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UTILIZATION OF METALLIC NANOPARTICLES BASED MATERIALS IN CANCER THERAPY: ADVANCING TARGETED DRUG DELIVERY AND REDUCING TOXICITY

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ABSTRACT
Cancer continues as a key factor in the health decline globally which can lead to one death among six deaths, making about 19.3 million recent cases as well as approximately 10 million annual deaths. Therefore, gallbladder cancer is quite unusual but it is one of the most dangerous gastrointestinal tumors that can be detected at advanced stages, having only a few therapeutic choices. The traditional techniques including radiotherapy, surgery as well as chemotherapy, can have many limitations such as considerable systemic toxicity and quite a low specificity. Recently, nanotechnology has provided innovation in the treatment of cancer through providing novel techniques to increase the treatment effectiveness while decreasing its side effects. This review emphasizes different applications of several nanoparticles in gallbladder cancer (GBC) treatment which include dendrimers, polymeric nanoparticles, liposomes, as well as gold nanoparticles. Such carriers allow particular functions such as controlled drug release, targeted drug delivery as well as enhanced bioavailability which eventually increase the effectiveness of the treatment while minimizing its hazardous effects to tissues. Furthermore, nanoparticle-based diagnostics along with prognostic biomarkers allow double abilities for the treatment as well as estimation of disease which eventually leads to the accurate imaging of cancer cells along with real-time monitoring of the therapy. This review also explains the integration of merged techniques such as photothermal therapy, chemotherapy as well as gene therapy along with nanoparticles to overcome the resistance of the drug while enhancing the effectiveness in the management of GBC. The nanoparticles allow the efficient, safer and specialized techniques for the GBC simply through overcoming the challenges faced by the traditional methods. Hence, further research along with clinical trials or translations may offer great assistance in the treatment of GBC.

KEYWORDS: Metallic materials**,** Gallbladder Cancer, Nanoparticle-Based Therapy, Targeted Drug Delivery, Toxicity

1. INTRODUCTION

Around the world, cancer is the leading cause of death, accounting for one in six deaths worldwide [1]. Specifically, gallbladder cancer (GBC) is considered as one of the most destructive cancers of the biliary tract which includes about 80-95% of such cancers globally and making it the fifth-ranking gastrointestinal cancer [2]. Worldwide, the rate of GBC fluctuates and moves to epidemic levels depending on different ethnicities and regions. It was noted to be quite highly found in regions such as Japan, Chile as well as northern India. The reason for such incidents may be various environmental conditions or genetic factors. There are many other symptoms involved in GBC along with chronic inflammation such as porcelain gallbladder, chronic Salmonella infection, abnormal pancreaticobiliary duct junction, congenital biliary cysts, etc. [3].

For many years, the only available treatments for cancer patients were chemotherapy, radiation therapy, and surgery, either separately or in combination [4]. Recent developments, however, have greatly expanded our knowledge of the pathways involved in cancer treatment and how to target them. As a result, combinatorial techniques have been

developed that employ several targeted therapies in addition to conventional chemotherapeutics, such as platinum compounds and taxanes, which have demonstrated a synergistic impact [5]. Even if the anticipated therapeutic levels that would lower mortality rates and increase survival durations for metastatic cancer have not yet been reached, new therapy approaches such as medications, biological molecules, and immune-mediated therapies are being used today [6]. Since the discovery of X-rays in 1896 and the advent of radiotherapy as the main cancer treatment, a great deal of research has been done on gallbladder cancer therapy. The second common traditional method for treating such cancer is chemotherapy, which uses cytotoxic medications to target growing cells [7]. Chemotherapy and radiotherapy are both known as "two-edged swords" because they often induce harm or genetic alterations in healthy tissues, nonspecific drug distribution, and the problem of multidrug resistance (MDR). Evidence-based medicine, which bases therapeutic outcomes on the findings of randomized trials, provides the foundation for advancements in these conventional treatments. The conventional treatments include the following:

Chemotherapy, which uses medications to destroy cancer cells, is thought to be the primary cancer treatment. These chemotherapy drugs are more effective against tumor cells because they target growing and dividing cells directly [8]. They can, however, also damage healthy cells. The patient's age, health, tumor type, size, location, and whether it has spread are all taken into consideration while designing a chemotherapy treatment plan [9]. The effectiveness of chemotherapy therapies is limited by several reasons. In addition to the prevalence of negative and side effects, these factors include the accumulation of mutations that result in tumor heterogeneity, drug resistance, the blood-brain barrier (BBB), and low selectivity [10].

Cancer is the third most common cause of morbidity and death globally, making it a serious public health concern [11]. More than 60% of cancer cases require radiation therapy (RT), making it a prominent therapeutic method even though there are no specific medications made specifically for treating cancer. RT, sometimes referred to as irradiation or X-ray therapy, stops cancer cells from growing and dividing by causing damage to their DNA, which eventually results in cell death. Radiation therapy's propensity to harm healthy cells around the cancerous tumor is one of its main drawbacks [12]. Numerous adverse effects, some of which may be quite serious, may result from this collateral harm. Indeed, nanoparticles have transformed the treatment of cancer, resulting in the creation of numerous medications and delivery methods based on nanoparticles that are now being used in clinical settings. Therapeutic medicines based on liposomes and polymers are noteworthy examples that have been thoroughly examined in scientific literature [13][14]. Paclitaxel, one of the most well-known anti-cancer drugs, is used to treat a variety of cancers, such as lung, ovarian, skin, and esophageal cancers [15] [16] [17] [18]. Paclitaxel works by keeping cancer cells' microtubules stable, which interferes with their regular activity and eventually causes apoptosis, or programmed cell death [19]. Paclitaxel is typically given as an ethanol-based solution (named Taxol®) mixed with a solvent known as polyoxyethylene castor oil (Cremophor® EL). The adverse effects of Cremophor®, which can include hypersensitivity responses, are one of the method's major disadvantages. Premedication with steroids and antihistamines is frequently necessary for these reactions [20] [21]. Abraxane®, a new paclitaxel formulation, received approval for clinical usage in the beginning of 2005. This formulation uses a high-pressure emulsification procedure to generate nanoparticles of the natural polymer albumin that contain paclitaxel. In addition to removing the negative effects associated with Cremophor®, this novel soluble version of paclitaxel has other advantages, including better drug delivery and increased effectiveness in destroying cancer cells. This development demonstrates how nanoparticle technology may improve the results of cancer treatment. Compared to conventional formulations like Taxol®, the use of albumin carriers greatly improves the delivery of medications from the bloodstream to tumor locations, enabling greater dosages of medications. This is an important development in the treatment of cancer since it helps to reduce side effects while simultaneously increasing the drug's effectiveness [22]. Gallbladder cancer (GBC) is quite uncommon; nevertheless, it is considered as one of the most destructive gastrointestinal cancers that can be diagnosed at advanced stages and has limited choices of therapy. Traditional methods such as chemotherapy, radiotherapy, as well as surgery can be non-specific as well as cause systemic toxicity which leads to the use of nanoparticles that enhance the targeted delivery of drugs while reducing side effects. This review offers the effective role of different nanoparticles including dendrimers, polymeric nanoparticles, gold nanoparticles, as well as liposomes in the treatment of cancer, particularly GBC. Such nanocarriers allow targeted drug delivery, less toxicity as well as more efficiency in GBC treatment. Furthermore, merging different techniques along with nanoparticles can also help in overcoming the challenges of conventional methods for GBC treatment. The novelty of this review focuses on the treatment of GBC along with several nanoparticle-assisted techniques to overcome the challenges of traditional approaches. Furthermore, this review also involves the prognostic biomarkers which can be helpful for drug delivery as well as the future prediction of GBC. Through carefully analyzing the merged techniques along with nanoparticles, this review contributes to develop efficient, as well as safe treatment approaches for GBC.

