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Review

Polymeric Nanoparticles—Tools in a Drug Delivery System in Selected Cancer Therapies

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Abstract: The increase in cancer cases is undoubtedly affecting the development of new therapeutic approaches. Polymeric nanoparticles are of great interest. Due to their relatively small size, the possibility of incorporating into them medicinal substances and the ease with which their physicochemical properties may be manipulated, they are being used as anticancer drug delivery systems. The aim of this review is to focus on the use of nanoscale polymeric particles in the treatment of colorectal cancer, breast cancer, ovarian cancer and glioblastoma multiforme, and to consider their potential use in cancer gene therapy. According to several reports, the use of polymer nanoparticles as drug carriers is promising in solid tumors. With their application, it is possible to precisely deliver medicinal substances to the tumor structure, to overcome the blood–brain barrier in the case of brain tumors, to reduce the side effects of anticancer agents on normal cells and to achieve a therapeutic effect with a lower drug dose. Additionally, a number of reports indicate that they can also be used in combination with other methods of cancer treatment, mainly radiotherapy.

Keywords: nanoparticles; nanospheres; nanoformulation; polymer; drug delivery system; breast cancer; colorectal cancer; ovarian cancer; glioblastoma multiforme; double emulsion

Citation: Madej, M.; Kurowska, N.; Strzalka-Mrozik, B. Polymeric Nanoparticles—Tools in a Drug Delivery System in Selected Cancer Therapies. *Appl. Sci.* **2022**, *12*, 9479. https://doi.org/10.3390/app12199479

Academic Editor: David Mills

Received: 16 August 2022
Accepted: 17 September 2022
Published: 21 September 2022

1. Introduction

Cancer is undoubtedly one of the most common causes of death among people worldwide [1]. Environmental factors, inappropriate lifestyles (i.e., lack of physical activity, inadequate diet) and genetic predisposition increase the possibility of neoplastic transformation, whereby cells acquire unique characteristics that promote its further development [2,3]. The ability to proliferate unlimitedly, evade the immune response and create new blood vessels to facilitate metastasis are just some of the many characteristics of cancer cells [2,4].

At present, the treatment process is mainly based on debilitating and burdensome chemotherapy, which is also not inert to normal cells and is often insufficient due to emerging cell resistance to the chemotherapeutic agent in question [3]. For this reason, combined methods are used in practice, involving the surgical removal of the tumor combination with pharmacotherapy or radiotherapy [3,5]. Such methods, although they have their advantages, also have limitations, which include the adverse destruction of normal cells, the short half-life of chemotherapeutic agents in the circulation or the difficult access to the medicinal substance in certain tumor types, e.g., glioblastoma multiforme [2,5].

Polymeric nanoparticles (PNPs) are increasingly being used as a drug delivery system (DDS) to solve some of the problems resulting from, among other things, difficulties in delivering the drug related to the location of tumor cells, as well as to reduce the risk of effects on neighboring unchanged cells [6].

Polymeric nanoparticles have small sizes, mainly ranging from 1 nm to 1000 nm [7]. Depending on the method of their formulation, they can take two different structural forms—nanocapsules and nanospheres. In the first case, the medicinal substance is entrapped in a core and surrounded by a polymer layer, but it can also be the core itself.

Nanospheres, however, take the form of a cross-linked polymer inside which the drug is loaded (Figure 1). The medicinal substance in either case can also be absorbed on the surface of the nanoparticle [7,8].

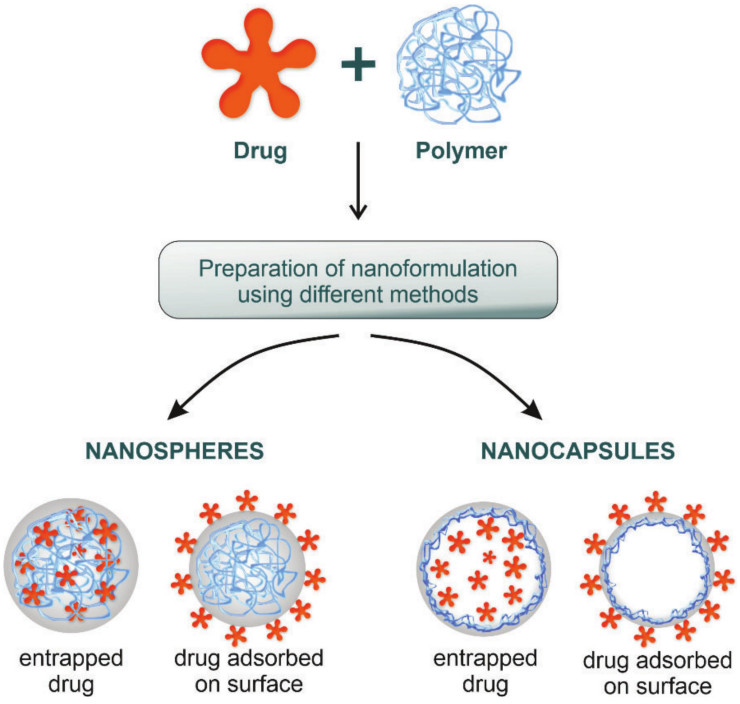

Figure 1. Types of structural forms of polymeric nanoparticles.

Biodegradable and biocompatible polymers are mainly used to produce PNPs. These include synthetic polymers, i.e., poly(lactide) (PLA) or poly(ε-caprolactone) (ε-PCL), as well as *co*-polymers such as poly(lactide-*co*-glycolide) (PLGA), which are currently approved by the Food and Drug Administration (FDA) [6–9]. Polymeric drug delivery systems also use biopolymers, mainly chitosan or collagen, due to their nonimmunogenic properties. This way, once the drug is released, the matrix is hydrolyzed into harmless products.

Another major advantage of PNPs is that it is possible to manipulate the properties of a given polymeric nanoparticle by appropriate modification of the polymer, as a result of which it is possible to control the release of the drug from the nanoparticle at a precise location in the body and also to make the carried water-soluble drug [7,9]. A short half-life, on the other hand, can be compensated for by encapsulating the drug into the nanoparticle [7,9].

Anticancer therapy using polymeric nanoparticles is increasingly being used in research, due to the fact that it is possible to target the therapeutic effect only on cancer cells. The small size undoubtedly mainly plays a role in cancer therapy, where access to the medicinal substance is limited. An example is brain diseases, where the main obstacle is the blood–brain barrier (BBB), which can be abolished in most cases, due to the ability of drug-loaded PNPs to interact on a ligand–receptor basis [5]. Polymeric nanoparticles are also being used in the treatment of colorectal cancer and women's cancers, and there have been in vitro attempts to use them as carriers for genome-editing tools. Therefore, the aim of this review is to present the latest information on the use of polymeric nanoparticles as a drug delivery system in selected cancer therapies and gene therapy.

2. Polymeric Nanoparticles—From Shape to Application

In the controlled delivery of a drug for cancer therapy, the properties of a specific polymeric nanoparticle are crucial. Its size, shape, molar mass, polymer molar ratio or zeta potential and stability in a biological system are highly dependent on the method used to produce PNPs [6,7,10–12].

The size of the nanoparticle should be suitable for the site of application so that it may act efficiently and penetrate biological barriers, but on the other hand, nanoparticles that are too small may be neutralized by the phagocytic system [7,13]. The most effective diameter for a polymeric nanoparticle is assumed to be around 100 nm for delivery to vascularized tumors, due to the ability of nanoparticles this size to pass through fenestrations in the endothelium of a blood vessel [6]. However, in the case of cancerous tumors in the brain's periphery, smaller diameters of polymeric nanoparticles of around 70 nm seem to be more effective, as confirmed by a study conducted by Gao et al. [14] in an animal model [14]. The shape of the PNPs is mainly responsible for their function and pharmacology; therefore, it is highly desirable to obtain PNPs with a spherical structure due to the fact of better uptake of a particular nanoparticle by the target cells [7,13]. In order to prolong the residence time of PNPs in the circulation and to prevent undesirable interaction with plasma proteins, polyethylene glycol (PEG) coating is used. Such modification is directly related to the increase in the half-life in the bloodstream and the improvement of the stability of the nanoparticles [7]. In addition to prolonging the residence time of the particles in the body, PEG coating also increases the hydrophilicity of the particles, and is used to encapsulate hydrophobic and hydrophilic drugs to achieve controlled release of the medicinal substance [7,13].

The most common polymers that are PEGylated are poly(D,L-lacide-*co*-glicolide) (D,L-PLGA) and PLA nanoparticles, which gives them the properties described earlier. Interestingly, studies report that the coating also reduces the effects of toxicity to normal cells [7,13]. In order to enhance selectivity, polymeric nanoparticles are functionalized with, e.g., folic acid, or conjugated with antibodies directed against surface receptors of cancer cells overexpressing a particular receptor [7].

Standard methods for obtaining nanoparticles can be divided into two different groups: top-down and bottom-up techniques (Figure 2).

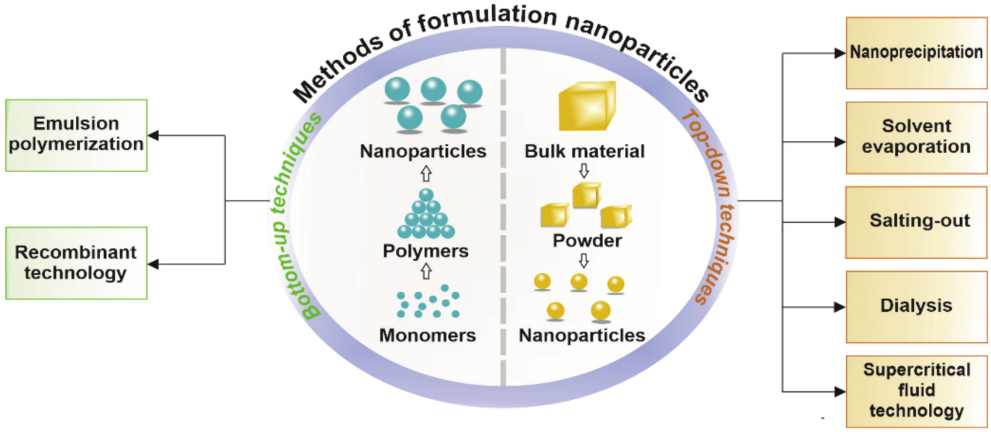

Figure 2. Methods of formulation nanoparticles.

Bottom-up techniques form nanoparticles from single monomers through polymers. This method includes emulsion polymerization and recombination technology, which is mainly used to produce PNPs for gene therapy (Table 1) [6,10–12].

The top-down technique can be distinguished by the formulation of nanoscale particles by: nanoprecipitation, solvent evaporation, salting out, dialysis or supercritical fluid technology (Table 2). The main idea of this method is based on reducing the dimensions of the starting material to a scale corresponding to nanostructures.

Table 1. Bottom-up techniques for formulation of polymeric nanoparticles.

Methods of Formulation	Description	Advantages	Disadvantages	Example	Cancer	Ref.
Emulsion polymerization	Two subgroups may be distinguished: using a continuous organic phase and using an aqueous phase. Dispersion of the monomer into an emulsion occurs, or the monomer is dissolved in an aqueous solution without surfactants, respectively	PNPs with a high molar mass Often used Does not require surfactants when using a continuous aqueous phase	For the continuous organic phase, it requires the use of surfactants and toxic solvents High cost Time-consuming	Cur-loaded PMMA NPs	Human lung cancer lines	[7,10,11,15,16]
Recombinant technology	The latest techniques, based on the use of living organisms, e.g., *Escherichia coli*, to produce a specific biopolymer by altering the expression of genes, result in various amino acid compositions and particle properties	Efficient method Formulates small sizes For gene delivery	Necessary use of living organisms Method under development	K_8-ELP /pDNA	Human breast cancer lines	[11,17]

PNPs—polymeric nanoparticles; Cur—curcuminoid; PMMA—poly (methyl methacrylate); NPs—nanoparticles; K_8—oligolisyne; ELP—elastine-like polypeptide; pDNA—plasmid DNA.

