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Exploring silver nanoparticles for cancer therapy and diagnosis

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ABSTRACT

Nanomaterials have emerged as promising candidates for cancer therapy and diagnosis as they can solve long-term issues such as drug solubility, systemic distribution, tumor acquired resistance, and improve the performance of diagnostic methods. Among inorganic nanomaterials, AgNPs have been extensively studied in the context of cancer treatment and the reported results have raised exciting expectations. In this review, we provide an overview of the recent research on AgNPs antitumoral properties, their application in different cancer treatment modalities, their potential in biosensors development, and also highlight the main challenges and possible strategies to enable its translation to clinical use.

1. Background

The World Health Organization estimates that in 2020 there were 19.3 million new cases of cancer in the world and almost 10 million deaths [1]. Despite the huge efforts and advances in cancer research, the standard treatment options remain chemotherapy, along with surgery and radiotherapy [2]. Treatment failure rates are high, mainly due to drug resistance, dose-limiting toxicity, and severe side effects [3,4]. Thus, effective strategies in cancer treatment that do not compromise patient's life quality are urgently needed. Also, to offer a good chance of recovery, early diagnosis is very important. In this regard, nanotechnology may open up new avenues for cancer therapy and diagnosis.

Nanotechnology emerges from the unique properties of materials in the nanoscale range and has a transformative potential for application in different fields of science and technology. Different types of nanomaterials have been explored to improve cancer therapy (e.g., drug nanocarriers, photodynamic therapy, gene-, and immunotherapy) and diagnostics (nanobiosensors and bioimaging agents) [5–9]. One of the main characteristics that make nanomaterials so interesting for cancer treatment is their tunable surface, which not only allows the nanoparticles to be synthesized with unique physico-chemical properties but also supports the attachment of a variety of molecules and drugs. As a consequence, these nanocarriers (NCs) may improve long-time issues such as poor drug solubility, drug metabolism, and systemic half-life [10]. In addition, NCs may enhance drug deposition in tumors by passive targeting, a phenomenon known as the Enhanced Permeability and Retention (EPR) effect [11]. The basis for the EPR effect relies on the leaky blood vessels and impaired lymphatic function of tumors, which facilitates the penetration and accumulation of NP into the tumor, compared to normal tissues [12].

Among the metallic nanomaterials, silver nanoparticles (AgNPs) stand out due to their broad range of applications. Given their unique physico-chemical properties (including optical, thermal, and electrical conductivity), as well as their activity against bacteria, fungus, and even viruses [13–16], AgNPs have been incorporated into textiles, health-care products, consumer goods, medical devices, biosensing, among others [17–22]. Most recently, AgNPs have gained a special interest in nanomedicine because several research groups reported that these NPs can induce antitumoral effects in in vitro and in vivo tumor models, which could benefit a number of oncotherapy modalities and diagnostic tools.

In this paper, we provide an overview of how the intrinsic properties of AgNPs and their potential as nanocarriers can improve current cancer therapies and diagnostics. We also present a discussion on the obstacles and possible solutions to enable the implementation of AgNPs into clinical use.

2. Antitumoral activity of AgNPs

AgNPs show great promise for cancer therapy due to their antitumoral effects demonstrated by several in vitro and in vivo studies (Table 1). Although the exact mechanisms through which AgNPs act against cancer cells are not yet fully elucidated, it is well known that their toxicity relies on the generation of reactive oxygen species (ROS) [23–27], both directly (by electron donation to molecular oxygen, generating $O_2^{\cdot}$) and indirectly (by interfering with mitochondrial structure and functions, leading to $O_2^{\cdot}$ leakage from the electron

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Table 1
Recent studies evaluating the potential of spherical AgNP as an anticancer agent.

AgNPs features			Exp. Duration	Tumor model	[c]Cell Viability (%)/IC_{50}	Antitumoral effect	Comments	Ref.
Size (nm)	[a]ZP (mV)	Surface coating						
10	-39	Citrate	24 h	Hepatocarcinoma cells (HepG2)	3.5 μg/mL: 75%	Reduction of glutathione metabolism and glycolysis-related proteins after exposure to 3.5 μg/mL	Protein levels in healthy THLE2 cells were not disturbed.	[31]
2.6 and 18	[b]*n.r*	[b]*n.r*	24 h	Pancreatic cancer cells (Panc-1)	IC_{50} 2.6 nm: 1.6 μg/mL; IC_{50}18 nm: 26.8 μg/mL	Both AgNPs sizes led to ROS increase, decreased antioxidants levels, mitochondrial damage and arrested cell cycle.	Levels of SOD1, SOD2, SOD3, GPX-4, and CAT were reduced for both NP sizes; ROS increase was lower in normal cells.	[32]
10	-30	Citrate	24 h	Hepatocarcinoma cells (HepG2)	3.5 μg/mL: 75%	Reduction of key proteins related to antioxidant defense and glucose metabolism, inactivation of NRF-2 and reduced ATP levels.	NRF-2 is a key transcription factor for the expression of antioxidant genes. Its inactivation is related to increased oxidative stress	[38]
28	-44	Citrate	24 h	Adenocarcinoma cells (Colo 205 and Colo 320)	IC_{50}Colo 205: 49.6 μM; IC_{50} Colo 320: 58.4 μM	Reduced expression and activity of PgP after 24 h at 60 μM in drug-resistant Colo 320 cells; Inhibition of proliferation after 72 and 96 h at 5 μM.		[40]
5 and 75	[b]*n.r*	Citrate	24 h	Breast adenocarcinoma cells (MCF-7/KCR)	IC_{50}5 nm: 244 μM; IC_{50}75 nm: 414 μM	Mitochondrial damage, cytochrome C release, decreased expression of PgP, ROS increase, ER stress.	5 nm AgNPs induced higher cell damages. Only 75 nm AgNP reduced PgP activity.	[46]
2	-23	Citrate	24 h	Hepatocarcinoma cells (HepG2)	3.5 μg/mL: 80%	Cytosolic and mitochondrial ROS increase;Decreased PgP functioning.		[43]
20	[b]*n.r*	[b]*n.r*		Liver and Lung adenocarcinoma cells (HepG2 and A549)	IC_{50} 72 h HepG2: 15.8 μg/cm^3; IC_{50} 72 h A549: 202.7 μg/cm^3	Decreased expression of several ABC transporter genes in both cell lines after 12 h.		[54]
40	-34.5	Biogenic (*G. biloba* leaves extract)		Cervical adenocarcinoma cells (HeLa)	4 μg/mL: 30%	Inhibition of proliferation after 36 h, at 6 μg/mL; Apoptosis, oxidative stress and cytochrome C release after 24 h, at 6 μg/mL.	Oxidative stress was marked by increased ROS, reduced SOD and GSH levels.	[45]
30 – 150	-24.5	Biogenic (*R fairholmianus*)	24 h	Breast adenocarcinoma cells (MCF-7)		Upregulation of apoptotic regulators (caspase 3 and 7), cytochrome C release, mitochondrial damage, reduction of cell proliferation and ROS increase (from 5 to 10 μg/mL).	Fibroblast cell line WS1 was more resistant to the AgNP.	[39]
74	-35.3	Curcumin derivate	30 days 15 I.P injections	EAC tumor-induced in mouse models		5 mg/kg (bw) led to inhibition of tumor growth and activation of apoptosis.	No histopathological alterations in major organs (liver, spleen, and kidney) after treatment.	[50]
9 – 25	-31.8	Biogenic (*N. linckia* pigment extract)	10 days daily I.P injections	EAC tumor-induced mouse model		5 mg/kg (bw) let to inhibition of tumor growth (tumor volume, cells count, and weight).		[51]
50	[b]*n.r*	Biogenic (*B. licheniformis*)	15 days I.P injection	DLA tumor - induced mouse model		500 nM led to a reduction in DLA cell count.	Increase of the survival time by 50%.	[52]
25	-15	PVP	10 weeks I.V injection 3 times/week	TNBC tumor-induced mice model		6 mg/kg (bw) led to significant tumor growth.	100% survival rate in AgNP-treated mice and only 30% in control groups.	[53]
[b]*n.r*	[b]*n.r*	Biogenic (*F. oxysporum)*	3 weeks I.Ve doses	Bladder cancer-induced mice		0.05 mg/mL led to 57% tumor regression.		[55]

I.P: intraperitoneal injection; I.V: intravenous injection; I.Ve: intravesical injection; bw: body weight; DLA: Dalton's lymphoma ascites; EAC: Ehrlich Ascites carcinoma; TNBC: Triple negative breast cancer; PVP: Polyvinylpolypyrrolidone.

[a] Zeta potential;

[b] *n.r*: Data not reported by the authors;

[c] Approximated values.

transport chain) [28]. ROS are by-products of the biological oxygen metabolism and include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO•) [29]. Under physiological conditions, these molecules are kept at low levels by the cell's antioxidants pool, being important in signaling pathways [29]. However, overproduction of ROS is associated with oxidative stress. The increase in the ROS levels caused by AgNPs exposure induces cytotoxicity, decreasing cell proliferation rates, inducing macromolecules and organelles damage, and ultimately leading to cell death (Fig. 1).

ROS inducers are particularly interesting for controlling cancer progression, as tumor cells generate higher ROS levels compared to healthy cells, making them more susceptible to oxidative stress-induced damage [30]. AgNPs may not only contribute to cell death by triggering ROS generation but also by interfering with the levels and activity of antioxidant molecules in the cells. It was recently reported that the treatment with 10 nm citrate-coated AgNPs resulted in downregulation of proteins related to glutathione metabolism in human hepatocarcinoma cells (HepG2), while no changes in the antioxidant pool were observed in healthy hepatocytes exposed to the same nanoparticles [31]. Consequently, higher ROS levels and cell death rates occurred for tumoral cells while the healthy ones were more resistant to the treatment. Similarly, Barcińska et al. also found that 2.6 and 18 nm AgNPs induced higher ROS levels in tumoral pancreatic cells than in normal cells from the same tissues [32]. The oxidative stress resulted from ROS increase and downregulation of antioxidants (superoxide dismutase (SOD), glutathione peroxidase, and catalase (CAT)), occurring both at protein and mRNA levels. The authors also showed that 2.6 nm AgNPs are more toxic than the 18 nm AgNPs, as the estimated IC_{50} was 1.67 μg/mL and 26.8 μg/mL for the smaller and the larger nanoparticles, respectively (Table 1). These results correlates with the fact that 2.6 nm AgNPs induced oxidative stress at lower concentrations compared to the 18 nm AgNPs. The influence of size in the ROS-induced cytotoxicity was also demonstrated by other authors [33–35]. Miethling-Graff et al., for example, showed that 20 nm AgNPs induced higher ROS levels than 100 nm ones in human LoVo colon carcinoma cell lines, which ultimately led to increased mitochondrial dysfunction and cell death [23]. In a recent study, Liu et al. reported that 20 nm AgNPs may interfere directly with CAT and SOD [36]. The authors demonstrated that AgNPs form complexes with these proteins and the interaction between CAT and the nanoparticles is strong enough to induce conformational changes in the protein structure and the loss of biological function.

AgNPs may also impair other cancer hallmarks such as energy metabolism and multidrug resistance, as demonstrated in recent studies [37–40]. Energy metabolism has gained increased attention for cancer treatment and drug design since the metabolism of tumoral cells differs significantly from that of the healthy ones; while oxidative phosphorylation is the main energy-generating pathway in normal cells, cancers are adapted for fast growth in hypoxic and acidic environments, thus glycolysis is the preferred pathway to synthesize ATP [41,42]. Lee et al. reported that exposure to 5 nm AgNPs affected negatively both glucose consumption and lactate production in HepG2 cells [37], while Miranda et al. observed, for the same cell line exposed to 10 nm AgNPs, a downregulation of key enzymes of the glycolysis pathway in hepatoma cell lines [36]. Moreover, AgNPs are also known for their deleterious action over mitochondria and the mitochondrial respiratory chain, which not only cause electron leakage and O_2^- generation but also triggers apoptosis pathways (via cytochrome c release and caspase activation), hindering another crucial ATP generating pathway [27,39,43–45]. These features might be useful for AgNPs to impair cancer cells