2. Types of Nanoparticles Used in Cancer Treatment

Different NPs will be employed to treat cancer. NPs used in drug delivery systems can be classified as organic, inorganic, or hybrid. The organic NPs include dendrimers, polymer-based NPs, and liposome-based NPs. Polymeric NPs and polymeric micelles are the two most commonly used forms of polymer-based NPs. Gold nanoparticles (Au NPs), carbon nanotubes, silica, magnetic nanoparticles, and quantum dots were among the inorganic NPs. Among the

NP hybrids are lipid–polymer hybrids, organic–inorganic hybrids, and NPs covered in cell membranes shown in Figure 1 [23].

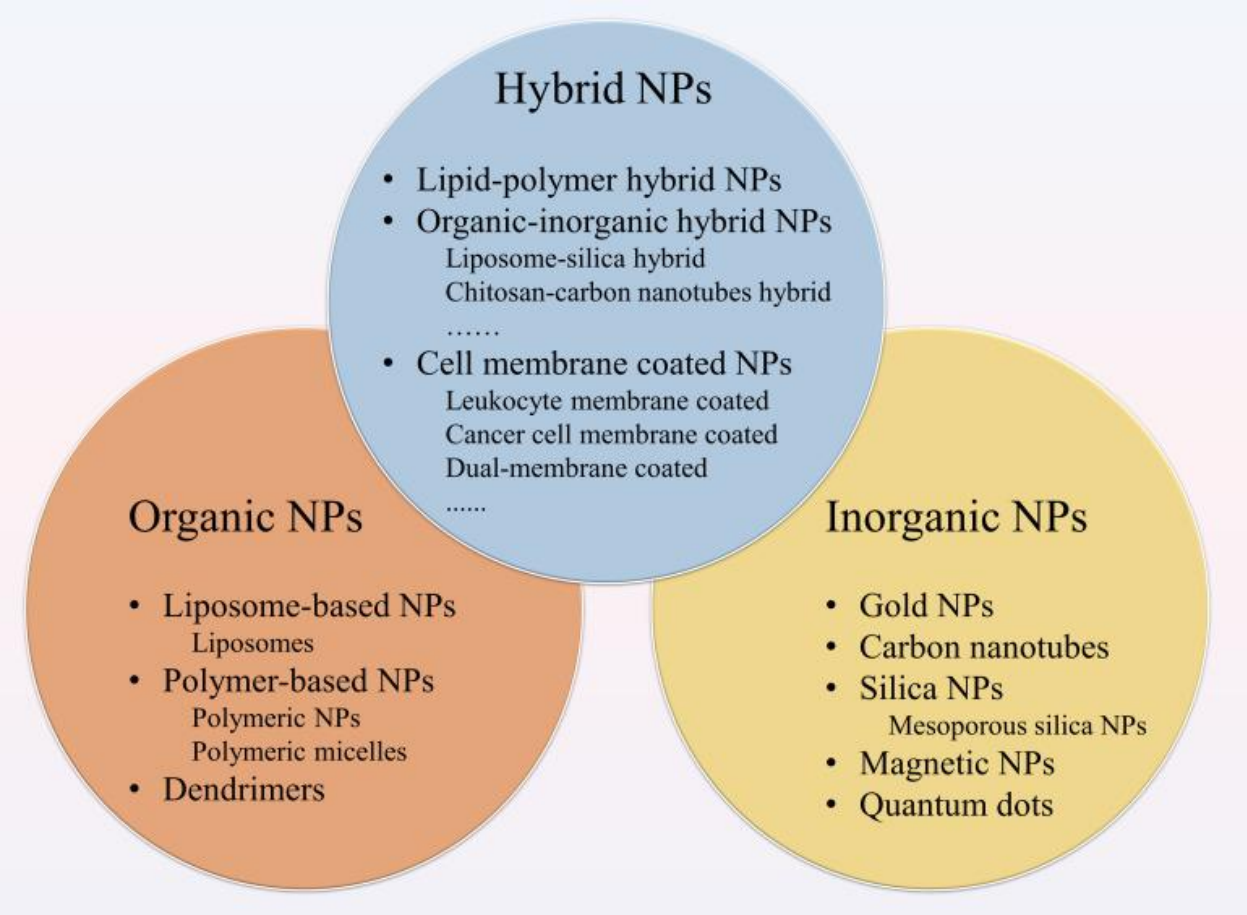


Figure 1: Different types of NPs used for cancer treatment [23].

2.1 Polymeric nanoparticles:

Polymeric nanoparticles, characterized by their distinctive properties, are essential in biomedical applications, facilitating collaboration among biologists, chemists, engineers, and healthcare professionals. The advent of polymeric nanoparticles signifies a transformative shift in medicine, resulting in significant biotechnological advancements in areas such as drug delivery, tissue engineering, biomaterials, and the development of medical devices [24]. This shift has led to the identification of more effective treatments involving proteins, nucleic acids, and various biologically active compounds [25]. These nanoparticles have many advantages over traditional non-mixed medications, especially when it comes to non-specific release kinetics, cycle duration, stability, structural integrity, encapsulation efficiency, and premature release. They also make it possible to combine elements with different chemical compositions, such as organic-inorganic and organic-organic pairings, to produce stronger synergistic effects. Nowadays, emulsion polymerization, solvent evaporation, salting-out, dialysis, and supercritical fluid technologies are the most used techniques for creating polymeric nanoparticles. Inorganic materials such as carbon nanotubes, polymers, silica, metal oxide nanoparticles, and graphene can be combined to form polymeric nanoparticles. On the other hand, natural or synthetic polymers can be combined with organic substances like lipids, proteins, and phospholipids to create novel polymeric nanoparticles, which have benefits over conventional non-mixed medications [26]. Combining various materials can change each one's properties, creating a composite with special qualities. System stability, solubility, and biological distribution can all be improved in this way. These materials' bonding properties can also prolong blood circulation while maintaining biological benefits. For instance, synthetic tunability enables the creation of intelligent nanoparticles that can co-encapsulate different therapeutic compounds with unique release patterns, serving a variety of therapeutic or imaging functions [27].