3. Nanoparticles in Cancer Therapy—Passive and Active Mechanisms

In the treatment of cancer, the main problem is that a medicinal substance does not target only cancer cells. Current therapy has a dualistic effect on the patient's body. On the one hand, it attacks cancer cells, causing inhibition of tumor growth or development, while on the other hand, it also destroys healthy cells [18]. In addition, the use of chemotherapy often does not completely eliminate tumor cells and contributes to their recurrence [18]. A significant advantage of polymeric nanoparticles is the possibility of freely modifying nanoparticles at the stage of their manufacture, as a result of which it is possible to obtain biodegradable PNPs formulated from D,L-PLGA or PLAs characterized by different sizes, rates of degradation and thus rates of release of the medicinal substance [19,20]. By increasing the size of the nanoparticle, the half-life of the drug at the target site, resulting from impaired elimination by the kidneys, can be prolonged [21]. In addition, by manipulating the surface area, the entire mechanism of action of a specific nanoparticle can undoubtedly also be altered [6]. For cancer, PNPs are used, which usually have a targeted mechanism of action [6,22]. Depending on the ability of nanoparticles to penetrate blood vessels, as well as the presence of a specific ligand on their surface, an active mechanism and a passive mechanism can be distinguished (Figure 3) [6,21–23].

Table 2. Top-down techniques for formulation of polymeric nanoparticles.

Methods of Formulation	Description	Advantages	Disadvantages	Example	Cancer	Ref.
Nanoprecipitation	Use of two mixing solutions, which results in the displacement of solvent and precipitation of nanoparticles	Single step Formulation of nanospheres and nanocapsules (~200 nm)	Only hydrophobic drugs can be encapsulated Solvent residues	BLC-PTX-loaded D,L-PLGA NPs	Human lung cancer lines	[7,24–27]
Solvent evaporation	PNPs are obtained by evaporation of the solvent from the polymer followed by diffusion through the continuous phase. Single or double emulsion can be carried out	Formulates nanospheres Simplicity	Requires homogenizer and heating Residual solvent may remain For lipid-dissolved drugs	DTX-loaded FA/D,L-PLGA NPs	Breast cancer lines	[3,7,11,24–26]
Salting out	Water with salt is rapidly added to a polymer solution with a drug and a water-soluble solvent, leading to the diffusion of the solvent and the formation of nanoparticles	For heat-sensitive drugs No heating required Encapsulates nucleic acid and protein molecules	Only for lipophobic drugs Time-consuming Stabilizer removal required	Meloxicam-loaded D,L-PLGA NPs	Human colorectal cancer lines	[7,19,26,28]
Dialysis	Uses a dialysis tube inside which a polymer dissolved in a solvent. Suspension of nanoparticles results in displacement of the solvent	Simplicity Easy manipulation of nanoparticle size	Time-consuming Does not require advanced equipment	DTX-loaded poly (N-vinyl-caprolactam) chitosan NPs	TNBC (in vivo)	[3,11,20]
Supercritical fluid technology	In this method, supercritical liquid is used and is based on two phenomena: the rapid expansion of the supercritical solution and the rapid expansion of the supercritical solution into the solvent	High purity of nanoparticles Environmentally friendly Possibility of formulating very small sizes (<20 nm)	Technique rarely used Limited solubility of compounds in supercritical fluid	CXB-loaded D,L-PLGA NPs	Metastatic cancers	[11,29,30]

BLC—baicalein; PTX—paclitaxel; D,L-PLGA—poly(D,L-lactide-*co*-glycolide); NPs—nanoparticles; PNPs—polymeric nanoparticles; DTX—docetaxel; FA—folic acid; TNBC—triple-negative breast cancer; CXB—celecoxib.

3.1. Passive Mechanism

As a tumor grows, the architecture at the tumor site is rearranged [31]. A so-called tumor microenvironment (TME) emerges, which is composed of multiple cell types, i.e., fibroblast-associated cells (CAFs), tumor-associated macrophages (TAMs) and other immune cells [31]. The possibility of tumor proliferation and the influx of cells into the TME is mainly due to the formation of new blood vessels [23,31,32]. The rate of their formation is rapid as a result of the irresistible need to supply nutrients and oxygen necessary for its growth [23,32]. The consequence of this is the appearance of abnormalities in the endothelium of blood vessels [23,32]. They become more permeable, allowing polymeric nanoparticles to enter the tumor more efficiently. Increased lymphatic drainage due to abnormal vascular structure further contributes to prolonged retention of the nanoparticle inside the tumor structure [21,23,32]. Both of these processes contribute to the so-called enhanced permeability and retention (EPR) effect, which directs polymeric nanoparticles to the tumor site [21,23,32]. PNPs up to 200 nm in size are assumed to diffuse best through the damaged endothelium [15]. However, this mechanism has its limitations mainly due to individual occurrences (differences in vascular permeability, cell receptor expression, etc., between patients with the same type of cancer), in which the EPR effect may not be present in humans in solid tumors or insufficiently so that diffusion of nanoparticles

into the tumor is limited [21,23,33]. In addition, it is acknowledged that the targeted action of PNPs through the EPR effect does not allow for the reduction in toxicity and triggering of side effects (Figure 4) [26,34,35]. One example of nanoformulation based on a passive mechanism is the Genexol PM® product, comprising Monomethoxy-poly (ethylene glycol)-*block*-poly(D,L-lactide) loaded with paclitaxel at a dose of 30 mg. Currently, its use is approved in South Korea for the treatment of metastatic breast cancer, while in the USA it is under phase II clinical trials as a potential pancreatic cancer drug [22].

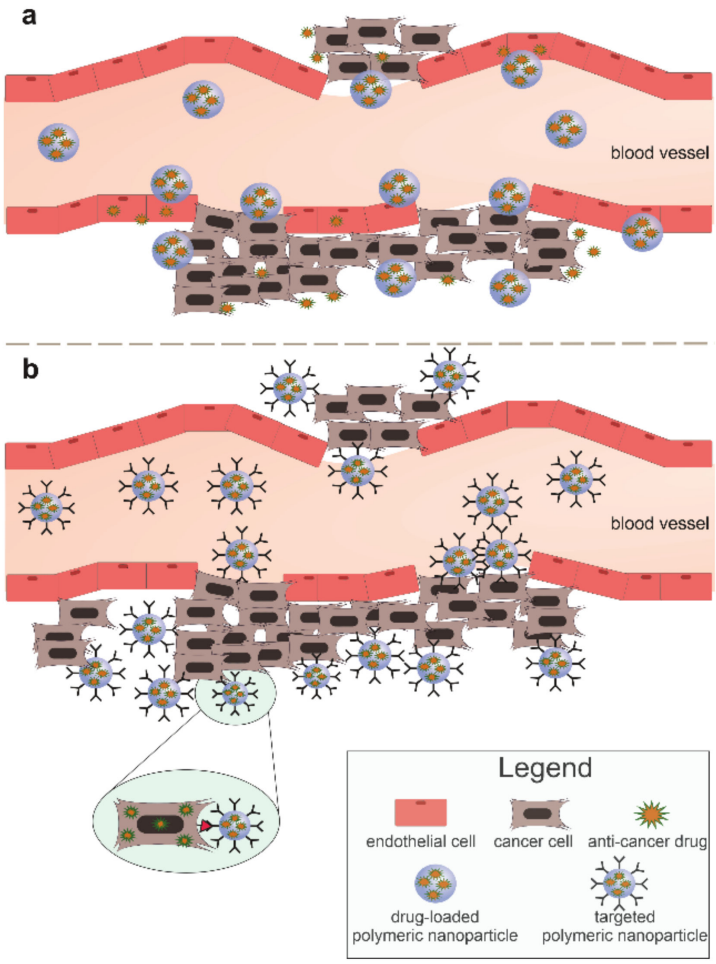

Figure 3. Mechanisms of action of polymeric nanoparticles: (**a**) passive mechanism; (**b**) active mechanism.

3.2. Active Mechanism

In cancer progression, an increase in the expression of certain receptors on the surface of the cancer cell is also observed [6]. The active mechanism, as compared to the passive one, is based on exploiting this phenomenon and applying a selected polymeric nanoparticle in combination with a cell-specific ligand [35,36]. Due to this effect, the polymeric nanoparticle with the incorporated drug can better reach the tumor site and also what is highly desirable, limiting the interaction only to tumor cells and thus causing a reduction in systemic toxicity [36]. The most commonly used ligands attached to PNPs are biotin, folic acid and antibodies directed against specific cellular antigens or proteins [26]. As an example, in 2015, a study by the team of Shi et al. [37] showed that the use of D,L-PLGA with paclitaxel (20% *w*/*w* dry weight of PLGA) nanoparticles conjugated with 50 µg of vascular endothelial growth factor (VEGF) formulated by single emulsion solvent evaporation better increases the affinity for human umbilical vein endothelial cells (HUVECs) than PLGA NPs without conjugation to VEGF. Additionally, they showed greater antiproliferative effects, which

is crucial for anticancer therapy [26,37]. However, the use of a combination of polymeric nanoparticles drug-loaded with a surface ligand has some limitations. The main one is the reduced circulation time in the bloodstream due to faster uptake by the phagocytic system, as well as the variability in the expression of selected receptors depending on the stage of the cancer [26,36]. Despite these disadvantages, this system is more commonly used than one based on a passive mechanism.

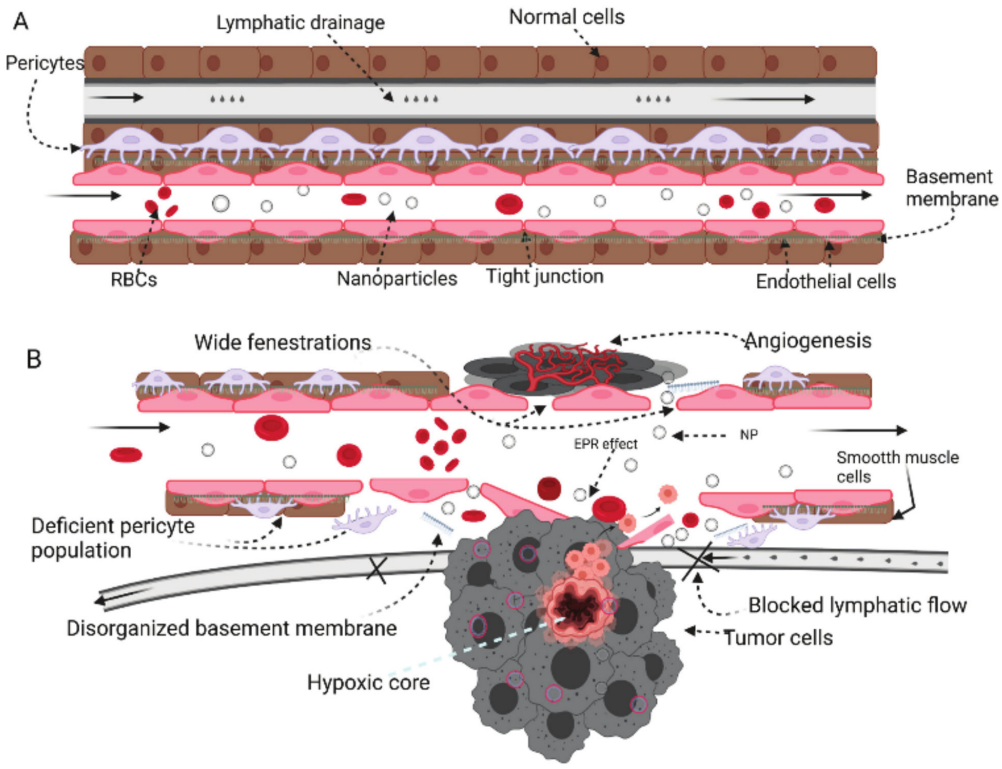

Figure 4. Comparison of properties of cancer cells used in treatment with polymeric nanoparticles with normal tissue structure: (**A**) normal tissue; (**B**) cancer tissue with microenvironment. Reprinted with permission from Ref. [34]. Copyright 2022 MDPI.

4. Polymeric Nanoparticles in Colorectal Cancer Treatment

Colorectal cancer (CRC) is classified as the second leading cause of cancer deaths worldwide and categorized as a solid tumor developed from an initial adenoma [38–40]. The most challenging issue is the therapy of CRC patients. As a result of progression and angiogenesis, a tumor microenvironment (TME) is formed, which makes treatment with currently available cytostatic agents more difficult due to limited access to tumor cells [39]. Standard therapy includes the administration of mixed cytostatic drugs, e.g., oxaliplatin application together with 5-fluorouracil (5-FU), or the use of irinotecan instead of oxaliplatin [41]. In some cases, additional monoclonal antibodies are also used, e.g., bevacizumab, cetuximab or panitumumab [41].

In the case of therapy and administration of medicinal substances in the treatment of CRC, it is necessary to consider and take into account all physiological as well as pathological aspects occurring in this type of malignancy [41]. Due to its location, the administration of anticancer drugs is carried out mainly by injection of a suspension of polymeric nanoparticles loaded with the drug [41]. Most frequently, additional coating with ligands specific for CRC neoplastic cells is used in this case. Another way of drug administration is the oral route, which involves the use of a pH-dependent drug delivery and release system [41]. The drug, when administered orally, overcomes a number of physiological barriers associated with changes in the pH scale. Therefore, for this purpose,

polymeric nanoparticles are coated with an enteric layer, which, at higher pH levels, is degraded, so that the drug can be released at a specific location (Figure 5) [41].