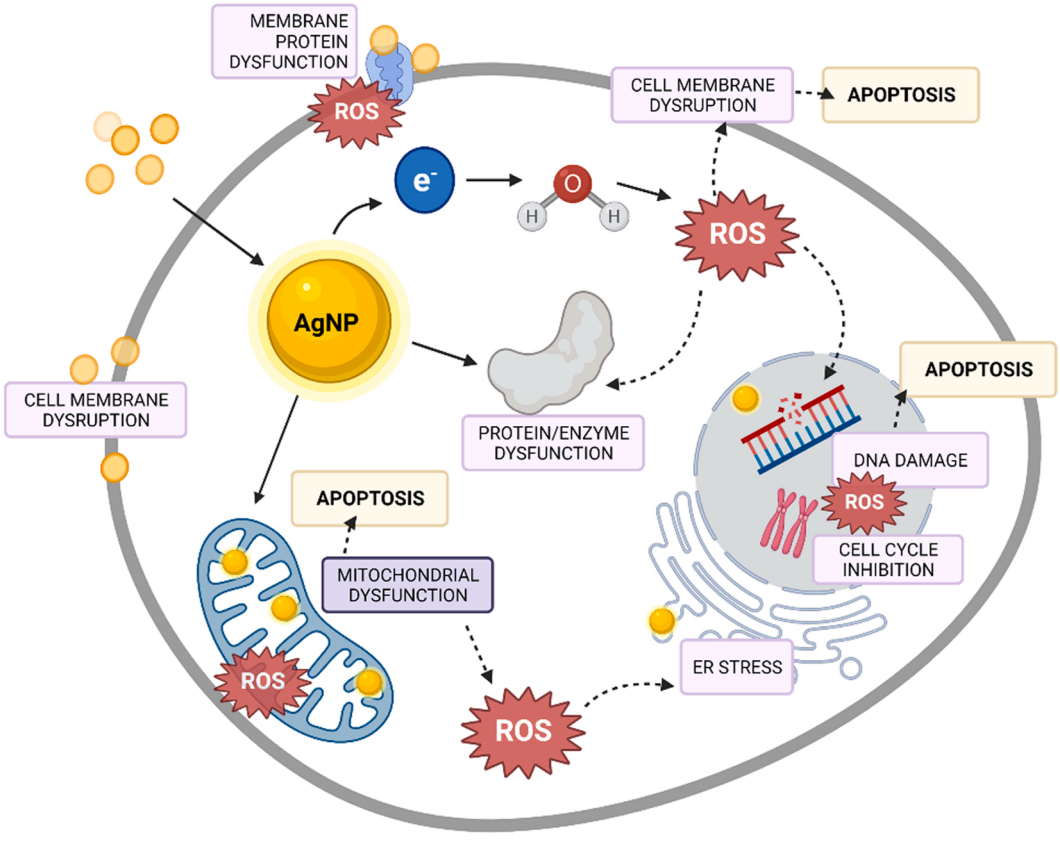

Fig. 1. The interaction of AgNPs with cellular membranes, macromolecules, and organelles results in structural and functional disruption. AgNPs also lead to excessive ROS production, which interacts with cellular components leading to lipid peroxidation, genomic damages, and protein oxidation. Consequently, several signaling pathways and cell functions are disturbed, resulting in reduced cell viability and proliferation, as well as increased apoptosis rates. Figure created with BioRender.com.

bioenergetics and trigger cell death.

AgNPs also interfere with the expression and activity of multidrug resistance (MDR) transporters in breast and colon MDR-cancer cells [40,43,46,47]. MDR transporters are membrane efflux pumps that belong to the ATP-binding cassette (ABC) transporter family (including PgP, MDR1, ABCB1) [48]. Cancer cells in which these proteins are overexpressed may develop chemoresistance, which is a major hurdle in chemotherapy, since the internalized drugs are pumped back to the extracellular environment [48]. The mechanisms by which AgNPs interfere with MDR are not fully elucidated; it is not clear whether AgNPs hinder the activity of the transporters by their direct contact with the proteins, or indirectly, as a consequence of oxidative stress or reduced ATP production. Thus, more studies are needed to confirm how these nanoparticles effectively contribute to overcome drug resistance, one of the main reasons for chemotherapy failure [49].

As displayed in Table 1, antitumoral effects of AgNPs in solid tumors of animal models have also been reported [50,51]. Sriram et al. showed that biologically synthesized AgNPs (intraperitoneally injected) significantly increased the survival rates and reduced the number of malignant cells in Dalton's lymphoma ascites tumor-bearing mice. The dose used

Table 2
Studies evaluating the potential of spherical AgNP as a combinatorial partner or NC system to traditional chemotherapy drugs.

AgNPs features			Drug	[c]Type of exposure	Exp. Duration	In vitro tumor model	[d]Cell Viability (%)/IC_{50}	Comments	Ref.
Size (nm)	[a]ZP (mV)	Surface coating							
28	-44	Citrate	Methotrexat, Cisplatin, Carmustine, Bleomycin, Vinblastine, Verapamil	Combination	24 h	Adenocarcinoma cells (Colo320)	MTX (500 μM): 75% NP (20 μM): 75% MTX+NP: 15% CAR (100 μM): 95% NP (20 μM): 75% CAR+NP: 10% VER (10 μM): 80% NP (20 μM): 75% VER+NP: 15%	AgNPs and all tested drugs decreased cell viability of Colo 320 cells in a synergic manner, even with lower AgNPs concentration (20 μM), possibly due to PgP expression and activity.	[40]
10	-39	Citrate	Cisplatin	Combination	24 h	Hepatocarcinoma cells (HepG2)	CIS (10 μM):75% NP (3.5 μg/mL): 75% CIS+NP: 50%	The combination of AgNPs and CIS led to reduced levels of glycolytic proteins and antioxidants in HepG2; Healthy THLE2 cells were more resistant to therapy.	[31]
20	[b]*n.r*	Biogenic *Bacillus clausii*	Salinomycin	Combination	24 h	Ovarian cancer cells (MDA-MB-231)	SAL (3 μM): 75% NP (4 μg/mL): 75% SAL+NP: 20%	Strong synergic effect of AgNPs and SAL; cytotoxicity, expression of pro-apoptotic genes, and mitochondrial dysfunction.	[60]
6	-21	[b]*n.r*	Gemcitabine	Combination	24 h	Ovarian cancer cells (A2780)	GEM (50 nM): 75% NP (50 nM): 75% GEM+NP: 30%	Synergic effects on viability, proliferation and ROS, expression of pro-apoptotic genes, DNA fragmentation.	[59]
2	23	PEI	Paclitaxel	Conjugation	24 h	Hepatocarcinoma cells (HepG2)	NP (2.5 μg/mL): 70% NP@PTX: 60%	Synergic effects on cell viability, apoptosis, proliferation, and ROS on HepG2 cells; NC was less cytotoxic to LO2 cells.	[62]
14.5 18.6 20 21	-12 -0.3 -2.3 -12	Bare PVA PEG PVP	Doxorubicin	Conjugation	48 h	Breast adenocarcinoma cells (MCF-7)	IC_{50} DOX: 3.7 μg/mL IC_{50} NP-PVP: 30 μg/mL IC_{50} NP-PVP@DOX: 0.1 (DOX) and 3.5 (NP)	NP-PVP@DOX NC was the most effective system and led to a strong synergic cytotoxicity in MCF-7 cells; Healthy fibrobaststs were more resistant.	[63]
130	-10	Biogenic *E. procera* leaves extract	Imatinib	Conjugation	24 h	Breast adenocarcinoma cells (MCF-7)	IC_{50} IMAB: 3 μg/mL IC_{50} NP: 9.6 μg/mL IC_{50} IMAB+NP: 1.7 μg/mL	Synergic effects on cell viability, expression of pro-apoptotic genes and apoptosis.	[67]
35	-44.4	Citrate	Trichostatin A	Combination	72 h	Cervical cancer cells (HeLa)	TSA (60 nM): 60% NP (8 μM): 60% TSA+NP: 10%	Synergic effects on cell viability, oxidative stress, DNA damage, and apoptosis.	[65]

MTX: Methotrexat; CAR: Carmustine; VER: Verapamil; CIS: Cisplatin; SAL: Salinomycin; GEM: Gemcitabine; PTX: Paclitaxel; DOX: Doxorubicin; IMAB: Imatinib; TSA: Trichostatin A; PVP: Polyvinylpyrrolidone; PVA: Poly(vinyl alcohol); PEG: Polyethylene glycol.

[a] Zeta potential;

[b] *n.r*: Data not reported by the authors;

[c] The exposure is either a combination of AgNPs and the drug, or the drug is conjugated to AgNPs, forming a NC system;

[d] Approximated cell viability values.

for the experiments was safe for control mice [52]. Swanner et al. reported that intravenous delivered AgNPs were effective in reducing tumor growth in triple-negative breast cancer xenografts in mice, at non-toxic doses [53]. The authors also reported a 100% survival rate of the AgNPs-treated mice group, whereas only 30% of animals in the control group survived.

3. The synergic combination of AgNPs and chemotherapy drugs

Combination chemotherapy refers to the administration of two or more drugs that target different cancer hallmarks to generate a synergic toxicity. This strategy can potentially enhance therapeutic efficacy, minimize drug resistance and side effects [56]. However, complicated dosage regimes, spatiotemporal delivery limitations, and differences in the pharmacokinetic and physicochemical properties of the drugs may affect the treatment's success rates in many cases [3,4]. Nanotechnology may offer a possibility to overcome these obstacles. Nanocarrier systems (NCs) are designed to transport clinically approved anticancer drugs to address drug solubility issues, increase circulation times and allow controlled drug release. In addition, NCs can also promote drug accumulation at the tumor site through passive (EPR effect) or active targeting [57,58].

Several research groups have investigated the potential of AgNPs as a combinatorial agent to act synergically with clinically approved chemotherapeutic drugs (Table 2). It has been shown that AgNPs may exert synergic toxicity upon combination with several antineoplastic drugs. Kovács et al. analyzed the potential of 28 nm, citrate-coated, AgNPs to increase the toxicity induced by anticancer agents (such as verapamil, cisplatin, carmustine, and methotrexate) and described a synergic toxicity for all tested combinations against MDR colon adenocarcinoma cancer cells [40]. The authors argue that the synergic interactions are related to the inhibitory action of the AgNPs to the efflux transporters activity and PgP proteins expression, leading to the intracellular accumulation of the cytotoxic drugs. AgNPs (citrate-coated, 75 nm) may also sensitize doxorubicin-resistant breast cancer cells: in the presence of AgNPs, lower concentrations of doxorubicin (DOX) are required to reach the IC50, compared to treatments with DOX alone [46]. The authors showed that the decreased function of PgP transporters possibly resulted from the endoplasmic reticulum stress induced by AgNPs (150 μM), which led to a reduced number of properly folded PgP proteins in the plasma membrane. AgNPs were also effective to enhance the responsiveness of human ovarian cancer cells to gemcitabine and salinomycin, [59,60]. Co-exposure of AgNPs and cisplatin induced a synergic toxic effect against HepG2 cells. The underlying molecular mechanisms induced by this combination, investigated by mass spectrometry-based proteomics, involved energy metabolism disruption, inhibition of cell proliferation pathways, oxidative stress, and increased cisplatin intracellular accumulation; although healthy hepatocytes were also affected, these cells were more resistant to treatment, possibly due to the increased level of antioxidant proteins found after co-exposure [31].

The potential of AgNPs as NCs for antineoplastic drugs has been demonstrated in vitro (Table 2). Benyettou et al. reported that AgNPs can be functionalized with alendronate (Ald) and DOX [61]. The system was efficiently endocytosed by HeLa cells and proliferation assays indicated that the treatment with the NCs for 48 h was more effective to reduce cell proliferation compared to Ald, AgNP-Ald, and DOX alone. Li et al. developed polyethylene imine (PEI)-based NCs combining AgNPs and paclitaxel, a potent anticancer drug that has limited usage due to its high hydrophobicity. The authors found that the nanosystems were more cytotoxic to HepG2 cells than to the healthy hepatocyte cell line LO2, and that the underlying molecular mechanisms involved the activation of caspase-3-mediated cell apoptosis via ROS generation [62]. Tumor specificity has also been reported for AgNP-DOX NCs, as developed by Elbaz et al. [63]. The drug was attached to AgNPs with different coatings (PEG, PVA, and PVP), and cell viability analysis revealed that the treatment using NCs at low concentrations resulted in high cytotoxicity against breast cancer MCF7 cells, while normal fibroblasts 1BR hTERT cells were more resistant to AgNP-DOX combinations [63].

Silver NCs may also be used to deliver and act synergically with cancer small molecule inhibitors (Table 2). For example, the histones deacetylases inhibitors (HDACis), which represent a promising class of molecules for cancer therapy. The HDACis activity can induce different biological outcomes in cancer cells such as apoptosis and suppression of cell proliferation. Moreover, the use of HDACis causes hyperacetylation of the chromatin, resulting in opened chromatin structure, turning the DNA more vulnerable to damaging agents [64]. Igaz et al. studied the biological outcomes of the combination of AgNPs and the HDACis - Trichostatin A, which resulted in a synergistic inhibitory effect in HeLa cells, affecting cell viability, proliferation, and migration [65]. The possible molecular mechanisms associated with these outcomes are increased ROS levels and double DNA strand breaks. Gurunathan et al. showed that the combination of AgNPs and HDACis-MS-275 is also effective. The authors found that the combined treatment leads to high cytotoxicity due to cell membrane disruption, oxidative stress, mitochondrial damage, and apoptosis [66]. Shandiz et al. demonstrated another successful example of silver nanocarriers for anticancer molecules [67] upon developing green synthetized AgNCs systems for imatinib, a kinase inhibitor currently used for chemotherapy against different cancer types. The authors reported that the use of NCs significantly reduced the viability of MCF-7 cells, compared to the cytotoxic effects caused by isolated AgNPs or imatinib. AgNPs are promising agents capable of improving combination chemotherapy, since they may act as active vehicles for anticancer drug delivery; however, in vivo studies are necessary for a deeper understanding of the systemic outcomes, metabolism, bioaccumulation, and long-term effects of AgNPs combined with anti-cancer drugs in the body.