2.2 Dendrimers:

Dendrimers are spherical, nanoscale, highly branching structures with an arm or branch configuration like a tree [28]. They are made up of an outer surface and an inner core, with the outer layer including functional groups that aid in

drug targeting and attachment. The inner layer promotes controlled release, lowers toxicity, and improves drug encapsulation efficiency [29]. Numerous engineering and modification techniques for dendrimers enable the production of hundreds of distinct molecules with specialized characteristics and uses. Dendrimer synthesis is carried out using "iterative synthesis methods," which have developed over time and comprise two primary strategies: "divergent" and "convergent." Dendrimers form many layers in the divergent technique as they develop outward from the center. Drugs' water solubility can be greatly increased by incorporating them into dendritic structures, which improves bodily functions without compromising efficacy. For example, Sandra and associates created a carbosilane dendrimer that increases the stability and lipophilicity of the nanostructures as well as their compatibility with lipophilic medications. Dendritic structures can also improve the efficacy of the medication. By binding the medication to a poly-amidoamine dendrimer, it is feasible to overcome the blood-brain barrier, which is a significant obstacle in drug delivery to the central nervous system [30] Polylysine dendrimers exhibit promise as biodegradable delivery systems for cytotoxic medications to solid tumors [31]. Dendrimers are promising smart nanoparticles for cancer therapy since they can also solve problems with toxicity, release mechanisms, and drug resistance [32].

2.3 Gold Nanoparticles:

Due to their distinct optical and physical characteristics, many types of gold nanoparticles, including nanorods, nanostars, nanocubes, nanocages, and nanospheres, are very useful for the diagnosis and treatment of cancer. They are perfect for applications including biosensing, photothermal therapy (PTT), photodynamic therapy (PDT), targeted drug administration, and photoimaging [33]. Because of their biological inertness and exceptional time and place resolution for imaging, gold nanoparticles, including nanorods, cages, and shells are extremely valuable as outstanding optical imaging nanoparticles for cancer treatment. These nanoparticles can be administered into tumors at predetermined intervals to optimize their therapeutic efficacy. Doctors can more easily differentiate between cancers and healthy tissue when gold nanoparticles are administered because they particularly target cancer cells and produce light [34]. The increasing interest in photothermal therapy (PTT) is due to the near-infrared absorption properties of gold nanoparticles. Recently [35]. Chang et al. presented a multipurpose nano platform that combines gold nanoparticles with Ti_3C_2-MXene. This technology included dual-mode photoacoustic (PA) and thermal imaging for in vivo applications, as well as the ability to combine PTT, enzyme kinetics treatment, and antitumor immune therapy [36].

2.4 Carbon nanotubes:

The last step, which can be completed by functionalizing these CNTs chemically or mechanically, gives them intelligent properties [37]. The PEGylation procedure is essential to increase its solubility, prevent RES, and reduce its toxicity [38]. For instance, the CsA demonstrated the promise of PEGylation of SWCNT-based systems for CsA administration when it was conjugated to the chain of amine-terminated phospholipid PEG via an ester bond with SWCNTs [39]. Additionally, recent research has demonstrated that functionalized CNTs can traverse the blood-brain barrier [40]. CNTs have shown promise in transfecting aptamers, antisense oligonucleotides, tiny interfering ribonucleic acid, and plasmid DNA. It can be utilized for thermal ablation of cancerous regions in addition to gene delivery. Functionalized CNTs can be used as diagnostic tools for the early diagnosis of cancer, but they can also [41].

3. Gallbladder Cancer: An Overview

3.1 Epidemiology and Risk Factors

The cancer of the gallbladder is the most common malignancy within the biliary tract, accounting for approximately 80% to 95% of all biliary cancers in the world, based on the studies found on autopsy [42]. It ranks as the sixth most common cancer among all the types of gastrointestinal malignancies. Notably, the global incidence of this type demonstrates substantial geographical and ethnic variability, reaching endemic levels in certain populated areas. This heterogeneity is believed to stem from a complex combination of environmental factors and inherent genetic susceptibilities influencing carcinogenesis. The distribution of these risk factors varies markedly across different regions and ethnic groups. Typically, gallbladder cancer evolves over a span of 5 to 15 years, starting with metaplasia and advancing towards dysplasia carcinoma in situ, and eventually culminating in invasive carcinoma [42]. The disease often progresses silently and aggressively, contributing to the poor prognosis of the disease. The chance to achieve a favorable outcome depends on early detection of disease and surgical removal of the tumor for curative results. however, only 10% of patients could be eligible for this curative surgery at diagnosis stage, and approximately 50% exhibit lymph node metastasis [43]. Furthermore, even after the seemingly successful surgery, the resurrection of the disease and even the development of metastasis disease could occur, underscoring the urgent need for more effective adjuvant therapies [44].

3.2 Molecular Mechanisms and Key Biomarkers

The incidence of gallbladder cancer (GBC) demonstrates significant geographic variation, with the highest incidence rates reported in regions of Central and East Asia (including Northern India, Pakistan, Bangladesh, Nepal, Japan, Korea, and China), Central Europe (Hungary, Slovakia, and Poland), and South America (notably Chile, Bolivia, and Peru) [45]. This huge variability is believed to arise from differences in environmental exposures and genetic aberrations, both considered as the major contributors to this variation (Figure 2). In the U.S., the highest rates of incidence and mortality cases are seen among American Indian and Alaska Native people. Over recent decades, the

incidence of GBC in the United States has shown a rising trend, with more than 1,000 new cases reported in 2013 [46]. Histologically, gallbladder adenocarcinomas represent the predominant subtype, accounting for 85%–97% of cases, primarily of the papillary or tubular variants, followed by squamous cell carcinoma, aden-squamous cell carcinoma, neuroendocrine carcinoma, anaplastic carcinoma, and sarcoma variant [47].