The application of chemotherapeutic agents, due to their physicochemical properties, bioavailability and lack of tissue and cell selectivity, results in the patient's normal cells also being destroyed during therapy [41,42]. Therefore, new methods of delivering a medicinal substance targeting only cancer cells are increasingly being investigated. To achieve this, researchers are attempting to use polymeric nanoparticles as drug delivery systems in colorectal cancer cells due to the small size of the nanoparticles, allowing them to freely penetrate blood vessels and achieve high stability and targeted release of the drug being carried [42].

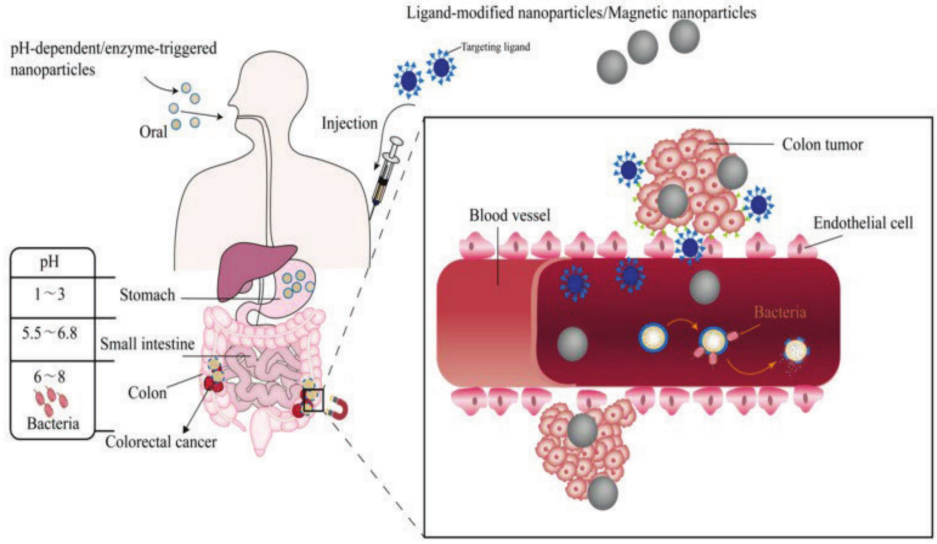

Figure 5. Administration routes for polymeric nanoparticles in the treatment of colorectal cancer. Reprinted with permission from Ref. [41]. Copyright 2022 MDPI.

An in vitro and in vivo study by the team of Wu et al. [43] in 2020 on the SW620 cell line and BALB/c mice showed that the use of PLGA nanoparticles loaded with 5 mg 5-FU and 2 mg perfluorocarbon (PFC) conjugated to EGF (EGF-PLGA@5FU/PFC NPs) formulated by the double emulsion solvent evaporation method resulted in the targeted delivery of the anticancer agent to tumor cells only via the active mechanism of the polymeric nanoparticle [43]. In addition, this formulation allows the chemoresistance of colorectal cancer cells to be abolished by locally increasing oxygen levels in the vicinity of the tumor tissues [43]. Such studies provide new information on the use of formulations in the delivery of drug combinations with synergistic effects. Consequently, the use of PNPs to deliver chemotherapeutics in CRC may prove crucial in the development of new strategies for targeted anticancer therapy, thereby reducing the adverse effects caused by the use of uracil-based drugs. In most cases, the polymers used to formulate nanoparticles such as D,L-PLGA are additionally coated with PEG in order to prolong their persistence in the circulation, which is important due to the difficulty of accessing tumor cells through the TME present in colorectal cancer [43]. Among polymeric nanoparticles, studies using the biopolymer chitosan for drug delivery systems in CRC can also be found [43]. Other studies using polymeric nanoparticles as drug delivery systems in colorectal cancer are presented in Table 3.

Table 3. Polymeric nanoparticles as drug delivery systems for colorectal cancer therapy.

PNPs	Formulation Method	Size (nm)	Drug	Dose	In Vitro/In Vivo	Ref.
PHBV/PLGA	Double emulsion solvent evaporation	~150	5-FU	3 mg/mL	In vitro—HT-29, CT-26 In vivo—BALB/c mice	[44]
PLGA-PEG-PLGA	Double emulsion solvent evaporation	~40	5-FU/Chrysin	10 mg/mL	In vitro—HT-29	[45]
HPMC phthalate	Nanoprecipitation	~478	Doxycycline	5 mg/kg, 10 mg/kg	In vivo—Swiss albino mice	[46]
D,L-PLGA	Single emulsion solvent evaporation	~191	Curcumin	10 mg, 20 mg	In vitro—HT-29	[47]
D,L-PLGA	Spontaneous emulsification	~310	SN-38	15 mg	In vitro—COLO-205	[48]
Poly-UA	Nanoprecipitation	~171	Mith-A	3 mg	In vitro—CT-26 In vivo—BALB/c mice	[49]
Chitosan polymeric	Ionic gelation technique	~200	Imatinib	5 mg	In vitro—CT-26 In vivo—Wistar rat	[50]
D,L-PLGA-PEG-FA	Double emulsion solvent evaporation	~201	Oxaliplatin	5 mg/kg	In vitro—CT-26 In vivo—BALB/c mice	[51]
D,L-PLGA	Single emulsion solvent evaporation	~237	Quercetin and CAPE	5 mg and 15 mg	In vitro—HT-29	[52]
v6 Fab-PLGA-PEG	Double emulsion solvent evaporation	~345	Bevacizumab	25 mg/mL	In vitro—MKN74-CD44std and CD44v6+	[53]
CS-Chitosan	Single emulsion solvent evaporation	~289	Camptothecin	6 mg	In vitro—CT-26 In vivo—BALB/c mice	[25,54]
PMMA	Single emulsion solvent evaporation	~154	Benznidazole	0.0125 mg/25 mL	In vitro—HT-29	[55]
PEG	Single emulsion solvent evaporation	~114	PTX and DHA	6 µg/mL	In vitro—HT-29	[56]
PCL-PEG-PCL	Double emulsion solvent evaporation	~95	Cur and MTX	4 mg and 2 mg	In vitro—CL-40, SW1417	[57]
D,L-PLGA	Modified salting-out	~200	Meloxicam	n/d	In vitro—HT-29	[28]
PEG-PLGA	Double emulsion solvent evaporation	~147	PTX	1 mg	In vitro—S174T, COLO205, HCT116	[58]
PEG-PLGA	Double emulsion solvent evaporation	~289	Sorafenib and PEDF	2 mg and 25 µg	In vitro—C26 In vivo—BALB/c mice	[59,60]

PHBV—poly(3-hydroxybutyrate-co-3-hydroxyvalerate); D,L-PLGA—poly(D,L-lactide-co-glycolide); 5-FU—5-fluorouracil; PEG—polyethylene glycol; HPMC—hydroxypropyl methyl cellulose; SN-38—7-ethyl-10-hydroxy-camptothecin; EGFR—epidermal growth factor receptor; mAb—monoclonal antibody; poly-UA—poly(ursolic acid); Mith-A—mithramycin-A; FA—folic acid; CAPE—caffeic-acid phenethyl ester; Fab—antibody fragment; CS—chondroitin sulfate; PMMA—poly(methyl methacrylate); PTX—paclitaxel; DHA—dihydroartemisinin; Cur—curcumin; MTX—methotrexate; PAA—poly(acrylic acid); ε-PCL—poly(ε-caprolactone); PEDF—pigment epithelium-derived factor.

5. Polymeric Nanoparticles in Breast and Ovarian Therapy

Undoubtedly, the most common type of cancer occurring in women is breast cancer [61–63]. Among the different types, triple-negative breast cancer (TNBC) appears to be the most malignant and most metastatic [61]. For therapy, the use of combinations of various taxanes, i.e., PTX or DTX, platinum-based compounds, e.g., cisplatin, or the application of drugs from the anthracycline group, is common, with doxorubicin leading the way [61,62].

The second type of cancer closely related to breast cancer is ovarian cancer [64]. The division of ovarian cancer is based on histopathological changes within the epithelium and includes five subtypes, 90% of which are high-grade serous carcinoma [64,65]. Treatment of ovarian cancer is based on a combination of surgical resection and chemotherapy [66]. The gold standard is the administration of platinum-based drugs, e.g., carboplatin, whose efficacy reaches up to 80% in combination with PTX. However, this treatment is not always sufficient, as recurrence of the disease is observed [66].

The problem of chemotherapy for treatment of breast and ovarian cancer is the non-selective mechanism of action of the platinum-based or cytostatic drugs concerned [61]. In addition, the drugs applied in therapy are poorly soluble, and also, in some cases, cell resistance to the drug may occur [67]. Multidrug resistance (MDR) is an increasingly common phenomenon in cancer therapy that complicates the treatment process [68]. The development of chemoresistance in tumor cells occurs either after treatment with cytostatic drugs or, surprisingly, in patients not treated with chemotherapeutic agents. In addition, the use of one type of drug may lead to the development of resistance not only to the drug used, but also to other subtypes [68]. This occurrence is one of the most challenging obstacles for sufficient treatment for both types of cancers. Therefore, there are increasing reports on the development of new formulations using polymeric nanoparticles in targeted drug delivery aimed at cancer cells [68].

A poly(D,L-lactide-*co*-glycolide) nanoparticle functionalized with 0.2 mg folic acid and loaded with 10 mg docetaxel was investigated by the team of Poltavets et al. [69]. In their study on breast cancer cell lines with overexpression of the folic acid receptor alpha (FRα), they found that the use of the polymeric carrier overcomes the chemopreventive effect. Additionally, increases in the cytotoxicity of docetaxel towards breast cancer cells, compared to the use of DTX in its native form, were observed [68,69]. This indicates that the polymeric nanocarriers have a significant effect on both distribution and selectivity, as well as reducing toxic effects on normal cells [68,69].

Currently, Abraxane®, an albumin-based nanoparticle loaded with 5 mg paclitaxel, is used for the treatment of metastatic breast cancer [61]. It should be noted here that it is commonly referred to as a polymeric nanoparticle, even though it should actually be classified as a nanoconjugate due to its physicochemical properties and structure. However, for relevance and illustration, several applications of nanoconjugates based on albumin-bound nanoparticles are also included in this review. However, the two terms should not be mixed up.

In addition, cancer stem cells (CSCs) also play an important role in the development of MDR, which is also the reason for cancer recurrence [68,70]. The major factor behind this process is an increase in the expression of selected ATP-binding cassette efflux transporters, which contributes to a greater pumping of the medicinal substance out of the cell, leading to a reduced cellular response to the chemotherapeutic agent [68,70]. However, this process can be abolished in some cases by using coadministration of cytostatic drugs with chemosensitizers [68]. In a study by Guo et al. [71] using solvent-based methods, mPEG-D,L-PLA nanoparticles loaded with docetaxel and resveratrol were obtained simultaneously. The study, conducted on MCF-7 breast cancer lines and in vivo, observed that the coadministration of these two substances increased the cytotoxic effect and abolished the MDR effect in tumor cells. This suggests that reducing the effect of resistance to chemotherapeutics can be achieved by combining drugs that exhibit synergistic effects, causing MDR to be eliminated in cancer cells [71].

The use of polymeric magnetic nanoparticles in the treatment of breast cancer also seems interesting, because it reduces the elimination of drug-loaded NPs by the reticuloendothelial system [72]. The team of Alsadat Vakilinezhad et al. [72] conducted a study to evaluate the potential of using PLGA NPs loaded with methotrexate (MTX)-functionalized magnetide against the SK-BR-3 line. The results of the study showed similar cytotoxicity to MTX. In addition, based on the accumulation of particles at the target site, they concluded that such a combination could reduce the side effects of MTX [72].

An overview of the PNPs used in the treatment of ovarian cancer and breast cancer is presented in Table 4.

Table 4. PNPs as a drug delivery system in breast and ovarian cancer treatment.

