MDPI

Review

Application of Non-Viral Vectors in Drug Delivery and Gene Therapy

Shuaikai Ren, Mengjie Wang, Chunxin Wang, Yan Wang, Changjiao Sun, Zhanghua Zeng [ID]**, Haixin Cui and Xiang Zhao** *

Institute of Environment and Sustainable Development in Agriculture, Chinese Academy of Agricultural Sciences, Beijing 100081, China; ren19801266562@163.com (S.R.); wangmengjie@caas.cn (M.W.); wangchunxin@caas.cn (C.W.); wangyan03@caas.cn (Y.W.); sunchangjiao@caas.cn (C.S.); zengzhanghua@caas.cn (Z.Z.); cuihaixin@caas.cn (H.C.)
* Correspondence: zhaoxiang@caas.cn

Academic Editors: José Miguel Ferri, Vicent Fombuena Borràs and Miguel Fernando Aldás Carrasco

Abstract: Vectors and carriers play an indispensable role in gene therapy and drug delivery. Non-viral vectors are widely developed and applied in clinical practice due to their low immunogenicity, good biocompatibility, easy synthesis and modification, and low cost of production. This review summarized a variety of non-viral vectors and carriers including polymers, liposomes, gold nanoparticles, mesoporous silica nanoparticles and carbon nanotubes from the aspects of physicochemical characteristics, synthesis methods, functional modifications, and research applications. Notably, non-viral vectors can enhance the absorption of cargos, prolong the circulation time, improve therapeutic effects, and provide targeted delivery. Additional studies focused on recent innovation of novel synthesis techniques for vector materials. We also elaborated on the problems and future research directions in the development of non-viral vectors, which provided a theoretical basis for their broad applications.

Keywords: non-viral vectors; polymers; liposomes; gold nanoparticles; mesoporous silica nanoparticles; carbon nanotubes

1. Introduction

With the development of biotechnology, drug delivery and gene therapy play an important role in the treatment of many diseases such as hereditary diseases, malignant tumors, cardiovascular diseases, infectious diseases, and neurodegenerative diseases [1–6]. However, there are some drawbacks containing rapid degradation [7–9], nontargeted delivery [10,11], unsatisfactory efficacy [12], multiple side effects [13,14] after nucleic acids, proteins, peptides, and other substances entering the body circulation. Therefore, suitable vectors, effective transport route, or chemical modification are necessary to improve the pharmacokinetic properties [15–18]. A growing number of vectors for gene therapy or vaccines and carriers for drug delivery have been extensively researched owing to their facile use, targeting ability, high bioavailability, and good biocompatibility [19–21].

Viruses, such as adenovirus, vesicular stomatitis virus, cytomegalovirus, lentivirus, and retrovirus, are commonly used vectors because of highly infectious, effective delivery, and efficient expression [22–25]. However, viral vectors have several limitations including toxicity, immunogenicity, carcinogenicity, high cost, and difficulty of large-scale production in clinical practice [26–28]. Consequently, more and more scientists have turned their attention to the development of non-viral vectors and carriers [29–31]. Recent studies have shown that non-viral vectors have the following advantages: low immunogenicity, biodegradability, easy synthesis, low cost of production, and no restriction on the size of the molecules to be introduced [32–36]. The most extensively researched non-viral vectors are mainly polymers, liposomes, and nanoparticles [37–42]. This review introduces several non-viral vectors that have been extensively studied in the past few decades and summarizes