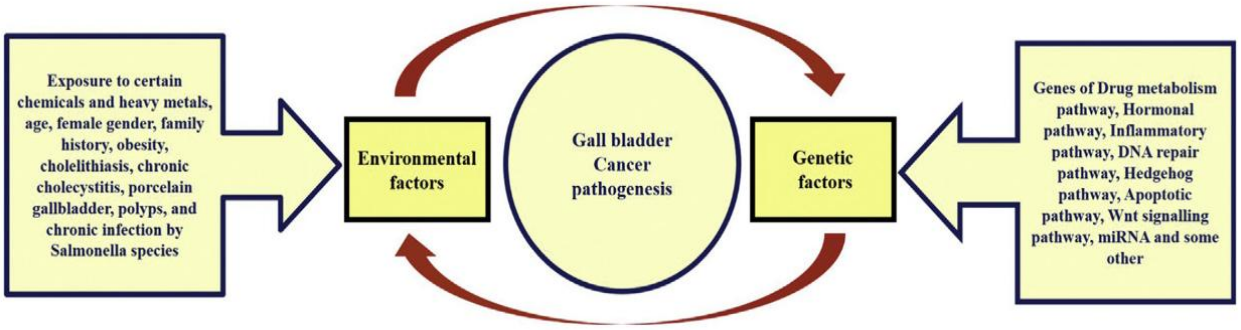


Figure 2: Factors involved in gallbladder cancer pathogenesis [48].

The number of patients with gallbladder cancers are diagnosed at an advanced stage, attributed to poor diagnosis which leads to the point where surgical resection is no longer feasible [49]. Furthermore, conventional therapeutic approaches, including chemotherapy and radiotherapy, offer only a thin line rate of survival for individuals with locally advanced or metastatic disease [50]. Consequently, the discovery and validation of novel diagnostic and prognostic biomarkers are essential for early detection and the development of more effective and targeted therapeutic processes among patients with GBC (Figure 3).

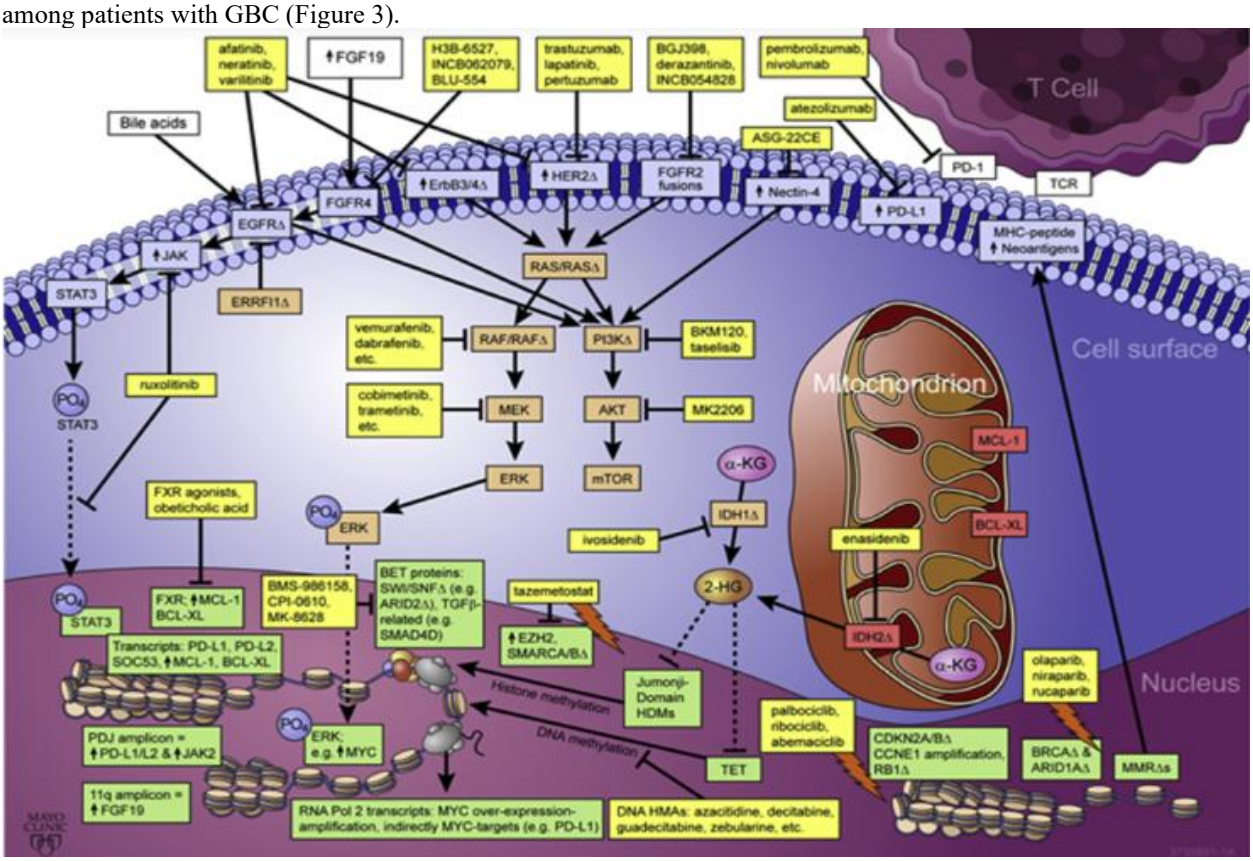


Figure 3: Gallbladder cancer carcinogenesis sequence and involved pathway [48].

Cancer antigens have been extensively employed as diagnostic tools in various gastrointestinal malignancies. With reference of gallbladder cancer (GBC), serum levels of tumor indicators such as Carcinoembryonic Antigen (CEA), Cancer Antigen 19-9 (CA 19-9), and CA 125 may be elevated, however, the diagnostic ability and specificity of these markers are still in a low range [51]. Furthermore, tumor antigen markers can be deceiving, particularly for benign gallbladder tumors. Yu et al. conducted a study on 37 patients, supposedly to have GBC based on elevated tumor

markers, but the pathological report concluded the presence of xanthogranulomatous cholecystitis [52]. Hence, Table 1 demonstrates an overview of prognostic biomarkers and their impact in GBC patient survival [53].

Table 1: Overview of prognostic biomarkers and their effect on GBC patient survival.