PNPs	Formulation Method	Size (nm)	Drug	Dose	In Vitro/In Vivo	Cancer	Ref.
D,L-PLGA	Modified nanoprecipitation	~70	Cur	1 mg	In vitro—A2780, A2780CP	Ovarian	[73]
PLGA-PEG-HA	Single emulsion solvent evaporation	~268	SN-38	3 mg/mL	In vitro—SKOV-3, CHO	Ovarian	[74]
PEG-*b*-PLA	Single emulsion solvent evaporation	~112	Bortezomib	500 µg	In vitro—MDA-MB-468, HCC1937 In vivo—NOD/SCID and ICR mice	TNBC	[75]
Chitosan-EGFRvIII	Ionotropic gelation technique	~146	Gemcitabine	5 mg	In vitro—OVAR-8	Ovarian	[76]
PEG-PLA	Single emulsion solvent evaporation	~88	DOX	10 mg	In vitro—MDA-MB-231 In vivo—NOD/SCI mice	Breast	[77]
PEG-PLA	Double emulsion solvent evaporation	~79	DAC	5 mg	In vitro—MDA-MB-231 In vivo—NOD/SCI mice	Breast	[77]
mPEG-PLGA	Nanoprecipitation	~101	Nos	5 mg	In vitro—4T1 In vivo—BALB/c mice	Breast	[78]
PCEC	Double emulsion solvent evaporation	~28	PTX and Cur	3 mg/mL	In vitro—MCF-7 In vivo—BALB/c mice	Breast	[79]
mPEG-PLGA	Single emulsion solvent evaporation	~165	Piperine	8.5 mg	In vitro—MDA-MB-488, BT-549	TNBC	[80]
PCL	Single emulsion solvent evaporation	~154	PTX and IR780	140 µg and 148 µg	In vitro—SKOV-3, ST30 In vivo—BALB/c mice	Ovarian	[81]
Chitosan-PLGA	Ionic gelation	~156	Carboplatin	n/d	In vitro—PEO1	Ovarian	[82]
PEG-PLA-FA	Nanoprecipitation	~192	PTX	50 mg	In vitro—SKOV-3, HO-89110, A2780 In vivo—BALB/c mice	Ovarian	[83]
PLGA-PEG-maleimide	Single emulsion solvent evaporation	~209	PTX	5 mg	In vitro—LM2 In vivo—BALB/c mice	TNBC	[84]
PLGA with anti-CD133 mAb	Single emulsion solvent evaporation	~320	PTX	6 mg	In vitro—MCF-7, MDA-MB-231-luc In vivo—BALB/c mice	Breast	[85]

D,L-PLGA—poly(D,L-lactide-co-glycolide); Cur—curcumin; HA—hialuronic acid; PEG—polyethylene glycol; SN-38—7-ethyl-10-hydroxy-camptothecin; PEG-*b*-PLA—poly(ethylene glycol)-block-poly(D,L-lactide); D,L-PLA—poly(D,L-lactide); TNBC—triple-negative breast cancer; EGFRvIII—epidermal growth factor receptor variant III; DOX—doxorubicin; DAC—decitabine; mPEG—methoxy polyethylene glycol; Nos—noscapine; PCEC—poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone); PTX—paclitaxel; ε-PCL—poly(ε-caprolactone); FA—folic acid; mAb—monoclonal antibody.

Increasingly, polymers are also being used to coat nanoparticles, with the aim of improving their potency. Undoubtedly, one such polymer is polyvinyl alcohol (PVA) [86]. In 2022, Shahrousvand et al. [86] obtained poly(vinyl alcohol-2-hydroxyethyl methacrylate) (PVA-PHEMA) nanoparticles by hydrolyzing PVAc-PHEMA copolymers. They observed that the nanoparticles prepared in this way acquired pH-sensitive properties and increased release of the drug in the acidic medium, which may contribute to the accumulation within the tumor [86]. In addition, the nanoparticles were shown to be biocompatible and, upon the staining of cells, it was shown that PVA-HEMA copolymer nanoparticles exhibited the properties of intelligent particles affecting the death of neoplastic cells [86]. PVA was also used as a coating for the nanoparticle codelivery of MTX and gemcitabine in the treatment of bone cancer [87].

Due to the fact that PNPs are increasingly being used in research on new potential methods for drug delivery to tumor cells, several clinical trials using PNPs have been conducted. An overview of clinical trials for breast, ovarian and colorectal cancer using nanoparticles for potential therapeutic applications is presented in Table 5, which was generated from data available in the database https://clinicaltrials.gov/ (accessed on 14 September 2022).

Table 5. Clinical trials using PNPs in selected cancer therapy based on https://clinicaltrials.gov/ (accessed on 10 September 2022).

Identifier	Drug Delivery System	Title	Cancer	Phase	Status
NCT03774680	PNPs	Targeted Polymeric Nanoparticle Loaded With Cetuximab and Decorated With Somatostatin Analogue to Colon Cancer	Colon Cancer	I	Unknown
NCT02010567	PNPs	Neoadjuvant Chemoradiotherpay With CRLX-101 and Capecitabine for Rectal Cancer	Rectal Cancer	II	Terminated
NCT03505528	Nab–paclitaxel	An Early Phase Study of Abraxane Combined With Phenelzine Sulfate in Paient With Metastatic or Adcanced Breast Cancer (Epi-PRIMED)	Breast Cancer	I	Completed
NCT02788981	Nab–paclitaxel	Abraxane® With or Without Mifepristone for Advanced, Glucocorticoid Receptor-Positive, Triple-Negative Breast Cancer	TNBC	I	Active
NCT04249167	Nab–paclitaxel	Cryoablation, Atezolizumab/Nab-paclitaxel for Locally Advanced or Metastatic Triple Negative Breast Cancer	TNBC	I	Withdrawn
NCT00499252	Nab-paclitaxel	Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Recurrent or Persistent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Ovarian Cancer	II	Completed
NCT03942068	Nab–paclitaxel	Apatinib With Albumin-bound Paclitaxel in Patients With Platinum-resistant Recurrent Ovarian Cancer	Ovarian Cancer	II	Unknown
NCT01652079	PNPs	CRLX101 in Combination With Bevacizumab for Recurrent Ovarian/Tubal/Peritoneal Cancer	Ovarian Canacer	II	Completed
NCT00313599	Nab–paclitaxel	Lapatinib and Paclitaxel in Treating Patients With Advanced Solid Tumors	Ovarian Cancer	I	Completed
NCT03719326	Nab–paclitaxel	A Study to Evaluate Safety/Tolerability of Immunotherapy Combinations in Participants With Triple-Negative Breast Cancer or Gynecologic Malignancies	TNBC, Ovarian Cancer	I	Completed
NCT00989131	PNPs	Study of Paclitaxel in Patients With Ovarian Cancer	Ovarian Cancer	III	Completed

PNPs—polymeric nanoparticles; Nab–paclitaxel—nanoparticle albumin-bound paclitaxel; TNBC—triple-negative breast cancer.

6. Polymeric Nanoparticles in Glioblastoma Multiforme Therapy

Glioblastoma multiforme (GBM) is a primary malignant brain tumor characterized by a high mortality rate [88,89]. Combination of surgery, radiotherapy and local chemotherapy consisting of implantable drug formulation appears to be most promising methods for treatment [90]. However, a significant disadvantage of commonly used chemotherapeutics is the short half-life in blood circulation, leading to difficulty in transporting and releasing the drug at the proper pathological lesion [91]. PNPs, due to their diversity and the possibility of loading them with various drugs, are of major interest. Furthermore, they can be modified to penetrate the BBB and reach cancer cells [88]. The above factors are associated with improved penetration of the drug into the tumor, reduced side effects on healthy tissues and increased concentration of the drug in the pathologically altered area [88]. Several routes of PNP administration for GBM can be distinguished, i.e., focused ultrasound, which uses the ability to temporarily open the BBB; convection-enhanced delivery, based on delivering the drug to the brain region using pump systems; intranasally,

whereby the nanoparticles are absorbed through the olfactory pathways; and the use of polymeric hydrogels intracranially (Figure 6) [92].

Liang et al. [93] developed anti-EGFRvIII-modified conjugated polymer nanoparticles. Poly [2-methoxy-5-(2-ethylhexyloxy)-*p*-phenylenevinylene] was used as the core. The developed system exhibited high reactive oxygen species generation ability under white-light irradiation. By studying their effect on the LN229 cell line, they observed not only that the fluorescent targeting effect can enable neurosurgeons to clearly identify the tumor boundary during the neurosurgical operation, but also that the release of reactive oxygen species promotes the death of EGRFvIII-positive cells, as well as adjacent cells not carrying this mutation [93]. Currently, the interest of many researchers is focused on the use of biodegradable polymers to produce nanoparticles [94–96]. Some other research on nanoparticles for GBM therapy is presented in Table 6.

Table 6. Polymeric nanoparticles in glioblastoma multiforme treatment.

PNPs	Formulation Method	Size (nm)	Drug	Dose	In Vitro/In Vivo	Ref.
D,L-PLGA	Nanoprecipitation	~250	Cur	1 mg	In vitro—DKMG/EGFRvIII, DK-MG^{low}	[94]
mPEG-PLGA	Nanoprecipitation	<150	PTX and etoposide	5 mg	In vitro—U87, C6 In vivo—Wistar rats	[95]
D,L-PLGA	Nanoprecipitation	~212	PTX and MTX	2.5 mg	In vitro—U87MG, B65	[96]
mPEG–PTMC	Single emulsion solvent evaporation	~49	PTX	10 mg	In vitro—U87MG In vivo—Sprague Dawley rats	[97]
mPEG-PLGA	Double emulsion solvent evaporation	~206	PTX and TMZ	0.2 mg/mL and 4.4 mg/mL	In vitro—U87, C6 In vivo—BALB/c mice	[98]
D,L-PLGA	Single emulsion solvent evaporation	~135	PTX	5 mg	In vitro—C6 In vivo—Sprague Dawley rats	[99]
D,L-PLGA	Double emulsion solvent evaporation	~110	DOX	23 mg/mL	In vivo—Wistar rats	[100]
mPEG-(LA)-(TBPC)	Nanoprecipitation	~68	DOX	2 mg/mL	In vitro—U87, GIN-8, GIN-28, GIN-31	[101]
Receptor -mediated D,L-PLGA	Modified single emulsion solvent evaporation	~187	TMZ	1 mg	In vitro—U87, U215, NHA	[102]
D,L-PLGA	Emulsion solvent evaporation techniques	~200	TMZ	3.3 mg/mL	In vitro—U87	[103]

D,L-PLGA—poly(D,L-lactide-*co*-glycolide); Cur—curcumin; mPEG—methoxy polyethylene glycol; PTMC—poly(trimethylene carbonate; LA—lactid acid; TBPC—t-butyloxycarbamoyl-protected cyclic carbonate; PTX—paclitaxel; MTX—methotrexate; TMZ—temozolomide; DOX—doxorubicin.

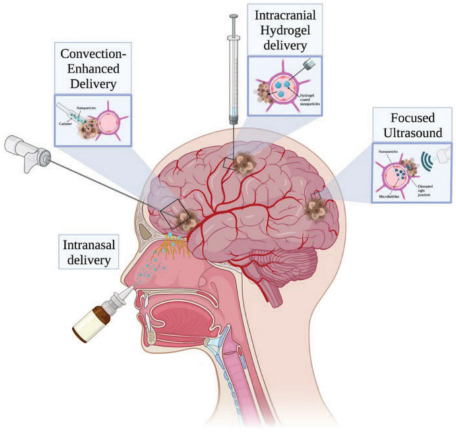

Figure 6. Administration routes for polymeric nanoparticles in the treatment of GBM. Reprinted with permission from Ref. [92]. Copyright 2022 MDPI.

7. PNPs as a Drug Delivery System in Cancer-Associated Gene Therapy

The main advantages of using a drug delivery system in cancer treatment are the possibility of reducing side effects of the drug, better acceptance by the patient, the use of a lower effective dose of the drug and the possibility of controlling the rate of drug release at a precise location, while increasing the stability and efficacy of the active substance [28]. Due to these features, as well as advances in genetic engineering and biotechnology, PNPs are increasingly being used as DDSs used to introduce molecules into cells [104,105]. Biopolymers such as chitosan, dextran or pullulan are of particular importance due to their easy production process and nonimmunogenicity, biocompatibility and biodegradability [104]. Synthetic polymers such as poly (beta-amino ester) (PBAE) or D,L-PLGA are also used [104,106]. Ease of interaction with DNA molecules is also provided by the use of cationic polymers, which are capable of interacting with anionic groups in nucleic acid [11,105]. The mechanism of action of polymeric nanoparticles as gene carriers in anticancer therapy works by overcoming both extracellular and intracellular barriers [107,108]. A PNP loaded with a molecule such as DNA, oligonucleotides (ONs), etc., binds to the surface-specific receptor of a cancer cell, undergoes endocytosis and in the form of an endosome is transported into the cytoplasm [107,108]. The degrading nanoparticle releases its contents. In the case of a DNA molecule, the particle is transported to the cell nucleus, where it affects the process of gene transcription [107]. In the case of mRNA, protein synthetase is disrupted, while in the case of siRNA or miRNA, it binds to the RISC protein complex, leading to silencing of gene expression [107]. Each of the events leads to inhibition of proliferation of the neovascular cells and ultimately their death (Figure 7) [108].

