ethylene glycol)-*b*-poly(γ-benzyl-L-glutamic acid) (PEG−PBLG), and triblock copolymers of poly(ethylene glycol)-*b*-poly(L-glutamic acid-*co*-L-leucine) (PEG−PGA−PLeu) were synthesized using sequential HMDS-mediated ring-opening polymerization. The copolymers formed nanomicelles, with increased polyleucine content resulting in greater PS, reduced CAC, and higher DLC. The release of PTX from these copolymers was significantly influenced by pH (Figure 3A).[161]

4.2.3. Micelles. Micellar nanoparticles, characterized by their size of around 100 nm or smaller, can be easily synthesized.[162] Micelles facilitate extensive tissue penetration for precise medication administration and often undergo rapid disintegration within the body. Amphiphilic molecules, such as surfactants, can interact to generate miceelles in an aqueous environment. Nevertheless, traditional surfactants exhibit a significantly elevated critical micelle concentration (CMC), which is the threshold at which the surfactant undergoes micelle formation. The presence of high CMCs indicates that the micelles have the ability to separate when they are diluted in the bloodstream or other biological fluids after being administered.[163] As a result of this constraint, researchers have produced alternative amphiphilic materials, such as amphiphilic copolymers, which have the ability to form micellar structures in aqueous environments, albeit at reduced concentrations.[164]

Micelles have been the subject of substantial research in the field of cancer, with their potential as drug delivery systems being presented.[165] Only a limited number of clinical trials are now underway for polymeric micelles, which are employed to enhance the solubility of medications with low solubility, such as anticancer therapies.[166] In recent times, the area of molecular biology has made significant progress in gene delivery using nanoparticles. This is due to the ability to carry and target a wide range of genes in cells,[167] which has great potential for cancer therapy.

Micelles are a type of nanoarchitecture that consists of an amphiphilic block copolymer and a core−shell that can transport hydrophobic and hydrophilic therapeutic medicines.[168,169] They are considered potential nanoparticles for ovarian cancer treatment due to their capacity for loading chemotherapeutic medicines and efficient targeting of specific areas.[170] Micelles with a size range of 10−100 nm can decrease nonspecific targeting of normal cells by increasing their penetrating capacity and promoting endocytosis toward ovarian cancer cells.[171] These nanomicelles are good for treating ovarian cancer because they can pass through tumors easily, are biocompatible, do not attract water, stay stable in living cells, and stay in the plasma for a long time.[172]

Edwards et al. developed a method to encapsulate suberoylanilide hydroxamic acid (SAHA) into F127 micelles modified with a hyaluronic acid moiety, specifically targeting endometrial cancer cells with high levels of CD44. In vitro evaluations using 2D and 3D models showed that encapsulation improved SAHA's transport and effectiveness, leading to higher cytotoxicity. In 2D models, high-content imaging demonstrated a higher uptake of nanoparticles, while in 3D models, CD44 facilitated improved penetration. The nanodelivery system also made it easier for spheroids to reach cells, which stopped them from growing and overcame an EMT-related phenotype in type II endometrial cancer cells that were given free medicine. This study suggests that targeting SAHA through nanoparticles could enhance its effectiveness in treating endometrial cancer.[173]

4.2.4. Dendrimers. Dendrimers are nanoparticles that have a three-dimensional, consistently branched, tree-like design surrounding an inner core molecule. The nanosized spherical molecules have a high molecular weight due to the steric limits of branch lengths. The drug molecules could be connected to the functional groups on the surface of dendrimers or taken up into the inner spherical microenvironment.[174] Dendrimers can integrate and host both hydrophilic and hydrophobic carrier molecules. Dendrimers are intricately structured molecules with a highly branching architecture. Examples of dendrimers such as poly(propyleneimine), polyesters, peptide dendrimers, triazine dendrimers, and polyamidoamine (PAMAM) show promise in biological uses because of their high loading capacity and minimal toxicity.[175,176] Dendrimers are considered to be excellent vehicles for drug delivery. Research has focused on reducing their toxicity and facilitating their use in clinical applications.[177]

Li et al. enhanced the water solubility of flavonoid analogues for cancer treatment using folate-modified dendrimers. The targeted drugs exhibited a higher intracellular accumulation and an enhanced apoptotic fraction in HeLa cells. Chlorin e6 (Ce6) is considered a promising candidate for photodynamic therapy due to its high phototoxicity and light absorption capabilities. Lee et al. developed a new hydrophilic nanocopolymer (DC) using polyamidoamine dendrimers to address the issues of low water solubility and unfavorable cell localization of Ce6. The spherical DC with an average particle size of 61.7 nm exhibited enhanced cellular uptake and increased cytotoxicity compared to Ce6 alone.[178]

Samreen Khatri and colleagues created MT-PAMAM dendritic nanoconjugates to study their impact on the cell viability in uterine sarcoma cells. Using a dicyclohexylcarbodiimide coupling process, they linked the G5 dendrimer with MTX carboxylic groups. MESSA cells, a uterine sarcoma cell line, tested the nanoconjugates and confirmed the formation of covalent bonds between the drug and dendrimer. They found

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that the nanoconjugates were more effective in inducing cell death compared to unbound MTX.[179]

4.3. Inorganic Nanoparticles. Inorganic nanoparticles can be categorized as nonmetallic materials like graphene oxide (GO), silica, or carbon and metallic carriers like gold and copper. Inorganic nanoparticles are commonly used in the field of biomedicine because of their chemical and physical stability, compatibility with most organic solvents, minimal hazardous effects, manageable production costs in laboratory settings, and extensive surface area.[180] Inorganic nanoparticles typically consist of an inorganic core and a surface coating.[181] The inorganic core possesses stable physicochemical features, can be meticulously manufactured, and serves as the rigid foundation for drug carriers.[182] Modifying the surface coating of inorganic delivery carriers can enhance their functioning and enable effective antitumor treatment. Nevertheless, the low degradation rates and probable toxicity are significant concerns that require structural optimization to ensure safe internal degradation and removal.

4.3.1. Metallic Nanoparticles. In recent years, there has been significant interest in producing metal nanoparticles such as iron, gold, silver, and metal oxide nanoparticles for treating ovarian cancer. The creation and modification of metal nanoparticles rely on their shape, size, and target accumulation to create an efficient nanotechnology strategy. They enhance permeability, diminish toxicity, and minimize adverse effects while simultaneously enhancing the targeted delivery of an anticancer medication. Moreover, it offers substantial surface area and enhances photosensitization for photothermal therapy. Iron-oxide nanoparticles (Fe2O3 NPs) are considered promising candidates in modern nanobiotechnology due to their potential uses in antioxidant, antibiofilm, antibacterial, and anticancer activities.[183,184]

Metallic nanoparticles have been extensively used to trigger immune responses, deliver genes, and enhance radiosensitivity.[185] A recent study demonstrated that spherical chitosan-coated oxide nanoparticles (CuONPs@CS) can stimulate macrophages and trigger strong antitumor immune responses. Chitosan was found to enhance the release of copper ions, leading to the destruction of cervical cancer cells without causing significant harm to lymphocytes at a concentration of 50 μg/mL in toxicological testing. The metal compounds significantly inhibited the growth of HeLa cells and tumors in Balb/C mice by releasing cytokines (TNF-α, IFN-γ, and IL-12) and stimulating Th1/2 cells.[186] Gold nanoparticles (AuNPs) are being used as carriers for delivering drugs such as siRNA, DNA, or proteins due to their high bioavailability, large surface area, and ability to disperse easily (Figure 3B).[187]

Chunbai and colleagues have developed nanoscale metal−organic frameworks (NMOFs) to deliver cisplatin and pooled small interfering RNAs (siRNAs) simultaneously, improving treatment effectiveness by suppressing multiple drug resistance genes and restoring the sensitivity of resistant ovarian cancer cells to cisplatin therapy. In cisplatin-resistant ovarian cancer cells, the NMOFs protect siRNAs from enzymatic breakdown, improve siRNA absorption, and facilitate siRNA release from endosomes to silence MDR genes. In laboratory tests, the simultaneous administration of cisplatin and siRNAs via NMOFs resulted in a 10-fold increase in chemotherapy efficacy. This study highlights the potential of NMOFs for delivering multiple therapies simultaneously to treat drug-resistant malignancies (Figure 3C).[188]

4.3.2. Carbon Nanoparticles. Carbon nanoparticles like graphenes, carbon nanotubes, fullerenes, carbon nanoparticles, nanodiamonds, carbon nanohorns, and carbon dots have garnered significant attention due to their potential uses in tumor theranostics, thanks to their distinctive π-electron cloud and structures.[189] Carbon nanoparticles are appealing for biological uses due to their ability to absorb light across a wide spectrum (UV-vis-NIR), exhibit NIR photoluminescence, produce unique Raman signals, show exceptional photothermal response, generate singlet oxygen through photosensitization, and provide a large surface area for attaching contrast agents, drugs, DNA, and RNA.[190] Carbon nanoparticles have become increasingly popular in the theranostics of malignant tumors, encompassing sensing, imaging, drug administration, and photothermal therapy.[191] Carbon nanoparticles are being increasingly used in the treatment of gynecologic cancers, with some even being effectively utilized in clinical settings, including carbon nanoparticle suspension injection.[192]

Carbon nanotubes (CNTs) are a type of carbon with a unique structure that cannot dissolve in water or other organic solvents. Their potential harm in biological fluids is a significant constraint. Nevertheless, it is possible to convert them into nanoparticles that are soluble in water through chemical alteration, thereby enhancing their biocompatibility and decreasing their toxicity. The material possesses distinct physicochemical characteristics, such as its hollow monolithic structure that can hold a large payload and its capacity to incorporate various functional groups. These traits make it an appropriate and efficient delivery system for chemotherapeutic drugs.[193]

Hui et al. synthesized a carbon-coated MoSe2 (MEC) nanoparticle using a one-step hydrothermal technique. The MEC + Laser group showed the lowest cell viability, suppressed human ovarian cancer cell proliferation, triggered apoptosis, and elevated intracellular ROS levels. MEC nanoparticles showed outstanding photothermal therapy in tumor-bearing mice without any negative effects on vital organs. The study revealed enhanced absorbance and heat generation under laser irradiation, leading to improved therapeutic efficacy against ovarian cancer. MEC nanoparticles, as photothermal agents, have strong anticancer properties, making them a potential candidate for treating ovarian cancer.[194]

Carbon-based nanotubes have been thoroughly researched since 1990 and are appealing nanoparticles for enhancing the pharmacological characteristics of many diagnostic and therapeutic substances. Currently, carbon nanotubes are categorized into single-walled carbon nanotubes (SWCNTs) and multiple-walled carbon nanotubes (MWCNTs), each possessing distinct properties. Their thermal, mechanical, and electrical properties have a significant impact on imaging and drug delivery.[195] The photothermic therapy of solid tumors with SWCNTs augmented by near-infrared light induces noninvasive cell killing without harmful side effects. SWCNTs and MWCNTs have shown effectiveness in treating and diagnosing cervical cancer early. However, concerns remain about their toxicity and biocompatibility due to a lack of selectivity in these treatments.[196]

4.3.3. Silica Nanoparticles (SiNPs). SiNPs are produced using femtosecond laser ablation in deionized water. SiNPs offer numerous benefits in cancer therapy because of their biocompatibility, biodegradability, minimal cytotoxicity, and genotoxicity. They can be fully broken down into cells and

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tissues. SiNPs can offer photodynamic therapy and radiofrequency hyperthermia for cancer treatment because of their room-temperature photoluminescence, singlet oxygen production when exposed to light, and ability to produce hyperthermia using infrared radiation and ultrasound. PSiNPs created through mechanical milling of porous silicon manufactured electrochemically exhibit biocompatibility, biodegradability, high drug loading capacity, and adaptable surface changes. Nanoparticles can serve as containers for carrying hydrophobic medications in large amounts within their pores while also enabling the attachment of targeted molecules to their surface.[197] PSiNPs show promise for several cancer treatments and diagnostics, including tumor imaging, chemotherapy, photodynamic therapy, gene therapy, immunotherapy, and targeted therapy.[198]

Pradip Das's study utilized direct stochastic optical reconstruction microscopy (dSTORM), a technique for super-resolution imaging at the single-molecule level, to measure the degradation of nanoPMOs induced by glutathione and the multivalency of antibody-conjugated nanoPMOs. Furthermore, the impact of these characteristics on the specific targeting of cancer cells, the capacity to load and release drugs, and the effectiveness in fighting against cancer are also examined. Thanks to its enhanced spatial resolution at the nanoscale, dSTORM imaging can accurately depict the structural characteristics, such as size and shape, of fluorescent and biodegradable nanoPMOs. The assessment of nanoPMOs' breakdown by dSTORM imaging reveals their remarkable degradation behavior, which is influenced by their structure, at an elevated concentration of glutathione. The surface properties of nanoPMOs coupled with anti-M6PR antibodies, as measured by dSTORM imaging, have a significant impact on labeling prostate cancer cells. Specifically, orientated antibodies are more effective than randomly oriented ones, and a high level of multivalency significantly enhances the effectiveness. Nanorods coupled with an orientated antibody (EAB4H) have enhanced biodegradability and the ability to specifically target cancer cells. This enables efficient delivery of the anticancer medication doxorubicin to cancer cells, resulting in powerful anticancer effects.[199]

Xue Wang et al. created mesoporous silica nanoparticles (DIMSNs) coloaded with DOX and indocyanine green. They added them to chitosan/poly to create composite nanofibers (DIMSN/F) by using electrospinning. When exposed to vaginal fluid erosion, DIMSN/F demonstrated targeted drug release. However, local application of the thermosensitive DIMSN-loaded gel did not achieve this. Researchers investigated the photothermal chemotherapy effects of DIMSN/F in subcutaneous and orthotopic cervical cancer models, finding a tumor inhibition rate (TIR) of 72.5%, suggesting potential for cervical cancer treatment.[200]

To address PGP-MDR, researchers have developed a new drug, MSN-Hydrazone-Dox, using endosomal pH-sensitive MSN to regulate the release of Do. The drug is taken up by human uterine sarcoma MES-SA/Dox-resistant tumors through endocytosis, avoiding efflux pump resistance. This enhances the drug's effectiveness and results in cell death and DNA breakdown. In living organisms, injecting MSN-Hydrazone-Dox directly into the tumor increases the level of programmed cell death in MES-SA/Dox-resistant cancer cells. However, MSN alone, without doxorubicin, is unable to trigger a programmed cell death. The study suggests MSN can act as a nanocarrier to enter cells easily, counteracting PGP-mediated multidrug resistance (Figure 3D).[201]

Magnetic nanoparticles (MNPs) are nanoscale carriers that consist of iron oxide. Magnetic particles are nanoparticles ranging in size from 1 to 100 nm. MNPs typically consist of a central magnetic core and a surface coating adjacent to the functional layer. Magnetic particles consist of pure metals like iron,[202] cobalt,[202] nickel,[203] and manganese.[204] The detection of MNPs has sparked significant research attention due to their capacity to carry out various activities at the same time, such as serving as colloidal carriers for drug delivery to tumor locations while monitoring in real-time. The basic medication delivery of a magnetic nanoparticle involves an inorganic core and a surface coating to improve stability and biocompatibility in the body. Magnetic nanoparticles are used in medicine for diagnostic and therapeutic purposes. When used for diagnosis, these substances have applications both inside a living organism and in a controlled environment, such as identifying different biomolecules,[205] fixing, purifying,[206] separating cells,[207] and perhaps acting as a contrast agent in MRI[208] or for gene transfer.[209] Magnetic nanoparticles offer detailed information about the skeletal structure, anatomy, and metabolic functions with precise temporal and spatial accuracy. It uses a strong magnetic field to align the nuclear magnetization of hydrogen atoms in the body, which is then manipulated using radiofrequency.[210]

In cervical cancer, Hu et al. used core−shell-type magnetic gold (Fe3O4@Au) nanoparticles to improve radio-photothermal therapy. These nanoparticles showed excellent surface plasmon resonance characteristics, superparamagnetic capabilities, biocompatibility, and high photothermal conversion efficiency. Studies done in the laboratory showed that cervical cancer cells that were exposed to low amounts of Fe3O4@Au NPs and near-infrared radiation died over time. The combination of RT and PTT showed synergistic anticancer benefits. An external magnetic field could enhance the nanoparticles' effectiveness.[211]

4.3.4. Quantum Dots. Quantum dots (QDs) are small inorganic semiconductor nanocrystals that have diameters ranging from 1 to 10 nm. Because of their distinctive surface chemistry that can be altered and their ability to emit light at multiple wavelengths with good stability, these materials have gained significant interest in tumor research and are considered an excellent choice for delivering drugs directly to specified areas.[212] QDs typically consist of a semiconductor core that is enveloped by a shell, which alters its physical and chemical characteristics and enhances its solubility. QD nanomaterials are often characterized by their small size yet possess diverse potential applications across several industries. The exceptional attributes of carbon-based quantum dots, such as their low toxicity and biocompatibility, enable amazing applications in biomolecule distribution, medication administration, biosensing, and bioimaging.