Biomarker	Hazard Ratio (95% C.I.)	p-value	Ref
CA 19-9 [54]	1.005 (1.002–1.009)	0.001	[54]
Combined CEA/CA 19-9 [55]	2.6 (1.8–3.6)	< 0.001	[55]
Combined VEGF-A/ER1	1.773 (1.021–3.080)	0.042	[56]
HDGF	4.298 (1.134–88.887)	0.038	[57]
Survivin	2.848 (0.959–8.463)	0.043	[58]
PTEN	0.26 (0.12–0.57)	0.009	[59]
MTA-1	3.06 (1.37–6.87)	0.007	[60]
SPOCK1	0.378 (0.164–0.871)	0.022	[61]
TSG101	3.083 (1.178–8.072)	0.022	[62]
PEG10	3.3 (1.273–8.555)	0.014	[62]
PKM2	2.68 (1.090–6.591)	0.032	[63]
ACVR 1C	0.366 (0.151–0.888)	0.026	[63]
SHP2	4.332 (1.527–12.289)	0.006	[64]
	4.62 (1.218–4.62)	0.011	
Pronomin-1	2.947 (1.447–5.718)	0.004	[65]
N-cadherin	2.664 (1.423–4.989)	0.002	[66]
ERp29	0.414 (0.189–0.92)	0.029	[67]
S1P1	4.513 (1.63–11.67)	0.004	[67]
EpCAM	2.9 (0.9–10.7)	0.005	[68]
S100A4	2.77 (1.119–6.837)	0.028	[69]
RCAS1	12.69 (1.216–132.423)	0.0337	[70]

4. Novel Nanoparticle Approaches for Gallbladder Cancer Therapy

At present, a number of cancer treatment technologies are there which are being subjected to rigorous preclinical investigation or as transition states to clinical studies. Genetic modification methods and nano-medicines are being utilized in lab-based research projects in order to trace cancer cells and to restrict their growth. Rao et al [71] proposed a single treatment strategy which is often insufficient to attain an optimal therapeutic effect in bladder cancer intervention, care and clinical management. Recent research investigations [72] demonstrate a combination therapy as a treatment strategy that utilizes several treatment interventions. Currently, a major part of the research community is integrating phototherapy with other therapeutic strategies by means of nanoparticles. Hence, the results suggest promising outcomes and validate the capability of nanoparticles in blood cancer combined treatment [73].

4.1 Nanoparticle-Assisted Photodynamic Therapy for Targeted Treatment of Gallbladder Cancer (GBC)

A noninvasive therapeutic strategy with extraordinary therapeutic efficiency has been gaining traction as a treatment for cancer [74]. It is often employed in the treatment of epithelial or superficial diseases or oncologic conditions like squamous cell skin cancer, actinic keratosis and basal cell skin cancer [75]. Antitumor treatments still show inadequate therapeutic outcomes in treating deep tumors because near-infrared (NIR) light penetrates to only limited tissue depth and is unable to penetrate enough to trigger or activate the phototherapeutic agents at the tumor site [76]. Though numerous investigations demonstrate that in order to enhance penetration depth by extending the wavelength range by shifting from NIR-I to NIR-II [77]. There is a major hurdle for the effectiveness of NIR-mediated therapies as it requires a penetration depth of more than 4 cm for the treatment of deep tumors (such as GBC) [77].

Persistent luminescence is reported in another research work to treat deep tumors which are termed ‘Stimuli-sensitive Tumor-targeted Photodynamic Nanoparticles (STPNs)’. Lanthanide-doped upconversion nanoparticles (UCNPs) show bio-imaging characteristics and have exceptional photostability leading to an improved photosensitizer efficacy, while a porphyrin derivative, Purpurin 18 (Pu18), serves as a photosensitizer to induce persistent luminescence in STPNs. NIR irradiation is utilized in order to stimulate the STPNs prior to intravenous administration and concentrate at the tumor site to penetrate the cells via HER2 receptor. As a result of the afterglow Pu18 luminescence properties, ROS can be constantly produced from STPNs to impair NFκB nuclear translocation, resulting apoptosis of tumor

cells. In addition to this, STPNs are capable of being employed for diagnostic purposes via intraoperative NIR navigation and MRI. The extraordinary and remarkable antitumor activities of STNPs integrated the strengths of persistent luminescence and UCNPs which offers a potential phototherapeutic approach for deep tumors. The design and mechanism of STPNs is illustrated in Figure 4 [78] .

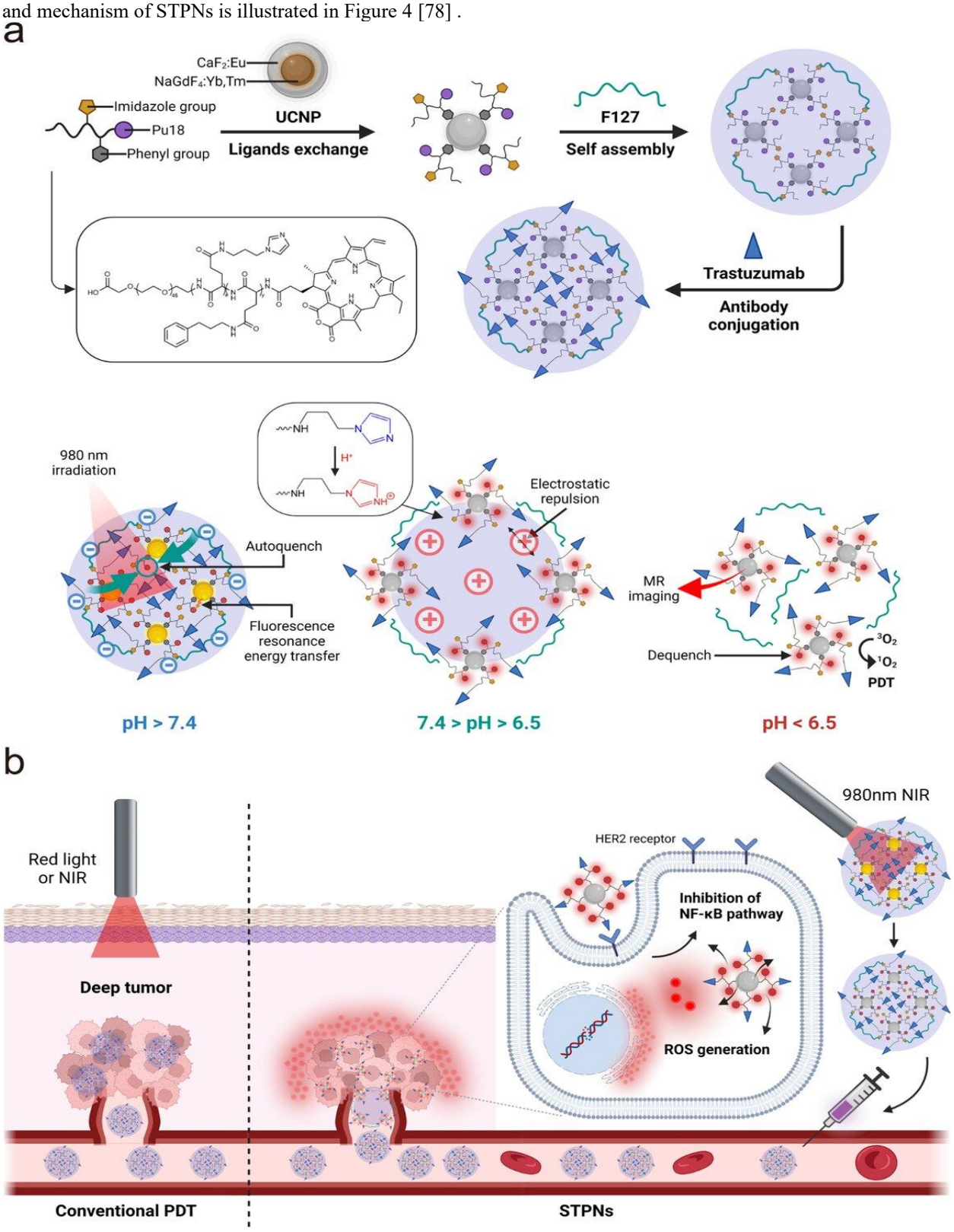


Figure 4: Design and mechanism of STPNs: a Schematic representation of self-assembled STPNs and pH-responsive mechanism of STPNs. b Schematic illustration of STPNs activation for deep tumor phototherapy [78].