their biomedical applications, providing a theoretical basis for the development of new non-viral vectors in the future (Figure 1). Table 1 shows the characteristics and commonly used preparation methods of several non-viral vectors. Table 2 shows the patent reports related to non-viral vectors in recent years.
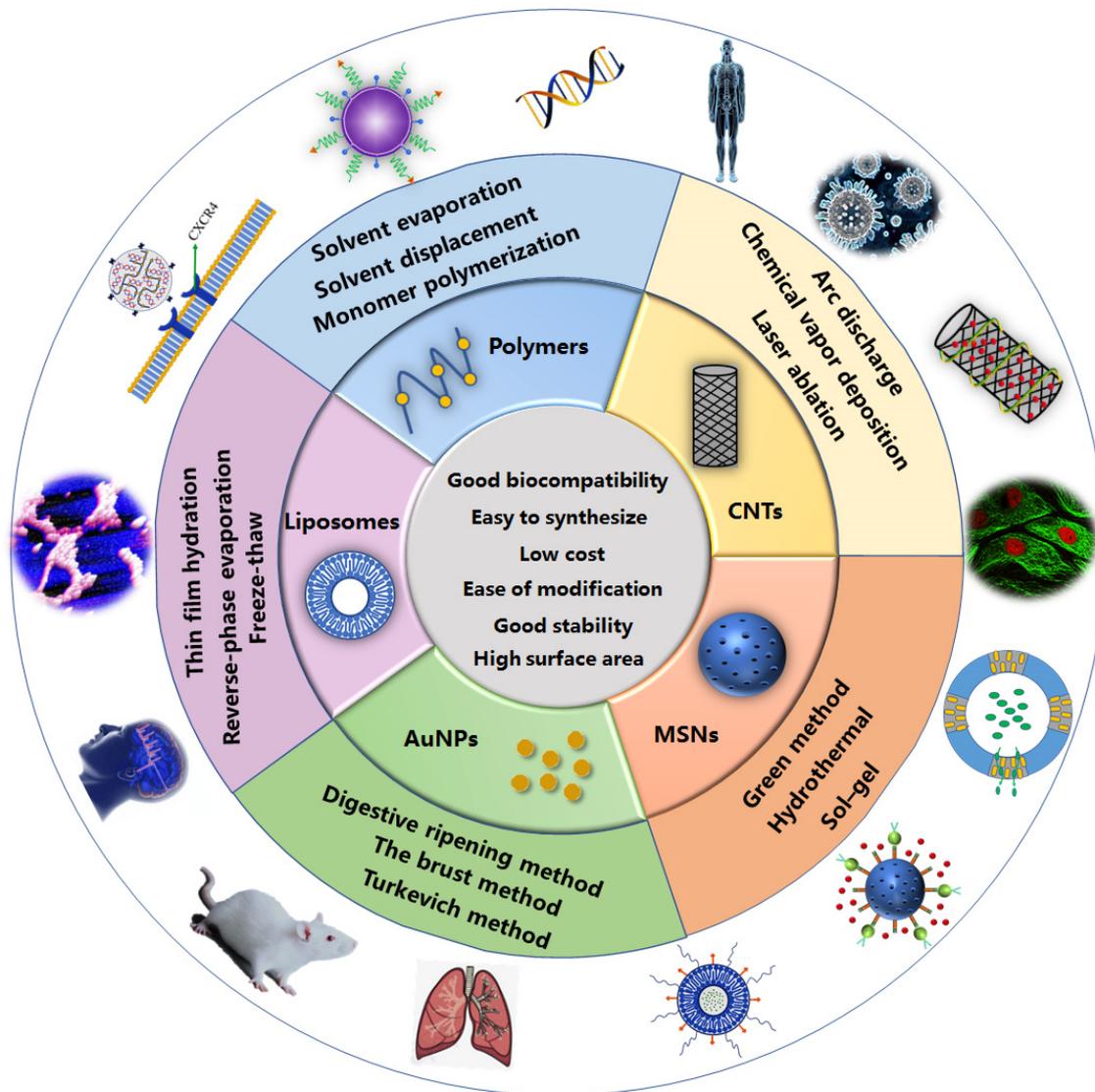

Figure 1. The characteristics, preparation methods, and biomedical applications of several non-viral vectors.

Table 1. The characteristics and preparation methods of several non-viral vectors.