Quantum dots, a novel use of nanotechnology, have potential uses in healthcare and research imaging. Their remarkable photophysical properties and occasionally multifunctional aspects make them suitable for various biological applications. QDs are being used for cancer imaging because of their distinctive and consistent fluorescence, absorption, and emission spectra, as well as their minimal photobleaching and sustained fluorescence.[213] Research studies have shown that QD-conjugated oligonucleotide sequences, linked via surface COOH groups, are designed to interact with DNA or

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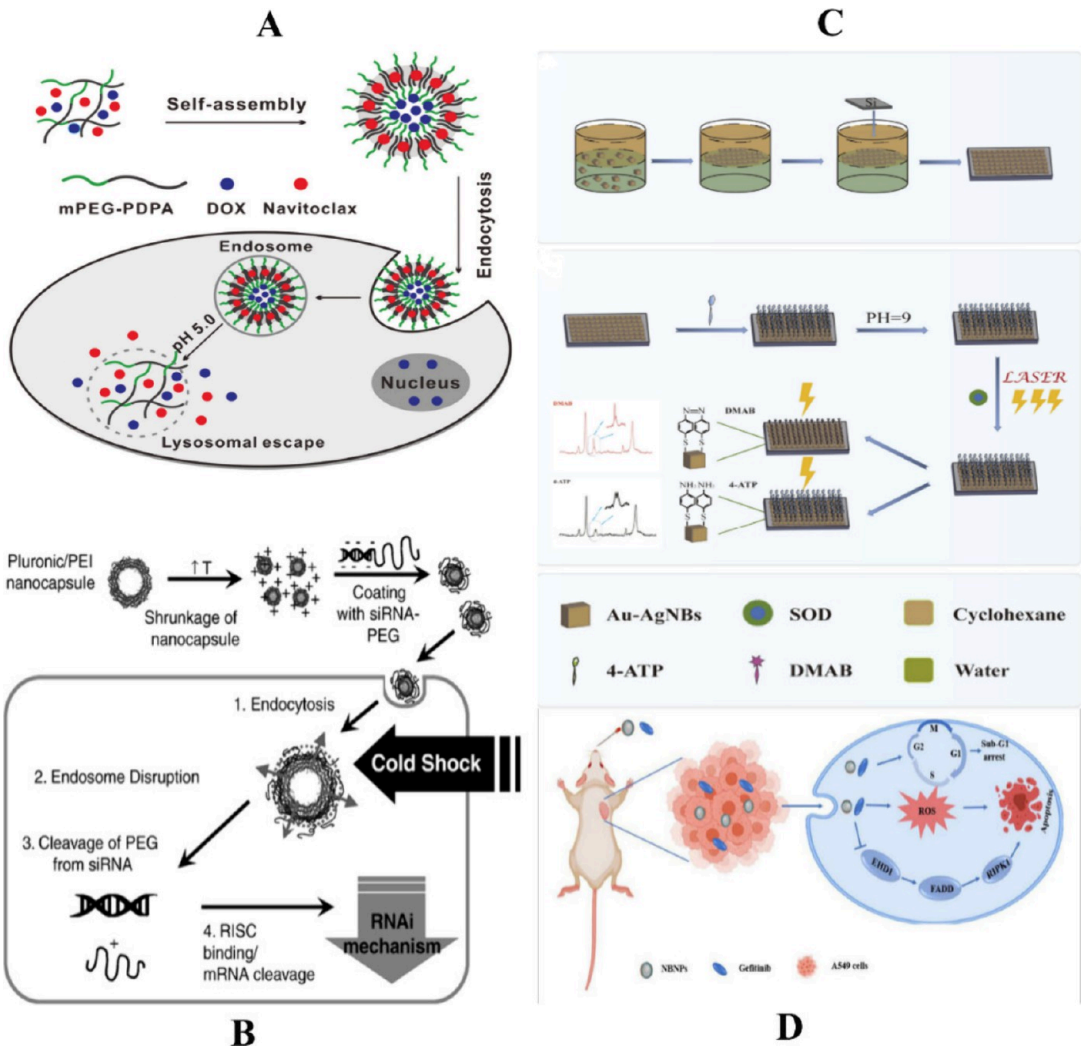

Figure 4. A. Co-delivery of DOX and navitoclax mediated by ultra pH-sensitive polymeric nanovesicles for synergetic therapy of endometrial carcinoma. Reprinted in part with permission from [Ding, J.; Zhang, X.; Chen, C.; Huang, Y.; Yu, X.; Li, X. Ultra pH-sensitive polymeric nanovesicles codeliver doxorubicin and navitoclax for synergetic therapy of endometrial carcinoma. *Biomater. Sci.* **2020**, *8* (8), 2264−2273].[229] B. Schematic illustration for intracellular delivery and gene inhibition of siRNA-PEG/NC complexes by endocytosis and subsequent cold shock induced disruption of the endosome compartment. Reprinted in part with permission from [Lee, S. H.; Choi, S. H.; Kim, S. H.; Park, T. G. Thermally sensitive cationic polymer nanocapsules for specific cytosolic delivery and efficient gene silencing of siRNA: swelling induced physical disruption of endosome by cold shock. *J. Control Release* **2008**, *125* (1), 25−32].[235] C. Preparation of self-assembled Au-AgNB arrays at the oil−water interface. SOD was detected by the SERS platform. Reprinted in part with permission from [Xia, J.; Chen, G. Y.; Li, Y. Y.; Chen, L.; Lu, D. Rapid and sensitive detection of superoxide dismutase in serum of cervical cancer by 4-aminothiophenol-functionalized bimetallic Au−Ag nanoboxs array. *Front Bioeng. Biotechnol.* **2023**, 11, 1111866].[243] D. Schematic illustration of the mechanism of the natural borneol nanoparticle (NBNP) enhanced gefitinib sensitivity in A549 cells when loaded with natural borneol. Reprinted in part with permission from [Li, J.; Xie, Q.; Ma, R.; Li, Y.; Yuan, J.; Ren, M.; Li, H.; Wang, J.; Lu, D.; Xu, Z.; Wang, J. Recent Progress on the Synergistic Antitumor Effect of a Borneol-Modified Nanocarrier Drug Delivery System. *Front Med (Lausanne)* **2021**, *8*, 750170].[271]

mRNA.[214] Biologically conjugated quantum dots are also being explored for targeted gene and medication delivery in cancer treatment. Various targeting molecules, including antibodies,[215] high-molecular-weight dextran,[216] aptamers,[217] peptides,[218] and folate,[219] can be coupled with QDs.

Xia and colleagues have developed FA-SeNPs that target cancer cells by overexpressing receptors on their surfaces. They attached the anticancer medication DOX to the surface of FA-SeNPs to enhance its effectiveness in treating human cervical carcinoma. The nanoparticles showed notable internalization in HeLa cells, overexpressing folate receptors, compared to A549 cells, which lack folate receptors. FA-Se@DOX effectively inhibited HeLa cell proliferation and induced apoptosis, compared to free DOX or Se@DOX. It selectively accumulates at the tumor site, producing potent in vivo anticancer effects.[220]

5. ENHANCING THE POTENTIAL OF NANOPARTICLES IN GYNECOLOGICAL MALIGNANCIES

The enhanced permeability and retention (EPR) effect is a distinct phenomenon observed in solid tumors, which arises from their anatomical and pathophysiological distinctions compared to normal tissues. Angiogenesis, the formation of new blood vessels, results in a high density of blood vessels in solid tumors. However, there are significant gaps between the endothelial cells in the blood vessels of tumors. Additionally, tumor tissues exhibit a specific process of macromolecular medicines crossing from the blood vessels into the surrounding

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tissue and being retained there. The EPR effect has been used as a foundation for the advancement of macromolecular anticancer therapy. Macromolecular anticancer drugs are currently gaining significant attention in cancer chemotherapy due to their ability to target tumors through the EPR effect. This targeting mechanism enhances the therapeutic effectiveness of the drugs and reduces the negative side effects, in contrast to conventional chemotherapy, which uses low-molecular-weight drugs. The EPR effect is a significant and essential phenomena that specifically occurs in tumor tissues. It is responsible for the morphological and pathological features of tumor blood vessels. The EPR effect is facilitated by several increased vascular factors, including kinin, NO, VEGF, and PGs. It seems plausible to employ a technique that enhances the EPR effect and, thus, improves the effectiveness of anticancer drugs by manipulating these parameters. AT-II-induced hypertension has been proven to be successful in both experimental and clinical investigations as a means to enhance the EPR effect. The NO-releasing molecule NG has potential in improving the EPR effect and subsequent therapeutic effects of anticancer medicines, particularly macromolecular medications. The EPR effect is considered a benchmark for the development of macromolecular anticancer drugs. Nevertheless, it is important to acknowledge the limits of the approach, including the PEG problem and the varied repercussions of its impact. These challenges can potentially be overcome by using alternative tactics, such as utilizing SMA micelles. As an illustration, we observed a significantly higher cellular uptake (about 5-fold better) for SMA micelles compared to that for PEG micelles. Therefore, we expect significant advancements in macromolecular therapies due to the benefits of the EPR effect.[221]

Nanoparticle-based drug delivery systems have demonstrated promising effectiveness in cancer treatment by leveraging the increased porosity of tumor vasculature and their compromised lymphatic drainage to concentrate drugs specifically at the tumor site through enhanced EPR effects.[222] One novel method for drug delivery involves using a stimulus-responsive nanoparticle. These systems offer extended circulation times, precise delivery to specific targets, increased transport of drugs into cells, and regulated release of drugs in terms of location, timing, and dosage.[69] The system operates by cellular or extracellular stimulation altering the composition or structural conformation of nanoparticle, leading to the release of active species in a specific biological milieu.[223] Stimulus-sensitive nanoparticles play a crucial role in disease pathology by responding particularly to pathogenic triggers, therefore reducing side effects and contributing to the effectiveness of these systems.[224] The stimulus can be classified as either internal or external. The internal stimuli are influenced by the pathological tumor microenvironment (TME), characterized by acidic pH, overexpressed enzymes, hypoxia, and increased reductive conditions within organelles.[225] Common external stimuli encompass magnetic, light, temperature, and ultrasonic.[226]

5.1. pH Triggered. The key aspect of this method is the physiological variations in pH. Internal cellular components like lysosomes have a lower pH of around 4, and certain malignant cells are more acidic than regular healthy cells. Materials with pH-responsive properties can react to changes in pH by collapsing, swelling, or altering the nanocarrier structure in response to a lower pH environment.[227] Certain chemical bonds, such as hydrazone bonds, Schiff-base bonds, acetal/ketal bonds, and ester bonds, are susceptible to breaking in acidic environments. Therefore, they are incorporated into nanosystems for pH-sensitive drug release in multidrug-resistant cells.[228]

A highly pH-responsive nanovesicle made of PEG−PDPA was developed to encapsulate the chemotherapy medication Doxorubicin and the antiapoptotic Bcl-2 inhibitor navitoclax. These nanovesicles accumulate in tumor tissue through the enhanced EPR effect and diffuse efficiently through endocytosis. They release drugs rapidly in response to the acidic environment in lysosomes, enhancing tumor-killing effects through combination therapy of DOX and Bcl-2 inhibitors. This medication codelivery system and microenvironment-triggered drug release could be an effective approach for endometrial cancer treatment (Figure 4A).[229]

Yao et al.[230] have devised a pH-responsive linker specifically designed for the pores of mesoporous silica nanoparticles. For the regulated release of doxorubicin, pegylated tetraphenylporphyrin zinc was employed as the gatekeeper. Upon reaching the acidic extracellular pH of malignant cells (pH = 6.8), the nanoplatform facilitated the cleavage of the conjugated acid-sensitive cis-aconitic anhydride bond between Zn and PEG, resulting in the release of DOX.

5.2. Thermoresponsive. Recent studies have highlighted the significance of thermoresponsive nanoparticles due to the aberrant temperatures found in tumors and inflammatory disorders caused by increased metabolic activity and cell proliferation in sick tissues.[231] Nanoparticles release medications due to a slight temperature change, as heat-responsive polymers alter their physical and chemical characteristics when exposed to heat.[232] Temperature fluctuations can be influenced by both sick tissue and external factors at specific locations.[233] Polymers can experience structural alterations due to temperature variations, leading to changes in solubility or hydrophobicity. They exhibit hydrophilic properties at temperatures below a given threshold and transition to hydrophobic characteristics beyond a specific temperature.[234]

Lee et al. created pluronic/poly(ethylenimine) nanocapsules to serve as siRNA carriers and as potent endosome-disrupting agents for delivery to the cytosol. The nanocapsules exhibited a responsiveness to a heat stimulus. When deflated, the average size is 118.9 ± 15.3 nm at 37 °C, whereas in a swelled state, it measures 412.3 ± 83.2 nm at 15 °C. The volume rapidly increased due to a cold shock within the nanocapsules when in an endosomal compartment, causing the endosomal membrane to physically tear and enabling proper delivery of the siRNA (Figure 4B).[235]

5.3. Light-Responsive. Light-sensitive nanoparticles react similarly to materials that respond to pH and temperature.[232] These drug delivery systems offer precise control over the timing and location of the triggered event, releasing the cargo only upon exposure to external radiation sources.[236] To ensure a successful release, the polymers utilized in the synthesis of these nanocapsules need to contain light- or radiation-sensitive functional groups that can induce conformational changes in the polymeric structure.[223] For in vivo use, the light must be harmless to healthy tissues, show low absorption and interaction with biological components, and offer significant tissue penetration.[223]

Near-infrared (NIR) light as an external stimulus provides precise regulation when needed without being invasive, with spatial and temporal accuracy.[237] NIR light is significantly safer than light from other wavelengths. The main tissue

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chromophores, such as hemoglobin, myoglobin, and melanin, absorb UV and visible light more effectively than NIR light, resulting in reduced tissue penetration.[238] When exposed to NIR light, nanoparticles can absorb photons and use them to break the chemical bonds of prodrug molecules, activating them through photothermal or photodynamic processes. Various nanoparticles, including noble metal nanoparticles,[239] carbon nanoparticles,[240] and upconversion nanoparticles,[241] have been studied as platforms for activating prodrugs using NIR light. They show minimal conversion until they reach tumor sites. These advancements heavily depend on their high extinction coefficient, ideal photostability, adjustable size and shape, simple surface modification, and synthetic adaptability.

Research has demonstrated that utilizing nanoparticles to encapsulate porphyrin sensitizers in photodynamic therapy for ovarian cancer can offer numerous benefits, for example, enhancing the stability and loading efficiency of photosensitizers, increasing the delivery capacity of porphyrin sensitizers, and generating higher quantum yield and phototoxicity.[242]

Ji Xia and colleagues developed a Raman spectroscopy (SERS) platform to quantitatively measure superoxide dismutase in the serum of cervical cancer patients. They created an array of Au−Ag nanoboxes using the oil−water interface self-assembly approach, which showed excellent homogeneity, selectivity, and reproducibility. A surface catalytic reaction at pH 9 with laser exposure oxidized the Raman signal molecule 4-aminothiophenol (4-ATP), to dithiol azobenzene. The platform accurately and quantitatively quantified SOD content in human serum within the range of 10 U mL^{-1} to 160 U mL^{-1}, with a quantitative limit of 10 U mL^{-1}. They used the platform to analyze serum samples from individuals with cervical cancer, cervical intraepithelial neoplasia, and healthy individuals (Figure 4C).[243]

5.4. Enzyme-Responsive. Specific enzymes such as proteases, glycosidases, and phospholipases are found in high concentrations in tumor tissue, while they are either not present or found in extremely low amounts in healthy tissues.[244] These enzymes, which are increased in the tumor's external environment, are especially attractive for creating drug delivery systems that respond to enzymes. Tumour extracellular enzyme-responsive nanoparticles remain stable without the specific enzyme, unlike tumor pH-responsive nanoparticles that may disintegrate even under normal physiological conditions.