4.2 Nanoparticle-Assisted Chemotherapy for Targeted Treatment of Gallbladder Cancer (GBC)

Gallbladder cancer (GBC) is rarely found cancer with extremely proliferative biliary tract malignancy, worsened prognosis linked to delayed diagnosis, elevated rates of chemo resistance and constrained treatment options and strategies [79]. Now, reduced effectiveness is found for Traditional chemotherapy (i.e. cisplatin, gemcitabine) due to systemic toxicity, drug resistance and specific distribution. In order to mitigate these limitations, a potentially effective approach, nanoparticle-assisted chemotherapy has been developed which is capable of efficient and targeted drug delivery in GBC [80].

Bortezomib (BTZ), a proteasome inhibitor displays remarkable antitumor activity in GBC. Even so, the sustained therapeutic efficacy is constrained by poor stability, high toxicity and its resistance. In a further investigation, pH-responsive BTZ-encapsulated copolymeric nanoparticles along with estrone (ES-NP (BTZ; Ce6)) GBC-focused targeted therapy is documented. ES-NP (BTZ; Ce6) are capable of entering the cells and aggregating near the nucleus by means of ES-mediated endocytosis which is because of excessive estrogen receptor presence in GBC. In case of acidic tumor microenvironment (TME) and irradiation with 808 nm laser, there is a discharge of BTZ and then ROS is released from Ce6 in order to inhibit the "bounce-back" signaling pathway proteins like p97 and DD12 which can efficiently prevent the proteasomes and enhance apoptosis. In comparison with conventional treatments utilizing BTZ monotherapy, ES-NP (BTZ; Ce6) substantially hinder the disease progression at reduced BTZ concentrations and enhances its resistance. Furthermore, ES-NP (BTZ; Ce6) exhibits comparable antitumor activities in a patient-specific xenograft models and also five additional types of solid tumor cell models illustrating its promise as a broad-spectrum antitumor formulation. Figure 5 illustrates the GBC cell interactions with different ES-NP$_{(BTZ;Ce6)}$ [81].

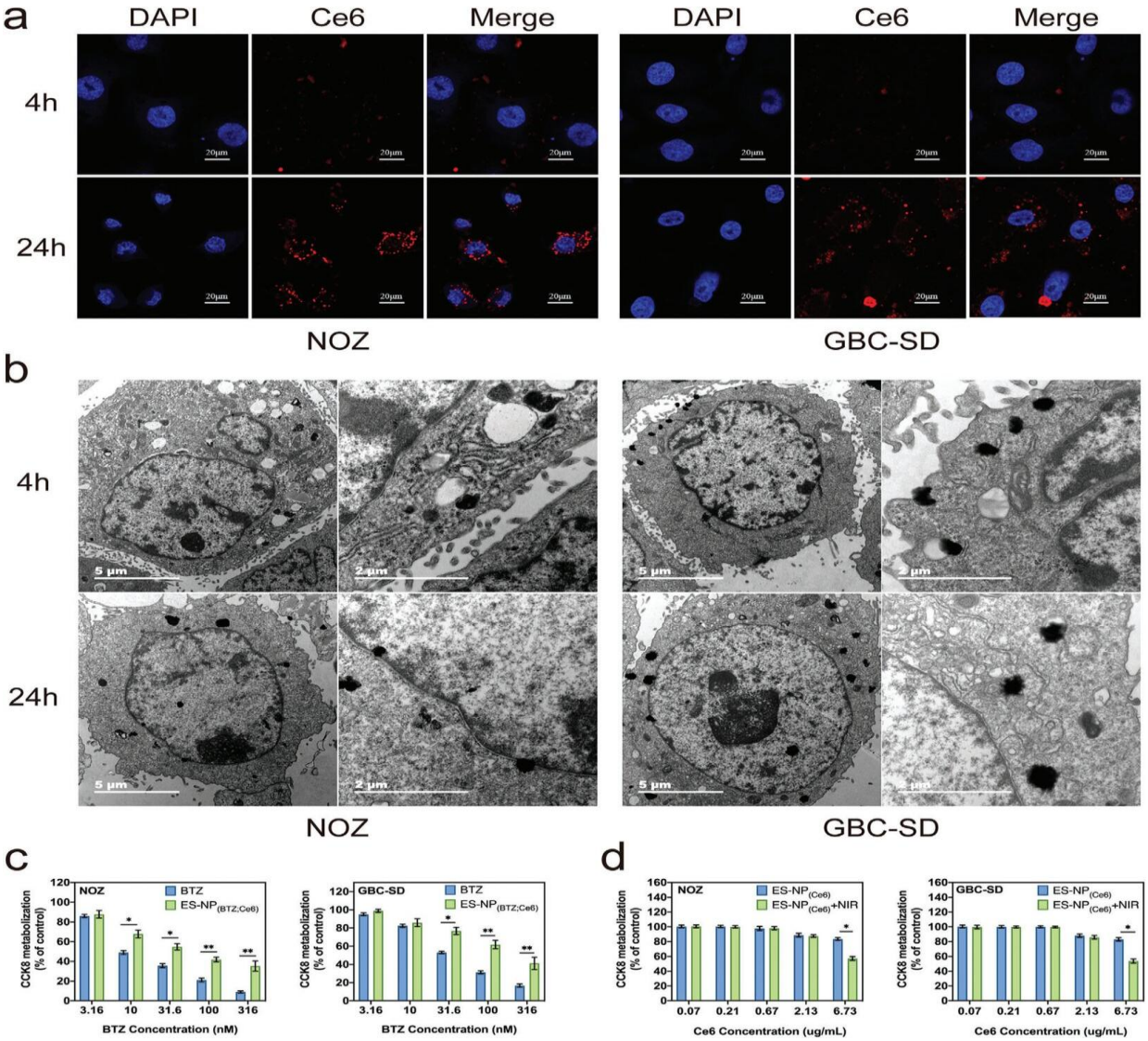


Figure 5: ES-NP$_{(BTZ;Ce6)}$ interactions with GBC cells. **a)** CLSM images to demonstrate ES-NP$_{(BTZ;Ce6)}$ cellular uptake by NOZ or GBC-SD cell sat different time points under acidic TME (pH6.5). DAPI-stained cells are shown in blue;ES-