Vector	Characteristics	Preparation Methods
Polymers	Easy to synthesize Low cost Biodegradable No immunogenicity Allow to be extensively modified	Solvent evaporation Emulsification–solvent diffusion Solvent displacement Monomer polymerization Double emulsion solvent evaporation
Liposomes	Low toxicity Good biocompatibility Improved pharmacokinetics Ease of synthesis	Thin film hydration Reverse-phase evaporation Injection Dehydration-rehydration Freeze-thaw

Table 1. *Cont.*

Vector	Characteristics	Preparation Methods
Gold nanoparticles	Good stability and biocompatibility High surface area-to-volume ratio Easy to modify	Turkevich method The brust method Digestive ripening method Green method
Mesoporous silica nanoparticles	Substa Ntial surface area Large pore size Low density Adsorption capacity Tunable pore size Ease of modification High biocompatibility	Sol–gel Hydrothermal Green method
Carbon nanotubes	Good adsorption ability Excellent chemical stability High tensile strength Significant electrical Thermal conductivity	Arc discharge Chemical vapor deposition (CVD) Laser ablation

Table 2. The patent reports related to non-viral vectors in recent years.

Vector	Summary	References
Polymer	Gene transfer composition using a tri-block polymer electrolyte being polyethyleneimine-polylactic-acid-polyethylene-glycol	[43]
Polymer	A methoxypolyethylene glycol-polylactic acid block copolymer was prepared to improve the drug encapsulation rate	[44]
Polymer	The chitosan modified with a carboxymethyl group and a hexanoyl group can be used as a material for a drug carrier	[45]
Polymer	Chitosan microspheres capable of precisely controlling the release of the drug	[46]
Polymer	Alginate extraction method	[47]
Polymer	Injectable hybrid alginate hydrogels	[48]
Liposomes	A method for preparing a Decoy nucleic acid cationic liposome carrier	[49]
Liposomes	An efficient, stable human lung tissues-active targeting immune nanoliposome, with specific active lung targeting	[50]
Liposomes	A liposome preparation, a preparation method and an application thereof in treatment for related diseases caused by abnormal expression of gene	[51]
Gold nanoparticles	A method for producing confeito-like gold nanoparticles using hydroxyl peroxide in an aqueous alkaline condition in the presence of a biocompatible protecting agent	[52]
Gold nanoparticles	Method for the size controlled preparation of these monodisperse carboxylate functionalized gold nanoparticles	[53]
Silica nanoparticles	Mesoporous silica nanoparticles and supported lipid bi-layer nanoparticles for biomedical applications	[54]
Silica nanoparticles	Mesoporous silica nanoparticles with lipid bilayer coating for cargo delivery	[55]
Carbon nanotubes	Payload molecule delivery using functionalized discrete carbon nanotubes	[56]
Carbon nanotubes	Carbon nanotubes for imaging and drug delivery	[57]

2. Polymers

Recent trends in biodegradable polymers, especially aliphatic polymers, indicate significant developments in terms of novel design strategies and clinical biomedicine applications [58]. Polymer as a non-viral vector has the following advantages: (1) easy

to synthesize and low cost [59]; (2) multiple polymers are biodegradable [60]; (3) no immunogenicity [61]; (4) allow being extensively modified [62]; (5) ability to protect the nucleic acid drugs from various enzymes by forming polyelectrolyte complexes [63]. There are four main types of production methods: solvent evaporation, emulsification–solvent diffusion, solvent displacement and monomer polymerization [59]. Various polymers such as dendrimers, polylactic acid (PLA), polyethylenimine (PEI), and chitosan (CS) have been widely used in delivery systems [51,64–68]. Table 3 summarizes the structural characteristics, synthesis methods and properties of several polymer materials.

Table 3. The information of several polymer materials.