4. AgNPs and radiotherapy

Recent in vivo and in vitro studies have highlighted the ability of AgNPs to enhance cell/tissue sensitivity to radiotherapy (RT). This oncotherapy modality is based on the interaction of ionizing energy (such as γ-ray, X-ray photons, or charged particles) with biomolecules to eliminate tumor cells. RT is a standard adjuvant treatment for many cancers and is currently administered in approximately 50% of all cancer patients [68]. However, its main drawbacks rely on tumor-acquired resistance, lack of selectivity, and dose escalation, which is limited due to severe side effects associated with ionizing radiation [69–71].

One of the main properties that renders AgNPs an increasing interest as radio sensitizers is their high atomic number (Z). High-Z elements possess high electron density around the central atom, therefore ionizing radiation can result in increased ionization and cross-section with biomolecules [72,73]. Similar to other high Z-number atoms [69], the interaction of AgNPs with X-ray photons results in the release of secondary electrons. These electrons either interact directly with the DNA, causing DNA double-strand breaks [74,75], or ionize water molecules to produce ROS, which can cause further damage (such as to the DNA, lipid peroxidation, ER stress, and mitochondrial dysfunction), leading to cell death [76,77] (Fig. 2A).

One of the pioneer's studies investigating AgNPs as potential radiosensitizers showed a size-dependent enhancement of the irradiation doses cytotoxicity in different glioma cell lines; the radiosensitizing effect of AgNPs decreases as particle size increases, 20 nm AgNPs performed better than 50 and 100 nm nanoparticles. The authors attributed this outcome to the release of silver ions from the particles, since smaller AgNPs tend to release more Ag^{+} ions [78]. Liu et al. investigated the in vivo radiosensitizer effect of AgNPs (PVP-coated, 21 nm, −15 mV) in C6 rat glioma models. Data showed that the combination of intratumorally injected AgNPs and radiotherapy (10 Gy) resulted in a better antitumor effect in terms of survival and cure rates compared to irradiation alone;

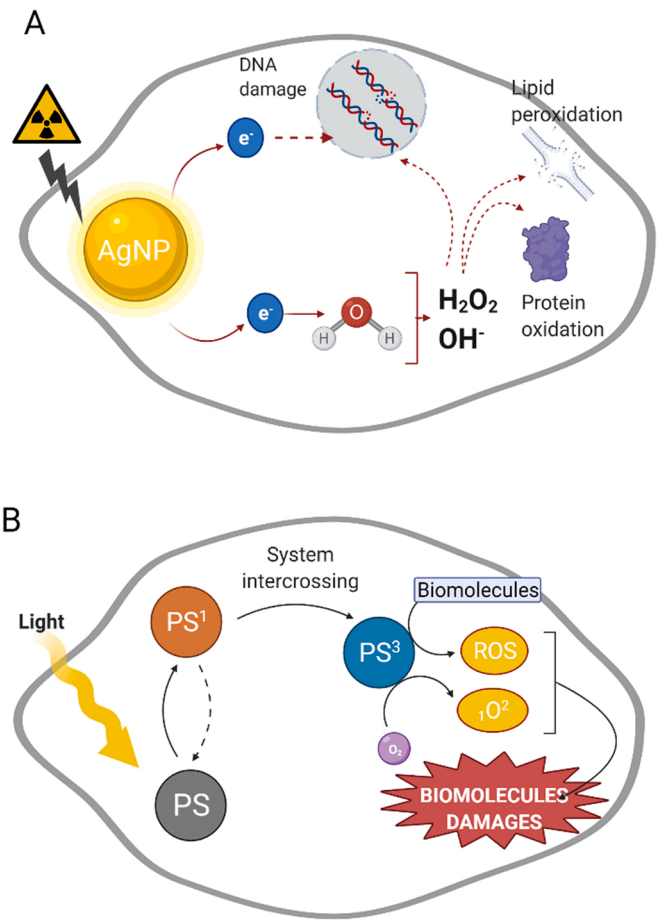

Fig. 2. (A) Schematic illustration of the proposed mechanism for radiotherapy in cells using AgNPs. Under ionizing radiation, high Z-elements such as AgNPs, releases secondary electrons that interact with cellular components, leading to biomolecules damages and cell death. (B) Schematic illustration of the proposed mechanism of PDT reaction in cells. Upon light irradiation, the PS undergoes physical changes, generating ROS in the presence of oxygen. According to recent studies, AgNPs may also act as a PS itself or as a NC. Figures created with BioRender.com.

the mean survival rate of irradiated controls was 24.5 days, while for animals treated with 10 μg of AgNP, followed by 10 Gy, was 100.5 days. It was also shown that the combination of AgNPs and ionizing radiation reduces tumor proliferation and increases apoptotic rates [79]. A comparison of PVP-coated AgNPs (27 nm) in normoxia and hypoxia in glioma cell lines revealed that the radiosensitizing performance of AgNPs in the hypoxic glioma cells was greater than cells kept in normoxia [80]. This result was attributed to higher apoptotic levels and destructive autophagy exhibited by the cells.

Stimulation of cancer cells with AgNPs in conjunction with ionizing radiation was also investigated for other cancer types. Habiba et al. investigated the effect of PEGylated silver nanoprisms as radiosensitizers on colorectal cancer, both in vitro and in vivo [81]. The authors demonstrated that the enhanced radiosensitization of silver nanoprisms in vitro was associated with increased ROS levels and DNA damage. For the in vivo experiment, tail-vein injection of 56 μg of AgNP followed by a single dose of 10 Gy, was ca. 175% more effective in inhibiting tumor growth compared to radiation therapy alone in nude mice bearing HCT116 tumors. Spherical AgNPs (130 nm, PVP-coated, 1 μg/mL) combined with ionizing radiation (1 – 6 Gy) were also effective against triple-negative breast cancer cell lines (TNBC), while non-tumorigenic breast cells were more resistant; the strategy (intratumorally injected AgNPs 0.2 μg/mm^3 tumor volume, combined with 4 Gy) also improved radiotherapy in mice TNBC xenografts [82].

Taken together, the studies cited above provide important evidence that AgNPs are promising agents to improve radiotherapy, not only because the nanoparticles act as radiosensitizers, releasing secondary electrons (increasing the damage of intracellular radiation), but also because they reduce cell proliferation and increase apoptosis and autophagy. Novel studies elucidating the detailed mechanisms through which AgNPs lead to radiotherapy enhancement and their effect in different types of cancer are necessary to allow their clinical application.

5. AgNPs and phototherapies

Photodynamic therapy (PTD), a type of phototherapy, is a medical non-invasive strategy for therapeutic purposes that has been successfully applied in cancer therapy due to its low toxicity, minimal invasiveness, and improved patient life quality [83–86].

Fig. 2B shows a schematic illustration of a typical PDT reaction. Briefly, this strategy is based on the accumulation of a photosensitizer (PS) in the tumor tissue. Upon local exposure to light at an appropriate wavelength, the PS achieves an excited singlet state (PS^1), which decays to the ground state or undergoes system intercrossing, forming a triplet state (PS^3). This molecule can induce irreversible cell damages either indirectly (by transferring a proton or electron to biomolecules forming a radical, which reacts with O_2 to produce ROS) or directly (PS^3 energy is transferred to O_2, leading to the formation of singlet oxygen), resulting in cell death [84,87]. However, many factors limit a wider application and efficacy of PTD such as the poor PS solubility, its concentration and localization in the tumor site at the time of irradiation, the time between PS administration and light irradiation, light fluence rate, tumor type, and its oxygenation level [84,86].

The application of nanoparticles in PDT has been a major evolution in overcoming some of the challenges associated with conventional photosensitizers [73]. Metal nanoparticles, for instance, can be designed as a PS delivery system, improving their biodistribution in physiological media or even acting as a PS [87]. To date, a few studies highlighted the potential applications of AgNPs in PTD.

Erdogan et al. investigated the potential of the green synthetized AgNPs (ca. 100 nm, +32 mV) as a PS system in the breast cancer cell line MCF-7. The authors reported a significant cell viability reduction of irradiated cells (0.5 mJ/cm^2) pre-treated with a non-cytotoxic concentration of AgNPs (10 μg/mL), while the viability of cells only irradiated or only treated with AgNPs was kept at control levels. Moreover, the AgNPs treated cells also exhibited a decreased activity of antioxidant enzymes, increased ROS, and apoptosis levels [88]. A multifunctional nanosystem based on AgNPs has been developed by Srinivasan et al. aiming at delivering DOX and PDT. The results highlighted the potential of AgNPs (70 nm, PEG-coated) to act as PS upon irradiation with NIR laser exposure of 808 nm at a fluence rate of 6.7 W/cm^2 [89]. Habiba et al. demonstrated that treatment with quantum dots-decorated AgNPs (33 nm) led to a drastic concentration-dependent (75 – 200 μg/mL) cell viability reduction of cervical (Hela) and prostate (DU145) cancer cells, upon irradiation with 425 nm LED (3 mW/cm^2) for 15 min [90]. It was also demonstrated that the AgNPs may enhance the photosensitization effects of riboflavin, 5-aminolevulinic acid, and hypocrellin B, resulting in increased cell death [91–93].

AgNPs exhibit surface plasmon resonance (SPR), an important optical property that consists of the collective oscillation of electrons in the conduction band after the incidence of a photon at a resonance frequency. This feature is very interesting for photothermal therapy (PTT), because plasmonic nanomaterials can be delivered to tumors and exposed to light at the resonant frequency so that the collective oscillation results in heat production. Consequently, the increased tumor temperature leads to cell death, a process known as photo-hyperthermia [94]. Unlike PDT, PTT does not require oxygen to kill cancer cells, which may be particularly interesting for cancers with poor oxygenation. Moreover, the radiation used for exciting the photothermic materials is

in the near-infrared region (NIR), therefore, is less harmful to healthy cells than that used in PDT [95–98]. Although gold-based nanoparticles are the most explored materials for PTT [99], recent studies have shown that this strategy may also benefit from the use of AgNPs. In a pioneer study, Boca et al. designed chitosan-coated silver nanotriangles (AgNT) that exhibited high specificity to human non-small lung cancer cells (NCI-H460). After pre-incubation with 0.39 μg/mL AgNT, the viability of cells irradiated at 800 nm laser (50 W/cm^2) reduced about 80%, while the viability of cells pre-incubated with gold nanorods and subjected to NIR stimulation, reduced only 20% [100]. AgNPs with triangular shape are also effective agents for photothermal therapy against both breast cancer cells (MCF7), and treatment-resistant triple-negative (MDA-MB-231) breast cancer cells, as treatments with concentrations above 50 μg/mL AgNT, followed by irradiation at 800 nm laser (2.94 W/cm^2) [101]. Hexagonal-shaped AgNPs stimulated with NIR light were also efficient to generate heat [102], and could be further explored in cancer therapy. In the latter studies, AgNPs were designed with unique morphologies, which caused a shift of the optical absorption from 400 nm (for spherical AgNPs) to the infrared region, making the nanomaterial ideal for PTT. Although they show the potential of AgNPs as an efficient light-to-heat converter, this field remains largely unexplored as more studies are needed to support these findings and to investigate whether other types of cells and in vivo cancer models can benefit from this strategy.

6. The use of AgNPs in biosensing

AgNPs are very attractive materials for application in diagnosis due to their high conductivity, catalytic activity, and plasmonic properties that can be exploited to improve the performance of biosensors. The sensitivity of the biosensors is a crucial factor for the detection of low concentrations of an analyte. AgNPs have been employed to increase the electroactive area of the electrodes and consequently the electron transfer rate, thus enhancing the biosensor's sensitivity. For this purpose, Douaki et al. modified silver screen-printed electrodes with AgNPs and showed that the electroactive area increased from 0.47 to 1.01 cm^2. These electrodes were functionalized with aptamers and used for the detection of furaneol, a widely used flavoring agent, obtaining a good analytical performance in the range from 2 pM to 200 nM [103]. Aiming to develop a highly sensitive electrochemical biosensor for the detection of exosomal miRNAs, Cheng et al. used functionalized-AgNPs for double signal amplification. First, a hairpin immobilized onto electrode is opened by the target miRNA which is displaced when a biotinylated hairpin is added. The second step consisted of the binding of AgNPs modified with streptavidin to the biotin on the electrode surface. This biosensor exhibited a lower limit of detection of 0.4 fM for miRNA-21 in human biological samples [22]. Based on a similar strategy, Li et al. developed a biosensor for alpha-fetoprotein-L3 detection by using functionalized AgNPs to label the target captured by the electrode, amplifying the signal to increase the sensitivity of the system [104].