$NP_{(BTZ;Ce6)}$ fluorescence signals are shown in red.b)Cyro-TEM images of ES-$NP_{(BTZ;Ce6)}$ cellular uptake by NOZ or GBC SD cell sat different time points under acidic TME(pH6.5).c)48h CCK-8 assays of NOZ or GBC-SD cells treated with different BTZ(equivalent to the dose loaded in ES-$NP_{(BTZ;Ce6)}$)or ES-$NP_{(BTZ;Ce6)}$ concentrations. d)48hCCK-8assaysofNOZor GBC-SD cells exposed to different concentrations of ES-$NP_{(Ce6)}$ or ES-$NP_{(Ce6)}$ with808nm laser irradiation (2Wcm^{-2} ,5min with every min interval). The data are represented as mean ± SD (n = 3).* $P < 0.05$,** $P < 0.01$ [81].

4.3 Nanoparticle-Assisted Gene-Editing for Targeted Treatment of Gallbladder Cancer (GBC)

Recently, nanomaterials have increasingly demonstrated unique benefits in gene delivery. Several nano-delivery strategies for CRISPR/Cas9 have been created, including cationic liposomes, lipid nanoparticles (LNPs), cationic polymers, vesicles, and gold nanoparticles [82].. Exosomes, the most promising non-viral nanocarrier, have the ability to efficiently delivering the CRISPR/Cas9 system both in vitro and in vivo. They serve as unique devices to increase the use of this strong gene-editing technique in the life sciences and therapeutic applications [82].

The CRISPR/Cas9 gene-editing process is unique in that it requires the co-delivery of two components, Cas9 and a single guide RNA (s). Currently, three types of cargoes are delivered (Figure 6) [83].

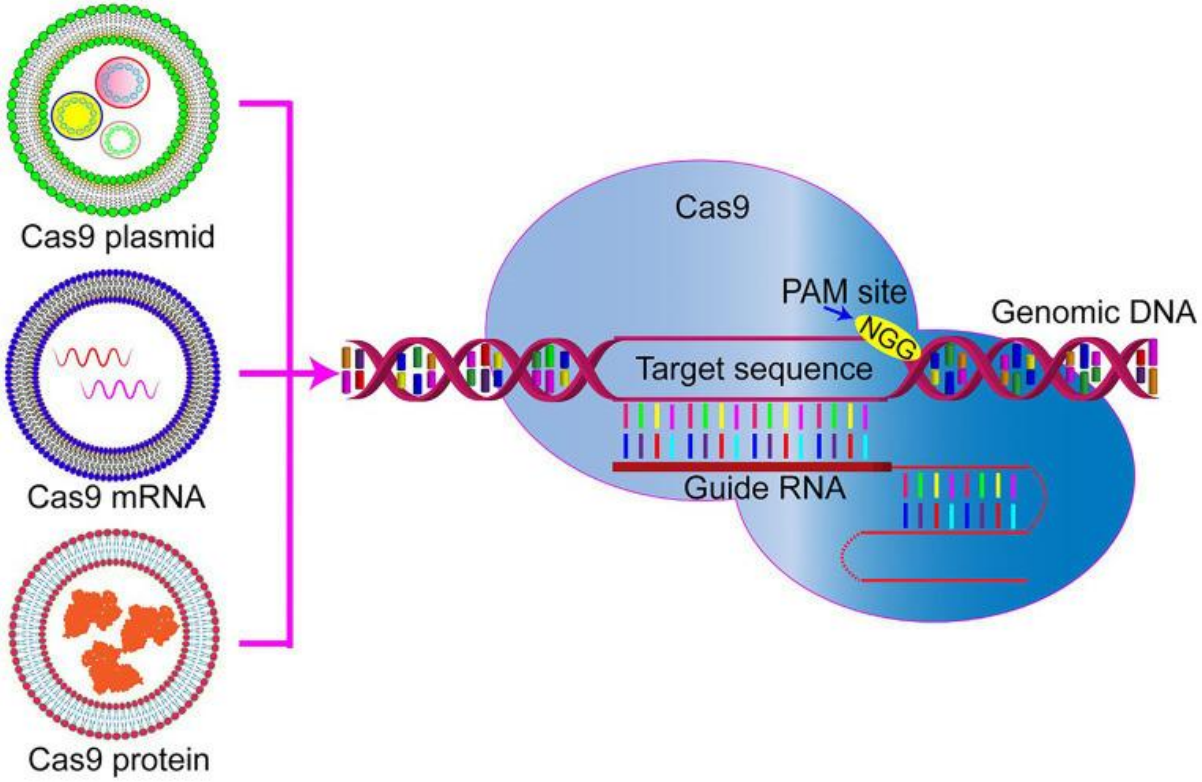


Figure 6: Representative genome editing by three forms of clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9. Cas9 plasmid DNA, RNA, or protein delivery *via* nanoparticles to be used for precise genome editing. PAM, protospacer adjacent motif [82].

4.4 Nanoparticle-Assisted Photothermal Therapy for Targeted Treatment of Gallbladder Cancer (GBC)

Near infrared (NIR) light-responsive nanomaterials have recently received a lot of interest as a developing nanomedicine for imaging, sensing, and therapeutic applications, such photoacoustic imaging (PAI) and photothermal therapy (PTT), as well as integrated theranostic applications [84]. Numerous NIR-absorbing nanomaterials, that extend from organic to inorganic nanoparticles (NPs) of various forms, have successfully demonstrated PAI and/or PTT capability in vivo. These include melanin nanoparticles, nanorods (e.g., Au), carbon nanotubes and nanosheets (e.g., Pd, MoOx, reduced graphene oxides), inorganic NPs (e.g., quantum dots, Fe_3O_4), and conductive polymer NPs (e.g., polypyrrole), among others [85]. Bilirubin (BR), a bile pigment with strong antioxidant and anti-inflammatory properties, is a primary component of black pigment gallstones seen in bile ducts under certain conditions. Inspired by the inherent metal-chelating properties of BR found in gallstones. A study described a cisplatin-chelated BR-based nanoparticle (cisPt@BRNP) for usage as a novel photonic nanomedicine for combined photoacoustic imaging and photothermal therapy of cancer. cisPt@BRNPs were created through the combination of cisplatin with BRNPs, resulting in nanoparticles of around 100 nm. Upon near-infrared laser irradiation at 808 nm, cisPt@BRNPs produced significant heat and caused cancer cells to die in vitro. Following intravenous injection into human colon cancer-

bearing mice, cisPt@BRNPs showed effective tumor visibility through photoacoustic imaging and extraordinary antitumor activity via photothermal therapy, suggesting their promise as a novel photonic nanomedicine for cancer therapy. The anticancer efficacy of cisPt@BRNPs based on PTT (shown in Figure 7) was investigated in xenograft tumor-bearing mice after a single i.v. injection of (a) saline (n = 5), (b) saline + laser irradiation (sham; n = 5), (c) cis@BRNPs (n = 5), or (d) cisPt@BRNPs + laser irradiation (n = 5) [86].