Polymer	Structure	Synthesis Methods	Characteristics	Limitations
Dendrimers	Linear polymers with dendron on each repeating unit	Divergent approaches, Convergent approaches	Uniform size, High degree of branching, Polyvalency, Water solubility, Available internal cavities	-
Polyethylenimine	Cationic polymer of ethylenediamine monomers	-	High transfection efficiency	High toxicity
Chitosan	Repeating β-(1,4)-2-amino-D-glucose and β-(1,4)-2-acetamido-D-glucose units	Chemical method, enzymatic	Good biocompatibility	Poor solubility in water, Low transfection efficiency
Polylactic acid	The polymerization of lactic acid	Direct condensation polymerization, Azeotropic dehydration condensation, Lactide ring-opening polymerization, Double emulsion solvent evaporation technique	Strong plasticity, Low price, Good versatility	Poor hydrophilicity
Amino acid derived biopolymers	Amino acid polymerization	Direct polycondensation, Solution or activated polycondensation, Ring-opening polymerization, Interfacial polymerization, Melt polycondensation, Chemoen-zymatic synthesis	Wide-range of functional groups, Good biocompatibility	Production of by-products in the synthesis process
Alginate	Linear copolymer	Ionic crosslinking, Covalent crosslinking, Phase transition, Cell crosslinking, Free radical polymerization, Click chemistry	easy availability, hydrophilicity, biodegradability, versatility	Aggregation tendency with protein at high pHs

2.1. Dendrimers

Dendrimers are linear polymers with dendron on each repeating unit and have a hyper-branched 3D structure [61,69]. Their size, degree of branching and functionality can be controlled and adjusted through the synthetic procedures [70]. Meanwhile, dendrimers contain a variety of peripheral functional groups, which can be functionally modified using

surface engineering technology such as antibody, transferrin, biotin, folic acid, galactose, and peptide [71–73]. A variety of dendrimers such as poly (propylene imine) (PPI) dendrimers, polyamidoamine (PAMAM) dendrimers, and poly-L-lysine (PLL) dendrimers were synthesized by divergent and convergent approaches [74]. Guan et al. prepared fluorescent PAMAM dendrimer by conjugating PAMAM dendrimers to fluorescein. The vector has low cytotoxicity and high siRNA binding affinity which can improve the efficiency of Cy5-siRNA delivery in A549 cells [75]. Mastorakos et al. prepared the hydroxyl PAMAM dendrimer-based gene vectors which had high gene transfection efficiency and the stability of compound can be improved after polyethylene glycol treatment [76]. Liaw et al. prepared targeted novel hydroxyl dendrimer to deliver CSF-1R inhibitor BLZ945 (D-BLZ), these dendrimers penetrated into orthotopic brain tumors and localize specifically within TAMs. In vivo experiments on mice showed that the dendritic polymer could improve the therapeutic effect of D-BLZ on glioblastoma [77].

2.2. Polyethylenimine

Various molecular weights of PEI can be synthesized by linear and branched forms [78]. Because PEI has a large amount of positive charge on its surface, it can be adsorbed together with negatively charged nucleic acid drugs through electrostatic action to protect them from lysosomal degradation [79–83]. However, PEI cannot be degraded in vivo, and its high toxicity limits its application development [84,85]. Various polyethylenimine derivatives containing coordination groups have been developed to reduce toxicity [86,87]. Mattheolabakis et al. used polyethylenimine, hyaluronic acid, and polyethylene glycol to produce a polymer with a good ability to deliver siRNA to A549 cells [88]. Zhou et al. prepared a PEI derivative modified by a cyclic amine derivative. Compared with unmodified PEI, modification with cyclic amine derivatives can significantly reduce cytotoxicity. At the same time, the polymer has a good antagonistic effect on Chemokine receptor CXCR4, and has a good inhibitory ability on tumor cell invasion (Figure 2) [83]. Low molecular weight PEI has lower toxicity, but the transfection efficiency is correspondingly lower [89]. More and more studies have been conducted to modify low molecular weight PEI to improve transfection efficiency [90,91]. Zhang et al. modified PEI 600 Da with aromatic rings in order to improve DNA affinity. Cell uptake experiments showed that the polymer had higher transfection efficiency for DNA compared with PEI 25 kDa. Meanwhile, the toxicity of the polymer has low toxicity in both 7702 and HeLa cells by CCK-8 assay [92].
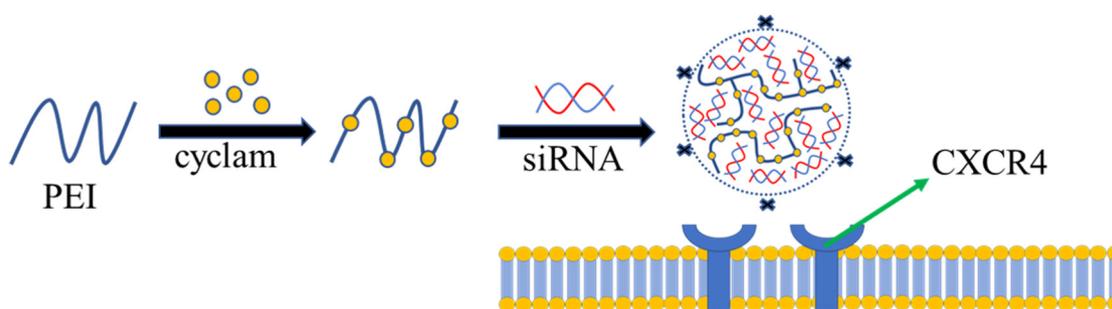