Peptide substrates with unique proteolytic properties can be used to construct prodrugs that are selectively activated by proteases in the tumor microenvironment.[245] Matrix metalloproteinases (MMPs), a kind of protease capable of degrading extracellular matrix components, such as overexpressed MMP2, are recognized for their role in the invasion, development, and metastasis of many human tumors.[246] Yamada et al. developed and created two PTX prodrugs by linking PTX to an octapeptide (AcGPLGIAGQ) at distinct locations. This octapeptide can be broken down by MMP2 enzymes specifically at tumor sites. Consequently, it is anticipated that PTX will be discharged at the tumor locations, taken up by the tumor cells, and consequently impede the growth of the tumor. The researchers assessed the effectiveness of the two medications in a range of cancer cell lines that are susceptible to or resistant to treatments in a laboratory setting. They also analyzed the drugs' effectiveness in a mouse model of HT1080 fibrosarcoma, which has an increased expression of MMP2. The results obtained from our laboratory experiments conducted outside of a living organism demonstrated that the PTX-AcGPLGIAGQ conjugates effectively suppressed the growth of cancer cells to a greater extent than free PTX. This suppression was achieved by causing a halt in the G (2)/M-phase of the cell cycle. Corroborating the findings from laboratory experiments, the administration of PTX-octapeptide combination led to significant areas of tissue death and a reduced proportion of actively dividing cells in tumor sections derived from xenograft models. Collectively, their findings suggest that the targeted delivery of PTX to tumors by exploiting the particular identification of MMP2 has the potential to minimize toxicity and selectively eradicate tumor cells.[247]

Cui et al.[248] developed a light-responsive backbone that was coated with polyethylene glycol (PEG) and linked to bromoisophosphoramide mustard intermediate (IPM-Br) by hypoxia-cleavable linkers. The fragmentation and release of IPM-Br, facilitated by nitroreductase, were specifically induced by hypoxia in cancer cells, resulting in the cellular demise.

5.5. Reduction/Oxidation (Redox) Reactions. Cells regulate ROS levels to maintain natural physiological baseline levels despite the presence of diverse redox processes. When cells become malignant, they change their surroundings, which can be used to create drug delivery systems. Cancerous cells contain unique microenvironments. Glutathione and reactive oxygen species levels are elevated in these cells compared to those in healthy ones. Redox-responsive drug delivery devices have been developed to improve the targeting of drugs to tumor cells based on their glutathione levels, aiming to reduce the side effects of treatment medicines.[249] The low reducing potential within cancer cells supports the use of reduction-responsive nanosystems to target and improve medication delivery inside multidrug-resistant cancer cells.[250] Reduction-sensitive nanotherapeutics offer distinct advantages over pH-sensitive counterparts, including enhanced stability against hydrolytic degradation, quick response to intracellular reducing conditions, and the ability to release drugs directly in the cytosol, where many anticancer drugs are most effective. The disulfide bond is commonly used as a cleavable and reversible linker in nanoparticles to make nanosystems sensitive to redox potential through the disulfide-to-thiol reduction reaction. Nanosystems capable of targeted drug delivery to the cytoplasm while minimizing negative effects on healthy tissues are frequently utilized to address multidrug resistance and improve treatment outcomes.[251]

Using various techniques, Vieira and her team developed a sustainable method for producing selenium nanoparticle. D-Fructose served as a reducing agent. In comparative experiments, the results showed significant toxicity against resistant cancer cells like MES-SA/Dx5 and MES-SA, but not against P4 fibroblast cells. The study highlights the potential of selenium nanoparticles in cancer treatment.[252]

The poly(ethylene glycol)-based dendrimers (G3) were created by Liu et al.[253] and subsequently conjugated to doxorubicin, an anticancer medication, and porphyrin, a photosensitizer, through disulfide bonds. The polymeric prodrug poly(ethylene glycol)-*b*-poly(5-methyl-5-propargyl-1,3-dioxan-2-one) was synthesized by Yi et al.[254] The medication and photosensitizer could be released by these nanoplatforms through their interaction with intracellular glutathione in cancer cells.[255]

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5.6. Various Surface Modifications of Nanoparticles. The elevated surface area of the nanoparticle enhances their reactivity, resulting in instability. Nanoparticles like CNTs, graphene, titanium dioxide NPs, and zinc oxide NPs have a tendency to combine, leading to increased cell death compared to when they are in a dispersed state.[256,257] Hence, it is crucial to functionalize nanoparticles to prevent their aggregation and enhance their biocompatibility. Coating nanoparticles with polymers like PEG, polyethylene imine (PEI), chitosan, polystyrenesulfonate (PSS), dextran, PLGA, and poly-ε-caprolactone (PCL) enlarges their dimensions, reduces their binding with proteins in living organisms, and hinders their uptake through endocytosis. Nanoparticles can be modified on their surface with biomolecules like nucleic acids, proteins, peptides, antibodies, aptamers, fluorescent molecules, drug moieties, and cell-penetrating peptides to enhance their properties and enable targeted delivery, stability, charge distribution, imaging, diagnosis, and internalization into cells. The surface functionalization type is determined by the nanostructure's characteristics and the intended use.

Proteins are organic compounds widely used in nanotechnology for their singular or numerous capabilities. To enhance targeting, the protein nanocarrier undergoes chemical modification to harm it, and then it is linked with the targeting ligand to improve precise distribution to cells or tissues. Albumin is a versatile protein with hydrophobic pockets that facilitate the binding of drugs to amphiphilic or hydrophobic compounds. Li et al. conducted phase 2 research utilizing nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and nedaplatin (NDP) in patients with advanced, recurring, and metastatic cervical cancer, yielding positive outcomes and manageable side effects.[258]

Cong et al. developed a targeted drug delivery system using a human chorionic gonadotropin (HCG) ligand−receptor interaction. They used an optimal HCG polypeptide fragment as the target head base and poly(ethylene glycol)−poly(lactic acid) copolymers as nanometer materials to carry the chemotherapy drug MTX. In vitro experiments showed that the peptide HCGβ81-95 selectively attached to HCG receptor-positive cells, while HCG81-NP effectively transported MTX to choriocarcinoma cells. The complex effectively suppressed cell growth and decreased the transition from G0/G1 to the S phase.[259]

Antibody-targeted nanoparticles play a crucial role in cancer therapy because of their specificity and significant benefits. Monoclonal antibodies are primarily used to direct nanoparticles toward cancer-specific antigens, transport chemotherapy and photosensitizers through antibody−drug conjugates, and attract cytotoxic T cells to fight against cancer cells.[260] Hana Krakovicová and colleagues[261] conducted a study on the combination treatment of HPMA copolymer-bound DOX and Mchlorin-e6 targeted with an OV-TL16 mAb in OVCAR-3 carcinoma xenografts. The OV-TL 16 antibody can detect the OA-3 antigen present in the OVCAR-3 cells and many human ovarian carcinomas, leading to a significant enhancement in the accumulation of nanoparticles in tumors.

Nanoparticles covered with cell membranes are considered a promising approach to biomimetic particle engineering.[262] Extracellular vesicles and membranes derived from cells can possess numerous characteristics of the original cells. Coating nanoparticles with these derivatives enhances their biocompatibility and imparts functionalities similar to those of their donor cells.[263] This top-down engineering method can be utilized in developing new therapeutic solutions.[264] Membranes suitable for coating nanoparticles have been found to include those from red blood cells,[265] immunological cells,[266] platelets,[267] stem cells,[268] macrophages,[269] and cancer cells.[270] These nanoparticles that interact with cell membranes have been documented for their application in targeted medicine, immunization, virus detection, and various other domains.

Borneol, a traditional Chinese medication, can improve treatment effectiveness by directing active components to specific sites. It enhances the permeability of nasal, corneal, transdermal, intestinal, and blood−brain barriers. Nanotechnology has revolutionized oncology by targeting tumor locations, but delivery efficiency is minimal. Using Borneol's ability to penetrate and stop drug efflux, changing nanoparticles with Borneol could make it easier for medicines to target and stay in tumor areas (Figure 4D).[271]

Hybrid nanomedicines consist of a combination of inorganic and organic components that facilitate the creation of hybrid nanoparticles and enable the system to adapt to accomplish certain outcomes. Lipid nanocapsules (LNCs) are composed of a liquid oily core and a shell made of surfactants, combining the features of polymeric nanocapsules and liposomes. LNCs can hold high levels of lipophilic medicines in their oily core.[272] LNCs are different from previous nanoparticles since they are produced using pharmaceutical-grade ingredients through a solvent-free, gentle energy method. Furthermore, LNCs exhibit a high drug-loading capacity, physical stability, and a prolonged drug release pattern.[273] Simply put, LNCs show great potential as nanoparticles for delivering drugs.

Nanoscale metal organic frameworks are hybrid porous nanoparticles created through the coordinated interaction of metal ions and bridging ligands. Metal−organic frameworks are promising for drug delivery systems because of their extensive surface area, high porosity, and customizable surface chemistry.[274] Metal−organic frameworks have been utilized in photodynamic treatment to create a combined impact for treating cancer. Zr6 clusters are coupled with terephthalic acid to generate UiO-66, which possesses microporous cages and exceptional stability, making it a promising option for drug encapsulation.[275]

Kayani and colleagues developed a new synthetic method to create doughnut-shaped bovine serum albumin nanoparticles (DBSA-NPs) with consistent size distributions and uniformity. The study compared DBSA-NPs' size, polydispersity, and Dox loading to those of spherical nanoparticles and doxorubicin-containing DBSA-NPs. The research discovered that Dox-DBSA-NPs could be a new and useful way to treat cancer cells that are not resistant to drugs or that are resistant to more than one drug.[276]

Zhao and colleagues developed a method to deliver chemotherapy medications to cancer cells in living organisms using a synthetic placental chondroitin sulfate-binding peptide (plCSA-BP) derived from VAR2CSA. They combined DGL with plCSA-BP to create a targeted delivery carrier and tested it on choriocarcinoma. The DGL/CSA-PNPs were more effective at fighting cancer. They caused apoptosis in JEG3 cells through caspase-3 and the P53 signaling pathway.[277]

5.7. Magnetic and Ultrasound-Responsive. Nanoparticles that respond to magnetic fields are created using magnetic, paramagnetic, or supermagnetic materials.[231] Nanosystems typically consist of a core−shell structure where a magnetic core is enveloped by polymers known for their exceptional biocompatibility.[69] Nanosystems can be exposed to

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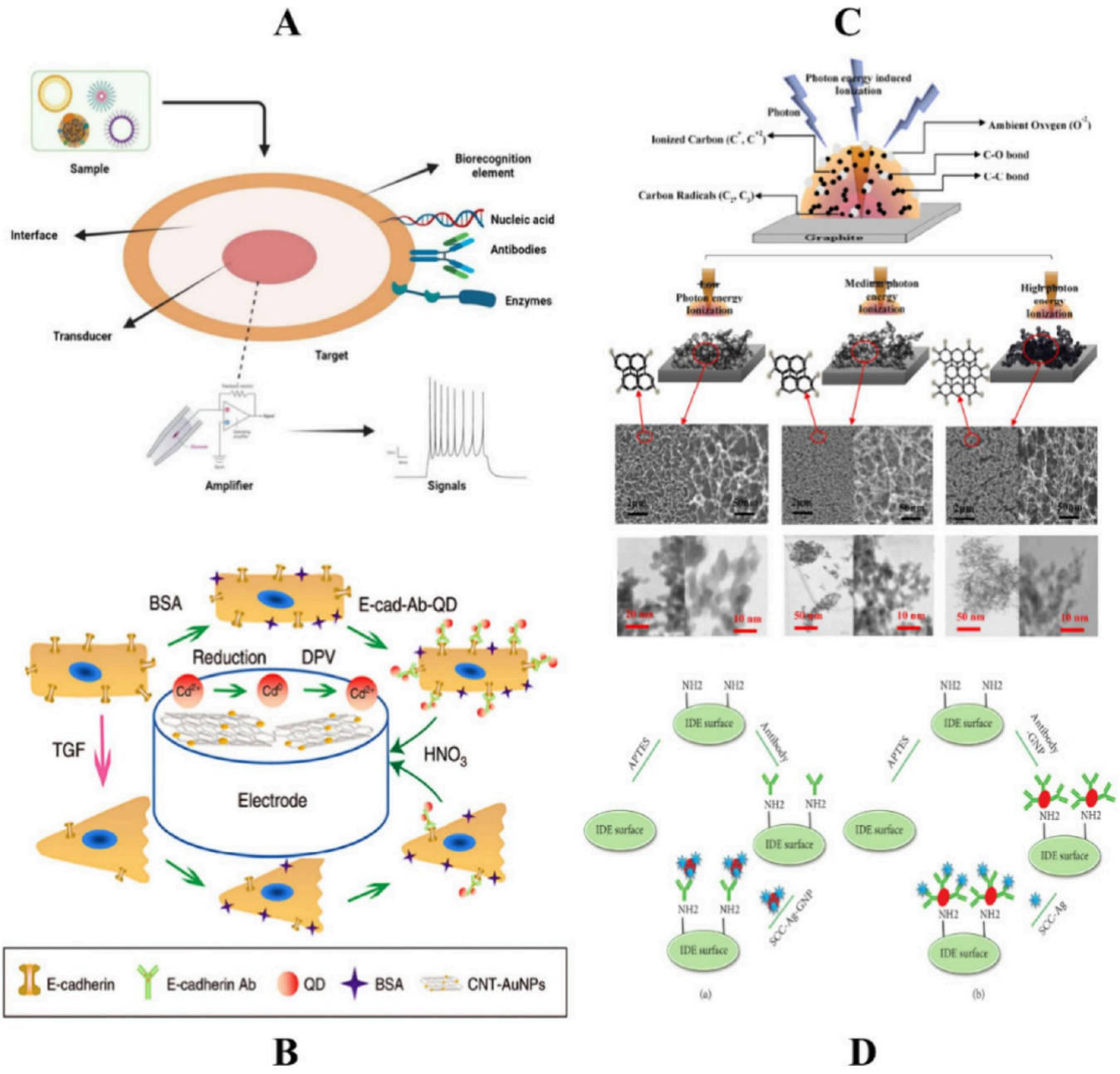

Figure 5. A. Schematic illustration of biosensor with optical biosensing applications. Reprinted in part with permission from [Ding, H.; Zhang, J.; Zhang, F.; Xu, Y.; Liang, W.; Yu, Y. Nanotechnological approaches for diagnosis and treatment of ovarian cancer: a review of recent trends. *Drug Deliv.* **2022**, *29* (1), 3218−3232].[390] B. Design of the electrochemical nanosensor for low detection of E-cadherin as an ovarian cancer biomarker. Reprinted in part with permission from [Cheng, J.C.; Klausen, C.; Leung, P.C.K. Activin A promotes ovarian cancer cell migration by suppressing E-cadherin expression. *Exp Cell Res.* **2019**, *382* (2), 111471].[288] C. Single-stage 3D INW platform synthesis illustrated schematically. The carbon−oxygen bond ratio in the INW nanostructure and its morphology were modulated accurately, in correspondence to the ionization energy changes. Reprinted in part with permission from [Chowdhury, A. K. M. R. H.; Tan, B.; Venkatakrishnan, K. SERS-Active 3D Interconnected Nanocarbon Web toward Nonplasmonic In Vitro Sensing of HeLa Cells and Fibroblasts. *ACS Appl Mater Interfaces* **2018**, *10* (42), 35715−35733].[290] D: Schematic representation of the detection of SCC-Ag on the amine-modified IDE surface. Reprinted in part with permission from [Liu, X.; Yang, X.; Shao, J.; Hong, Y.; Gopinath, S. C. B.; Chen, Y.; Wey, M. C.; Wang, Y. Coordination of Nanoconjugation with an Antigen/Antibody for Efficient Detection of Gynecological Tumors. *J Anal. Methods Chem.* **2020**, *2020*, 6528572].[291]

either permanent or alternating magnetic fields, depending on the specific application.[69] Alternating magnetic fields are intriguing for regulating the timing and frequency of the discharged charge amount of these nanoparticles.[278] An important part is conducting magnetic resonance imaging of nanoparticles to integrate diagnostics and treatments into a unified system.[279]

Ultrasound has been used in diagnostic imaging for an extended period of time.[85,95] The ultrasonic impulse can induce drug release with spatial and temporal control due to its noninvasive nature.[278] Ultrasonic effects in biological systems are categorized into two primary physical mechanisms: thermal and mechanical pressure.[280] Nanocapsule degradation can be induced by lengthy, high-energy pulsed signals with temper-

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ature or by shorter pulsed signals without temperature.[280] Ultrasound is appealing because it does not involve ionizing radiation and allows for easy control of tissue penetration depth by adjusting the frequency, duty cycles, and exposure time.[69]

6. NANOPARTICLES AND THEIR POTENTIAL APPLICATIONS OF GYNECOLOGICAL MALIGNANCIES

The main goal of nanotechnology is to find new ways to treat various diseases, including OC. Nanocarrier applications offer several benefits such as targeted delivery of hydrophobic compounds, stabilization of delivery carriers, reduction of systemic toxicity of antineoplastic drugs, and improved biodistribution and pharmacokinetics. Contrast agents, such as iron oxide and magnetic particles, can also be used. Nanoparticles such as carbon nanotubes, magnetic nanoparticles, and gold nanoparticles as well as fluorescent agents like quantum dots are used for imaging and diagnostics. These carriers can be loaded with targeting moieties. Some nanoparticles have inherent optical characteristics, including fluorescence and Raman. It is important to note that any subjective evaluations were excluded from this text. Scattering makes these materials advantageous for optical imaging and sensing applications.