For electrochemical biosensors, AgNPs are especially interesting to be used as redox mediators, since they exhibit a well-defined oxidation peak in buffer solution [105]. Feng et al. developed a biosensor for the detection of a leukemia-related gene using a structure generated in the presence of the DNA target as a template for the in-situ synthesis of AgNPs. As consequence, an electrochemical signal is generated. By using the differential pulse voltammetry technique, the authors demonstrated a linear relationship between the oxidation current produced by the AgNPs and the logarithm of the target concentration [106]. Although the oxidation peak of AgNPs is promising to monitor the biorecognition reactions on the electrode surface, the current produced by them alone is low, making it difficult to detect low concentrations of the analyte [107]. To overcome this limitation, many studies have proposed the association of AgNPs with other materials to obtain a synergic effect, increasing the oxidation current [108]. Recently, Zhao et al. reported a nanocomposite formed by Fe-based metal-organic frameworks (Fe-MOFs) decorated with AgNPs as an efficient redox mediator. Due to their porosity, MOFs can be coated with a large amount of AgNPs, resulting in an amplified oxidation current. The functionalized nanocomposite was applied for the detection of carbohydrates indicated as tumor biomarkers [107]. In another study, Xu et al. developed a hybrid nanostructure containing AgNPs deposited onto multi-wall carbon nanotubes (MWCNTs) as a non-enzymatic electrochemical sensor to determine H_2O_2 concentration. Also benefiting from the excellent conductivity of the MWCNTs, this nanocomposite exhibited a great electrocatalytic activity toward H_2O_2 [109].

The SPR property exhibited by AgNPs is also widely explored in biosensors [110,111]. Since the SPR band is influenced by the nanoparticle's size and the dielectric constant of the surrounding medium, the position and intensity of the band can be monitored to determine the analyte biorecognition. Upon exploring the SPR features of AgNPs, Mohammadi et al. proposed the use of AgNPs coated with thiomalic acid (TMA-AgNPs) to detect cystamine, a neuroprotective molecule. The authors demonstrated that as the cystamine concentration is increased, the intensity of the SPR band at 395 nm decreases and a new absorption band is observed around 560 nm. This phenomenon occurred due to the cystamine binding to two TMA-AgNPs, causing aggregation [112]. Varghese et al. reported the use of green synthesized AgNPs for application in SPR-based biosensors. To prove the sensing potential, the absorption spectrum of the AgNPs was evaluated after the addition of different concentrations of mancozeb, a widely used pesticide. A blue shift in the SPR band was observed and a linear relationship between the band position and the mancozeb concentration was achieved [111].

AgNPs are also attractive to be applied in colorimetric biosensors since these nanoparticles may undergo a shift in the SPR band resulting in color changes of the suspensions. Dewangan et al. have used AgNPs modified with cholesterol oxidase (ChOx) as colorimetric probes for cholesterol detection. The system was based on the oxidation of free cholesterol by ChOx which resulted in the production of hydrogen peroxide (H_2O_2). The generated H_2O_2 oxidizes the AgNPs (Ag^0) to Ag^+, causing a color change in the solution from yellow to colorless [113]. Chen et al. reported the development of modified AgNPs for the detection of human telomerase activity. AgNPs were conjugated to telomerase binding substrates partially hybridized with the complementary DNA strand. When the active telomerase binds to its domain, the conjugate stability is increased, reducing salt-induced aggregation, so that the color of the solution remains yellow. However, if telomerase is inactive, the conjugates aggregate, which results in the color change from yellow to gray [114]. These studies show how the physical-chemical properties of AgNPs have been explored in the development of different types of biosensors, especially for biomedical applications, contributing to the point-of-care diagnosis of several diseases. These methodologies can be used to detect cancer biomarkers, aiding early diagnosis, which is important to define the best treatment and to increase the chances of recovery for cancer patients. Fig. 3 summarizes the applications of AgNPs in biosensors.

7. The safe use of AgNPs in oncotherapy

Despite the efforts of many research groups to investigate and develop silver nanomaterials to improve oncotherapy modalities, its translation into clinical applications has not yet occurred. One of the main reasons for this drawback is related to the biosafety aspects of using AgNPs in humans and how to avoid harmful and unwanted side effects.

It is important to understand the molecular mechanisms underlying the possible AgNPs interactions with biomolecules and cells, as well as the pharmacokinetic parameters, such as absorption routes, tissue biodistribution, bioaccumulation, long-term effects, metabolism, and nanoparticles excretion. The challenges, however, are more complex than that of small molecules [115], because all these factors are highly dependent on the particles physico-chemical properties, which are

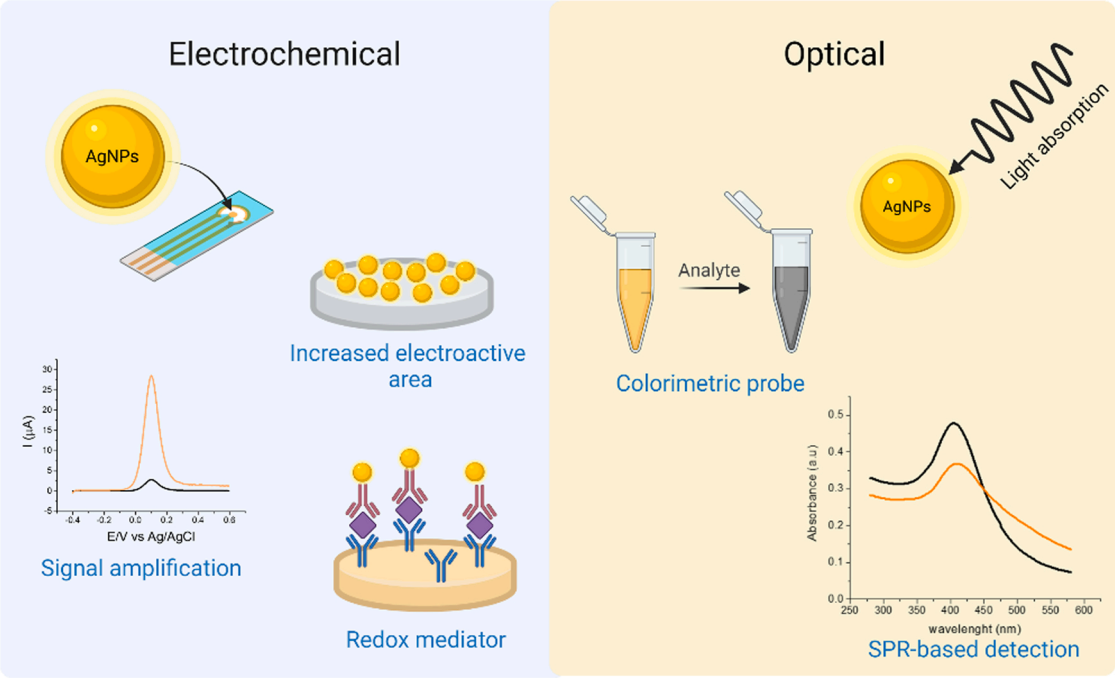

Fig. 3. The main applications of AgNPs in biosensors. For electrochemical detection, AgNPs are exploited as redox mediators, signal amplifiers, and also to increase the electroactive area of the electrodes, improving analytical performance. In optical biosensors, they are mainly used as colorimetric probes or for SPR-based detection. Figure created with BioRender.com.

synthesized in a variety of sizes, shapes, and surface functionalizations.

Several research groups have investigated the AgNPs toxicity and pharmacokinetic parameters in animal models (Table 3). The studies revealed that after systemic, oral, or nasal administration, AgNPs could accumulate in several organs, such as liver, kidney, spleen, lungs, heart, and testis [116–118]. Histopathological alterations, biochemical disturbances, geno- and immunotoxicity were detected in many soft tissues after AgNPs administration during short or prolonged exposure periods [119–122]. In contrast, some research groups found no detectable histopathological or biochemical alterations after AgNPs administration [123–125]. These conflicting results highlight the importance of the complete characterization of AgNPs and the appropriate control of the experimental designs according to the safe-by-design concept; these parameters are essential to perform interlaboratory comparison studies and also to share data across laboratories to reach a complete comprehension of the AgNPs systemic toxicity [126].

Regardless the AgNPs toxicity, minimizing nonspecific interactions and systemic biodistribution, as well as increasing particle tumor uptake are essential for reaching optimized treatments and successful translation into clinics. Although AgNPs may benefit from the EPR effect, their tumor targetability can be further enhanced. One of the main advantages of nanomedicines is the possibility to decorate the nanoparticles' surface for active target delivery. For this purpose, the NP's surface is functionalized with ligands, which interact with specific receptors and biomarkers typically overexpressed in tumor cells, resulting in higher specificity and delivery efficacy [127]. Several targeting ligands, such as proteins, peptides, vitamins, and nucleic acid are being exploited for the development of cancer-targeted nanocarriers [10, 128–132]. Some of these strategies have been applied to AgNPs. Cell-penetrating peptides (CPP) have been successfully anchored to AgNPs surface and the results showed that this strategy enhanced cellular uptake and cytotoxicity in glioblastoma and breast cancer in vitro models [133,134]. Liu et al. have investigated the in vitro and in vivo uptake and activity of CPP-functionalized AgNPs [47]. The CPP-AgNPs were more efficiently internalized by Caco-2 cells, compared to bare AgNPs, consequently, CPP-AgNPs induced higher toxicity to several cell lines. For in vivo studies, the nanoparticles were administered peritumorally in melanoma-bearing mice, and it was observed that not only CPP-AgNPs were more therapeutically efficient against the tumor, but also induced fewer side effects compared to DOX-treated mice. Wang et al. designed a silver nanocarrier functionalized with folic acid (FA); in vitro tests indicated that AgNPs-FA exhibit excellent targeting specificity and ability to kill cancer cells overexpressing FA-receptors [135].

An alternative method that has been recently explored to increase NP biocompatibility and specificity is the development of biomimetic nanoparticles. Briefly, this strategy comprises the coating of the nanoparticles with cell membrane (CM) vesicles, isolated from cell culture or tissue. As a result, the coated nanoparticles exhibits increased biocompatibility, prolonged circulation, and tumor specificity depending on the cell membrane nature [139]. CMs from different cell types, such as erythrocytes, white blood cells, platelets, stem cells, and cancer cells have been used to develop cell membrane-coated nanoparticles [8140–143]. For oncotherapy, membranes derived from cancer cells (CCM) are particularly interesting because they retain the membrane proteins from the source cancer cells, therefore the nanoparticles coated with CCM may benefit from the homologous binding and natural immune-evading properties [57]. Fig. 4 summarizes the main features that CCM-coated nanoparticles may exhibit.

AuNPs and magnetic nanoparticles have been successfully coated with cell membranes and exhibited improved therapeutic properties compared with the non-coated counterparts [8144–146]. For example, Xie et al. coated AuNPs with HeLa cell-derived membrane to build a plasmonic imaging probe [147]. They observed a 7- fold increase of plasmonic signal spots in HeLa cells treated with AuNPs-CCM, compared to cells treated only with AuNPs, which confirms the homotypic biding capability of the AuNP biomimetic probe. In another study, Marangoni et al. coated gold nanorods (AuNRs) with lung adenocarcinoma cells (A549) membranes [8]. The system also acted as a carrier for β-lapachone, which was loaded in the isolated membranes prior to AuNRs coating. Due to the plasmonic properties of AuNRs, irradiation with near-infrared laser led to disruption of the vesicles, releasing the

Table 3
Studies evaluating the toxic potential of different spherical AgNPs in animal models. While toxicity is observed by several research groups, there are also data revealing that AgNP may not induce toxic effects at given experimental conditions.

AgNPs features			Dose	Animal model	Exposure route	Exposure duration	Tissue distribution	Results	Ref.
Size (nm)	[a]ZP (mV)	Surface coating							
27.3 – 106.2	-40	[b]*n.r*	5 mg/kg (bw)	Sprague Dawley rats (female)	I.V, single injection	24 h	Lung, spleen, liver, kidney, thymus, and heart (ICP-MS).	Organ damage (liver, kidney, spleen and thymus); Chromosome and chromatid breakage in bone marrow cells; Alteration of biochemical biomarkers (ALT, BUN, TBil, and Cre).	[121]
7.9 ± 0.9	-17.5 ± 4.1	Citrate	0.5 and 5 mg/kg (bw)	Rabbit (male)	I.V, single injection	7 and 28 days	[b]*n.r*	Liver toxicity (tissue injury, cell death, oxidative stress, and DNA damage); Dose-dependent toxicity; Pathway analysis of microarray data indicate a correlation with inflammation, hepatotoxicity, and cancer.	[122]
21 ± 2.6 and 107 ± 7.6	-40.8 and -38.7	[b]*n.r*	0.0082 – 6 mg/kg (bw)	Winstar rats (male and female)	I.V, daily injections	28 days	Spleen, liver, venous cells, and lymph nodes (histopathological analysis).	Dose-dependent toxicity; Alteration of biochemical biomarkers (ALP, ALT, and AST); Histopathological lesions not observed; Immunotoxicity (suppression of NK cells activity and altered immunological biomarkers); Similar effects induced by 20 and 100 nm AgNPs.	[120]
10 ± 2.6	[b]*n.r*	Citrate	0.25 and 1 mg/kg (bw)	CD-1 mice (male)	Oral (daily, 5 days/ week)	28 days and 28 days + 28 days recovery (rec)	Brain, testis, liver and spleen (ICP-MS); after rec. limited decrease in brain and testis.	Higher Ag concentration in the brain; Histopathological lesions not observed; Dose-dependent decrease of WBCs and lymphocytes after rec. period; immunoreactivity in hippocampus and cortex, which were reduced after rec.	[136]
20	+66	Chitosan	50, 25, and 10 mg/kg (bw)	Winstar rats (male)	I.P (daily)	14 days	[b]*n.r*	Dose-dependent toxicity; 50 mg/kg: severe toxicity; 25 mg/kg: mild toxicity; 10 mg/kg: no toxicity; Decreased immunoglobulin levels; Histopathological alterations in spleen and lymphocytes; Oxidative stress.	[137]
25.2 ± 3	*n.r**	PVP	50, 100 or 200 mg/kg (bw)	Sprague Dawley rats (male)	Oral (daily)	90 days	Ileum, liver, kidneys, brain, thymus, and spleen (ICP-MS).	No hematological toxicity; No histopathological changes in the brain, thymus, spleen, ileum, and kidney; altered Cu and Zn levels in thymus and brain.	[138]
11 – 75	[b]*n.r*	Biogenic *E. faecalis*	I.V: 124–132 ug/ kg (bw); I.P: 97.6–105.4 ug/ kg (bw)	Winstar rats (male)	I.V and I.P	14 and 28 days	[b]*n.r*	No hematological toxicity; No histopathological changes; No liver, spleen, and kidney toxicity; I.P injection-induced mild toxicity.	[123]

I.P: Intraperitoneal injection; I.V: intravenous injection; bw: body weight; PVP: Polyvinylpolypyrrolidone; ICP-MS: Inductively coupled plasma mass spectrometry.
[a] Zeta potential;
[b] *n.r*: Data not reported by the author.

nanoparticles and drugs. The combination of PTT and the drug resulted in increased cytotoxicity to A549 cells and could be further explored for future clinical therapies.