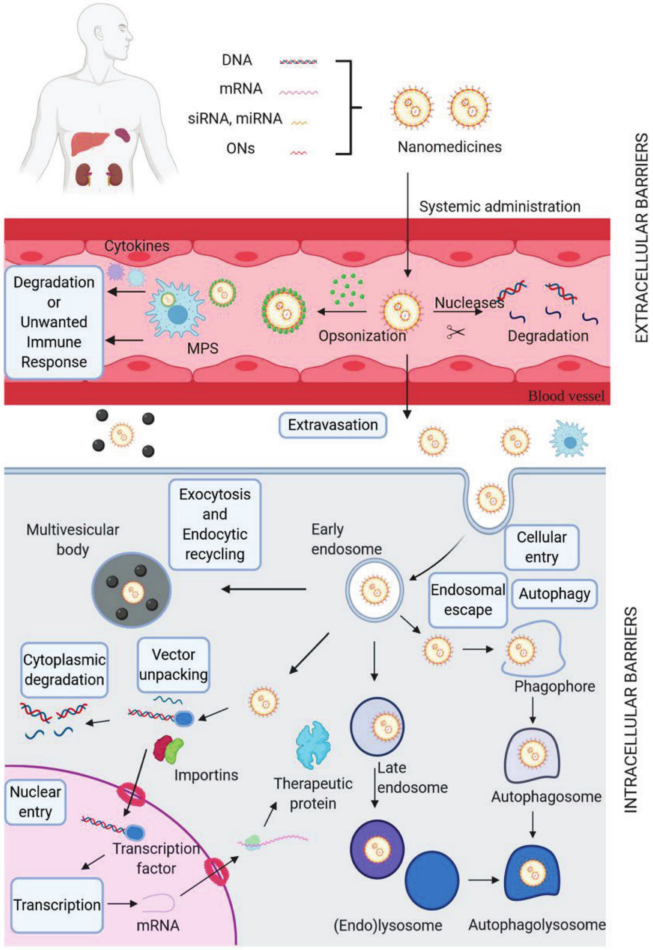

Figure 7. Mechanism of action of PNPs as gene delivery systems for cancer treatment. Reprinted with permission from Ref. [108]. Copyright 2021 MDPI.

In order to better eradicate the cancer tumor, immunotherapy is also widely used, focusing in particular on the activation of cells of the immune system, mainly T lymphocytes and cells with a CD8+ surface antigen, to eliminate cancer cells of a specific tumor type [109]. The most commonly used technique is the so-called adoptive T-cell immunotherapy, which is based on the use of patient-derived cells, their modification and reintroduction into the patient's body [110]. Inherent in the course of neoplastic diseases, as mentioned earlier, is the presence of TME, which consists of many cell types that produce both growth factors, chemotactic factors and cytokines. Due to this, a chronic presentation of the neoplastic antigen is produced, resulting in the acquisition of tolerance by T cells, which is associated with a decrease in the level of activation and proliferation of T cells involved in the eradication of neoplastic cells through receptor-related disorders, i.e., programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [109,110]. Therefore, a promising approach seems to be the use of methods based on antibodies that block receptors contributing to PD-1 inhibition and simultaneously activate T cells. One solution is to use nanoparticles that target both of these elements and, at the same time, avoid nonspecific binding to the receptors. In a study conducted by Mi et al. [111] on C57BL/6 mice, the effect of mPEG-PLGA nanoparticles conjugated with PD-1 and OX40 antibodies obtained by nanoprecipitation on the ability to activate T lymphocytes was evaluated. The results of the study showed that the use of such a combination allows better activation of the mentioned cells, and thus increased therapeutic efficacy compared to antibodies administered in free form. Thus, the possibility of combining immunotherapy methods and nanotechnology undoubtedly broadens the scope of research into new potential anticancer therapies [111]. Examples of the use of PNPs in gene therapy are presented in Table 7.

Table 7. Examples of PNPs as gene delivery system in cancer therapy.

PNPs	Formulation Method	Size (nm)	Molecule	Dose	In Vitro/In Vivo	Cancer	Ref.
D,L-PLGA	Double emulsion solvent evaporation	~197	BLC2 siRNA	50 μg	In vitro—SKOV3-TR. A2780-CP20	Ovarian	[112]
HA-PLGA	Double emulsion solvent evaporation	~232	PTX; FAK siRNA	900 μg and 125 μg	In vitro—SKOV3, TR, HeyA8, MDR In vivo—BALB/c mice	Ovarian	[113]
Chitosan	Solvent evaporation method	~135	NEAT siRNA	1:1	In vitro—LoVo, SW480, HCT116	CRC	[114]
Chitosan	Polyelectrolyte complexation	~172	DOX,CMD and siRNA	2.5 μg/mL, 1 mg/mL and 5 μL	In vitro—HCT-116	CRC	[115]
D,L-PLGA	Double emulsion solvent evaporation	~159	AFP siRNA	100 μL	In vitro—HepG2, HeLa, MDA-MB-231	HCC, cervical breast	[116]
PBAE-PEI-HA	Solvent evaporation technique	~182	EMB and pTRAIL	1.33 mg	In vitro—MCF-7, MDA-MB-231	TNBC	[117]
D,L-PLGA	Double emulsion solvent evaporation	~145	PNA targeting miRNA-155	1 μM	In vitro—HeLa, SUDHL-5,	Cervical, lymphoma	[118]
PLGA/PLA-PEG-FA	Single emulsion solvent evaporation	~232	miRNA-204-5p	n/d	In vitro—HT-29, HCT-116 In vivo—BALB/c mice	CRC	[119]
PLGA-chitosan with 5TR1	Double emulsion solvent evaporation	~222	Epirubicin	2 mg/mL	In vitro—MCF7, CHO In vivo—BALB/c mice	Breast	[120]
AS1411 aptamer PLGA-PEG	Double emulsion solvent evaporation	~113	Cisplatin; miR-21	8.4 mg/mL; 10 mg/mL	In vitro—A2780 S/R	Ovarian	[121]
PCL-AC	Nanoprecipitation	~194	LCS-1	n/d	In vitro—HCT116	CRC	[122]
AS1411 aptamer PLGA	Single emulsion solvent evaporation	~200	Paclitaxel	10 μg/mL	In vitro—GI-1	Glioblastoma	[123]

D,L-PLGA—poly(D,L-lactide-co-glycolide); siRNA—small interfering RNA; HA—hialuronic acid; PTX—paclitaxel; FAK—focal adhesion kinase; CRC—colorectal cancer; DOX—doxorubicin; CMD—carboxymethyl dextran; AFP—α-fetoprotein; HCC—hepatocellular carcinoma; PBAE—poly(beta-amino ester); PEI—polyethyleneimine; EMB—embelin; pTRAIL—tumor necrosis factor-related apoptosis-inducing ligand plasmid; TNBC—triple-negative breast cancer; PNA—peptide nucleic acid, miRNA—microRNA; D,L-PLA—poly(D,L-lactide); PEG—polyethylene glycol; FA—folic acid; ε-PCL—poly(ε-caprolactone); AC—aminocellulose; LCS-1—superoxide dismutase inhibitor.

Undoubtedly, the use of polymeric nanoparticles as molecule delivery system is one of the most promising. The reason for this is that in the case of gene therapy, polymer nanoparticles have less toxicity and immunogenicity than traditional methods based on vector systems [105]. In addition, due to the use of nanoparticles, it is possible to transport molecules such as miRNAs, siRNAs or gene-editing systems, etc., which directly affect transcription or correction of an abnormal gene [105]. However, despite this, there are still some limitations, mainly related to the lower efficiency of cell transfection compared to viral systems, which may be resolved in the future due to the significant development of biotechnology and nanomedicine [105].

8. Conclusions

Cancer is one of the most common causes of death worldwide, and current treatments are not fully effective and have many negative side effects. Because of this, alternative drug delivery methods are currently being sought to help overcome the limitations of cancer therapy, reduce systemic toxicity and prevent multidrug resistant on cytostatic agents. The use of polymeric nanoparticles in cancer therapy appears promising, especially those derived from D,L-PLGA, a copolymer approved by the FDA for use in active pharmaceutical ingredient delivery systems. These carriers act in an active or passive mechanism and have been proven effective against a variety of cells. The results of numerous studies show great potential for the use of PNPs as chemotherapeutic delivery systems in colorectal cancer, breast cancer, ovarian cancer and glioblastoma multiforme. In addition, PNPs are currently being investigated as carriers in gene therapy. Additionally, worthy of much attention is the fact that some of the PNPs are being evaluated in clinical trials, and some are approved by the FDA for treatment.

Based on a review of the literature, it should be noted that there are a growing number of studies on improving the effectiveness of polymeric nanoparticles. A considerable amount of research suggests that by manipulating the structure and coating of compounds, i.e., PEG, it is possible to significantly control the residence time in the system and reduce undesirable interactions with plasma proteins. This is an important aspect, as it can be concluded that it has a significant impact on the process of drug delivery. Depending on the type of tumor, the location and target site of nanoparticle delivery should also be taken into account. In the case of gastrointestinal cancers, the main limitation is the varying environment depending on the gastrointestinal tract. Therefore, it is suggested that in such a situation it is best to use pH-sensitive nanoparticles coated with an enteric coating to protect the PNPs from early degradation. In addition, to improve the efficacy of nanoparticles, it is necessary to take into account individual patient factors arising from variability in the number and expression of surface receptors of neoplastic cells, as well as individual morphological and structural features of the entire tumor microenvironment. In this aspect, it is undoubtedly important to assess the occurrence of MDR, which, as studies indicate, can be abolished by using codelivery of drugs with synergistic effects. Therefore, in order to improve the overall quality and efficacy of treatment with polymeric nanoparticles, it is crucial to precisely analyze the patient's profile, tumor type and genetic status, as well as to select the appropriate polymer and manufacturing method depending on the encapsulated drug. However, the problem in this aspect is still the high individual variability of tumor heterogeneity, as well as difficulties at the production stage related mainly to the low encapsulation efficiency of some chemotherapeutics.

Nevertheless, nanotherapy is a rapidly developing scientific field, and the results of published research in recent years demonstrate that PNPs can be used as carriers for anticancer drugs, giving hope for the development of more effective treatment methods and regimens for cancer patients.