6.1. Nanoparticles in Biosensors for Gynecological Malignancies. Sensors are analytical devices that consist of receptors, transducers, and reading systems (Figure 5A). They are used to identify and quantify the concentration of analytes in a sample. The biological receptor's specific interactions with the analyte are converted into a detectable signal by the transducer.[281] Nanobiotechnology encompasses pharmaceuticals and biology-based nanotechnology, which produce nanomedicines for medical purposes, and also includes the development of nanoelectronic sensors.[282] Nanomedicine encompasses the use of nanoparticles with biological systems in medical applications, as well as nanoelectronic biosensors and potential future uses of nanoscale materials like biological robots.[283] Nanoparticles with different configurations, chemical properties, surface chemistry, and crystallinity have been widely used in energy, biosensing, and drug delivery applications.[284] A nanosensor is a diagnostic device that translates data about the existence of chemical molecules (analytes) into an evaluatable signal. Nanosensors can be categorized based on the signal transduction mechanism.[285] The nanobiotechnology cell biosensor can rapidly and accurately identify various tumor cell types and assess their treatment resistance levels with great sensitivity. A dependable foundation for diagnosing and treating cancer can be established.[286]

6.1.1. Electrochemical Nanosensors. Electrochemical nanosensors have demonstrated the ability to accurately identify biomarkers in ovarian cancer in very small amounts.[287]

Electrochemical sensors were used with nanoparticles to detect ovarian cancer biomarkers, offering increased sensitivity and several detection pathways. E-cadherin expression was found to have a negative correlation with the pathological identification and display of ovarian cancer, making it a useful biomarker for tumor diagnosis (Figure 5B).[288] Du et al. conducted a study using QD nanocomposite materials and carbon nanotube (CNT)-AuNP-conjugated GCE to create an electrochemical nanosensor that can detect notable variations in E-cadherin, a biomarker for ovarian cancer.[289] The study demonstrated that the response of electrochemical signals was quick and efficient because of the combined effect of carbon nanotubes, gold nanoparticles, and QD nanoparticles.

Carbon-based nanohybrids may detect normal fibroblasts and HeLa carcinoma cells using surface-enhanced SERS by including noble metal nanoparticles, as documented by Venkatakrishnan et al.[290] A novel SERS-active nanoplasmonic-sensing platform was developed by using a self-functionalized biocompatible 3D interconnected nanocarbon web (INW) structure. The sub-10 nm physical morphology of the INW facilitates the endocytic uptake of INW clusters by cells, resulting in significantly enhanced factors of 3.66×10^4 and 9.10×10^3 for crystal violet and Rhodamine 6G dyes, respectively. Recent results indicate that graphene and carbon nanotubes primarily boost sensitivity and biocompatibility in biosensors used for detecting different biosignals of gynecologic malignancies (Figure 5C).

Gynecological tumors contain the serum biomarker squamous cell carcinoma antigen (SCC-Ag). Researchers used an amine-modified electrode sensor and an antibody to identify SCC-Ag. Researchers used gold nanoparticles to enhance detection. They tested two methods: SCC-Ag-GNP on SCC-Ag-antibody and SCC-Ag on SCC-Ag-antibody-GNP. Method 2 showed superior sensitivity and performance in SCC-Ag-spiked serum samples. Gold-conjugated probes can help identify and quantify the severity of gynecological tumors (Figure 5D).[291]

The CRISPR molecular system has become a viable tool for detecting nucleic acids. Zheng et al. described the invention of a surface plasmon resonance (SPR) sensor that is coated with a locally generated graphdiyne film. When combined with catalytically deactivated CRISPR-associated protein 9 (dCas9), this sensor achieved exceptional sensing capabilities. The dCas9 protein is fixed to the sensor surface and combined with a particular single-guide RNA, allowing for the identification of target sequences within genomic DNA without the need for amplification. The CRISPR-SPR-Chip sensor effectively detects recombinant plasmids with three-base alterations, with a remarkably low limit of detection of 1.3 fM. The CRISPR-SPR-Chip is utilized for real-time monitoring to analyze clinical samples from individuals with Duchenne muscular dystrophy who have two exon deletions. This analysis does not require any preamplification step and produces highly positive results within a 5 min time frame. The unique CRISPR-eSPR sensing technology demonstrates the capability to quickly, accurately, sensitively, and specifically identify a target gene sequence. This platform offers a new optical technique for clinical gene analysis, integrated on a microchip.[292]

6.1.2. Optical Biosensors. Optical biosensors possess biorecognition and sensing skills, thanks to their integrated optical transducer system, rendering them a versatile analysis instrument. The primary goal of an optical biosensor is to generate a signal that correlates directly with a specific substance or biomarker.[293] Various optical biosensors have been created, including those based on fluorescence, chemiluminescence, surface plasmon resonance, and electrochemiluminescence.

Al-Ogaidi et al. created an immunoassay to detect the ovarian cancer biomarker CA-125 by transferring energy from chemiluminescence resonance to a graphene quantum dot nanoparticle. The nanosensor detected CA-125 in the range of

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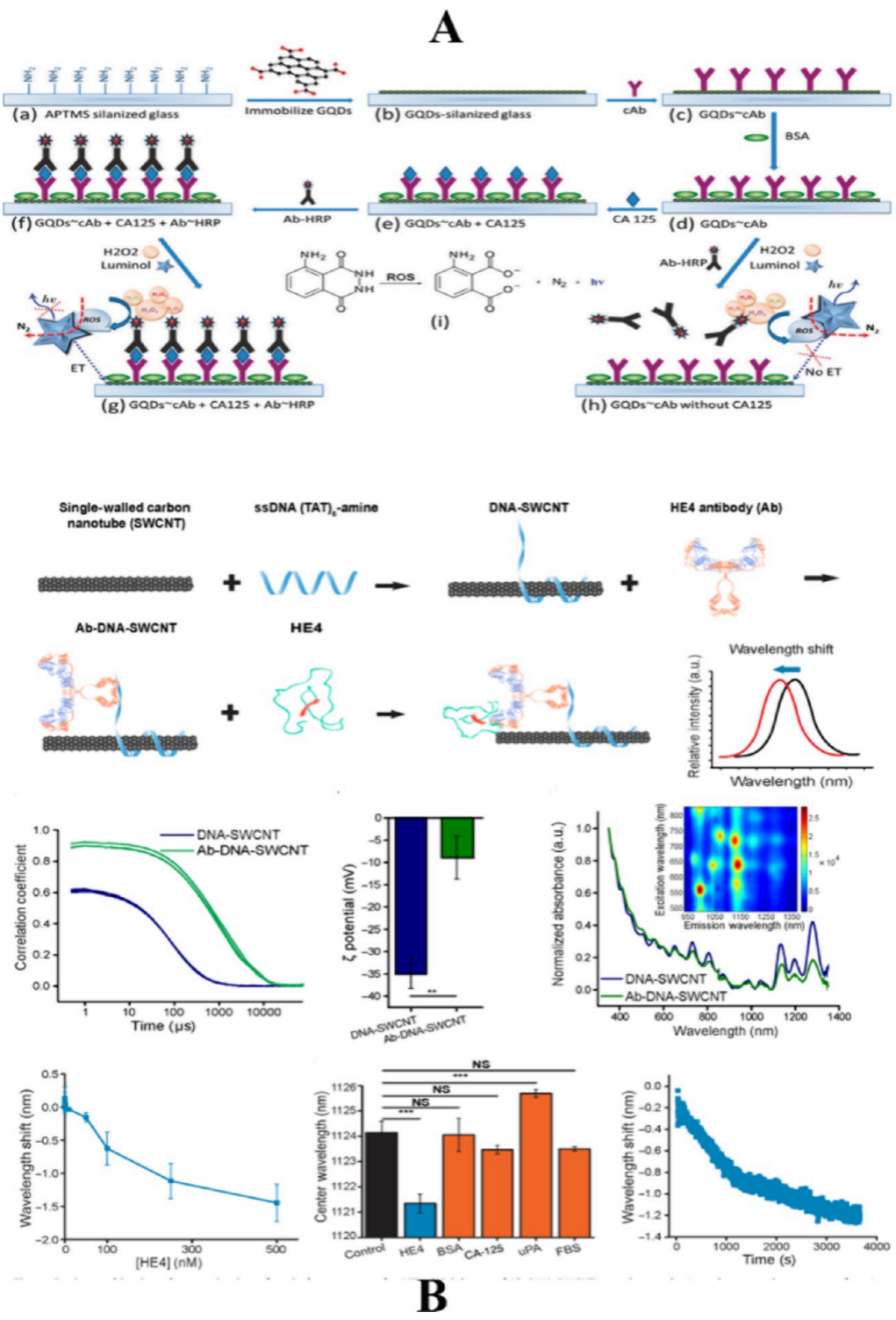

Figure 6. A. Scheme of the assembly of the immunoassay and the detection principle. Reprinted in part with permission from [Al-Ogaidi, I.; Gou, H.; Aguilar, Z. P.; Guo, S.; Melconian, A. K.; Al-Kazaz, A. K.; Meng, F.; Wu, N. Detection of the ovarian cancer biomarker CA-125 using chemiluminescence resonance energy transfer to graphene quantum dots. *Chem Commun (Camb).* **2014**, *50* (11),1344−6].[294] B. Design and in vitro characterization of optical nanosensor for HE4. Reprinted in part with permission from [Williams, R. M.; Lee, C.; Galassi, T. V.; Harvey, J. D.; Leicher, R.; Sirenko, M.; Dorso, M. A.; Shah, J.; Olvera, N.; Dao, F.; Levine, D. A.; Heller, D. A. Noninvasive ovarian cancer biomarker detection via an optical nanosensor implant. *Sci. Adv.* **2018**, *4* (4), eaaq1090].[296]

0.1 to 600 U/mL with a detection limit of 0.05 U/mL (Figure 6A).[294]

Carbon nanotubes are ideal for biological uses, including molecular imaging and in vivo biosensing, because they naturally emit light in the NIR-II region.[295] Williams et al. developed implantable membranes containing anti-HE4 carbon nanotube complexes specifically for detecting HE4 in ovarian cancer. These membranes act as a variable-wavelength sensor for HE4 detection (Figure 6B).[296] Nanotubes cause a noticeable change toward blue in the emitted light after HE4

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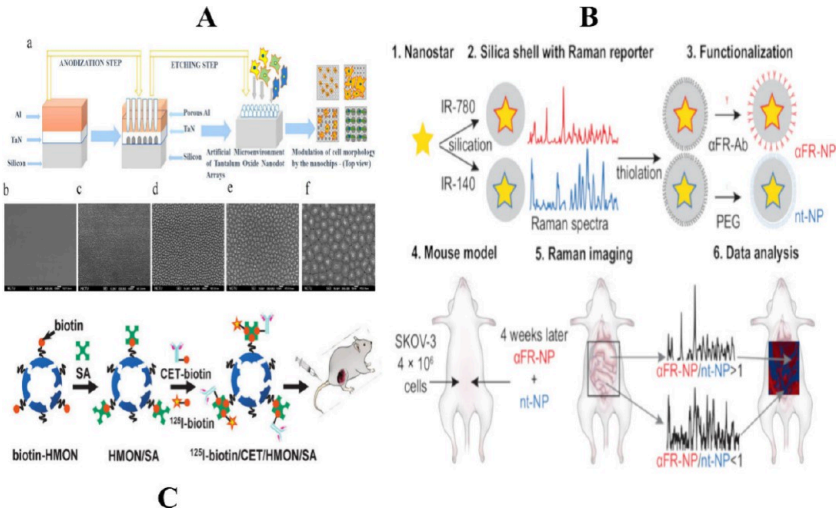

Figure 7. A. Scanning electron microscopy (SEM) of tantalum oxide nanodots. Reprinted in part with permission from [Dhawan, U.; Wang, S. M.; Chu, Y. H.; Huang, G. S.; Lin, Y. R.; Hung, Y. C.; Chen, W. L. Nanochips of Tantalum Oxide Nanodots as artificial-microenvironments for monitoring Ovarian cancer progressiveness. *Sci. Rep.* **2016**, *6*, 31998].[307] B: Schematic of the synthesis and application of ratiometric SERRS nanoprobe imaging. Reprinted in part with permission from [Andreou, C.; Oseledchyk, A.; Nicolson, F.; Berisha, N.; Pal, S.; Kircher, M. F. Surface-enhanced Resonance Raman Scattering Nanoprobe Ratiometry for Detecting Microscopic Ovarian Cancer via Folate Receptor Targeting. *J. Vis. Exp.* **2019**, 145, 10.3791/58389].[327] C: The synthesis and employment of a HMON/SA platform for the target-specific multimodality imaging agent. Reprinted in part with permission from [Ha, T. L.; Kim, H. J.; Shin, J.; Im, G. H.; Lee, J. W.; Heo, H.; Yang, J.; Kang, C. M.; Choe, Y. S.; Lee, J. H.; Lee, I. S. Development of target-specific multimodality imaging agent by using hollow manganese oxide nanoparticle as a platform. *Chem. Commun. (Camb).* **2011**, *47* (32), 9176−8].[329]

antigens bind in HGSOC fluids in a laboratory setting. They can differentiate between tumors that upregulate HE4, and those that do not in a xenograft model where nanotubes enclosed in membranes are placed in the peritoneal cavity. HE4 resulted in a noticeable emission blueshift of up to 1 nm, with a detection limit of 10 nM. The implanted sensors were effective for up to 38 days after implantation. Studies on identical carbon nanotubes showed no symptoms of toxicity for periods of up to 4 months, indicating potential long-term stability in mouse models.[297] Recently, nanotubes with similar structures have been used to detect many disease-related biomolecules like DNA,[298] RNA,[299] protease,[300] and proteins.[301] The advancement of carbon nanotube probes could enable the easy monitoring of particular biomarkers, which could be crucial for the early detection of ovarian cancer in high-risk groups and cases of recurrence.

6.1.3. Microfluidic Laboratory-on-Chip Nanosensors. Microfluidic and nanofluidic devices often regulate the movement of liquid droplets in biomedical research and biochemical processes. Micro/nanofluidic platforms offer various advantages like effective fluid processing, miniaturization, easy integration, quick analysis, and little sample usage, therefore providing significant prospects for cell analysis.[302]

In a study by Das et al., an investigation was conducted on a strategy for a bioassay based on fluorescence resonance energy transfer (FRET). This strategy utilizes modified cellulose paper to detect the presence of an EpCAM. EpCAM is a transmembrane glycoprotein that is commonly found in various tumors of epithelial origin and is known to be overexpressed in these tumors. The paper matrix functioned as a surface for the attachment of quantum dots (QDs-Apt) and cDNA labeled with Cy3. The quantum dots acted as a donor, while the cDNA served as an acceptor. The cDNA was displaced by competitive binding of EpCAM, leading to a decrease in FRET. The paper-based bioassay successfully identified the presence of EpCAM in both buffer solution and a 10% bovine serum solution within a response time of 60 min or less. The range of values that the system can accurately measure was from 1 to 100 nM when tested in a buffer solution with a precision of less than 4%. The lowest concentration that the system could reliably detect was 250 pM in a buffer solution and 600 pM in a solution containing 10% serum.[303]

Exosomes are small particles found in many bodily fluids that are crucial for cell communication and include biomolecules that indicate their source cells.[304] Microfluidic devices have demonstrated efficient exosome capture using biomarkers; however, releasing the trapped exosomes for testing remains a hurdle.[305] Hissey et al. introduced a microfluidic technology that was chemically modified with antibodies targeting general and cancer exosome membrane biomarkers (CD9 and EpCAM) to isolate exosomes from small amounts of high-grade serous ovarian cancer (HGSOC) serum. Their research showed the effective isolation of exosomes without labels and in their original state. It was shown that both the overall number of exosomes and those with EpCAM increased as HGSOC progresses. Additionally, they illustrated the subsequent uptake of the isolated exosomes by OVCAR3 cells.[306]

To study how to influence cancer cell behavior in artificial microenvironments, Dhawan and his team created nanochips with tantalum oxide nanodot arrays. They collected ovarian cancer samples, created primary cultures, and placed them on different nanochips. Immunofluorescence analysis showed that the nanochips changed their shape, viability, focal adhesions, microfilament bundles, and cell area. This means that they can be used to study how cancer grows. They can easily fabricate the nanochips for mass manufacture, which could potentially advance markerless surveillance of ovarian cancer progression and enhance prognosis (Figure 7A).[307]

6.1.4. Other Nanosensor. Saadati et al. developed a paper-based nanosensor for detecting the CA 125 biomarker in serum. The anti-CA 125 antibody was adsorbed onto the

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surface of the nanomatrix. The matrix consisted of silver nanoparticles attached to graphene quantum dots and CysA-Au NPs. Under optimal conditions, a linear range of 0.001−400 U/mL and a low detection limit of 0.001 U/mL were achieved.[308]

Giant magnetoresistive biosensors have the distinctive ability to simultaneously test numerous biomarkers within a portable instrument. Furthermore, other benefits include integrated circuit connections, high precision, and straightforward biomolecular detection. A portable, gigantic magnetoresistive nanosensor was created in a research investigation to diagnose various malignancies and their associated protein biomarkers. The method demonstrated the detection of multiple biomarkers: CA-125 II cancer antigen (3.6 U/mL), interleukin (7.2 U/mL), and epididymis protein 4 (7.3 U/mL).[309]

Nanosensors with high sensitivity offer distinct methods for detecting and amplifying signals, allowing for detection limits as low as zM concentrations. The ability to sense biomarkers and detect diseases early or after treatment can be highly beneficial. Some applications of nanosensors include identifying DNA damage, detecting cancer, identifying virus infections, diagnosing cardiovascular disorders, and detecting Alzheimer's disease. Nevertheless, the efficacy of nanosensors remains unverified in a clinical environment or in samples that are clinically significant. High salt concentrations typically hinder electrical detection measurements. However, the accumulation of nanoparticles also poses a problem for other transducer principles because of the presence of slats. The nanomaterial's purity can potentially give rise to problems. From a theoretical standpoint, mechanical sensors have the potential to be globally applicable due to the fact that almost everything possesses mass. Nevertheless, the act of manipulating liquids still presents a challenge when it comes to mechanical detection. While there are several techniques to address this problem, the sensor performance in liquid environments remains inferior to that under vacuum conditions. The extent of mass production is significantly restricted due to the lack of scaled-up nanosensors and the high costs associated with manufacturing. Nanosensors can be enhanced with additional capabilities to extend their use beyond diagnostics and toward therapeutic applications, resulting in what is known as theranostics. Prior to their utilization in medical applications, rigorous toxicity studies are necessary to comprehensively examine the entire life cycle of a nanoparticle within a living organism, including its absorption, metabolism, and removal.