The use of cell-derived membranes and extracellular vesicles (EVs) as smart and biocompatible coatings for nanoparticles remains largely unexplored for AgNPs. However, as exemplified by Zhao et al. this technique holds an enormous potential to overcome AgNPs limitations for clinical use [148]. In their study, the authors coated AgNPs with FA-functionalized red blood cells membranes and for both in vitro and in vivo models the system presented good biocompatibility, tumor targetability, and anti-lymphoma properties. The authors found no side effects induced by the system in vivo [148]. Given the enormous promise that CM-NP holds in oncotherapy, more studies are urgently needed, since they could improve AgNPs tumor specificity and the ability to overcome biological barriers.

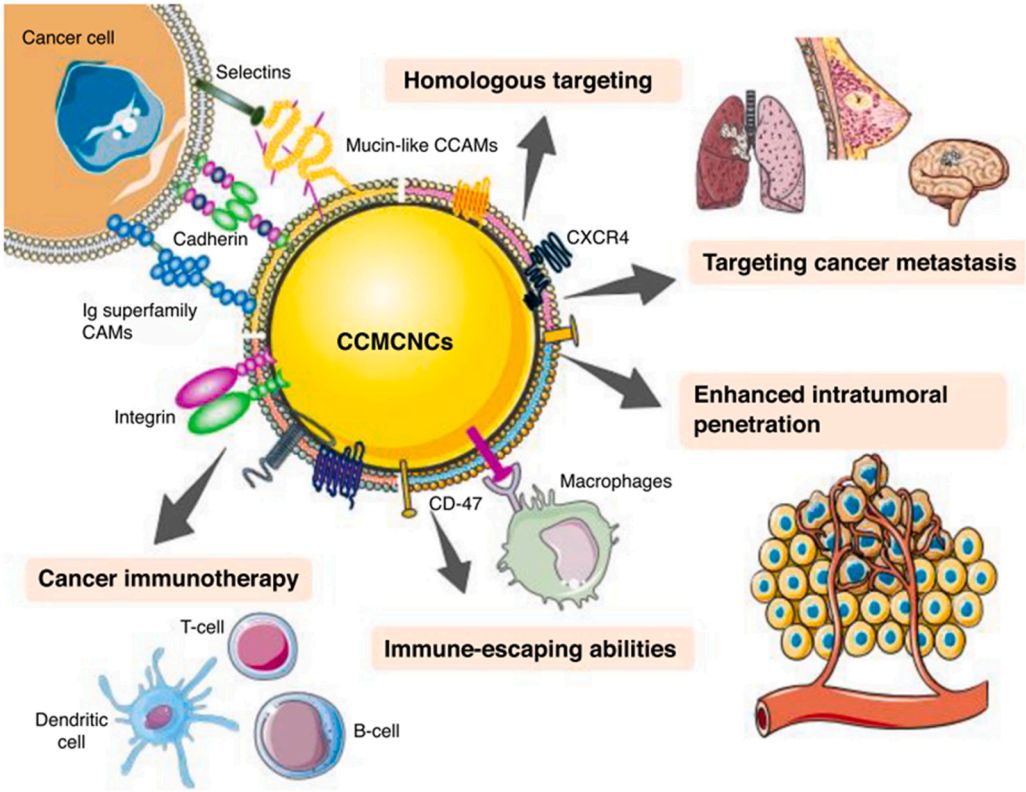

Fig. 4. Schematic overview of the advantages and applications of cancer cell membrane-coated nanocarriers (CCMCNCs) for the targeted delivery of nanotheranostics in cancer therapy. The figure details the proteins present in the membrane of tumor cells involved in the interaction of CCMCNCs with cancer cells. Homotypic binding (i.e., the affinity that tumor cells, especially metastatic cells, have to bind to each other) and adhesion proteins, such as cadherins and selections, confer greater specificity to CCMCNCs; the presence of antigens, such as CD47, provide CCMCNCs the ability to escape from the immune system; particles up to 200 nm benefit from the EPR effect (enhanced permeability and retention) and are more likely to accumulate in solid tumors due to fenestrations in blood vessels. Figure extracted from [57], copyright 2018, with permission from Elsevier.

8. Conclusions and perspectives

AgNPs are highly attractive materials for the development of new diagnostics and therapeutic systems for cancer. In diagnosis, AgNPs can improve the performance of biosensors, increasing the electroactive area and the electron transfer rate in electrochemical electrodes, or acting as redox mediators. AgNPs can also be explored as colorimetric probes or in SPR-based biosensors. For therapeutic purposes, AgNPs possess antitumoral properties that can tackle different cancer hallmarks, such as oxidative stress, energy metabolism, and drug resistance. Moreover, AgNPs may induce toxicity in cancer cells upon their combined use with different conventional chemotherapeutic drugs. These features may be useful to overcome limitations of the typical combination chemotherapy including drug solubility, differences in drugs pharmacokinetics, and spatiotemporal delivery, especially because AgNPs-based nanocarrier systems can be modified for smart drug delivery. In addition to chemotherapy, AgNPs have also shown promising results to enhance radiotherapy and photodynamic therapy against different cancer types.

Despite the optimistic results of AgNPs as a new therapeutic strategy, they have not yet been implemented into clinical use, mainly due to the limited knowledge regarding their behavior and toxicity to humans. Full nanoparticle characterization and standardized experimental design are essential to compare results from different laboratories and to reach a consensus regarding their toxicity and pharmacokinetics. In addition, novel targeting and biomimetic strategies, such as AgNPs coated with cancer cell membranes, should be explored for AgNPs to advance towards their clinical implementation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 0 (2021) 1–41, https://doi.org/10.3322/caac.21660.

[2] C. Zhao, R. Cheng, Z. Yang, Z. Tian, Nanotechnology for cancer therapy based on chemotherapy, Molecules 23 (2018) 1–29, https://doi.org/10.3390/molecules23040826.

[3] S. Rawal, M.M. Patel, Threatening cancer with nanoparticle aided combination oncotherapy, J. Control Release 301 (2019) 76–109, https://doi.org/10.1016/j.jconrel.2019.03.015.

[4] R. Xue, H. Lun, H. Yi, J. Young, X. Yu, R.X. Zhang, et al., Nanomedicine of synergistic drug combinations for cancer therapy – Strategies and perspectives, J. Control Release 240 (2016) 489–503, https://doi.org/10.1016/j.jconrel.2016.06.012.

[5] P. Severino, M. Szymanski, M. Favaro, A.R. Azzoni, M.V. Chaud, M.H.A. Santana, et al., Development and characterization of a cationic lipid nanocarrier as non-viral vector for gene therapy, Eur. J. Pharm Sci. 66 (2015) 78–82, https://doi.org/10.1016/j.ejps.2014.09.021.

[6] K. Mcnamara, S.A.M. Tofail, K. Mcnamara, S.A.M. Tofail, Advances in physics: X nanoparticles in biomedical applications, Adv. Phys. X 2 (2017) 1–35, https://doi.org/10.1080/23746149.2016.1254570.

[7] E. Salvati, F. Stellacci, S. Krol, Nanosensors for early cancer detection and for therapeutic drug monitoring, Nanomedicine 10 (2015) 3495–3512, https://doi.org/10.2217/nnm.15.180.

[8] V.S. Marangoni, J.C. Bernardi, I.B. Reis, W.J. Fa, Photothermia and activated drug release of natural cell membrane coated plasmonic gold nanorods and β -lapachone, ACS Appl. Bio. Mater. 2 (2019) 728–736, https://doi.org/10.1021/acsabm.8b00603.

[9] K. Cherukula, K.M. Lekshmi, S. Uthaman, K. Cho, C. Cho, I. Park, Multifunctional inorganic nanoparticles: recent progress in thermal therapy and imaging, Nanomaterials 6 (2016) 1–26, https://doi.org/10.3390/nano6040076.

[10] P. Kumari, B. Ghosh, S. Biswas, Nanocarriers for cancer-targeted drug delivery, J. Drug Target 00 (2015) 1–13, https://doi.org/10.3109/1061186X.2015.1051049.