Author Contributions: Conceptualization, B.S.-M. and M.M.; literature review, M.M. and N.K.; writing—original draft preparation and review and editing, all the authors; supervision, B.S.-M.; funding acquisition, B.S.-M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Li, B.; Li, Q.; Mo, J.; Dai, H. Drug-loaded polymeric nanoparticles for cancer stem cell targeting. *Front. Pharmacol.* **2017**, *8*, 51. [CrossRef] [PubMed]
2. Niculescu, A.G.; Grumezescu, A.M. Novel tumor-targeting nanoparticles for cancer treatment-a review. *Int. J. Mol. Sci.* **2022**, *23*, 5253. [CrossRef]
3. Sartaj, A.; Qamar, Z.; Qizilbash, F.F.; Annu, M.S.; Alhakamy, N.A.; Baboota, S.; Ali, J. Polymeric nanoparticles: Exploring the current drug development and therapeutic insight of breast cancer treatment and recommendations. *Polymers.* **2021**, *13*, 4400. [CrossRef]
4. Ahmad, R.; Singh, J.K.; Wunnava, A.; Al-Obeed, O.; Abdulla, M.; Srivastava, S.K. Emerging trends in colorectal cancer: Dysregulated signaling pathways (review). *Int. J. Mol. Med.* **2021**, *47*, 14. [CrossRef] [PubMed]
5. Mahmoud, B.S.; AlAmri, A.H.; McConville, C. Polymeric nanoparticles for the treatment of malignant gliomas. *Cancers* **2020**, *12*, 175. [CrossRef]
6. Gagliardi, A.; Giuliano, E.; Venkateswararao, E.; Fresta, M.; Bulotta, S.; Awasthi, V.; Cosco, D. Biodegradable polymeric nanoparticles for drug delivery to solid tumors. *Front. Pharmacol.* **2021**, *12*, 601626. [CrossRef] [PubMed]
7. Zielińska, A.; Carreiró, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Durazzo, A.; Lucarini, M.; Eder, P.; Silva, A.M.; et al. Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology. *Molecules* **2020**, *25*, 3731. [CrossRef] [PubMed]
8. Zhang, G.M.; Nie, S.C.; Xu, Z.Y.; Fan, Y.R.; Jiao, M.N.; Miao, H.J.; Liang, S.X.; Yan, Y.B. Advanced polymeric nanoagents for oral cancer theranostics: A mini review. *Front. Chem.* **2022**, *10*, 927595. [CrossRef]
9. Parveen, S.; Sahoo, S.K. Polymeric nanoparticles for cancer therapy. *J. Drug Target.* **2008**, *16*, 108–123. [CrossRef]
10. Pulingam, T.; Foroozandeh, P.; Chuah, J.A.; Sudesh, K. Exploring various techniques for the chemical and biological synthesis of polymeric nanoparticles. *Nanomaterials* **2022**, *12*, 576. [CrossRef]
11. Rai, R.; Alwani, S.; Badea, I. Polymeric nanoparticles in gene therapy: New avenues of design and optimization for delivery applications. *Polymers* **2019**, *11*, 745. [CrossRef]
12. Cruz-Nova, P.; Ancira-Cortez, A.; Ferro-Flores, G.; Ocampo-García, B.; Gibbens-Bandala, B. Controlled-release nanosystems with a dual function of targeted therapy and radiotherapy in colorectal cancer. *Pharmaceutics* **2022**, *14*, 1095. [CrossRef] [PubMed]
13. Truong, N.P.; Whittaker, M.R.; Mak, C.W.; Davis, T.P. The importance of nanoparticle shape in cancer drug delivery. *Expert Opin. Drug Deliv.* **2015**, *12*, 129–142. [CrossRef] [PubMed]
14. Gao, K.; Jiang, X. Influence of particle size on transport of methotrexate across blood brain barrier by polysorbate 80-coated polybutylcyanoacrylate nanoparticles. *Int. J. Pharm.* **2006**, *310*, 213–219. [CrossRef] [PubMed]
15. Niza, E.; Ocaña, A.; Castro-Osma, J.A.; Bravo, I.; Alonso-Moreno, C. Polyester polymeric nanoparticles as platforms in the development of novel nanomedicines for cancer treatment. *Cancers* **2021**, *13*, 3387. [CrossRef] [PubMed]
16. Sahu, A.; Solanki, P.; Mitra, S. Curcuminoid-loaded poly(methyl methacrylate) nanoparticles for cancer therapy. *Int. J. Nanomed.* **2018**, *13*, 101–105. [CrossRef]
17. Chen, T.H.; Bae, Y.; Furgeson, D.Y. Intelligent biosynthetic nanobiomaterials (IBNs) for hyperthermic gene delivery. *Pharm. Res.* **2008**, *25*, 683–691. [CrossRef]
18. Behranvand, N.; Nasri, F.; Zolfaghari Emameh, R.; Khani, P.; Hosseini, A.; Garssen, J.; Falak, R. Chemotherapy: A double-edged sword in cancer treatment. *Cancer Immunol. Immunother.* **2022**, *71*, 507–526. [CrossRef]
19. Dang, Y.; Guan, J. Nanoparticle-based drug delivery systems for cancer therapy. *Smart Mater. Med.* **2020**, *1*, 10–19. [CrossRef]
20. Hickey, J.W.; Santos, J.L.; Williford, J.M.; Mao, H.Q. Control of polymeric nanoparticle size to improve therapeutic delivery. *J. Control. Release* **2015**, *219*, 536–547. [CrossRef]
21. Kaps, A.; Gwiazdoń, P.; Chodurek, E. Nanoformulations for delivery of pentacyclic triterpenoids in anticancer therapies. *Molecules* **2021**, *26*, 1764. [CrossRef] [PubMed]
22. Gavas, S.; Quazi, S.; Karpiński, T.M. Nanoparticles for cancer therapy: Current progress and challenges. *Nanoscale Res. Lett.* **2021**, *16*, 173. [CrossRef] [PubMed]
23. Karlsson, J.; Vaughan, H.J.; Green, J.J. Biodegradable polymeric nanoparticles for therapeutic cancer treatments. *Annu. Rev. Chem. Biomol. Eng.* **2018**, *9*, 105–127. [CrossRef] [PubMed]
24. Crucho, C.I.C.; Barros, M.T. Polymeric nanoparticles: A study on the preparation variables and characterization methods. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *80*, 771–784. [CrossRef] [PubMed]
25. Neerooa, B.N.H.M.; Ooi, L.T.; Shameli, K.; Dahlan, N.A.; Islam, J.M.M.; Pushpamalar, J.; Teow, S.Y. Development of polymer-assisted nanoparticles and nanogels for cancer therapy: An update. *Gels* **2021**, *7*, 60. [CrossRef]

26. Rezvantalab, S.; Drude, N.I.; Moraveji, M.K.; Güvener, N.; Koons, E.K.; Shi, Y.; Lammers, T.; Kiessling, F. PLGA-based nanoparticles in cancer treatment. *Front. Pharmacol.* **2018**, *9*, 1260. [CrossRef]
27. Gad, A.; Kydd, J.; Piel, B.; Rai, P. Targeting cancer using polymeric nanoparticle mediated combination chemotherapy. *Int J Nanomed. Nanosurg.* **2016**, *2*. [CrossRef]
28. Şengel-Türk, C.T.; Hasçiçek, C.; Dogan, A.L.; Esendagli, G.; Guc, D.; Gönül, N. Preparation and in vitro evaluation of meloxicam-loaded PLGA nanoparticles on HT-29 human colon adenocarcinoma cells. *Drug Dev. Ind. Pharm.* **2012**, *38*, 1107–1116. [CrossRef]
29. Chakravarty, P.; Famili, A.; Nagapudi, K.; Al-Sayah, M.A. Using supercritical fluid technology as a green alternative during the preparation of drug delivery systems. *Pharmaceutics* **2019**, *11*, 629. [CrossRef]
30. Margulis, K.; Neofytou, E.A.; Beygui, R.E.; Zare, R.N. Celecoxib nanoparticles for therapeutic angiogenesis. *ACS Nano* **2015**, *9*, 9416–9426. [CrossRef]
31. Kim, S.J.; Khadka, D.; Seo, J.H. Interplay between solid tumors and tumor microenvironment. *Front. Immunol.* **2022**, *13*, 882718. [CrossRef]
32. Pérez-Herrero, E.; Fernández-Medarde, A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *Eur. J. Pharm. Biopharm.* **2015**, *93*, 52–79. [CrossRef]
33. Danhier, F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? *J. Control. Release* **2016**, *244*, 108–121. [CrossRef] [PubMed]
34. Ejigah, V.; Owoseni, O.; Bataille-Backer, P.; Ogundipe, O.D.; Fisusi, F.A.; Adesina, S.K. Approaches to improve macromolecule and nanoparticle accumulation in the tumor microenvironment by the enhanced permeability and retention effect. *Polymers* **2022**, *14*, 2601. [CrossRef]
35. Rasool, M.; Malik, A.; Waquar, S.; Arooj, M.; Zahid, S.; Asif, M.; Shaheen, S.; Hussain, A.; Ullah, H.; Gan, S.H. New challenges in the use of nanomedicine in cancer therapy. *Bioengineered* **2022**, *13*, 759–773. [CrossRef]
36. Naki, T.; Aderibigbe, B.A. Efficacy of polymer-based nanomedicine for the treatment of brain cancer. *Pharmaceutics* **2022**, *14*, 1048. [CrossRef]
37. Shi, Y.; Zhou, M.; Zhang, J.; Lu, W. Preparation and cellular targeting study of VEGF-conjugated PLGA nanoparticles. *J. Microencapsul.* **2015**, *32*, 699–704. [CrossRef] [PubMed]
38. Malki, A.; ElRuz, R.A.; Gupta, I.; Allouch, A.; Vranic, S.; Al Moustafa, A.E. Molecular mechanisms of colon cancer progression and metastasis: Recent Insights and Advancements. *Int. J. Mol. Sci.* **2020**, *22*, 130. [CrossRef]
39. Al-Joufi, F.A.; Setia, A.; Salem-Bekhit, M.M.; Sahu, R.K.; Alqahtani, F.Y.; Widyowati, R.; Aleanizy, F.S. Molecular pathogenesis of colorectal cancer with an emphasis on recent advances in biomarkers, as well as nanotechnology-based diagnostic and therapeutic approaches. *Nanomaterials* **2022**, *12*, 169. [CrossRef] [PubMed]
40. Aleksandrova, K.; Reichmann, R.; Kaaks, R.; Jenab, M.; Bueno-de-Mesquita, H.B.; Dahm, C.C.; Eriksen, A.K.; Tjønneland, A.; Artaud, F.; Boutron-Ruault, M.C.; et al. Development and validation of a lifestyle-based model for colorectal cancer risk prediction: The LiFeCRC score. *BMC Med.* **2021**, *19*, 1. [CrossRef] [PubMed]
41. Wang, K.; Shen, R.; Meng, T.; Hu, F.; Yuan, H. Nano-drug delivery systems based on different targeting mechanisms in the targeted therapy of colorectal cancer. *Molecules* **2022**, *27*, 2981. [CrossRef] [PubMed]
42. Ying, K.; Bai, B.; Gao, X.; Xu, Y.; Wang, H.; Xie, B. Orally administrable therapeutic nanoparticles for the treatment of colorectal cancer. *Front. Bioeng. Biotechnol.* **2021**, *9*, 670124. [CrossRef]
43. Wu, P.; Zhou, Q.; Zhu, H.; Zhuang, Y.; Bao, J. Enhanced antitumor efficacy in colon cancer using EGF functionalized PLGA nanoparticles loaded with 5-fluorouracil and perfluorocarbon. *BMC Cancer* **2020**, *20*, 354. [CrossRef]
44. Handali, S.; Moghimipour, E.; Rezaei, M.; Ramezani, Z.; Dorkoosh, F.A. PHBV/PLGA nanoparticles for enhanced delivery of 5-fluorouracil as promising treatment of colon cancer. *Pharm. Dev. Technol.* **2020**, *25*, 206–218. [CrossRef]
45. Khaledi, S.; Jafari, S.; Hamidi, S.; Molavi, O.; Davaran, S. Preparation and characterization of PLGA-PEG-PLGA polymeric nanoparticles for co-delivery of 5-fluorouracil and chrysin. *J. Biomater. Sci. Polym. Ed.* **2020**, *31*, 1107–1126. [CrossRef]
46. Alshaman, R.; Alattar, A.; El-Sayed, R.M.; Gardouh, A.R.; Elshaer, R.E.; Elkazaz, A.Y.; Eladl, M.A.; El-Sherbiny, M.; Farag, N.E.; Hamdan, A.M.; et al. Formulation and characterization of doxycycline-loaded polymeric nanoparticles for testing antitumor/antiangiogenic action in experimental colon cancer in mice. *Nanomaterials* **2022**, *12*, 857. [CrossRef]
47. Akl, M.A.; Kartal-Hodzic, A.; Oksanen, T.; Ismael, H.R.; Afouna, M.M.; Yliperttula, M.; Samy, A.M.; Viitala, T. Factorial design formulation optimization and in vitro characterization of curcumin-loaded PLGA nanoparticles for colon delivery. *J. Drug Deliv. Sci. Technol.* **2016**, *32*, 10–20. [CrossRef]
48. Essa, S.; Daoud, J.; Lafleur, M.; Martel, S.; Tabrizian, M. SN-38 active loading in poly(lactic-co-glycolic acid) nanoparticles and assessment of their anticancer properties on COLO-205 human colon adenocarcinoma cells. *J. Microencapsul.* **2015**, *32*, 784–793. [CrossRef] [PubMed]
49. Hassanzadeh, P.; Arbabi, E.; Rostami, F. Development of a novel nanoformulation against the colorectal cancer. *Life Sci.* **2021**, *281*, 119772. [CrossRef] [PubMed]
50. Bhattacharya, S. Fabrication and characterization of chitosan-based polymeric nanoparticles of imatinib for colorectal cancer targeting application. *Int. J. Biol. Macromol.* **2020**, *151*, 104–115. [CrossRef] [PubMed]
51. Oliveira, A.L.C.S.L.; Zerillo, L.; Cruz, L.J.; Schomann, T.; Chan, A.B.; de Carvalho, T.G.; Souza, S.V.P.; Araújo, A.A.; de Geus-Oei, L.F.; de Araújo Júnior, R.F. Maximizing the potency of oxaliplatin coated nanoparticles with folic acid for modulating tumor progression in colorectal cancer. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2021**, *120*, 111678. [CrossRef]