6.2. Nanoparticle for Imaging Gynecological Malignancies. Integrating imaging technologies with nanomedicine early on is expected to enhance preclinical development and clinical application, resulting in better therapeutic results. Visualizing and quantifying the biodistribution and pharmacokinetics of nanomedicines at the whole-body level offers crucial insights throughout both the early and late phases of their preclinical development. Considering the widespread presence of patient and disease variability in cancer, imaging can have a significant theranostic impact in medical settings by aiding in the identification and selection of patients who are more likely to benefit from treatment with nanomedicines, thus enabling the concept of "personalized nanomedicine".[310] Various imaging modalities are accessible in clinical settings to provide this information. Only nuclear imaging techniques like positron emission tomography (PET) and single-photon emission computed tomography (SPECT), and, to a lesser degree, MRI and CT, possess the essential characteristics needed. Detecting and visualizing are crucial elements in identifying and determining the extent of gynecological cancers, including advancements in nanomedical molecular imaging and contrast agents. Nanoparticle functionals in at least one detection modality are present in different modes of detection, including fluorescence, ultrasound, and magnetic resonance imaging.

Effective imaging agents need to demonstrate improved pharmacokinetic profiles and reduced toxicity to be clinically significant. Various types of nanoparticles have been utilized in nanomedicine to overcome the limitations of traditional contrast agents.[311] Iron and iron-based magnetic nanoparticles have a high T2 and T1 relaxation ratio, and their retention time can be adjusted by modifying their size and surface functionalization with different moieties.[312] Semiconductor quantum dots have been used to track cells and medicinal molecules in real-time. Quantum dots are characterized by their wide absorption and excitation spectrum, making them useful for simultaneously tracking and photographing different cell components with distinct colors for precise elineation.[313] Furthermore, QDs have excellent stability, eliminating the concern of photobleaching commonly associated with traditional fluorescent dyes. Gold nanoparticles like nanocages, nanorods, and core−shell nanoparticles are being utilized as contrast agents in MRI, PET, and two-photon luminescence imaging due to their unique optical properties and surface plasmon resonance (SPR), which traditional contrast agents like iodine, barium, and lead do not possess.

Photoacoustic imaging is a noninvasive imaging technique that combines the molecular sensitivity of optical imaging with the spatial resolution of ultrasound imaging. It is portable and noninvasive, offering high molecular sensitivity, excellent spatial resolution, and significant measurement depth. You can load high-absorption optical contrast agents into nanobubbles to enhance contrast, minimize interactions, and prolong the cycle life. Additionally, metal nanobubbles can undergo PEGylation and conjugation for disease-specific imaging. Various imaging agents and combination medications can be included in nanobubbles for image-guided collaborative treatment.[314]

Das et al. present a straightforward and precise approach for synthesizing hydrophobic silicon nanoparticles in the size range of 1−10 nm using a simple colloid-chemical process at moderate temperatures. The silicon nanoparticles exhibit size-dependent adjustable visible emission ranging from blue to red, with a fluorescence quantum yield ranging from 6% to 13%. The fluorescence properties of these silicon nanoparticles remain mostly unaffected, even after undergoing substantial surface chemistry. The red emitting nanoparticles, which were initially synthesized, have been converted into water-soluble functional nanoprobes. These nanoprobes have a hydrodynamic diameter of 18 nm and a fluorescence quantum yield of 5%. They are utilized as fluorescent biological markers.[315]

Research has demonstrated that the nanoscale nanobubble ultrasonic contrast agent (UCA) is a precise and visible technique for treating cancer.[316] Several studies have shown that the nanobubble contrast agent they developed exhibits superior stability and acoustic performance compared to the definity microbubble commonly used in clinical settings.[317] Additionally, combining nanobubbles with specific targeting molecules like aptamers can result in precise and sensitive ultrasonic imaging focused on specific areas.[318] Due to the

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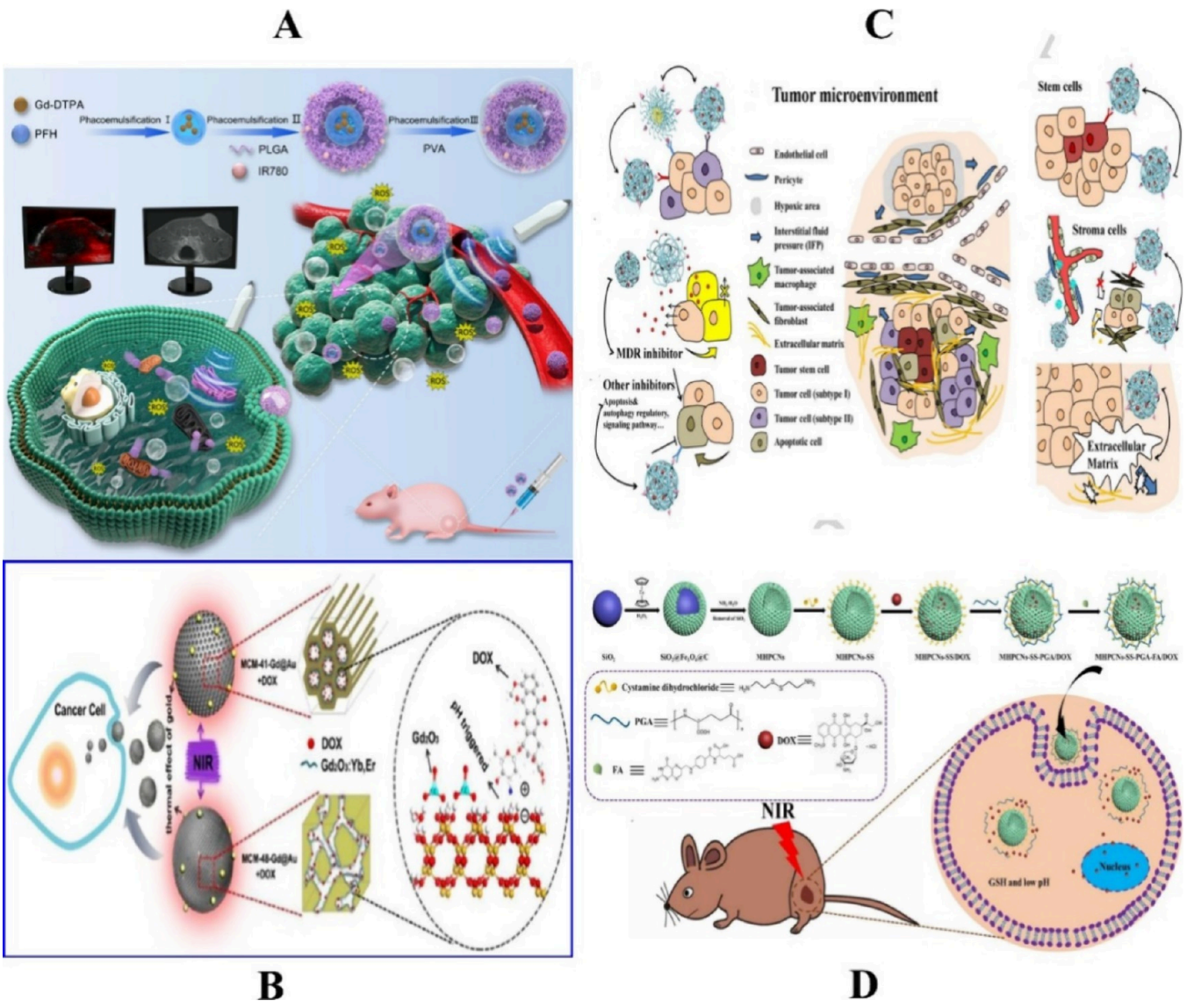

Figure 8. A. Schematic diagram of the preparation of the IGP@P NPs, the cascade-amplifying sequential therapeutic impacts of ROS generation and ADV effects caused by LIFU irradiation on tumors, and real-time monitoring of the targeted penetration and therapeutic effects with the help of PA and MR imaging. Reprinted in part with permission from [Zhou, J.; Hou, J.; Liu, S.; Xu, J.; Luo, Y.; Zheng, J.; Li, X.; Wang, Z.; Ran, H.; Guo, D. Theranostic Nanoplatform with Sequential SDT and ADV Effects in Response to Well-Programmed LIFU Irradiation for Cervical Cancer. *Int. J. Nanomedicine* **2021**, *16*, 7995−8012].[330] B. Diagram showing the structure of DOX loaded MCM-41-Gd@Au and MCM-48-Gd@Au. Reprinted in part with permission from [Niu, N.; He, F.; Ma, P.; Gai, S.; Yang, G.; Qu, F.; Wang, Y.; Xu, J.; Yang, P. Up-conversion nanoparticle assembled mesoporous silica composites: synthesis, plasmon-enhanced luminescence, and near-infrared light triggered drug release. *ACS Appl Mater Interfaces* **2014**, *6* (5), 3250−62].[332] C. Schematic illustration of the current treatment strategies using combination therapy based on targeted nanomedicines. D. Synthetic procedure of stimuli-responsive MHPCN-based drug delivery systems for synergistic photothermal and chemotherapy of tumor. Reprinted in part with permission from [Wu, F.; Zhang, M.; Lu, H.; Liang, D.; Huang, Y.; Xia, Y.; Hu, Y.; Hu, S.; Wang, J.; Yi, X.; Zhang, J. Triple Stimuli-Responsive Magnetic Hollow Porous Carbon-Based Nanodrug Delivery System for Magnetic Resonance Imaging-Guided Synergistic Photothermal/Chemotherapy of Cancer. *ACS Appl Mater Interfaces* **2018**, *10* (26), 21939−21949].[341]

presence of nanoscale UCA in both the circulatory system and tissues like tumor tissues, combining passive and active targeting techniques is possible when these UCAs target cancer cells.[319]

Carbon nanoparticles can be introduced into living cells or supplied in vivo, with or without bioconjugation. Some carbon nanoparticles, like graphenes, carbon nanotubes, and CDs, have a wide absorption band in the UV-vis-NIR range, NIR photoluminescence, a strong photoacoustic response, and distinctive Raman/SERS bands. These properties could enable the spectral imaging of tumor cells.[320] Conversely, the dark hue of carbon nanoparticles can vividly stain particular tissues, aiding in tumor-related surgeries apparent to the naked eye.[321] CDs and their derivatives are used for photoluminescence imaging of several gynecological malignancies due to their distinctive structural and optical characteristics. CD-based nanoparticles can detect biological signals, label HE4-positive ovarian cancer cells,[322] image OVCAR-3 line cells selectively,[323] and perform multicolor imaging of Hela cells.[324] Zarghami et al. recently discovered two nitrogen-doped green carbon dots (N-CDs) derived from lemon and tomato extraction using hydroxylamine. These N-CDs showed

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improved fluorescence efficiency, intensity, and biocompatibility, making them suitable for biolabeling and bioimaging of Hela cells.[325] Ma et al.[326] discovered that linking the functional groups of CDs with other nanoparticles like hydroxyapatite (HAp) can achieve long-lasting fluorescence by preventing easy diffusion and quenching.

Researchers have developed nanoprobes using surface-enhanced Raman scattering for molecular imaging during surgery. These nanoprobes, coated with gold nanostars and an organosilica layer, contain a Raman reporter and a surface folate receptor for targeting tumors. To minimize background signal, nanoprobes with a different reporter and an affinity ligand were used in equal proportions. The folate-targeted nanoprobes attached to tumor cells through the folate receptor, while nonspecific nanoprobes were used to minimize nonspecific signals (Figure 7B).[327]

QDs have shown progress in reducing their acute toxicity, making them more significant in biology, especially in oncology research. A study by Wang et al. used monoclonal antibodies against CA125 attached to ZnS-capped CdSe quantum dots for imaging human ovarian cancer cells. They found that cells exposed to CA125-conjugated QDs exhibited strong fluorescence, unlike cells exposed to FITC. In tests that were not done on living things, tissue samples that were treated with CA125-conjugated QDs gave off strong fluorescence that could be seen without a microscope.[328]

A platform procedure utilizing hollow manganese oxide nanoparticles was created to create multimodal diagnostic agents. These agents enable the selective detection of vulva cancer using T1-weighted in vivo MRI. Ha and colleagues have created a methodology for a nanoparticle platform called HMON, which is linked to streptavidin proteins on its surface. This technology facilitates the easy combination of active targeting materials, including antiepidermal growth factor receptor (EGFR) antibodies (Cetuximab, CET), and other imaging agents for multimodal imaging. The HMON-based technique can be utilized to create multimodal diagnostic agents for detecting target diseases using various imaging approaches, as shown by their successful imaging of vulva cancer (Figure 7C).[329]

Zhou and his team have developed a nanoplatform containing IR780 and PFH for treating cervical cancer. They demonstrated that IR780 was delivered to mitochondria in HeLa cells and used LIFU irradiation to penetrate tumors in 3D MCTSs and living organisms. The ADV effect increased with time and had the largest anticancer impact. The researchers can monitor nanocarrier targeting and deep penetration using multisequence MR molecular imaging (Figure 8A).[330]

Functionalized Fe3O4@SiO2 nanoparticles have been documented to be effective in treating ovarian cancer. The iron oxide nanoparticle (IONP) in the core−shell has increased the relaxivity value to around 24.3, suggesting that nanoparticles can serve as MRI contrast agents. Additionally, the silica coating has enhanced the intensity of fluorescence imaging.[331] Niu et al. have presented a nanocomposite system containing silica, gold, and gadolinium for dual therapy (chemotherapy and photothermal therapy) to effectively cure ovarian cancer (Figure 8B).[332] The system relies on the near-infrared absorption properties of gold nanoparticles and the porous structure of silica nanoparticles for loading DOX. The synergistic effect of DOX and heat is more pronounced on SKOV3 cells compared to DOX alone. Wu et al. used noninvasive silica core-gold nanoshells with an antihuman CD47 antibody to induce intraperitoneal hyperthermia and photoablation therapy.[333] Gold nanoshells improved the efficiency of photoablation on nanocomposite-exposed cells, reducing the time needed to kill malignant cells by increasing the local temperature. An anti-CD47 antibody caused selective harm to CD47-expressing tumor cells within 18 h of treatment, in contrast to tumors treated with nontargeted nanocomposites.