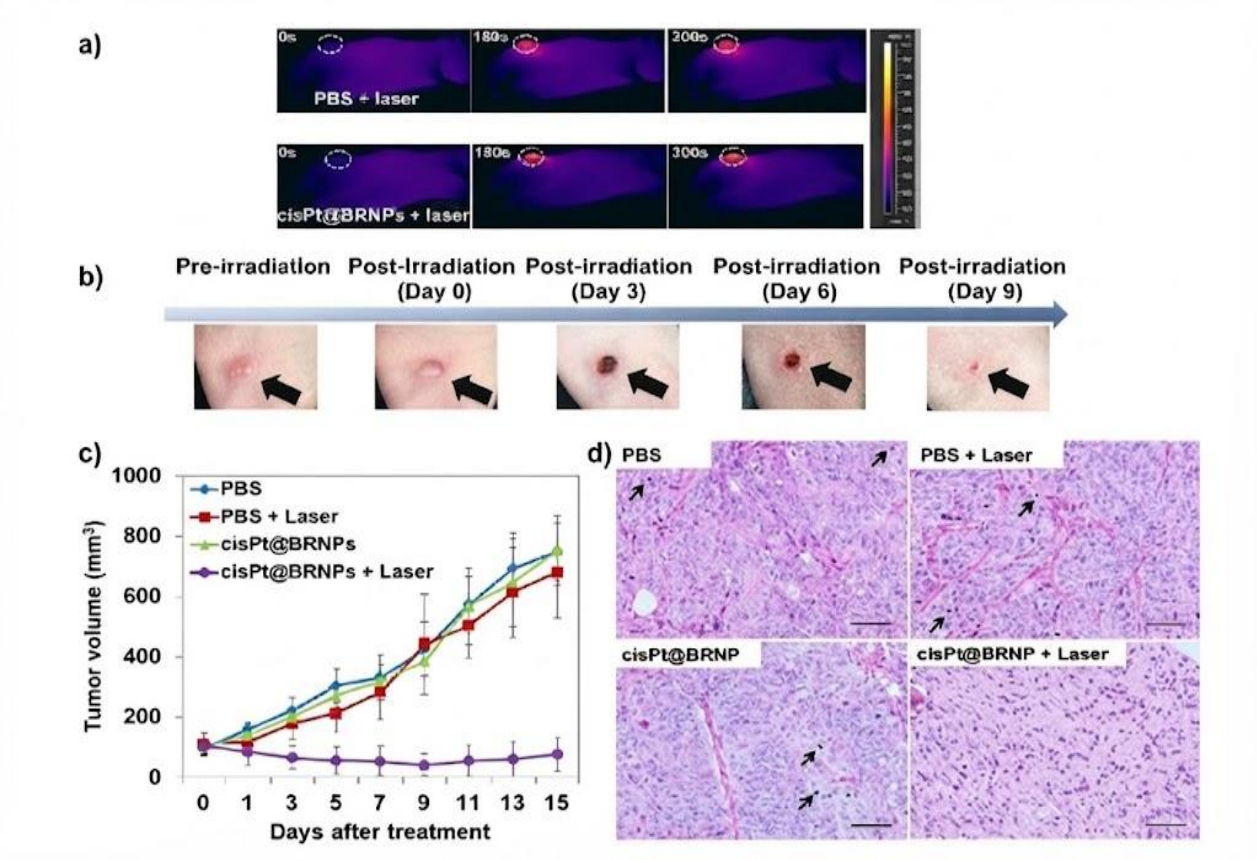


Figure 7. IR thermal images of HT-29 tumor-bearing mice 6 hours after intravenous injection of PBS (upper panel) or cisPt@BRNPs (bottom panel; PEG-BR, 15 mg kg-1; cisplatin, 1 mg kg-1), followed by irradiation (1.0 W cm-2 for 10 min). b) Illustrations of tumor shrinkage in a cisPt@BRNP-injected mouse before and after irradiation. Black arrows indicate the tumor's position. b) Tumor growth curves for each group following intravenous injection with and without irradiation. The data is presented as mean ± standard deviation (n = 5). d) H&E-stained pictures of HT-29 tumor slices from each indicated group were obtained about two weeks following therapy. The black arrows in each image represent mitotic figures in actively developing tumor cells [86].

5. CONCLUSION AND FUTURE ASPECTS

Nanoparticle-based drug delivery devices represent a promising and novel approach to improving the treatment of gallbladder cancer (GBC), an aggressive tumor with few therapeutic choices and a dismal prognosis. Nanoparticles such as gold nanoparticles, polymeric nanoparticles, liposomes, and dendrimers lower systemic toxicity while increasing the therapeutic efficacy of anticancer medications by allowing for the targeted delivery of chemotherapeutic agents directly to tumor locations. These nanocarriers not only improve medication stability and bioavailability, but they also enable regulated and stimuli-responsive release mechanisms, which are very useful in the complicated tumor microenvironment of GBC. Furthermore, the use of combination techniques, such as co-delivery of chemotherapeutic medicines with gene therapy, immunotherapy, or photothermal agents using multifunctional nanoparticles, shows significant potential for overcoming multidrug resistance and enhancing therapeutic outcomes. These cooperative methods could pave the way for more personalized and effective gallbladder cancer treatment regimens. Future research should concentrate on the creation of extremely specialized and biocompatible nanoparticle systems tailored to the molecular profile of GBC. Advances in biomarker identification and tumor-targeting ligands will be critical in improving the selectivity of these systems. Furthermore, clinical translation remains a considerable issue due to concerns about toxicity, long-term safety, reproducibility, and large-scale manufacture within regulatory limits. As a result, broad preclinical validation and clinical studies are required to determine the efficacy and safety of nanoparticle-based therapeutics in real-world applications. Theranostic nanoparticles that combine therapy and imaging have the potential for facilitating real-time monitoring and individualized treatment adjustments. As

interdisciplinary collaborations in nanotechnology, oncology, and biomedical engineering grow, nanoparticle-based strategies are likely to alter cancer care and provide new hope to gallbladder cancer patients.

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