[11] A.A. Gabizon, R.T.M.De Rosales, N.M. La-beck, Translational considerations in nanomedicine: the oncology perspective, Adv. Drug Deliv. Rev. (2020), https://doi.org/10.1016/j.addr.2020.05.012.
[12] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat. Publ. Gr. 7 (2010) 653–664, https://doi.org/10.1038/nrclinonc.2010.139.
[13] H.H. Lara, E.N. Garza-Treviño, L. Ixtepan-Turrent, D.K. Singh, Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds, J. Nanobiotechnol. 9 (2011) 1–8, https://doi.org/10.1186/1477-3155-9-30.
[14] S. Galdiero, A. Falanga, M. Vitiello, M. Cantisani, V. Marra, M. Galdiero, Silver nanoparticles as potential antiviral agents, Molecules 16 (2011) 8894–8918, https://doi.org/10.3390/molecules16108894.
[15] A.H. Alshehri, M. Jakubowska, A. Młozìniak, M. Horaczek, D. Rudka, C. Free, et al., Enhanced electrical conductivity of silver nanoparticles for high frequency electronic applications, ACS Appl. Mater. Interfaces 4 (2012) 7007–7010, https://doi.org/10.1021/am3022569.
[16] A.J. Haes, R.P. Van Duyne, A nanoscale optical biosensor: sensitivity and selectivity of an approach based on the localized surface plasmon resonance spectroscopy of triangular silver nanoparticles, J. Am. Chem. Soc. 124 (2002) 10596–10604, https://doi.org/10.1021/ja020393x.
[17] T. Baygar, N. Sarac, A. Ugur, I.R. Karaca, Antimicrobial characteristics and biocompatibility of the surgical sutures coated with biosynthesized silver nanoparticles, Bioorg. Chem. 86 (2019) 254–258, https://doi.org/10.1016/j.bioorg.2018.12.034.
[18] E.I. Alarcon, B. Vulesevic, A. Argawal, A. Ross, P. Bejjani, J. Podrebarac, et al., Coloured cornea replacements with anti-infective properties: expanding the safe use of silver nanoparticles in regenerative medicine, Nanoscale 8 (2016) 6484–6489, https://doi.org/10.1039/c6nr01339b.
[19] B. Tang, J. Li, X. Hou, T. Afrin, L. Sun, X. Wang, Colorful and antibacterial silk fiber from anisotropic silver nanoparticles, Ind. Eng. Chem. Res. (2013), https://doi.org/10.1021/ie3033872.
[20] S. Kokura, O. Handa, T. Takagi, T. Ishikawa, Y. Naito, T. Yoshikawa, Silver nanoparticles as a safe preservative for use in cosmetics, Nanomed. Nanotechnol., Biol. Med. 6 (2010) 570–574, https://doi.org/10.1016/j.nano.2009.12.002.
[21] L. Xu, Y.Y. Wang, J. Huang, C.Y. Chen, Z.X. Wang, H. Xie, Silver nanoparticles: synthesis, medical applications and biosafety, Theranostics 10 (2020) 8996–9031, https://doi.org/10.7150/thno.45413.
[22] W. Cheng, J. Ma, P. Cao, Y. Zhang, C. Xu, Y. Yi, et al., Enzyme-free electrochemical biosensor based on double signal amplification strategy for the ultra-sensitive detection of exosomal microRNAs in biological samples, Talanta 219 (2020), 121242, https://doi.org/10.1016/j.talanta.2020.121242.
[23] R. Miethling-Graff, R. Rumpker, M. Richter, T. Verano-Braga, F. Kjeldsen, J. Brewer, et al., Exposure to silver nanoparticles induces size- and dose-dependent oxidative stress and cytotoxicity in human colon carcinoma cells, Toxicol. In Vitro 28 (2014) 1280–1289, https://doi.org/10.1016/j.tiv.2014.06.005.
[24] Govender R., Phulukdaree A., Gengan RM, Anand K., Chuturgoon AA. Silver nanoparticles of Albizia adianthifolia: the induction of apoptosis in human lung carcinoma cell line 2013:1–9.
[25] D. Guo, L. Zhu, Z. Huang, H. Zhou, Y. Ge, W. Ma, et al., Anti-leukemia activity of PVP-coated silver nanoparticles via generation of reactive oxygen species and release of silver ions, Biomaterials 34 (2013) 7884–7894, https://doi.org/10.1016/j.biomaterials.2013.07.015.
[26] G. Raja, Y.-K. Jang, J.-S. Suh, H.-S. Kim, S.H. Ahn, T.-J. Kim, Microcellular environmental regulation of silver nanoparticles in cancer therapy: a critical review, Cancers 12 (2020) 664, https://doi.org/10.3390/cancers12030664.
[27] P. Chairuangkitti, S. Lawanprasert, S. Roytrakul, S. Aueviriyavit, D. Phummiratch, K. Kulthong, et al., Silver nanoparticles induce toxicity in A549 cells via ROS-dependent and ROS-independent pathways, Toxicol Vitr. 27 (2013) 330–338, https://doi.org/10.1016/j.tiv.2012.08.021.
[28] L.Z. Flores-López, H. Espinoza-Gómez, R. Somanathan, Silver nanoparticles: electron transfer, reactive oxygen species, oxidative stress, beneficial and toxicological effects. Mini review, J. Appl. Toxicol. 39 (2019) 16–26, https://doi.org/10.1002/jat.3654.
[29] P.D. Ray, B.W. Huang, Y. Tsuji, Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling, Cell Signal 24 (2012) 981–990, https://doi.org/10.1016/j.cellsig.2012.01.008.
[30] D. Trachootham, J. Alexandre, P. Huang, Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat. Rev. Drug Discov. 8 (2009) 579–591, https://doi.org/10.1038/nrd2803.
[31] R. Rank Miranda, M. Pereira da Fonseca, B. Korzeniowska, L. Skytte, K. Lund Rasmussen, F. Kjeldsen, Elucidating the cellular response of silver nanoparticles as a potential combinatorial agent for cisplatin chemotherapy, J. Nanobiotechnol. 18 (2020) 164, https://doi.org/10.1186/s12951-020-00719-x.
[32] E. Barcińska, J. Wierzbicka, A. Zauszkiewicz-Pawlak, D. Jacewicz, A. Dabrowska, I. Inkielewicz-Stepniak, Role of oxidative and nitro-oxidative damage in silver nanoparticles cytotoxic effect against human pancreatic ductal adenocarcinoma cells, Oxid Med. Cell Longev 2018 (2018) 1–15, https://doi.org/10.1155/2018/8251961.
[33] A. Avalos, A.I. Haza, D. Mateo, P. Morales, Cytotoxicity and ROS production of manufactured silver nanoparticles of different sizes in hepatoma and leukemia cells, J. Appl. Toxicol. 34 (2014) 413–423, https://doi.org/10.1002/jat.2957.
[34] A. Fehaid, A. Taniguchi, Size-dependent effect of silver nanoparticles on the tumor necrosis factor α-induced dna damage response, Int. J. Mol. Sci. (2019) 20, https://doi.org/10.3390/ijms20051038.
[35] A. Onodera, F. Nishiumi, K. Kakiguchi, A. Tanaka, N. Tanabe, A. Honma, et al., Short-term changes in intracellular ROS localisation after the silver nanoparticles exposure depending on particle size, Toxicol. Reports 2 (2015) 574–579, https://doi.org/10.1016/j.toxrep.2015.03.004.
[36] W. Liu, I. Worms, V.I. Slaveykova, Interaction of silver nanoparticles with antioxidant enzymes, Environ. Sci. Nano 7 (2020) 1507–1517, https://doi.org/10.1039/c9en01284b.
[37] M.J. Lee, S.J. Lee, S.J. Yun, J.-Y. Jang, H. Kang, K. Kim, et al., Silver nanoparticles affect glucose metabolism in hepatoma cells through production of reactive oxygen species, Int. J. Nanomed. (2015) 55, https://doi.org/10.2147/IJN.S94907.
[38] R.R. Miranda, V. Gorshkov, B. Korzeniowska, S.J. Kempf, F.F. Neto, F. Kjeldsen, Co-exposure to silver nanoparticles and cadmium induce metabolic adaptation in HepG2 cells, Nanotoxicology 12 (2018) 781–795, https://doi.org/10.1080/17435390.2018.1489987.
[39] B. Plackal Adimuriyil George, N. Kumar, H. Abrahamse, S.S. Ray, Apoptotic efficacy of multifaceted biosynthesized silver nanoparticles on human adenocarcinoma cells, Sci. Rep. 8 (2018) 14368, https://doi.org/10.1038/s41598-018-32480-5.
[40] D. Kovács, K. Szőke, N. Igaz, G. Spengler, J. Molnár, T. Tóth, et al., Silver nanoparticles modulate ABC transporter activity and enhance chemotherapy in multidrug resistant cancer, Nanomed. Nanotechnol., Biol. Med. 12 (2016) 601–610, https://doi.org/10.1016/j.nano.2015.10.015.
[41] S. Rodríguez-Enríquez, O. Juárez, J.S. Rodríguez-Zavala, R. Moreno-Sánchez, Multisite control of the Crabtree effect in ascites hepatoma cells, Eur. J. Biochem. 268 (2001) 2512–2519, https://doi.org/10.1046/j.1432-1327.2001.02140.x.
[42] M.V. Liberti, J.W. Locasale, The Warburg effect: how does it benefit cancer cells? Trends Biochem. Sci. 41 (2016) 211–218, https://doi.org/10.1016/j.tibs.2015.12.001.
[43] R.R. Miranda, A.G. Bezerra, C.A.O. Ribeiro, M.A.F. Randi, C.L. Voigt, L. Skytte, et al., Toxicological interactions of silver nanoparticles and non-essential metals in human hepatocarcinoma cell line, Toxicol Vitr 40 (2017) 134–143, https://doi.org/10.1016/j.tiv.2017.01.003.
[44] S. Aueviriyavit, D. Phummiratch, R. Maniratanachote, Mechanistic study on the biological effects of silver and gold nanoparticles in Caco-2 cells–induction of the Nrf2/HO-1 pathway by high concentrations of silver nanoparticles, Toxicol Lett. 224 (2014) 73–83, https://doi.org/10.1016/j.toxlet.2013.09.020.
[45] Z. Xu, Q. Feng, M. Wang, H. Zhao, Y. Lin, S. Zhou, Green biosynthesized silver nanoparticles with aqueous extracts of ginkgo biloba induce apoptosis via mitochondrial pathway in cervical cancer cells, Front Oncol. 10 (2020) 1–10, https://doi.org/10.3389/fonc.2020.575415.
[46] M.K. Gopisetty, D. Kovács, N. Igaz, A. Rónavári, P. Bélteky, Z. Rázga, et al., Endoplasmic reticulum stress: major player in size - dependent inhibition of P - glycoprotein by silver nanoparticles in multidrug - resistant breast cancer cells, J. Nanobiotechnol. (2019) 1–15, https://doi.org/10.1186/s12951-019-0448-4.
[47] J. Liu, Y. Zhao, Q. Guo, Z. Wang, H. Wang, Y. Yang, et al., TAT-modified nanosilver for combating multidrug-resistant cancer, Biomaterials 33 (2012) 6155–6161, https://doi.org/10.1016/j.biomaterials.2012.05.035.
[48] M.M. Gottesman, T. Fojo, S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters, Nat. Rev. Cancer 2 (2002) 48–58, https://doi.org/10.1038/nrc706.
[49] Y.A. Luqmani, Mechanisms of drug resistance in cancer chemotherapy, Med. Princ Pract. 14 (2005) 35–48, https://doi.org/10.1159/000086183.
[50] K. Murugesan, J. Koroth, P.P. Srinivasan, A. Singh, S. Mukundan, S.S. Karki, et al., Effects of green synthesised silver nanoparticles (ST06-AgNPs) using curcumin derivative (ST06) on human cervical cancer cells (HeLa) in vitro and EAC tumor bearing mice models, Int. J. Nanomed. 14 (2019) 5257–5270.
[51] N.E.A. El-Naggar, M.H. Hussein, A.A. El-Sawah, Bio-fabrication of silver nanoparticles by phycocyanin, characterization, in vitro anticancer activity against breast cancer cell line and in vivo cytotxicity, Sci. Rep. 7 (2017) 1–20, https://doi.org/10.1038/s41598-017-11121-3.
[52] M.I. Sriram, S. Barath, M. Kanth, K. Kalishwaralal, S. Gurunathan, Antitumor activity of silver nanoparticles in Dalton ' s lymphoma ascites tumor model, Int. J. Nanomed. 5 (2010) 753–762, https://doi.org/10.2147/IJN.S11727.
[53] J. Swanner, J.J. Sears, R. Singh, A. Hooker, G.L. Donati, C.M. Furdui, et al., Silver nanoparticles selectively treat triple - negative breast cancer cells without affecting non - malignant breast epithelial cells in vitro and in vivo, FASEB BioAdvances 1 (2019) 639–660, https://doi.org/10.1096/fba.2019-00021.
[54] D. Krzyzanowski, M. Kruszewski, A. Grzelak, Differential action of silver nanoparticles on ABCB1 (MDR1) and ABCC1 (MRP1) activity in mammalian cell lines, Materials 14 (2021) 3383, https://doi.org/10.3390/ma14123383.
[55] L.A.B. Ferreira, F. Garcia-Fossa, A. Radaic, N. Durán, W.J. Fávaro, M.B. de Jesus, Biogenic silver nanoparticles: in vitro and in vivo antitumor activity in bladder cancer, Eur. J. Pharm. Biopharm. 151 (2020) 162–170, https://doi.org/10.1016/j.ejpb.2020.04.012.
[56] R.B. Mokhtari, T.S. Homayouni, N. Baluch, Therapy in combating cancer, Oncotarget 8 (2017) 38022–38043.
[57] R.J.C. Bose, R. Paulmurugan, J. Moon, S. Lee, H. Park, Cell membrane-coated nanocarriers: the emerging targeted delivery system for cancer theranostics, Drug Discov. Today 23 (2018) 891–899, https://doi.org/10.1016/j.drudis.2018.02.001.
[58] L. Bregoli, D. Movia, J.D. Gavigan-Imedio, J. Lysaght, J. Reynolds, A. Prina-Mello, Nanomedicine applied to translational oncology: A future perspective on cancer treatment, Nanomed. Nanotechnol., Biol. Med. 12 (2016) 81–103, https://doi.org/10.1016/j.nano.2015.08.006.
[59] D. Press, Y.G. Yuan, Q.L. Peng, S. Ggurunathan, Silver nanoparticles enhance the apoptotic potential of gemcitabine in human ovarian cancer cells: Combination