6.3. Nanoparticles for Drug and Gene Delivery in Gynecological Malignancies. Nanotechnology has extensively penetrated various fields of biomedical research and technology due to significant investment and quick advancements in recent years. Nanotechnology offers a novel method for delivering drugs, particularly for targeting tumors. Various types of nanoparticles have been utilized for delivering anticancer drugs, such as liposomes, organic, inorganic, or hybrid nanoparticles, polymeric micelles, polymer−drug conjugates, nanogels, and others. Nanoparticles loaded with drugs, known as nanomedicines, have the ability to enhance drug solubility, prevent drug degradation in the body, extend the presence of drugs in circulation, and target specific areas for treatment such as tumor tissues, cells, and subcellular organelles.[68] Additionally, nanomedicines allow for controlled release of pharmaceuticals in a specific location and time, ensuring that the drugs only act at the intended place.[334] Nanotechnology-based anticancer drugs like Doxil and Abraxane have been FDA-approved for over a decade.[335]

Nanoparticle drug delivery methods have demonstrated antitumor effects but face limited application in tumor therapy due to challenges in targeting particular locations, multidrug resistance, and high drug toxicity. RNAi technology has enabled the targeted delivery of nucleic acids to replace or repair faulty genes or suppress certain genes. Synergistic therapeutic effects can be achieved through combination medication administration, which is more successful in overcoming multidrug resistance in cancer cells. Combination therapies have superior therapeutic outcomes compared to administering nucleic acids or chemotherapeutic medications individually. The field of combined drug delivery has broadened to include drug−drug, drug−gene, and gene−gene interactions (Figure 8C).

6.3.1. Nanoparticles for Drug Delivery in Gynecological Malignancies. The optimal clinical goal of anticancer treatment is to attain a high therapeutic effectiveness with minimal adverse effects. Traditional pharmaceutical-based chemotherapeutic drugs tend to spread throughout the entire body, resulting in low concentrations within tumors. Nanoparticles provide several advantages over directly administering chemotherapeutic drugs. The benefits are as follows: 1) Nanoparticles can deliver drugs with low solubility by enclosing them in hydrophobic interfaces or acting as carriers in the blood. 2) They can reduce the systemic toxicity of chemotherapeutic agents. 3) Nanoparticles stabilize drugs by improving biodistribution and pharmacokinetics, reducing renal clearance, and extending circulation time through encapsulation and protection from metabolic enzymes. 4) They can overcome drug resistance by targeting cancer cells during uptake via endocytic pathways and delivering multiple chemotherapeutic agents to the tumor while avoiding drug efflux pumps.[336] Tumour-targeted nanomedicines can be classified into passive targeting, active targeting, and stimulus-responsive categories based on their targeting

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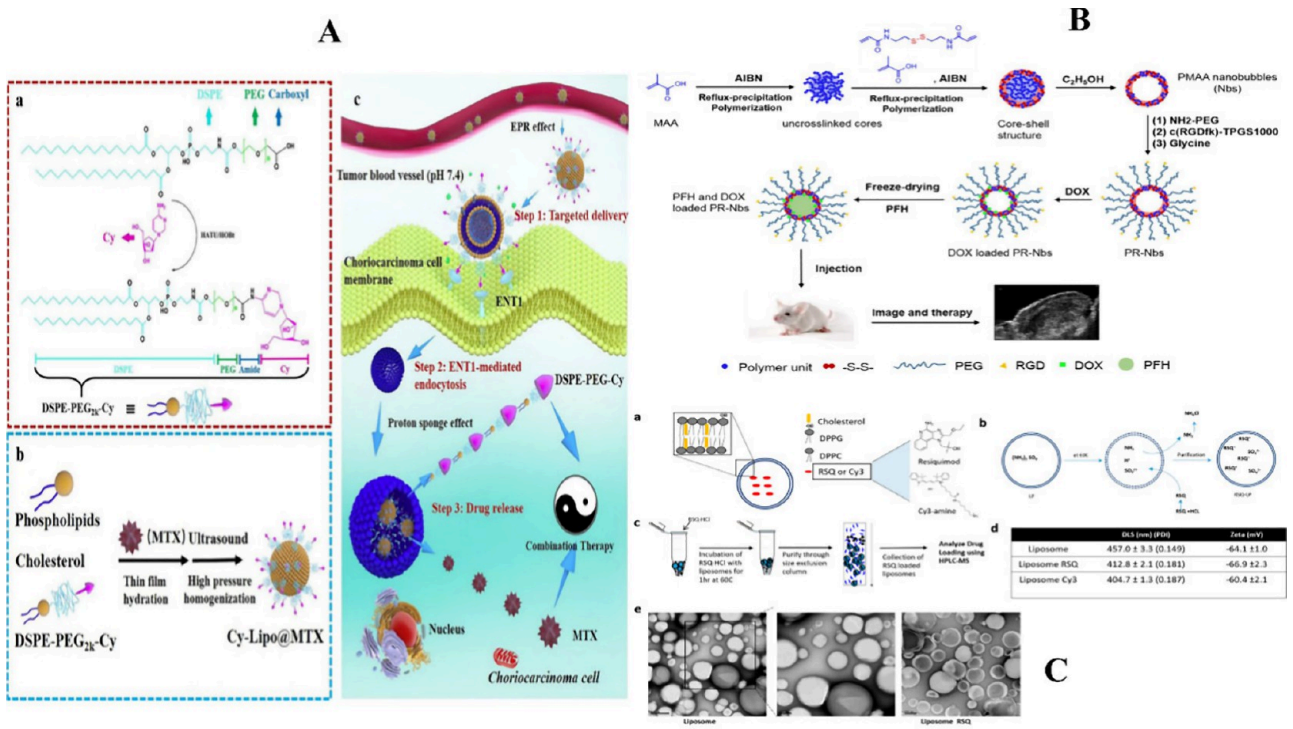

Figure 9. A. Synthesis diagram of DSPE-PEG2k-Cy (a). Preparation process of Cy-Lipo@MTX (b). Schematic illustration of Cy-Lipo@MTX for choriocarcinoma therapy (c). Reprinted in part with permission from [Fei, W.; Zhao, Y.; Wu, X.; Sun, D.; Yao, Y.; Wang, F.; Zhang, M.; Li, C.; Qin, J.; Zheng, C. Nucleoside transporter-guided cytarabine-conjugated liposomes for intracellular methotrexate delivery and cooperative choriocarcinoma therapy. *J. Nanobiotechnology* **2021**, *19* (1), 184].[342] B. Preparation and applications of the PFH-loaded Gly/PEG/RGD-modified PMAA nanobubbles for theranostic applications. Reprinted in part with permission from [Li, Y.; Wan, J.; Zhang, Z.; Guo, J.; Wang, C. Targeted Soft Biodegradable Glycine/PEG/RGD-Modified Poly(methacrylic acid) Nanobubbles as Intelligent Theranostic Vehicles for Drug Delivery. *ACS Appl Mater Interfaces* **2017**, *9* (41), 35604−35612].[345] C. Synthesis and characterization of large, anionic liposomes loaded with RSQ. Reprinted in part with permission from [Kang, Y.; Flores, L.; Ngai, H. W.; Cornejo, Y. R.; Haber, T.; McDonald, M.; Moreira, D. F.; Gonzaga, J. M.; Abidi, W.; Zhang, Y.; Hammad, M.; Kortylewski, M.; Aboody, K. S.; Berlin, J. M. Large, Anionic Liposomes Enable Targeted Intraperitoneal Delivery of a TLR 7/8 Agonist To Repolarize Ovarian Tumors' Microenvironment. *Bioconjugate Chem.* **2021**, *32* (8), 1581−1592].[357]

mechanisms.[337] Local delivery of nanomedicines for cancer therapy can ensure that the entire medication remains in the tumor or surrounding tissue, leading to outcomes comparable to targeted nanomedicines.

Initial research discovered that carbon nanoparticles like graphene oxides and mesoporous carbon nanoparticles may effectively transport membrane-impermeable chemical agents or genes into eukaryotic cells (HeLa) with high cellular absorption efficiency and biocompatibility.[338] Graphene oxides covered with cationic lipids were used as carriers to transport double-stranded DNA into HeLa and HEK-293 cells.[339] Genes like siRNA attached to carbon nanoparticles can be released using NIR irradiation to achieve the photoacoustic transport of siRNA into ovarian cancer cells at a high concentration.[340] Wu et al. developed a new targeted nanocarrier that responds to GSH, pH, and NIR using magnetic hollow and porous carbon-based nanoparticles for cancer treatment. The nanoparticles efficiently gathered at tumor locations and suppressed tumor growth (HeLa) with few side effects (Figure 8D).[341]

Cytarabine-grafted liposomes (Cy-Lipo) were used to deliver methotrexate to choriocarcinoma cells (JEG-3) by overexpressing human equilibrative nucleoside transporter 1 (ENT1). ENT1 is attracted to Cy-Lipo, allowing it to enter JEG-3 cells. The ENT1 protein sustains its transport function through endocytosis. Cy-lipo-based formulations showed significant tumor accumulation and retention in biodistribution experiments. The DSPE-PEG2k-Cy conjugation strategy showed synergistic therapeutic impact (Figure 9A).[342]

Utilizing ultrasound imaging along with tailored nanobubble delivery of drugs to the tumor spot shows great promise as a therapy method. It can transport medications to the tumor site, visualize the tumor shape, provide adjuvant therapy, and serve for both diagnosis and treatment. Many experiments have substantiated this, as referenced in sources.[343] the amine group of DOPE in liposomes and the carboxylate group of stearic acid in NBs were used to create an amide linkage for ultrasound imaging and ultrasound-triggered medication delivery in cancer cells.[344] Li et al.'s experiment utilized DOX as an anticancer medicine and perfluorohexane as an ultrasound probe to create glycine/PEG/RGD-modified NBs. These NBs demonstrated exceptional cancer treatment effectiveness and produced high-quality ultrasonic images. The new theranostic NBs combine diagnostic and therapeutic capabilities in one unit, providing a promising approach to assess treatment outcomes and improve drug delivery precision using ultrasound in biomedical applications (Figure 9B).[345]

Polyaspartamides possess biocompatibility, biodegradability, and little cytotoxicity, making them suitable for a wide range of biomedical applications. So far, the majority of these polyaspartamide derivatives have been used for creating bioimaging nanoprobes, developing nanocarriers for transporting various medicinal medicines, and preparing tissue

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engineering scaffolds.[346] Han et al. present a new approach for creating a self-assembled structure with spike-like features, specifically tailored to improve UV blocking capabilities. The synthesis of poly(2-hydroxyethyl aspartamide) (PHEA) replaced with octadecyl chains and menthyl anthranilate (C18-M-PHEA) was achieved by adjusting the quantity of grafted groups, allowing for control over their shape and UV absorbance. In aqueous solution, the self-aggregates of C18-M-PHEA were used to incorporate polymerized rod-like TiO2, resulting in the formation of spike-like self-assemblies (TiO2@C18-M-PHEA) with a chestnut burr structure. The findings demonstrated that the spike-like self-assemblies combined with TiO2 NPs had a significant 9-fold enhancement in UV protection. This improvement was achieved through the combined mechanisms of UV absorption and scattering in contrast to the pure TiO2 NPs produced through a bulk mixing method. This study presents an innovative approach for shielding against UV radiation by incorporating functional nanoparticles into self-assembling derivatives of poly(amino acid)s, therefore controlling their structure and arrangement.[347]

6.3.2. Nanoparticles for Gene Delivery in Gynecological Malignancies. Due to the intricate tumor environment, single chemotherapeutic medications or sequence-specific nucleic acids may not be sufficient for successful therapy, thereby prompting the administration of many therapeutic agents simultaneously.[348] One frequent strategy to enhance tumor sensitivity to therapeutic agents is by utilizing nanoparticles to administer several cytotoxic medicines.[349] Combining cytotoxic medicines with nucleic acids could be an effective anticancer strategy that may lower drug dosages and overcome drug resistance.[350] The simultaneous administration of genes and gene agents is a new approach that is gaining popularity for establishing coordinated control of gene expression in tumor cells.[351]

DNA nanoparticles possess strong structural programmability, excellent biocompatibility, customizable forms, and huge volume. DNA nanostructure carriers are being thoroughly investigated for drug delivery and illness therapy.[352] RNA nanoparticles can be created through bottom-up self-assembly, offering excellent biocompatibility and precise control over content, structure, and function. To achieve an effective tumor treatment with minimal toxicity or immune stimulation, DNA, RNA, and peptide therapy through nanomedicine offer a promising approach despite ongoing challenges in cancer treatment and diagnosis.

Gene therapy alters gene expression for therapeutic benefit. Because naked siRNA lacks physiological stability, its systemic administration is difficult, necessitating the use of siRNA carriers for targeted delivery to tumors.[353] Both viral and nonviral carriers have been created to aid in the transportation of siRNA. Positively charged lipids and polymers are the main choice for nonviral carriers as they can create stable electrostatic complexes with negatively charged siRNAs.[354] An optimal gene delivery method should possess stability, biocompatibility, nontoxicity, cost-effectiveness, and the ability to transport external, highly negatively charged genetic materials (such as DNA, antisense oligodeoxynucleotides [AS-ODNs], and short interfering RNAs) to particular tissue locations. The main objective of gene therapy is to effectively deliver vectors and target genes to specific cell types. An efficient nanodelivery technology that is safe and nontoxic can improve gene transfection efficacy. NBs can bind DNA to their surfaces, allowing them to circulate in the bloodstream for longer periods, collect in tumor tissues (by the enhanced permeability and retention effect), and facilitate transit into cells. Ultrasound combined with DNA-bound bubbles can enhance DNA transfection.[355,356]

Delivering genes to endothelial cells in tumors is challenging due to concerns related to nonspecific dispersion and toxicity. Hood et al. used $\alpha v\ \beta 3$-targeted cationic nanoparticles to transport the mutant Raf gene, which inhibits endothelial signaling and the development of new blood vessels in response to various growth stimuli. Injecting these nanoparticles systemically into a CT-26 cell-induced xenograft mouse model led to the depletion of tumor endothelium cells, subsequently causing apoptosis of tumor cells.[352] Gene transfection led to a decreased level of angiogenesis.

Yi et al. created a targeted delivery system for siRNA to tumor locations using a monodispersed unimer polyion complex (uPIC) made of therapeutic siRNA, cyclic RGD, and block antiomers. This uPIC was then attached to 20 nm AuNPs. The nanocarrier method efficiently administered siRNA targeting the HPV E6 gene and successfully reduced xenograft tumors grown specifically from HeLa cells. Moreover, there is growing evidence indicating that metallic nanoparticles might enhance radiosensitivity and reduce systemic toxicity simultaneously.[359]

The study by Kang et al. shows that large, anionic liposomes given intraperitoneally effectively target tumor-associated macrophages (TAMs) and can be used to deliver resiquimod. Targeted delivery of resiquimod stimulated M1 macrophages and T cell infiltration while decreasing the presence of Tregs in the tumor microenvironment. Liposome-formulated resiquimod greatly improved the effectiveness of PD1 blockage against syngeneic ovarian tumors. They expect that improving our liposomal delivery method further can create a clinically significant approach for enhancing the effectiveness and safety of immunotherapy for ovarian cancer patients (Figure 9C).[357]

Gao and colleagues have developed a supramolecular nanoassembly that targets tumors and addresses the challenges of distributing corilagin, an anticancer medication. They created stable nanoparticles around 100 nm in size through the covalent conjugation of hydrophobic linoleic acid with the carboxylic group. They studied the structure of corilagin-NPs by using electron microscopy methods. They assessed the anticancer effects of corilagin and corilagin-NPs on CaSki and HeLa cancer cell lines. The study found corilagin-NPs to have superior biocompatibility compared to corilagin, suggesting it could be a promising strategy for cervical cancer treatment (Figure 11C).[358]

Huining and colleagues synthesized magnetic nanoparticles and used them as a gene vector to transfect Hpa ASODNs into choriocarcinoma JEG-3 cells. Fe3O4-dextran-anti-βHCG loaded with Hpa ASODN reduced the invasive and proliferative capacity of choriocarcinoma, resulting in a notable inhibition of transplanted choriocarcinoma tumor growth. Fe3O4-dextran-anti-βHCG with Hpa ASODN is an efficient gene therapy, and Fe3O4-dextran-anti-βHCG nanoparticles serve as a safe and efficient gene carrier.[359]

Cationic liposomes are regarded as promising carriers for DNA cancer vaccines due to the negative properties of DNA. The lipidic HPV vaccination PDS0101, containing HPV16 peptides and cationic lipid (R-DOTAP), was found to enhance the infiltration of CD8+ T cells.[360]