52. Colpan, R.D.; Erdemir, A. Co-delivery of quercetin and caffeic-acid phenethyl ester by polymeric nanoparticles for improved antitumor efficacy in colon cancer cells. *J. Microencapsul.* **2021**, *38*, 381–393. [CrossRef]
53. Baião, A.; Sousa, F.; Oliveira, A.V.; Oliveira, C.; Sarmento, B. Effective intracellular delivery of bevacizumab via PEGylated polymeric nanoparticles targeting the CD44v6 receptor in colon cancer cells. *Biomater. Sci.* **2020**, *8*, 3720–3729. [CrossRef]
54. Zu, M.; Ma, L.; Zhang, X.; Xie, D.; Kang, Y.; Xiao, B. Chondroitin sulfate-functionalized polymeric nanoparticles for colon cancer-targeted chemotherapy. *Colloids. Surf. B Biointerfaces.* **2019**, *177*, 399–406. [CrossRef] [PubMed]
55. Dos Santos-Silva, A.M.; de Caland, L.B.; do Nascimento, E.G.; Oliveira, A.L.C.S.L.; de Araújo-Júnior, R.F.; Cornélio, A.M.; Fernandes-Pedrosa, M.F.; da Silva-Júnior, A.A. Self-assembled benznidazole-loaded cationic nanoparticles containing cholesterol/sialic acid: Physicochemical properties, in vitro drug release and in vitro anticancer efficacy. *Int. J. Mol. Sci.* **2019**, *20*, 2350. [CrossRef] [PubMed]
56. Phung, C.D.; Le, T.G.; Nguyen, V.H.; Vu, T.T.; Nguyen, H.Q.; Kim, J.O.; Yong, C.S.; Nguyen, C.N. PEGylated-paclitaxel and dihydroartemisinin nanoparticles for simultaneously delivering paclitaxel and dihydroartemisinin to colorectal cancer. *Pharm. Res.* **2020**, *37*, 129. [CrossRef]
57. Zhang, D.; Jiang, L.; Liu, C. A convergent synthetic platform for polymeric nanoparticle for the treatment of combination colorectal cancer therapy. *J. Biomater. Sci. Polym. Ed.* **2021**, *32*, 1835–1848. [CrossRef]
58. Zhong, Y.; Su, T.; Shi, Q.; Feng, Y.; Tao, Z.; Huang, Q.; Li, L.; Hu, L.; Li, S.; Tan, H.; et al. Co-administration of iRGD enhances tumor-targeted delivery and anti-tumor effects of paclitaxel-loaded PLGA nanoparticles for colorectal cancer treatment. *Int. J. Nanomed.* **2019**, *14*, 8543–8560. [CrossRef] [PubMed]
59. Chen, Y.; Li, N.; Xu, B.; Wu, M.; Yan, X.; Zhong, L.; Cai, H.; Wang, T.; Wang, Q.; Long, F.; et al. Polymer-based nanoparticles for chemo/gene-therapy: Evaluation its therapeutic efficacy and toxicity against colorectal carcinoma. *Biomed. Pharmacother.* **2019**, *118*, 109257. [CrossRef]
60. Cabeza, L.; Perazzoli, G.; Mesas, C.; Jiménez-Luna, C.; Prados, J.; Rama, A.R.; Melguizo, C. Nanoparticles in colorectal cancer therapy: Latest in vivo assays, clinical trials, and patents. *AAPS PharmSciTech.* **2020**, *21*, 178. [CrossRef] [PubMed]
61. Fraguas-Sánchez, A.I.; Lozza, I.; Torres-Suárez, A.I. Actively targeted nanomedicines in breast cancer: From pre-clinal investigation to clinic. *Cancers* **2022**, *14*, 1198. [CrossRef] [PubMed]
62. Miglietta, F.; Bottosso, M.; Griguolo, G.; Dieci, M.V.; Guarneri, V. Major advancements in metastatic breast cancer treatment: When expanding options means prolonging survival. *ESMO Open* **2022**, *7*, 100409. [CrossRef] [PubMed]
63. Kashyap, D.; Pal, D.; Sharma, R.; Garg, V.K.; Goel, N.; Koundal, D.; Zaguia, A.; Koundal, S.; Belay, A. Global increase in breast cancer incidence: Risk factors and preventive measures. *Biomed. Res. Int.* **2022**, *2022*, 9605439. [CrossRef]
64. Huang, J.; Chan, W.C.; Ngai, C.H.; Lok, V.; Zhang, L.; Lucero-Prisno, D.E.; Xu, W.; Zheng, Z.J.; Elcarte, E.; Withers, M.; et al. On Behalf Of Ncd Global Health Research Group Of Association Of Pacific Rim Universities Apru. worldwide burden, risk factors, and temporal trends of ovarian cancer: A global study. *Cancers* **2022**, *14*, 2230. [CrossRef] [PubMed]
65. Akter, S.; Rahman, M.A.; Hasan, M.N.; Akhter, H.; Noor, P.; Islam, R.; Shin, Y.; Rahman, M.D.H.; Gazi, M.S.; Huda, M.N.; et al. Recent advances in ovarian cancer: Therapeutic strategies, potential biomarkers, and technological improvements. *Cells* **2022**, *11*, 650. [CrossRef] [PubMed]
66. Zhang, H.; Zhang, Y. Olaparib and paclitaxel in combination with carboplatin in treatment of ovarian cancer: Influence on disease control. *Am. J. Transl Res.* **2022**, *14*, 468–475.
67. Ahmed, M.M.; Anwer, M.K.; Fatima, F.; Aldawsari, M.F.; Alalaiwe, A.; Alali, A.S.; Alharthi, A.I.; Kalam, M.A. Boosting the anticancer activity of sunitinib malate in breast cancer through lipid polymer hybrid nanoparticles approach. *Polymers* **2022**, *14*, 2459. [CrossRef]
68. Jurczyk, M.; Kasperczyk, J.; Wrześniok, D.; Beberok, A.; Jelonek, K. Nanoparticles loaded with docetaxel and resveratrol as an advanced tool for cancer therapy. *Biomedicines* **2022**, *10*, 1187. [CrossRef]
69. Poltavets, Y.I.; Zhirnik, A.S.; Zavarzina, V.V.; Semochkina, Y.P.; Shuvatova, V.G.; Krasheninnikova, A.A.; Aleshin, S.V.; Dronov, D.O.; Vorontsov, E.A.; Balabanyan, V.Y.; et al. In vitro anticancer activity of folate-modified docetaxel-loaded PLGA nanoparticles against drug-sensitive and multidrug-resistant cancer cells. *Cancer Nanotechnol.* **2019**, *10*, 2. [CrossRef]
70. Wong, S.H.D.; Xu, X.; Chen, X.; Xin, Y.; Xu, L.; Lai, C.H.N.; Oh, J.; Wong, W.K.R.; Wang, X.; Han, S.; et al. Manipulation of the nanoscale presentation of integrin ligand produces cancer cells with enhanced stemness and robust tumorigenicity. *Nano Lett.* **2021**, *21*, 3225–3236. [CrossRef]
71. Guo, X.; Zhao, Z.; Chen, D.; Qiao, M.; Wan, F.; Cun, D.; Sun, Y.; Yang, M. Co-delivery of resveratrol and docetaxel via polymeric micelles to improve the treatment of drug-resistant tumors. *Asian J. Pharm. Sci.* **2019**, *14*, 78–85. [CrossRef] [PubMed]
72. Alsadat Vakilinezhad, M.; Alipour, S.; Montaseri, H. Fabrication and in vitro evaluation of magnetic PLGA nanoparticles as a potential methotrexate delivery system for breast cancer. *J. Drug Deliv. Sci. Technol.* **2018**, *44*, 467–474. [CrossRef]
73. Yallapu, M.M.; Maher, D.M.; Sundram, V.; Bell, M.C.; Jaggi, M.; Chauhan, S.C. Curcumin induces chemo/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth. *J. Ovarian Res.* **2010**, *3*, 11. [CrossRef] [PubMed]
74. Vangara, K.K.; Liu, J.L.; Palakurthi, S. Hyaluronic acid-decorated PLGA-PEG nanoparticles for targeted delivery of SN-38 to ovarian cancer. *Anticancer Res.* **2013**, *33*, 2425–2434. [PubMed]
75. Shen, S.; Du, X.J.; Liu, J.; Sun, R.; Zhu, Y.H.; Wang, J. Delivery of bortezomib with nanoparticles for basal-like triple-negative breast cancer therapy. *J. Control. Release* **2015**, *208*, 14–24. [CrossRef]

76. Bhattacharya, S.; Anjum, M.M.; Patel, K.K. Gemcitabine cationic polymeric nanoparticles against ovarian cancer: Formulation, characterization, and targeted drug delivery. *Drug Deliv.* **2022**, *29*, 1060–1074. [CrossRef]
77. Li, S.Y.; Sun, R.; Wang, H.X.; Shen, S.; Liu, Y.; Du, X.J.; Zhu, Y.H.; Jun, W. Combination therapy with epigenetic-targeted and chemotherapeutic drugs delivered by nanoparticles to enhance the chemotherapy response and overcome resistance by breast cancer stem cells. *J. Control. Release* **2015**, *205*, 7–14. [CrossRef]
78. Esnaashari, S.S.; Muhammadnejad, S.; Amanpour, S.; Amani, A. A combinational approach towards treatment of breast cancer: An analysis of noscapine-loaded polymeric nanoparticles and doxorubicin. *AAPS PharmSciTech.* **2020**, *21*, 166. [CrossRef]
79. Xiong, K.; Zhang, Y.; Wen, Q.; Luo, J.; Lu, Y.; Wu, Z.; Wang, B.; Chen, Y.; Zhao, L.; Fu, S. Co-delivery of paclitaxel and curcumin by biodegradable polymeric nanoparticles for breast cancer chemotherapy. *Int. J. Pharm.* **2020**, *589*, 119875. [CrossRef]
80. Rad, J.G.; Hoskin, D.W. Delivery of apoptosis-inducing piperine to triple-negative breast cancer cells via co-polymeric nanoparticles. *Anticancer Res.* **2020**, *40*, 689–694. [CrossRef] [PubMed]
81. Pan, Q.; Tian, J.; Zhu, H.; Hong, L.; Mao, Z.; Oliveira, J.M.; Reis, R.L.; Li, X. Tumor-targeting polycaprolactone nanoparticles with codelivery of paclitaxel and IR780 for combinational therapy of drug-resistant ovarian cancer. *ACS Biomater. Sci. Eng.* **2020**, *6*, 2175–2185. [CrossRef]
82. Alassaif, F.R.; Alassaif, E.R.; Kaushik, A.K.; Dhanapal, J. Enhanced anti-proliferative effect of carboplatin in ovarian cancer cells exploiting chitosan-poly (lactic glycolic acid) nanoparticles. *Recent Pat. Nanotechnol.* **2022**. [CrossRef]
83. Yao, S.; Li, L.; Su, X.T.; Wang, K.; Lu, Z.J.; Yuan, C.Z.; Feng, J.B.; Yan, S.; Kong, B.H.; Song, K. Development and evaluation of novel tumor-targeting paclitaxel-loaded nano-carriers for ovarian cancer treatment: In vitro and in vivo. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 29. [CrossRef]
84. Khanna, V.; Kalscheuer, S.; Kirtane, A.; Zhang, W.; Panyam, J. Perlecan-targeted nanoparticles for drug delivery to triple-negative breast cancer. *Future Drug Discov.* **2019**, *1*, FDD8. [CrossRef]
85. Swaminathan, S.K.; Roger, E.; Toti, U.; Niu, L.; Ohlfest, J.R.; Panyam, J. CD133-targeted paclitaxel delivery inhibits local tumor recurrence in a mouse model of breast cancer. *J. Control. Release* **2013**, *171*, 280–287. [CrossRef] [PubMed]
86. Shahrousvand, M.; Hajikhani, M.; Nazari, L.; Aghelinejad, A.; Shahrousvand, M.; Irani, M.; Rostami, A. Preparation of colloidal nanoparticles PVA-PHEMA from hydrolysis of copolymers of PVAc-PHEMA as anticancer drug carriers. *Nanotechnology* **2022**, *33*, 275603. [CrossRef]
87. Ram Prasad, S.; Jayakrishnan, A.; Sampath Kumar, T.S. Hydroxyapatite-poly(vinyl alcohol) core-shell nanoparticles for dual delivery of methotrexate and gemcitabine for bone cancer treatment. *J. Drug Deliv. Sci. Technol.* **2019**, *51*, 629–638. [CrossRef]
88. Yang, J.; Shi, Z.; Liu, R.; Wu, Y.; Zhang, X. Combined therapeutic strategies synergistically potentiate glioblastoma multiforme treatment *via* nanotechnology. *Theranostics* **2020**, *10*, 3223–3239. [CrossRef] [PubMed]
89. Kurowska, N.; Strzalka-Mrozik, B.; Madej, M.; Pająk, K.; Kruszniewska-Rajs, C.; Kaspera, W.; Gola, J.M. Differences in the expression patterns of TGFβ isoforms and associated genes in astrocytic brain tumors. *Cancers* **2022**, *14*, 1876. [CrossRef]
90. Turek, A.; Stoklosa, K.; Borecka, A.; Paul-Samojedny, M.; Kaczmarczyk, B.; Marcinkowski, A.; Kasperczyk, J. Designing biodegradable wafers based on poly(L-lactide-co-glycolide) and poly(glycolide-co-ε-caprolactone) for the prolonged and local release of idarubicin for the therapy of glioblastoma multiforme. *Pharm. Res.* **2020**, *37*, 90. [CrossRef] [PubMed]
91. Rajaratnam, V.; Islam, M.M.; Yang, M.; Slaby, R.; Ramirez, H.M.; Mirza, S.P. Glioblastoma: Pathogenesis and current status of chemotherapy and other novel treatments. *Cancers* **2020**, *12*, 937. [CrossRef] [PubMed]
92. Caraway, C.A.; Gaitsch, H.; Wicks, E.E.; Kalluri, A.; Kunadi, N.; Tyler, B.M. Polymeric nanoparticles in brain cancer therapy: A review of current approaches. *Polymers* **2022**, *14*, 2963. [CrossRef] [PubMed]
93. Liang, Y.; Li, Z.; Yuan, H.; Wang, L.; Gao, L.H. Poly(p-phenylenevinylene) nanoparticles modified with antiEGFRvIII for specific glioblastoma therapy. *Sci. Rep.* **2021**, *11*, 4449. [CrossRef] [PubMed]
94. Jamali, Z.; Khoobi, M.; Hejazi, S.M.; Eivazi, N.; Abdolahpour, S.; Imanparast, F.; Moradi-Sardareh, H.; Paknejad, M. Evaluation of targeted curcumin (CUR) loaded PLGA nanoparticles for in vitro photodynamic therapy on human glioblastoma cell line. *Photodiagnosis Photodyn. Ther.* **2018**, *23*, 190–201. [CrossRef] [PubMed]
95. Maleki, H.; Hosseini Najafabadi, M.R.; Webster, T.J.; Hadjighassem, M.R.; Sadroddiny, E.; Ghanbari, H.; Khosravani, M.; Adabi, M. Effect of paclitaxel/etoposide co-loaded polymeric nanoparticles on tumor size and survival rate in a rat model of glioblastoma. *Int. J. Pharm.* **2021**, *604*, 120722. [CrossRef]
96. Madani, F.; Esnaashari, S.S.; Bergonzi, M.C.; Webster, T.J.; Younes, H.M.; Khosravani, M.; Adabi, M. Paclitaxel/methotrexate co-loaded PLGA nanoparticles in glioblastoma treatment: Formulation development and in vitro antitumor activity evaluation. *Life Sci.* **2020**, *256*, 117943. [CrossRef]
97. Jiang, X.; Xin, H.; Sha, X.; Gu, J.; Jiang, Y.; Law, K.; Chen, Y.; Chen, L.; Wang, X.; Fang, X. PEGylated poly(trimethylene carbonate) nanoparticles loaded with paclitaxel for the treatment of advanced glioma: In vitro and in vivo evaluation. *Int. J. Pharm.* **2011**, *420*, 385–394. [CrossRef]
98. Xu, Y.; Shen, M.; Li, Y.; Sun, Y.; Teng, Y.; Wang, Y.; Duan, Y. The synergic antitumor effects of paclitaxel and temozolomide co-loaded in mPEG-PLGA nanoparticles on glioblastoma cells. *Oncotarget* **2016**, *7*, 20890–20901. [CrossRef]
99. Wang, X.; Gao, J.; Ouyang, X.; Wang, J.; Sun, X.; Lv, Y. Mesenchymal stem cells loaded with paclitaxel-poly(lactic-co-glycolic acid) nanoparticles for glioma-targeting therapy. *Int. J. Nanomed.* **2018**, *13*, 5231–5248. [CrossRef]