therapy for effective cancer treatment, Int. J. Nanomed. 12 (2017) 6487–6502, https://doi.org/10.2147/IJN.S135482.
[60] Xi-Feng Zhang, Sangiliyandi Gurunathan, Combination of salinomycin and silver nanoparticles enhances apoptosis and autophagy in human ovarian cancer cells: an effective anticancer therapy, Int. J. Nanomed. 11 (2016) 3655–3675.
[61] F. Benyettou, R. Rezgui, F. Ravaux, T. Jaber, K. Blumer, M. Jouiad, et al., Synthesis of silver nanoparticles for the dual delivery of doxorubicin and alendronate to cancer cells, J. Mater. Chem. B 3 (2015) 7237–7245, https://doi.org/10.1039/c5tb00994d.
[62] Y. Li, M. Guo, Z. Lin, M. Zhao, M. Xiao, C. Wang, et al., Polyethylenimine-functionalized silver nanoparticle-based co-delivery of paclitaxel to induce HepG2 cell apoptosis, Int. J. Nanomed. 11 (2016) 6693–6702, https://doi.org/10.2147/IJN.S122666.
[63] N.M. Elbaz, L. Ziko, R. Siam, W. Mamdouh, Core-shell silver/polymeric nanoparticles-based combinatorial therapy against breast cancer in-vitro, Sci. Rep. 6 (2016) 1–9, https://doi.org/10.1038/srep30729.
[64] A.J. Frew, R.W. Johnstone, J.E. Bolden, Enhancing the apoptotic and therapeutic effects of HDAC inhibitors, Cancer Lett. 280 (2009) 125–133, https://doi.org/10.1016/j.canlet.2009.02.042.
[65] N. Igaz, D. Kovács, Z. Rázga, Z. Kónya, I.M. Boros, M. Kiricsi, Modulating chromatin structure and DNA accessibility by deacetylase inhibition enhances the anti-cancer activity of silver nanoparticles, Colloids Surf. B Biointerfaces 146 (2016) 670–677, https://doi.org/10.1016/j.colsurfb.2016.07.004.
[66] S. Gurunathan, M.H. Kang, J.H. Kim, Combination effect of silver nanoparticles and histone deacetylases inhibitor in human alveolar basal epithelial cells, Molecules (2018) 23, https://doi.org/10.3390/molecules23082046.
[67] S.A. Sadat Shandiz, M. Shafiee Ardestani, D. Shahbazzadeh, A. Assadi, R. Ahangari Cohan, V. Asgary, et al., Novel imatinib-loaded silver nanoparticles for enhanced apoptosis of human breast cancer MCF-7 cells. Artif Cells, Nanomedicine, Biotechnol 45 (2017) 1082–1091, https://doi.org/10.1080/21691401.2016.1202257.
[68] C. Allen, S. Her, D.A. Jaffray, Radiotherapy for cancer: present and future, Adv. Drug Deliv. Rev. 109 (2017) 1–2, https://doi.org/10.1016/j.addr.2017.01.004.
[69] D. Kwatra, A. Venugopal, S. Anant, Nanoparticles in radiation therapy: a summary of various approaches to enhance radiosensitization in cancer 2 (2013) 330–342, https://doi.org/10.3978/j.issn.2218-676X.2013.08.06.
[70] J. Sia, R. Szmyd, E. Hau, H.E. Gee, A. Burgess, R.C. Death, Molecular mechanisms of radiation-induced cancer cell death: a primer, Front. Cell Dev. Biol. 8 (2020) 1–8, https://doi.org/10.3389/fcell.2020.00041.
[71] J. Wei, B. Wang, H. Wang, L. Meng, Q. Zhao, X. Li, et al., Radiation-induced normal tissue damage: oxidative stress and epigenetic mechanisms, Oxid Med. Cell Longev 2019 (2019) 1–11, https://doi.org/10.1155/2019/3010342.
[72] J.D. Carter, N.N. Cheng, Y. Qu, G.D. Suarez, T. Guo, Nanoscale energy deposition by X-ray absorbing nanostructures, J. Phys. Chem. B 111 (2007) 11622–11625, https://doi.org/10.1021/jp075253u.
[73] S. Pinel, N. Thomas, C. Boura, M. Barberi-Heyob, Approaches to physical stimulation of metallic nanoparticles for glioblastoma treatment, Adv. Drug Deliv. Rev. 138 (2019) 344–357, https://doi.org/10.1016/j.addr.2018.10.013.
[74] M.E. Lomax, L.K. Folkes, P.O. Neill, Biological consequences of radiation-induced DNA damage: relevance to radiotherapy statement of search strategies used and sources of information why radiation damage is more effective than endogenous damage at killing cells ionising radiation-induced do, Clin. Oncol. 25 (2013) 578–585, https://doi.org/10.1016/j.clon.2013.06.007.
[75] J. Biau, E. Chautard, P. Verrelle, M. Dutreix, D.N.A. Altering, Repair to improve radiation therapy: specific and multiple pathway targeting, Front. Oncol. 9 (2019) 1–10, https://doi.org/10.3389/fonc.2019.01009.
[76] H. Wang, H. Jiang, M.Van De Gucht, M.De Ridder, Hypoxic radioresistance: Can ROS Be the Key to, Cancers 11 (2019) 23, https://doi.org/10.3390/cancers11010112.
[77] W. Kim, S. Lee, D. Seo, D. Kim, K. Kim, E. Kim, et al., Cellular stress responses in radiotherapy, Cells 8 (2019) 1–18.
[78] R. Xu, J. Ma, X. Sun, Z. Chen, X. Jiang, Z. Guo, et al., Ag nanoparticles sensitize IR-induced killing of cancer cells, Cell Res. 19 (2009) 1031–1034, https://doi.org/10.1038/cr.2009.89.
[79] P. Liu, Z. Huang, Z. Chen, R. Xu, H. Wu, F. Zang, et al., Silver nanoparticles: a novel radiation sensitizer for glioma? Nanoscale 5 (2013) 11829–11836, https://doi.org/10.1039/c3nr01351k.
[80] Z. Liu, H. Tan, X. Zhang, F. Chen, Z. Zhou, X. Hu, et al., Enhancement of radiotherapy efficacy by silver nanoparticles in hypoxic glioma cells. Artif Cells, Nanomedicine, Biotechnol 46 (2018) S922–S930, https://doi.org/10.1080/21691401.2018.1518912.
[81] K. Habiba, K. Aziz, K. Sanders, C.M. Santiago, L.S.K. Mahadevan, V. Makarov, et al., Enhancing colorectal cancer radiation therapy efficacy using silver nanoprisms decorated with graphene as radiosensitizers, Sci. Rep. 9 (2019) 1–9, https://doi.org/10.1038/s41598-019-53706-0.
[82] J. Swanner, J. Mims, D.L. Carroll, S.A. Akman, C.M. Furdui, S.V. Torti, et al., Differential cytotoxic and radiosensitizing effects of silver nanoparticles on triple-negative breast cancer and non-triple-negative breast cells, Int. J. Nanomed. 10 (2015) 3937–3953, https://doi.org/10.2147/IJN.S80349.
[83] M. Chudy, K. Tokarska, E. Jastrzębska, M. Bułka, S. Drozdek, Ł. Lamch, et al., Lab-on-a-chip systems for photodynamic therapy investigations, Biosens. Bioelectron. 101 (2018) 37–51, https://doi.org/10.1016/j.bios.2017.10.013.
[84] S.S. Lucky, K.C. Soo, Y. Zhang, Nanoparticles in photodynamic therapy, Chem. Rev. 115 (2015) 1990–2042, https://doi.org/10.1021/cr5004198.
[85] P. Agostinis, K. Berg, K.A. Cengel, T.H. Foster, A.W. Girotti, S.O. Gollnick, et al., Photodynamic therapy of cancer: an update, CA Cancer J. Clin. 61 (2011) 250–281, https://doi.org/10.3322/caac.20114.
[86] M. Cheng, Y. Cui, J. Wang, J. Zhang, L. Zhu, D. Kong, G-quadruplex/porphyrin composite photosensitizer: a facile way to promote absorption redshift and photodynamic therapy efficacy, ACS Appl. Mater. Interfaces 11 (2019) 13158–13167, https://doi.org/10.1021/acsami.9b02695.
[87] J. Sun, S. Kormakov, Y. Liu, Y. Huang, D. Wu, Z. Yang, Recent progress in metal-based nanoparticles mediated photodynamic therapy, Molecules (2018) 23, https://doi.org/10.3390/molecules23071704.
[88] O. Erdogan, M. Abbak, G.M. Demirbolat, F. Birtekocak, M. Aksel, S. Pasa, et al., Green synthesis of silver nanoparticles via Cynara scolymus leaf extracts: the characterization, anticancer potential with photodynamic therapy in MCF7 cells, PLoS One 14 (2019) 1–15, https://doi.org/10.1371/journal.pone.0216496.
[89] S. Srinivasan, V. Bhardwaj, A. Nagasetti, A. Fernandez-Fernandez, A.J. McGoron, Multifunctional surface-enhanced raman spectroscopy-detectable silver nanoparticles for combined photodynamic therapy and pH-triggered chemotherapy, J. Biomed. Nanotechnol. 12 (2016) 2202–2219, https://doi.org/10.1166/jbn.2016.2312.
[90] K. Habiba, J. Encarnacion-Rosado, K. Garcia-Pabon, J.C. Villalobos-Santos, V. I. Makarov, J.A. Avalos, et al., Improving cytotoxicity against cancer cells by chemo-photodynamic combined modalities using silver-graphene quantum dots nanocomposites, Int. J. Nanomed. 11 (2015) 107–119, https://doi.org/10.2147/IJN.S95440.
[91] M.B. Rivas Aiello, D. Castrogiovanni, J. Parisi, J.C. Azcárate, F.S. García Einschlag, T. Gensch, et al., Photodynamic therapy in hela cells incubated with riboflavin and pectin-coated silver nanoparticles, Photochem. Photobiol. 94 (2018) 1159–1166, https://doi.org/10.1111/php.12974.
[92] A. Shivashankarappa, K.R. Sanjay, Photodynamic therapy on skin melanoma and epidermoid carcinoma cells using conjugated 5-aminolevulinic acid with microbial synthesised silver nanoparticles, J. Drug Target 27 (2019) 434–441, https://doi.org/10.1080/1061186X.2018.1531418.
[93] S. Natesan, V. Krishnaswami, C. Ponnusamy, M. Madiyalakan, T. Woo, R. Palanisamy, Hypocrellin B and nano silver loaded polymeric nanoparticles: Enhanced generation of singlet oxygen for improved photodynamic therapy, Mater. Sci. Eng. C 77 (2017) 935–946, https://doi.org/10.1016/j.msec.2017.03.179.
[94] O. Santos, J. Cancino-Bernardi, P.M. Pincela Lins, D. Sampaio, T. Pavan, V. Zucolotto, Near-infrared photoactive theragnostic gold nanoflowers for photoacoustic imaging and hyperthermia, ACS Appl. Bio. Mater. (2021), https://doi.org/10.1021/acsabm.1c00519.
[95] J.R. Melamed, R.S. Edelstein, E.S. Day, Elucidating the fundamental mechanisms of cell death triggered by photothermal therapy, ACS Nano 9 (2015) 6–11, https://doi.org/10.1021/acsnano.5b00021.
[96] J. Estelrich, M. Antònia Busquets, Iron oxide nanoparticles in photothermal therapy, Molecules (2018) 23, https://doi.org/10.3390/molecules23071567.
[97] A.C.V. Doughty, A.R. Hoover, E. Layton, C.K. Murray, E.W. Howard, W.R. Chen, Nanomaterial applications in photothermal therapy for cancer, Materials ((Basel)) (2019) 12, https://doi.org/10.3390/ma12050779.
[98] Z. Li, Y. Chen, Y. Yang, Y. Yu, Y. Zhang, D. Zhu, et al., Recent advances in nanomaterials-based chemo-photothermal combination therapy for improving cancer treatment, Front Bioeng Biotechnol 7 (2019) 1–19, https://doi.org/10.3389/fbioe.2019.00293.
[99] H.S. Kim, D.Y. Lee, Near-infrared-responsive cancer photothermal and photodynamic therapy using gold nanoparticles, Polymers 10 (2018) 1–14, https://doi.org/10.3390/polym10090961.
[100] S.C. Boca, M. Potara, A.M. Gabudean, A. Juhem, P.L. Baldeck, S. Astilean, Chitosan-coated triangular silver nanoparticles as a novel class of biocompatible, highly effective photothermal transducers for in vitro cancer cell therapy, Cancer Lett. 311 (2011) 131–140, https://doi.org/10.1016/j.canlet.2011.06.022.
[101] E.A. Thompson, E. Graham, C.M. Macneill, M. Young, G. Donati, E.M. Wailes, et al., Differential response of MCF7, MDA-MB-231, and MCF 10A cells to hyperthermia, silver nanoparticles and silver nanoparticle-induced photothermal therapy, Int. J. Hyperth 30 (2014) 312–323, https://doi.org/10.3109/02656736.2014.936051.
[102] N. Levi-Polyachenko, R. Jacob, C. Day, N. Kuthirummal, Chitosan wound dressing with hexagonal silver nanoparticles for hyperthermia and enhanced delivery of small molecules, Colloids Surfaces B Biointerfaces 142 (2016) 315–324, https://doi.org/10.1016/j.colsurfb.2016.02.038.
[103] A. Douaki, B.D. Abera, G. Cantarella, B. Shkodra, A. Mushtaq, P. Ibba, et al., Flexible screen printed aptasensor for rapid detection of furaneol: a comparison of CNTs and AgNPs effect on aptasensor performance, Nanomaterials 10 (2020) 1–18, https://doi.org/10.3390/nano10061167.
[104] J. Li, T. Gao, S. Gu, J. Zhi, J. Yang, G. Li, An electrochemical biosensor for the assay of alpha-fetoprotein-L3 with practical applications, Biosens. Bioelectron 87 (2017) 352–357, https://doi.org/10.1016/j.bios.2016.08.071.
[105] P. Miao, K. Han, H. Sun, J. Yin, J. Zhao, B. Wang, et al., Melamine functionalized silver nanoparticles as the probe for electrochemical sensing of clenbuterol, ACS Appl. Mater. Interfaces 6 (2014) 8667–8672, https://doi.org/10.1021/am501473m.
[106] C. Feng, J. Guo, G. Li, B. Ye, L. Zou, Novel multiple strand displacement reaction coupled hybridization chain reaction for label-free and ultrasensitive electrochemical Type b3a2 biosensing, Sensors Actuators, B Chem. 326 (2021), 128972, https://doi.org/10.1016/j.snb.2020.128972.
[107] Y. Zhao, J. Chen, H. Zhong, C. Zhang, Y. Zhou, W. Mao, et al., Functionalized Ag/Fe-MOFs nanocomposite as a novel endogenous redox mediator for determination