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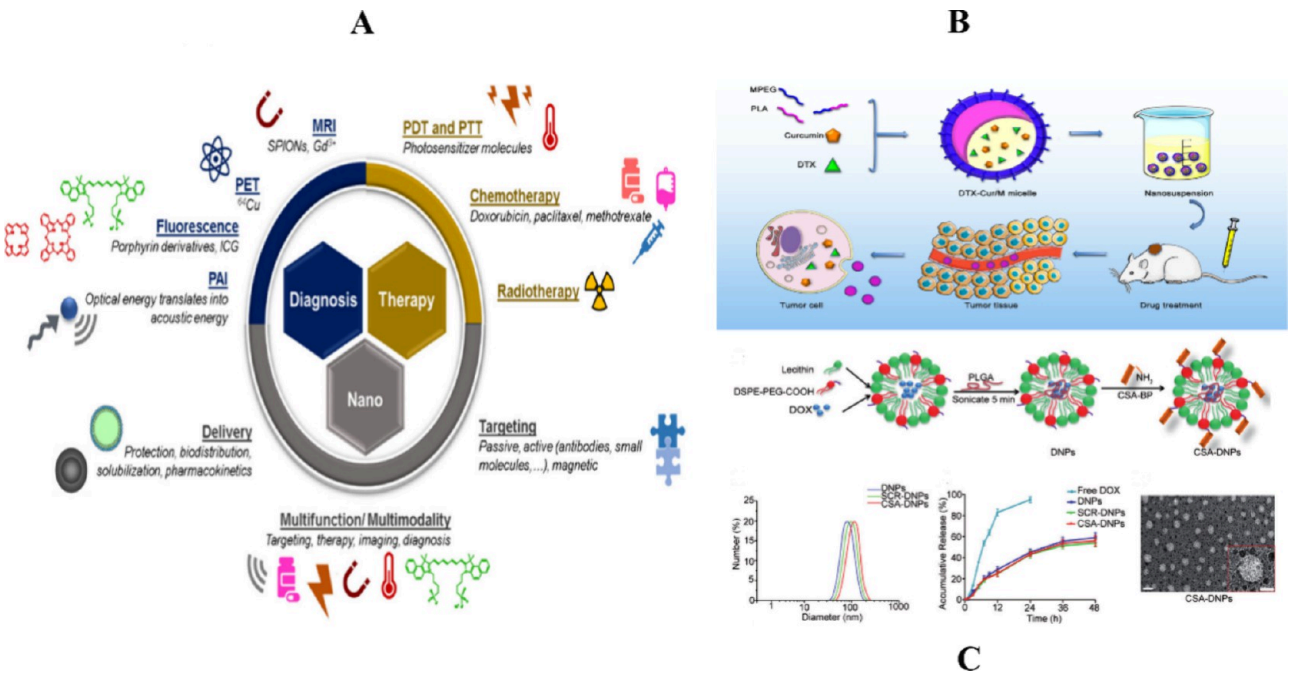

Figure 10. A. Schematic illustration of triple features in theranostic nanoplatforms, namely, nanosized particle, therapeutic, and diagnostic agents. Reprinted in part with permission from [Pacheco, C.; Baião, A.; Ding, T.; Cui, W.; Sarmento, B. Recent advances in long-acting drug delivery systems for anticancer drug. *Adv Drug Deliv Rev.* **2023**, 194, 114724].[361] B. Schematic illustration of synthesis and application of DTX-Cur/M nanomicelles. Reprinted in part with permission from [Hu, Y.; Ran, M.; Wang, B.; Lin, Y.; Cheng, Y.; Zheng, S. Co-Delivery of Docetaxel and Curcumin via Nanomicelles for Enhancing Anti-Ovarian Cancer Treatment. *Int. J. Nanomedicine* **2020**, *15*, 9703−9715].[363] C. Synthesis and characterization of CSA-DNPs. Reprinted in part with permission from [Zhang, B.; Cheng, G.; Zheng, M.; Han, J.; Wang, B.; Li, M.; Chen, J.; Xiao, T.; Zhang, J.; Cai, L.; Li, S.; Fan, X. Targeted delivery of doxorubicin by CSA-binding nanoparticle for choriocarcinoma treatment. *Drug Deliv.* **2018**, *25* (1), 461−471].[367]

6.4. Nanoparticles in the Treatment of Gynecological Malignancies. NanoDDSs have been extensively used in preclinical research for intratumoral administration in different therapeutic methods, such as chemotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), and radiation therapy. This approach has shown better treatment results compared to systemic administration (Figure 10A).[361]

6.4.1. Chemotherapy. Chemotherapy involves the use of medications to target and disrupt genetic material, growth cycles, and metabolic pathways of rapidly dividing cells, leading to their destruction. Chemotherapy is a conventional method for treating cancer; however, it is associated with severe adverse effects when administered systemically. Due to the complexity of drug resistance, various sophisticated methods have been developed for anticancer treatments to address drug resistance and enhance therapy effectiveness. Nanoparticles are being studied as a potential solution for several types of drug resistance in medication delivery.[362] Nanoparticles offer significant advantages over conventional pharmaceuticals, including increased bioavailability, controlled drug release, reduced medication dosage, and improved treatment efficacy.

Hu et al. created a core−shell structure of MPEG-PLA copolymers to encapsulate and codeliver DTX and Cur for treating ovarian cancer. The nanomicelles showed uniform particle size and sustained drug release, reducing ovarian cancer cell viability and causing apoptosis in a laboratory setting. In vivo drug evaluation showed improved inhibition of tumor cell growth, reduced blood vessel formation, and cell death (Figure 10B).[363]

Chemothermal therapy is an innovative method for treating cervical cancer. A multifunctional FePt-Fe3O4 nanocarrier (CNA) was developed to enhance tumor-killing effectiveness. These nanoparticles are stable in water and have a high concentration of carboxyl groups, allowing for a 90% loading capacity. They can release DOX with a pH-responsive release, which can be increased by applying an alternating-current magnetic field. Carbon nanotubes generate reactive oxygen species, selectively eliminating tumor cells while sparing normal cells.[364]

Gawde and his team enhanced the bioavailability and targeting efficiency of hydrophobic PTX and difluorinated curcumin by encapsulating them in bovine serum albumin nanoparticles called FA-BSA-PTX and FA-BSA-CDF. Both formulations produced consistent nanosized particles with smooth surfaces and good drug loading efficiency. The use of combination regimens as conventional treatments for lethal cancers is growing due to their targeted absorption through folate receptors and apoptosis.[365]

Ebeid and his team used nanoparticles to improve the effectiveness of PTX, the primary treatment for endometrial cancer, in mutant p53 tumors. They found that PTX-loaded nanoparticles outperformed PTX alone, and when combined with the antiangiogenic molecular inhibitor BIBF 1120, they induced synthetic lethality in cells with the p53 mutant. This combination therapy significantly inhibited tumor growth and prolonged survival in a xenograft model of endometrial cancer.[366]

Chondroitin sulfate A (CSA)-binding nanoparticles were developed to deliver DOX to choriocarcinoma cells using a synthetic CSA-binding peptide (CSA-BP). These nanoparticles quickly attached to JEG3 cells and were effectively taken up into lysosomes. Modifying CSA-BP significantly enhanced the

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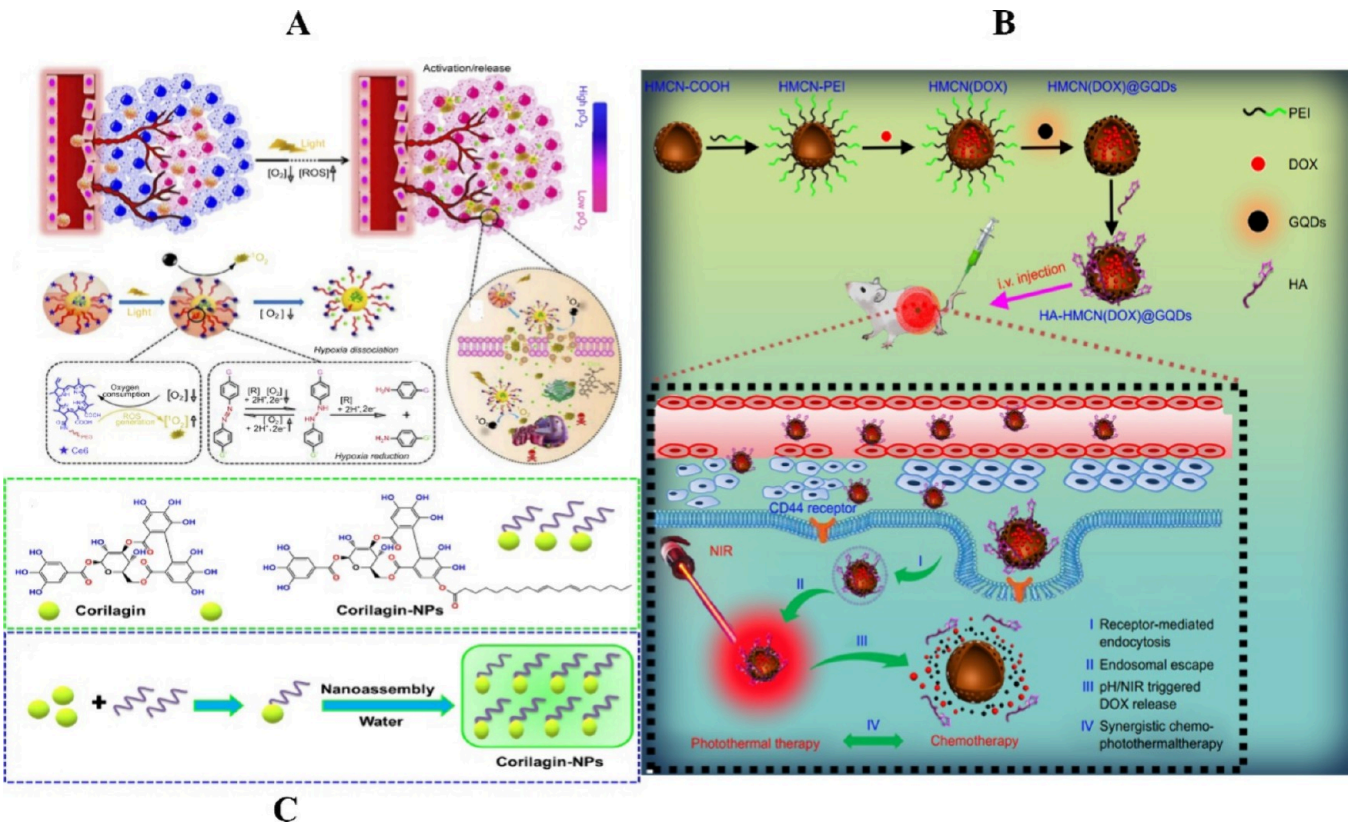

Figure 11. A. Schematic of how the light-activated Dox@NP nanoparticle worked in combining hypoxia-triggered and PDT treatment strategy. Reprinted in part with permission from [Theek, B.; Rizzo, L. Y.; Ehling, J.; Kiessling, F.; Lammers, T. The Theranostic Path to Personalized Nanomedicine. *Clin. Transl. Imaging* **2014**, *2* (1), 66−76].[310] B. Schematic illustration of the HA-HMCN(DOX) @GQDs nanoplatform for targeting drug delivery and synergistic chemo-photothermal therapy. Reprinted in part with permission from [Fang, J.; Liu, Y.; Chen, Y.; Ouyang, D.; Yang, G.; Yu, T. Graphene quantum dots-gated hollow mesoporous carbon nanoplatform for targeting drug delivery and synergistic chemo-photothermal therapy. *Int. J. Nanomedicine* **2018**, *13*, 5991−6007].[379] C. Graphical description of Corilagin-NPs affecting cervical cancer cells. Reprinted in part with permission from [Li, X.; Gao, Y.; Zhang, Y.; Li, J.; Zhang, H. Precise Engineering of Nanoassembled Corilagin Small Molecule into Supramolecular Nanoparticle for the Treatment and Care against Cervical Carcinoma. *Process Biochemistry* **2021**, *106*, 103].[358]

anticancer efficacy of DOX-loaded nanoparticles in vitro. CSA-BP-conjugated nanoparticles containing indocyanine green (CSA-INPs) were injected intravenously, effectively hindering tumor growth and reducing cancer spread in live subjects (Figure 10C).[367]

6.4.2. Radiation Therapy (RT). RT is a treatment modality that utilizes high-energy photon beams, classified as external beam radiotherapy (EBRT) and internal radioisotope therapy (RIT).[368] EBRT uses high-energy X-rays, γ-rays, or electron beams to irradiate the tumor externally, whereas RIT involves delivering radioactive isotopes (RIs) that produce β-particles or γ-rays directly into the tumor tissues.[369] Due to the high toxicity of both RSs and Ris, as well as the extended half-lives of some chemicals like I, Ra, and tirapazamine in the human body, it is crucial for radiation therapy to administer precise quantities of RSs and RIs while reducing their spread to healthy tissues. Multiple studies have demonstrated that using nano DDSs in radiation therapy has led to moderate success by enhancing the targeted distribution of radiosensitizers or radioprotectors to tumors.

Liu et al.[368] developed an X-ray-sensitive nanosystem using a PEGylated gold nanoparticle, nitroimidazole, and cell-penetrating peptides. The nanoparticles can be remotely controlled by X-rays, potentially reducing radiotherapy toxicity and enhancing radiosensitization at the target site. Laboratory conditions have demonstrated these nanosystems on resistant hypoxia cells, suggesting potential applications in cancer radiation (Figure 11A).[370]

Yang et al.[377] created a biocompatible material known as PEGylated platinum nanoflowers (Pt NFs). Pt NFs integrated with radiation-induced molecular and grafted polymers in the cytoplasm of HeLa cells significantly enhanced radiotherapy-induced apoptosis by increasing the sensitizing enhancement ratio by 23% in HeLa cells. Furthermore, these platinum nanofibers can undergo surface modification with molecules such as radionuclides, enzymes, or fluorescein. Synthesized AuNPs can enhance the effects of radiotherapy on HeLa cells by acting as radiosensitizers, increasing cytotoxicity by 9.93 times compared to radiotherapy alone.[371]

A new immunotherapy method combining RT with immunostimulatory cowpea mosaic virus (CPMV) was tested in a preclinical mouse model of ovarian cancer. The combination significantly improved tumor growth delay compared to placebo, single-agent RT, or CPMV. The study also showed an increase in tumor-infiltrating lymphocytes post-treatment with CPMV. The results suggest that using CPMV particles with RT can transform immunologically inactive tumors into immunologically active ones, indicating potential for insitu tumor vaccination.[372]

6.4.3. Photothermal Therapy. Hyperthermia is a treatment method that uses heat produced by different energy sources such as lasers, ultrasounds, and microwaves.[373] Lasers are the

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ideal energy sources for hyperthermic therapy because they can accurately focus light on the target tumor site with low energy loss.

Significant advancements have been achieved in PTT in recent years.[374] PTT works by transforming light energy into heat energy in a specific area using photothermal agents, which can be used to eliminate tumors through thermal ablation.[375] Its noninvasive operation and great specificity make it a viable option for cancer therapy, as highlighted by several studies.[376] Many PTT agents with high photoconversion efficiency (PCE) have been documented. Temperatures exceeding 50 °C could result in negative effects, including skin burns. Compared with traditional PTT, mild hyperthermia below 45 °C is preferred for clinical use instead of high operation temperatures. Moreover, PTT using excitation light in the NIR II window (1000−1700 nm) is receiving significant interest because of the decreased absorption and tissue scattering. It can effectively infiltrate deep tumor tissue, making it more appropriate for clinical use.[377]

Carbon nanoparticles offer highly promising phototherapies as therapeutic treatments. When exposed to near-infrared light, oxidized mesoporous carbon nanoparticles (OMCNs) produce a thermal effect that can cause the thermal destruction of cancer cells and facilitate the conversion of perfluoropentane into gas. This process boosts tumor ultrasound and photoacoustic imaging signals and improves the effectiveness of photothermal therapy on HeLa cells.[378] Fang et al. utilized hyaluronic acid (HA)-modified and graphene dots (CDs)-gated hollow mesoporous carbon nanoparticles (HMCNs) to achieve a high DOX-loading capacity of 410 mg/g and efficient dual-responsive targeting drug delivery (Figure 11B). These nanoparticles also demonstrated excellent light-to-heat conversion properties, enabling synergistic chemo-photothermal therapy for CD44 receptor-overexpressed cervical carcinoma cells.[379] Furthermore, combining phototherapy with chemotherapy helps to overcome multidrug resistance caused by chemotherapy using multifunctional magnetic hollow and porous carbon-based nanoparticles.[341] Carbon shells are efficient in magnetic fluid hyperthermia, reducing magnetic aggregation and protecting particles from oxidation. This method can be applied to the magnetic hyperthermia treatment of cervical cancer.[380]

A novel delivery system that combines photothermal therapy with platinum medicines shows promise for treating ovarian cancer. A reduction-sensitive polymer was used to encapsulate a Pt IV prodrug and a near-infrared II (NIR II) photothermal agent IR1048 in order to create nanoparticles, which were found to improve the effectiveness of ovarian cancer treatment. Endoplasmic reticulum stress signifies a disruption in proteostasis, likely triggered by external factors, such as chemotherapy and fluctuations in temperature. The effectiveness of nanoparticles containing Pt (IV) and IR1048 under NIR II light may be due to elevated DNA damage and endoplasmic reticulum (ER) stress.[381]

6.4.4. Photodynamic Therapy. PDT is a treatment method that uses photosensitizers (PSs) and light irradiation to create ROS that target and destroy cancer cells. When photosensitizers absorb light at a particular wavelength, they transition from the ground state to the singlet or triplet state. The energy from this transition is promptly transferred to nearby oxygen molecules, leading to the production of reactive oxygen species such as superoxide radicals and hydroxyl radicals.[382] Semiconductor nanoparticles often exhibit strong photocatalytic activity and can serve as a photosensitizer in tumor PDT.[383] PDT can selectively eliminate local aberrant tissue, including tumors, by utilizing a photosensitizer to induce a specific photodynamic reaction. The fundamental process involves the activation of the photosensitizer located in certain cells or tissues, leading to the generation of ROS such as singlet oxygen and oxygen-free radicals. Various biological components in tumor tissues and cells can interact with ROS, resulting in cytotoxic effects that ultimately cause tumor cell death and the elimination of tumor tissues. PDT is becoming more significant in cancer treatment.[384]

Michy and his team have developed a photosensitizer, verteporfin, in nanolactam (NLC) for targeted photodynamic therapy of ovarian cancer. The compounds were tested in vitro and in live mice. Results showed that both compounds were taken up by ovarian cancer cells and effectively reduced the tumor cell viability when exposed to laser light. The nanostructured NLC had a prolonged circulation duration and was effectively taken up by the tumors. However, administering 2 mg kg^{1} of free verteporfin resulted in significant phototoxic side effects, leading to the death of 5 out of 8 mice.[385]

Zhou et al. developed a Au@TiO2 core−shell nanoparticle for photodynamic therapy for cervical cancer. Initially filled with DOX, a pH-responsive polymer enhanced the nanoparticles. By binding with Mn2+, the nanoparticle created a distinct picture contrast in T1/T2-weighted MRI. This versatile nanoplatform demonstrated high effectiveness in eliminating tumors with few adverse effects.[386]

7. CHALLENGES AND PERSPECTIVES OF NANOPARTICLES IN GYNECOLOGICAL MALIGNANCIES

Research and understanding of nanotechnology-based formulations have significantly advanced in recent years, but only a limited number of these formulations have been effectively implemented in clinical settings. Many of these formulations do not show consistent outcomes when tested in living organisms; therefore, they do not advance to clinical trials. Nanoformulations have specific problems in clinical translation including biological, technological, and study-design-related obstacles.