100. Maksimenko, O.; Malinovskaya, J.; Shipulo, E.; Osipova, N.; Razzhivina, V.; Arantseva, D.; Yarovaya, O.; Mostovaya, U.; Khalansky, A.; Fedoseeva, V.; et al. Doxorubicin-loaded PLGA nanoparticles for the chemotherapy of glioblastoma: Towards the pharmaceutical development. *Int. J. Pharm.* **2019**, *572*, 118733. [CrossRef]
101. Vasey, C.E.; Cavanagh, R.J.; Taresco, V.; Moloney, C.; Smith, S.; Rahman, R.; Alexander, C. Polymer pro-drug nanoparticles for sustained release of cytotoxic drugs evaluated in patient-derived glioblastoma cell lines and in situ gelling formulations. *Pharmaceutics* **2021**, *13*, 208. [CrossRef] [PubMed]
102. Ramalho, M.J.; Sevin, E.; Gosselet, F.; Lima, J.; Coelho, M.A.N.; Loureiro, J.A.; Pereira, M.C. Receptor-mediated PLGA nanoparticles for glioblastoma multiforme treatment. *Int. J. Pharm.* **2018**, *545*, 84–92. [CrossRef] [PubMed]
103. Ananta, J.S.; Paulmurugan, R.; Massoud, T.F. Temozolomide-loaded PLGA nanoparticles to treat glioblastoma cells: A biophysical and cell culture evaluation. *Neurol. Res.* **2016**, *38*, 51–59. [CrossRef] [PubMed]
104. Hamimed, S.; Jabberi, M.; Chatti, A. Nanotechnology in drug and gene delivery. *Naunyn. Schmiedebergs Arch. Pharmacol.* **2022**, *395*, 769–787. [CrossRef] [PubMed]
105. Roma-Rodrigues, C.; Rivas-García, L.; Baptista, P.V.; Fernandes, A.R. Gene therapy in cancer treatment: Why go nano? *Pharmaceutics* **2020**, *12*, 233. [CrossRef]
106. Charbe, N.B.; Amnerkar, N.D.; Ramesh, B.; Tambuwala, M.M.; Bakshi, H.A.; Aljabali, A.A.A.; Khadse, S.C.; Satheeshkumar, R.; Satija, S.; Metha, M.; et al. Small interfering RNA for cancer treatment: Overcoming hurdles in delivery. *Acta Pharm. Sin. B* **2020**, *10*, 2075–2109. [CrossRef]
107. Chen, J.; Guo, Z.; Tian, H.; Chen, X. Production and clinical development of nanoparticles for gene delivery. *Mol. Ther. Methods Clin. Dev.* **2016**, *3*, 16023. [CrossRef]
108. Torres-Vanegas, J.D.; Cruz, J.C.; Reyes, L.H. Delivery systems for nucleic acids and proteins: Barriers, cell capture pathways and nanocarriers. *Pharmaceutics* **2021**, *13*, 428. [CrossRef]
109. Wong, W.K.; Yin, B.; Lam, C.Y.K.; Huang, Y.; Yan, J.; Tan, Z.; Wong, S.H.D. The interplay between epigenetic regulation and CD8+ T cell differentiation/exhaustion for T cell immunotherapy. *Front. Cell Dev. Biol.* **2022**, *9*, 783227. [CrossRef]
110. Wong, W.K.; Yin, B.; Rakhmatullina, A.; Zhou, J.; Wong, S.H.D. Engineering advanced dynamic biomaterials to optimize adoptive T-cell immunotherapy. *Eng. Regen.* **2021**, *2*, 70–81. [CrossRef]
111. Mi, Y.; Smith, C.C.; Yang, F.; Qi, Y.; Roche, K.C.; Serody, J.S.; Vincent, B.G.; Wang, A.Z. A dual immunotherapy nanoparticle improves T-cell activation and cancer immunotherapy. *Adv. Mater.* **2018**, *30*, e1706098. [CrossRef]
112. Risnayanti, C.; Jang, Y.S.; Lee, J.; Ahn, H.J. PLGA nanoparticles co-delivering MDR1 and BCL2 siRNA for overcoming resistance of paclitaxel and cisplatin in recurrent or advanced ovarian cancer. *Sci. Rep.* **2018**, *8*, 7498. [CrossRef]
113. Byeon, Y.; Lee, J.W.; Choi, W.S.; Won, J.E.; Kim, G.H.; Kim, M.G.; Wi, T.I.; Lee, J.M.; Kang, T.H.; Jung, I.D.; et al. CD44-targeting PLGA nanoparticles incorporating paclitaxel and FAK siRNA overcome chemoresistance in epithelial ovarian cancer. *Cancer Res.* **2018**, *78*, 6247–6256. [CrossRef]
114. Li, T.; Deng, N.; Xu, R.; Fan, Z.; He, J.; Zheng, Z.; Deng, H.; Liao, R.; Lv, X.; Pang, C. NEAT1 siRNA packed with chitosan nanoparticles regulates the development of colon cancer cells via lncRNA NEAT1/miR-377-3p Axis. *Biomed. Res. Int.* **2021**, *2021*, 5528982. [CrossRef]
115. Sadreddini, S.; Safaralizadeh, R.; Baradaran, B.; Aghebati-Maleki, L.; Hosseinpour-Feizi, M.A.; Shanehbandi, D.; Jadidi-Niaragh, F.; Sadreddini, S.; Kafil, H.S.; Younesi, V.; et al. Chitosan nanoparticles as a dual drug/siRNA delivery system for treatment of colorectal cancer. *Immunol. Lett.* **2017**, *181*, 79–86. [CrossRef] [PubMed]
116. Pho-Iam, T.; Punnakitikashem, P.; Somboonyosdech, C.; Sripinitchai, S.; Masaratana, P.; Sirivatanauksorn, V.; Sirivatanauksorn, Y.; Wongwan, C.; Nguyen, K.T.; Srisawat, C. PLGA nanoparticles containing α-fetoprotein siRNA induce apoptosis and enhance the cytotoxic effects of doxorubicin in human liver cancer cell line. *Biochem. Biophys. Res. Commun.* **2021**, *553*, 191–197. [CrossRef] [PubMed]
117. Xu, Y.; Liu, D.; Hu, J.; Ding, P.; Chen, M. Hyaluronic acid-coated pH sensitive poly (β-amino ester) nanoparticles for co-delivery of embelin and TRAIL plasmid for triple negative breast cancer treatment. *Int. J. Pharm.* **2020**, *573*, 118637. [CrossRef] [PubMed]
118. Malik, S.; Lim, J.; Slack, F.J.; Braddock, D.T.; Bahal, R. Next generation miRNA inhibition using short anti-seed PNAs encapsulated in PLGA nanoparticles. *J. Control. Release* **2020**, *327*, 406–419. [CrossRef]
119. Zheng, B.; Chen, L.; Pan, C.C.; Wang, J.Z.; Lu, G.R.; Yang, S.X.; Xue, Z.X.; Wang, F.Y.; Xu, C.L. Targeted delivery of miRNA-204-5p by PEGylated polymer nanoparticles for colon cancer therapy. *Nanomedicine* **2018**, *13*, 769–785. [CrossRef]
120. Taghavi, S.; Ramezani, M.; Alibolandi, M.; Abnous, K.; Taghdisi, S.M. Chitosan-modified PLGA nanoparticles tagged with 5TR1 aptamer for in vivo tumor-targeted drug delivery. *Cancer Lett.* **2017**, *400*, 1–8. [CrossRef]
121. Vandghanooni, S.; Eskandani, M.; Barar, J.; Omidi, Y. AS1411 aptamer-decorated cisplatin-loaded poly(lactic-co-glycolic acid) nanoparticles for targeted therapy of miR-21-inhibited ovarian cancer cells. *Nanomedicine* **2018**, *13*, 2729–2758. [CrossRef] [PubMed]
122. Ahmad, A.; Ansari, M.M.; Verma, R.K.; Khan, R. Aminocellulose-grafted polymeric nanoparticles for selective targeting of CHEK2-deficient colorectal cancer. *ACS Appl. Bio. Mater.* **2021**, *4*, 5324–5335. [CrossRef] [PubMed]
123. Aravind, A.; Varghese, S.H.; Veeranarayanan, S.; Mathew, A.; Nagaoka, Y.; Iwai, S.; Fukuda, T.; Hasumura, T.; Yoshida, Y.; Maekawa, T.; et al. Aptamer-labeled PLGA nanoparticles for targeting cancer cells. *Cancer Nanotechnol.* **2012**, *3*, 1–12. [CrossRef] [PubMed]