of α2,6-sialylated glycans in serum, Microchim. Acta (2020) 187, https://doi.org/10.1007/s00604-020-04608-w.
[108] F. Hakimian, H. Ghourchian, Ultrasensitive electrochemical biosensor for detection of microRNA-155 as a breast cancer risk factor, Anal. Chim. Acta 1136 (2020) 1–8, https://doi.org/10.1016/j.aca.2020.08.039.
[109] D. Xu, B. Hou, L. Qian, X. Zhang, G. Liu, Non-enzymatic electrochemical sensor based on sliver nanoparticle-decorated carbon nanotubes, Molecules 24 (2019) 1–11, https://doi.org/10.3390/molecules24183411.
[110] A. Loiseau, V. Asila, G. Boitel-Aullen, M. Lam, M. Salmain, S. Boujday, Silver-based plasmonic nanoparticles for and their use in biosensing, Biosensors (2019) 9, https://doi.org/10.3390/bios9020078.
[111] K. Varghese Alex, P. Tamil Pavai, R. Rugmini, M. Shiva Prasad, K. Kamakshi, K. C. Sekhar, Green synthesized ag nanoparticles for bio-sensing and photocatalytic applications, ACS Omega 5 (2020) 13123–13129, https://doi.org/10.1021/acsomega.0c01136.
[112] S. Mohammadi, G. Khayatian, Silver nanoparticles modified with thiomalic acid as a colorimetric probe for determination of cystamine, Microchim. Acta 184 (2017) 253–259, https://doi.org/10.1007/s00604-016-1991-4.
[113] L. Dewangan, J. Korram, I. Karbhal, R. Nagwanshi, V.K. Jena, M.L. Satnami, A colorimetric nanoprobe based on enzyme-immobilized silver nanoparticles for the efficient detection of cholesterol, RSC Adv. 9 (2019) 42085–42095, https://doi.org/10.1039/c9ra08328f.
[114] W. Chen, L. Wang, R. He, X. Xu, W. Jiang, Convertible DNA ends-based silver nanoprobes for colorimetric detection human telomerase activity, Talanta 178 (2018) 458–463, https://doi.org/10.1016/j.talanta.2017.09.057.
[115] P. Mathur, S. Jha, S. Ramteke, N.K. Jain, Pharmaceutical aspects of silver nanoparticles. Artif Cells, Nanomedicine, Biotechnol 46 (2018) 115–126, https://doi.org/10.1080/21691401.2017.1414825.
[116] M. Van Der Zande, R.J. Vandebriel, E. Van Doren, E. Kramer, Z. Herrera Rivera, C. S. Serrano-Rojero, et al., Distribution, elimination, and toxicity of silver nanoparticles and silver ions in rats after 28-day oral exposure, ACS Nano 6 (2012) 7427–7442, https://doi.org/10.1021/nn302649p.
[117] K. Dziendzikowska, J. Gromadzka-ostrowska, A. Lankoff, M. Oczkowski, A. Krawczy, J. Chwastowska, et al., Time-dependent biodistribution and excretion of silver nanoparticles in male Wistar rats, J. Appl. Toxicol. 32 (2012) 920–928, https://doi.org/10.1002/jat.2758.
[118] J.H. Sung, J.H. Ji, J.U. Yoon, D.S. Kim, M.Y. Song, J. Jeong, et al., Lung function changes in Sprague-Dawley rats after prolonged inhalation exposure to silver nanoparticles, Inhal. Toxicol. 20 (2008) 567–574, https://doi.org/10.1080/08958370701874671.
[119] H. Guo, J. Zhang, M. Boudreau, J. Meng, J. jie Yin, J. Liu, et al., Intravenous administration of silver nanoparticles causes organ toxicity through intracellular ros-related loss of interendothelial junction, Part Fibre Toxicol 13 (2016) 1–13, https://doi.org/10.1186/s12989-016-0133-9.
[120] W.H. De Jong, L.T.M. Van Der Ven, A. Sleijffers, M.V.D.Z. Park, E.H.J.M. Jansen, H. Van Loveren, et al., Systemic and immunotoxicity of silver nanoparticles in an intravenous 28 days repeated dose toxicity study in rats, Biomaterials 34 (2013) 8333–8343, https://doi.org/10.1016/j.biomaterials.2013.06.048.
[121] H. Wen, M. Dan, Y. Yang, J. Lyu, A. Shao, X. Cheng, et al., Acute toxicity and genotoxicity of silver nanoparticle in rats, PLoS One 12 (2017) 1–16, https://doi.org/10.1371/journal.pone.0185554.
[122] Y.J. Kim, M.M. Rahman, S.M. Lee, J.M. Kim, K. Park, J.H. Kang, et al., Assessment of in vivo genotoxicity of citrated-coated silver nanoparticles via transcriptomic analysis of rabbit liver tissue, Int. J. Nanomed. 14 (2019) 393–405, https://doi.org/10.2147/IJN.S174515.
[123] C. Ashajyothi, R.K. Chandrakanth, A pilot toxicology study of biogenic silver nanoparticles: in vivo by intraperitoneal and intravenous infusion routes in rats, J. Exp. Nanosci. 14 (2019) 89–106, https://doi.org/10.1080/17458080.2018.1502479.
[124] J.H. Lee, M. Gulumian, E.M. Faustman, T. Workman, K. Jeon, I.J. Yu, Blood biochemical and hematological study after subacute intravenous injection of gold and silver nanoparticles and coadministered gold and silver nanoparticles of similar sizes, Biomed. Res. Int. (2018) 2018, https://doi.org/10.1155/2018/8460910.
[125] L. Yang, H. Kuang, W. Zhang, Z.P. Aguilar, H. Wei, H. Xu, Comparisons of the biodistribution and toxicological examinations after repeated intravenous administration of silver and gold nanoparticles in mice, Sci. Rep. 7 (2017) 1–12, https://doi.org/10.1038/s41598-017-03015-1.
[126] Z. Ferdous, A. Nemmar, Health impact of silver nanoparticles: a review of the biodistribution and toxicity following various routes of exposure, Int. J. Mol. Sci. 21 (2020) 1–31, https://doi.org/10.3390/ijms21072375.
[127] X. Yu, I. Trase, M. Ren, K. Duval, X. Guo, Z. Chen, Design of nanoparticle-based carriers for targeted drug delivery, J. Nanomater. (2016) 2016, https://doi.org/10.1155/2016/1087250.
[128] M.P. Alvarez-Berríos, J.L. Vivero-Escoto, In vitro evaluation of folic acid-conjugated redox-responsive mesoporous silica nanoparticles for the delivery of cisplatin, Int. J. Nanomed. 11 (2016) 6251–6265, https://doi.org/10.2147/IJN.S118196.
[129] K. Zhao, D. Li, G. Cheng, B. Zhang, J. Han, J. Chen, et al., Targeted delivery prodigiosin to choriocarcinoma by peptide-guided dendrigraft poly-l-lysines nanoparticles, Int. J. Mol. Sci. 20 (2019) 1–18, https://doi.org/10.3390/ijms20215458.
[130] Y. Li, L. Hao, F. Liu, L. Yin, S. Yan, H. Zhao, et al., Cell penetrating peptide-modified nanoparticles for tumor targeted imaging and synergistic effect of sonodynamic/HIFU therapy, Int. J. Nanomed. 14 (2019) 5875–5894, https://doi.org/10.2147/IJN.S212184.
[131] L. Xu, X. He, B. Liu, C. Xu, S. Ai, R. Zhuo, et al., Colloids and surfaces b: biointerfaces aptamer-functionalized albumin-based nanoparticles for targeted drug delivery, Colloids Surfaces B Biointerfaces 171 (2018) 24–30, https://doi.org/10.1016/j.colsurfb.2018.07.008.
[132] C. Mamot, D.C. Drummond, C.O. Noble, V. Kallab, Z. Guo, K. Hong, et al., Epidermal growth factor receptor – targeted immunoliposomes significantly enhance the efficacy of multiple anticancer drugs in vivo, Cancer Res. 65 (2005) 11631–11639, https://doi.org/10.1158/0008-5472.CAN-05-1093.
[133] S. Mussa Farkhani, A. Asoudeh Fard, P. Zakeri-Milani, J. Shahbazi Mojarrad, H. Valizadeh, Enhancing antitumor activity of silver nanoparticles by modification with cell-penetrating peptides. Artif Cells, Nanomed. Biotechnol. 45 (2017) 1029–1035, https://doi.org/10.1080/21691401.2016.1200059.
[134] P. Säälik, P. Lingasamy, K. Toome, I. Mastandrea, L. Rousso-Noori, A. Tobi, et al., Peptide-guided nanoparticles for glioblastoma targeting, J. Control Release 308 (2019) 109–118, https://doi.org/10.1016/j.jconrel.2019.06.018.
[135] Y. Wang, B.B. Newell, J. Irudayaraj, Folic acid protected silver nanocarriers for targeted drug delivery, J. Biomed. Nanotechnol. 8 (2012) 751–759, https://doi.org/10.1166/jbn.2012.1437.
[136] C. Recordati, M. De Maglie, C. Cella, S. Argentiere, S. Paltrinieri, S. Bianchessi, et al., Repeated oral administration of low doses of silver in mice: tissue distribution and effects on central nervous system, Part Fibre Toxicol. 18 (2021) 1–18, https://doi.org/10.1186/s12989-021-00418-x.
[137] E.I. Hassanen, A.A. Khalaf, A.F. Tohamy, E.R. Mohammed, K.Y. Farroh, Toxicopathological and immunological studies on different concentrations of chitosan-coated silver nanoparticles in rats, Int. J. Nanomed. 14 (2019) 4723–4739, https://doi.org/10.2147/IJN.S207644.
[138] T. Garcia, D. Lafuente, J. Blanco, D.J. Sánchez, J.J. Sirvent, J.L. Domingo, et al., Oral subchronic exposure to silver nanoparticles in rats, Food Chem. Toxicol. 92 (2016) 177–187, https://doi.org/10.1016/j.fct.2016.04.010.
[139] Y. Zhai, J. Su, W. Ran, P. Zhang, Q. Yin, Z. Zhang, et al., Preparation and application of cell membrane- camouflaged nanoparticles for cancer therapy, Theranostics 7 (2017) 2575–2592, https://doi.org/10.7150/thno.20118.
[140] A. Narain, S. Asawa, V. Chhabria, Y. Patil-sen, Cell membrane coated nanoparticles: next-generation therapeutics, Nanomedicine 12 (2017) 2677–2692, https://doi.org/10.2217/nnm-2017-0225.
[141] R.H. Fang, C.J. Hu, B.T. Luk, W. Gao, J.A. Copp, Y. Tai, et al., Supporting Information Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery, Nano Lett. 14 (2014) 2181–2188, https://doi.org/10.1021/nl500618u.
[142] Xiuli Hu Qing Pei, Shi Liu Xiaohua Zheng, X.J. Yawei Li, and ZX. light-activatable red blood cell membrane- camou fl aged dimeric prodrug nanoparticles for synergistic photodynamic/chemotherapy, ACS Nano 12 (2018) 1630–1641, https://doi.org/10.1021/acsnano.7b08219.
[143] Y. Zhang, K. Cai, C. Li, Q. Guo, Q. Chen, X. He, et al., Macrophage-membrane-coated nanoparticles for tumor-targeted chemotherapy, Nano Lett. (2018), https://doi.org/10.1021/acs.nanolett.7b05263.
[144] J.Y. Zhu, D.W. Zheng, M.K. Zhang, W.Y. Yu, W.X. Qiu, J.J. Hu, et al., Preferential cancer cell self-recognition and tumor self-targeting by coating nanoparticles with homotypic cancer cell membranes, Nano Lett. 16 (2016) 5895–5901, https://doi.org/10.1021/acs.nanolett.6b02786.
[145] H. Sun, J. Su, Q. Meng, Q. Yin, L. Chen, W. Gu, Cancer cell membrane-coated gold nanocages with hyperthermia-triggered drug release and homotypic target inhibit growth and metastasis of breast cancer, Adv Funct Mater. 121 (2017) 800, https://doi.org/10.1002/adfm.201604300.
[146] L. Rao, B. Cai, L. Bu, Q. Liao, S. Guo, X. Zhao, et al., Micro fl uidic electroporation-facilitated synthesis of erythrocyte membrane-coated magnetic nanoparticles for enhanced imaging-guided cancer therapy, ACS Nano 11 (2017) 3496–3505, https://doi.org/10.1021/acsnano.7b00133.
[147] X. Xie, X. Hu, Q. Li, M. Yin, H. Song, J. Hu, et al., Unraveling cell-type-specific targeted delivery of membrane-camouflaged nanoparticles with plasmonic imaging, Nano Lett. 20 (2020) 5228–5235, https://doi.org/10.1021/acs.nanolett.0c01503.
[148] Q. Zhao, X.Y. Sun, B. Wu, Y. Shang, X. Huang, H. Dong, et al., Construction of biomimetic silver nanoparticles in the treatment of lymphoma, Mater Sci. Eng. C 119 (2021), 111648, https://doi.org/10.1016/j.msec.2020.111648.