The physical and chemical characteristics (dimensions, morphology, electric charge, and properties) of nanoparticles significantly influence their effectiveness in medical treatment within a living organism. Therefore, it is necessary to analyze the physicochemical properties of nanoparticles to create a pharmacological formulation with improved therapeutic effectiveness. The design of the experiment approach is a valuable tool for preformulation screening design and optimizing process and formulation parameters of nanocarrier systems, as indicated by several studies.[387,388] It is crucial to conduct this initial screening to identify an optimized system that could potentially facilitate the efficient transport of anticancer drugs to the central nervous system. Despite obstacles, nanotechnology offers a potential strategy to efficiently target brain tumor locations.

Combination therapy is very important in fighting cancer. Combining targeted nanomedicines with combination therapy enhances therapeutic effectiveness, addresses drug resistance, and reduces side effects compared to the use of targeted nanomedicines alone. The anticancer effect of combining targeted nanomedicines depends on factors such as the specific

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pharmaceuticals used, their mechanism of action, the design of the nanomedicines, targeting tactics, the type and condition of the tumor, the administration schedule, and other related factors. Significant advancements have been achieved in this field in recent years, although a critical obstacle persists for this innovative therapy approach because of the intricate and resistant characteristics of malignancies. A comprehensive knowledge of cancer biology, chemoresistance, cancer relapse, and metastasis is crucial for the effective advancement of combination therapy with targeted nanomedicines. Advancements in gene sequencing, systems biology, and personalized medicine are leading to the rapid discovery of new molecular disease targets and treatments. These will serve as valuable additions to targeted nanomedicines for future combination therapy. Nanomedicines require more optimization to enhance their targeting efficiency and minimize the effects of tumor heterogeneity. Biomimetic nanoparticles could be a favorable option. It is crucial to investigate preclinical evaluation methodologies and models in order to reduce the disparity between preclinical and clinical results and speed up translation from research to clinical practice. Research on combination therapy using targeted nanomedicines is a growing area, particularly with a focus on administering different nanomedicines simultaneously. Significant advancements in tumor biology, nanotechnology, and targeted drug delivery suggest that a big breakthrough is anticipated in the near future.

The toxicity of nanoparticles, particularly for QDs, is a major hindrance to creating an effective anticancer drug delivery system. Ongoing research aims to reduce the toxicity of current nanoparticles and investigate new nanoparticles with lower toxicity levels. Quantum dots mostly consist of semiconductors containing cadmium, which have excellent optical properties. However, cadmium is likely detrimental, and the toxicity of cadmium-containing quantum dots in human cells has not been thoroughly assessed. Therefore, the search for safe chemicals with similar targeting and optical qualities is a top priority. Carbon nanotubes show potential for delivering anticancer drugs due to their ability to be covalently functionalized on the surface, allowing them to transport multiple drug molecules simultaneously, leading to enhanced cancer treatment.

The advancement of RNAi technology has made gene-level cancer treatment possible, utilizing nucleic acids like siRNA, miRNA, shRNA, etc. as therapeutic agents for cancer. Although single-drug delivery has seen significant success, the complexity of MDR necessitates the use of combination chemotherapy. However, the potential for higher risks of adverse events and reduced compliance must be taken into account, particularly when multiple drugs are given simultaneously. Consequently, a delivery carrier capable of simultaneously delivering numerous medications could greatly enhance patient adherence and therapeutic outcomes. Utilizing nanoparticles for drug delivery shows promise in achieving precise and targeted release of medicines. Chemotherapeutic medications vary in physical and chemical properties, such as hydrophilicity and hydrophobicity, leading to variances in positive and negative charges between gene drugs and chemotherapy treatments. Future research in this sector should prioritize the development of multifunctional nanoparticles and delivery methods using suitable materials to encapsulate medications or genes. It should also involve making the necessary adjustments to ensure precise delivery. Despite challenges in coordinated delivery, advances have been achieved in synergistic therapy.

The TME is a hostile and markedly different environment from the neighboring healthy tissue. Different levels of blood vessel development influenced by the kind of tumor, blood flow dynamics, permeability of the blood vessel lining, and movement of substances within the tumor all provide significant challenges to effective nanoparticle administration. We should not solely concentrate on eradicating cancer cells but also stimulate immune cells in the body to combat cancer by altering antibodies or enzyme inhibitors on the surface of nanoparticles. The tumor stroma is a very intricate network where immune cells, stromal cells, and tumor cells communicate through autocrine and paracrine signaling pathways as well as direct interactions. We now have an incomplete understanding of the immune regulation mechanisms of tumors, leading to challenges and misunderstandings when trying to address antitumor concerns from an immunological standpoint. A thorough comprehension of the interactions and immune characteristics of the components infiltrating the tumor stroma will aid in identifying more targets for immunotherapy to modulate stromal nanoparticles. This knowledge will also be essential for developing smart nanomedicine delivery systems that respond to the environment. Exploring the complex network of stromal signals that support immune tolerance and tumor evasion from immune surveillance can assist in developing new strategies for stromal immunomodulation by NPs. This can enhance the effectiveness of immunotherapy by reducing the suppressive impact of the tumor stromal environment.

The emphasis is often on the material advancement of NP systems, ensuring bioactivity and preventing degradation. However, it is essential to also take into account the financial and production costs. Approximately 6% of small-molecule medications successfully advance to commercialization, and nanoparticle delivery technologies have shown comparable outcomes. Like medication development, the design, formulation, and experimentation of nanoparticles are costly and time-consuming, leading many university research laboratories to limit nanoparticle development due to insufficient funds. Manufacturing, while not a developmental concern, can lead to significant production challenges and impede the transition of a new product from laboratory testing to practical use. Complex NP systems with multiple components might be challenging to manufacture on a large scale. Failure to account for manufacturing intricacies throughout the design and testing phases can lead to problems, including inadequate quality control, increased expenses, pollution, and reduced reproducibility. Therefore, it is essential to include careful planning for nanoparticle manufacturing in the design of drug delivery systems to enhance the transition of nanoparticle-based therapeutics into clinical trials.

Nanomedicine has promise for cancer therapy, but it is currently unregulated and consists of a variety of items, some of which may not be suitable for pharmaceutical use. Utilizing immune system interactions, leveraging PK and imaging studies for safety enhancement and efficacy prediction, and combining nanomedicines with other therapeutic approaches will advance nanomedicine in oncology and early cancer treatment.

In the future, medical advancements may focus more on universally applicable and sustainable ways rather than personalized, resource-intensive, and time-consuming meth-

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ods. This is particularly important when medications must be quickly and widely distributed to significant segments of the population. In our efforts to provide cancer treatment that is both safe and effective, grounded in solid pharmacological principles, to a growing and aging population at risk of developing cancer, there is a demand to reduce the medical burden, hospital visits, and related costs. This will create new possibilities for sustainable and secure medical technologies. Nanomedicine is a moderately priced and sustainable technology with enhanced safety features that is expected to become more prominent in cancer treatment.

8. CONCLUSION

Conventional treatments such as chemotherapy, radiation, and surgery are still effective, but there is a need for further advancements in treatment methods for gynecological malignancies due to their unique negative effects on healthy tissues. An urgent requirement exists for the creation of innovative treatment approaches that target specific tumor types and have low side effects for gynecological malignancies. This review provides an overview of the latest advancements in using nanoparticles for theranostics in gynecological malignancies, covering scientific breakthroughs in sensing, imaging, drug transport, therapy, and biotoxicity. Nanoparticles and their derivatives, combined with other nanoparticles and functional molecules, were studied to enhance the sensitivity of tumor markers, improve imaging quality, increase drug effectiveness, and enable direct photothermal therapy for various gynecological cancers, aiming for high diagnostic accuracy and therapeutic outcomes. Nanoparticles such as liposomes, polymers, dendrimers, and inorganic materials show promise for clinical use. However, a single type of nanoparticle cannot solve challenges such as dose-dependent toxicities, drug biocompatibility, and controlled release during in vivo drug delivery. Nanotechnology in gynecological malignancies focuses on site-specific drug delivery and offers advanced targeted therapy options. While many formulations yield promising results, only a select handful will advance to clinical trials and eventual use in clinics. The majority of formulations are impeded in the preclinical phases by several causes. Each nanoformulation has specific hurdles in terms of biology, research design, or technology. Theranostic nanoparticles with various functions for diagnosing and treating cancer by targeting many sites simultaneously are considered the future of cancer treatments, and more research should be carried out. Furthermore, the study of the toxicity, biotransformation, and excretion of nanoparticles in treating gynecological cancers would provide a problematic issue. Hence, it is important to address these factors throughout the design phase to create carrier systems that are biocompatible and nontoxic. Studying recent advancements in nanomedicines for various cancers will aid in creating efficient nanomedicines for gynecological malignancies in future studies. It is crucial to distinguish the therapeutic impact of nanomedicines on gynecological malignancies from that on other cancers in order to create tailored nanomedicines for gynecological malignancies. Furthermore, it is recommended that more obstetricians and gynecologists engage in the research and advancement of new nanomedicines to evaluate their viability in treating gynecological cancers. Nanomedicines are anticipated to significantly enhance clinical theranostics for gynecological cancers due to recent advancements in the sector.

■ ASSOCIATED CONTENT

Data Availability Statement

All data analyzed during the current study are available from the corresponding author upon reasonable request.

■ AUTHOR INFORMATION

Corresponding Author

Jing Tian − *University-Town Hospital of Chongqing Medical University, Chongqing 401331, China*; Phone: +086-18084014036; Email: fengwonderful@163.com

Author

Yingfeng Zhang − *University-Town Hospital of Chongqing Medical University, Chongqing 401331, China*; orcid.org/0000-0003-3284-952X

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c04573

Author Contributions

Yingfeng Zhang was a major contributor in writing the manuscript. Jing Tian provided guidance and supervision for the entire work, and she is the corresponding author. All authors have read and agreed to the published version of the manuscript.

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Notes

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■ ABBREVIATION LIST

OC, ovarian cancer; CC, cervical cancer; HPV, human papillomavirus; EC, endometrial carcinoma; USC, uterine serous carcinoma; LG-ESS, low-grade endometrial stromal sarcoma; HG-ESS, high-grade ESS; CNTs, carbon nanotubes; QDs, quantum dots; MSNPs, mesoporous silica NPs; SPIONs, superparamagnetic iron oxide nanoparticles; GNPs, gold nanoparticles; Ag-NPs, silver nanoparticles; EPR, enhanced permeability and retention; SLN, solid lipid nanoparticle; NLC, nanostructured lipid carriers; SCSs, short-chain sphingolipids; Dxr, doxorubicin; LHRH, luteinizing hormone-releasing hormone; SAHA, suberoylanilide hydroxamic acid; NC@PDA-NH2, imatinib nanocrystals modified with amino groups; TPP, tripolyphosphate; BSA, bovine serum albumin; CPT, camptothecin; CCM, curcumin; 2-APBA, 2-acetylphenylboronic acid; PPIs, protein−protein interactions; PB NPs, Prussian blue nanoparticles; HCPT, hydroxycamptothecin; IVIS, in vivo imaging system; CQ, chloroquine; PGA−PLeu, hybrid diblock copolymers of poly(L-glutamic acid-*b*-L-leucine); PEG−PLeu, methoxy poly(ethylene glycol)-*b*-poly(L-leucine); PEG−PBLG, methoxy poly(ethylene glycol)-*b*-poly(γ-benzyl-L-glutamic acid); PEG−PGA−PLeu, triblock copolymers of poly(ethylene glycol)-*b*-poly(L-glutamic acid-*co*-L-leucine); ROP, ring-opening polymerization; GPC, gel permeation chromatography; PTX-NPs, PTX-loaded nanoparticles; MES-SA/DX5, multidrug-resistant uterine sarcoma cells; GO, graphene oxide; Fe2O3 NPs, iron-oxide nanoparticles; CuONPs@CS, chitosan-coated oxide nanoparticles; AuNPs, gold nanoparticles; NMOFs, nanoscale metal−organic

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frameworks; siRNAs, small interfering RNAs; MDR, multiple drug resistance; SWCNTs, single-walled carbon nanotubes; MWCNTs, multiple-walled carbon nanotubes; SiNPs, Silicon nanoparticles; DIMSN, developed mesoporous silica nanoparticle; DOX, doxorubicin; ICG, indocyanine green; TIR, tumor inhibition rate; MNPs, magnetic nanoparticles; SeNPs, selenium nanoparticles; FA, folic acid; PAMAM, polyamidoamine; DC, nanocopolymer; MTX, methotrexate; UV, ultraviolet; ^{1}H NMR, ^{1}H nuclear magnetic resonance; EPR, enhanced permeability and retention; TME, tumor microenvironment; PEG−PDPA, polyethylene glycol−poly(diisopropylamino)ethyl methacrylate; EPR, permeability and retention; SERS, Raman spectroscopy; 4-ATP, 4-aminothiophenol; MMPs, matrix metalloproteinases; a-SeNPs, amorphous selenium; t-SeNPs, trigonal selenium; HRTEM, high-resolution transmission electron microscopy; EDX, energy-dispersive X-ray spectroscopy; XRD, powder X-ray diffraction analysis; ICP OES, inductively coupled plasma optical emission spectrometry; DLS, dynamic light scattering; PEG, polyethylene glycol; PEI, polyethylene imine; PSS, polystyrenesulfonate; PLGA, polylactide-*co*-glycolide; PCL, poly-ε-caprolactone; NDP, nedaplatin; HCG, human chorionic gonadotropin; LNCs, lipid nanocapsules; DMSO, dimethyl sulfoxide; MOLT-4, lymphoblastic leukemia; MES-SA/DX-5, multidrug-resistant uterine sarcoma; plCSA-BP, placental chondroitin sulfate (CSA)-binding peptide; DGL, dendrigraft poly-L-lysine; SCC-Ag, squamous cell carcinoma antigen; IF, immunofluorescence; PET, positron emission tomography; SPECT, single-photon emission computed tomography; MRI, magnetic resonance imaging; CT, computed tomography; HAp, hydroxyapatite; ROS, reactive oxygen species; IONP, iron oxide nanoparticle; UCA, ultrasonic contrast agent; TAMs, tumor-associated macrophages; PTT, photothermal therapy; PDT, photodynamic therapy; CDF, difluorinated curcumin; CSA, chondroitin sulfate A; RT, radiation therapy; EBRT, external beam radiotherapy; RIT, radioisotope therapy; EBRT, external beam radiation therapy; CPMV, cowpea mosaic virus; TILs, tumor-infiltrating lymphocytes; PCE, photoconversion efficiency; OMCNs, oxidized mesoporous carbon nanoparticles

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