Figure 2. Cyclam modified PEI is used for the delivery of siRNA.

2.3. Chitosan

Chitosan (CS) is one of the most abundant biopolymers derived from natural chitin that commonly exists in the exoskeletons of arthropods, crustacean shells, insects, and fungal cell walls [93]. CS can be degraded by internal enzymes, which makes chitosan have good biocompatibility [94,95]. Like other cationic polymers, chitosan is linked to nucleic acids by electrostatic interaction [96,97]. However, the poor solubility in water and low transfection efficiency are the main factors limiting its application [98–100]. The presence of amino and hydroxyl groups makes chitosan easy to modify, modification of

chitosan with other substances such as PEI, gold nanoparticles, PLGA, and PEG have been widely reported [101]. Chen et al. incorporated hydrophobic deoxycholic acid (DCA) onto the chitosan backbone of poly (amidoamine) dendronized chitosan derivative (PAMAM-Cs) to obtain an amphiphilic derivative-PAMAM-Cs-DCA. Doxorubicin was wrapped inside the particle, and pDNA was electrostatically adsorbed on the surface of the particle. The system delivered both pDNA and drugs at the same time, and the transfection efficiency reached 74%. These results suggested that PAMAM-Cs-DCA NPs hold great promise to co-deliver chemotherapeutics and nucleic acid drugs [102]. Lee et al. prepared the triphenylphosphonium-glycol chitosan derivative (GME-TPP) with 36% substitution by Michael addition. GME-TPP microspheres successfully targeted DOX delivery to mitochondria in cells, which indicated the microsphere possess great potential as effective drug delivery carrier [103]. Babii et al. synthesized mannosyl chitosan with a degree of substitution of 15%. The particle has high encapsulation efficiency for CpG oligodeoxynucleotides (CpG ODN) and can target CpG ODN to immune cells, which indicated the particle may be used as an efficient carrier for intracellular CpG ODN delivery [104]. Masjedi et al. prepared targeted nanoparticles by modifying N, N, N-trimethyl chitosan with hyaluronic acid, which had low toxicity and high transfection efficiency for siRNA. The particle loaded with siRNA can block the proliferation of cancer cells by inhibiting the expression of IL-6/STAT3 [105].

2.4. Polylactic Acid/Poly (Lactic-Co-Glycolic Acid)

PLA and PLGA are biodegradable functional polymer organic compounds with good biocompatibility and encapsulation properties which can be metabolized in the body [106,107]. The synthesis of polylactic acid by direct condensation is described in the following four ways: (1) direct condensation polymerization; (2) azeotropic dehydration condensation; (3) lactide ring-opening polymerization; (4) double emulsion (water/oil/water) solvent evaporation technique [108–110]. The characteristics of strong plasticity, low price and good versatility have enabled them to be developed for biomedical applications such as drug delivery [111–113]. Zabihi et al. prepared poly (lactide-co-glycerol) (PLG) particles by combining hyperbranched polyglycerol and PLA. The encapsulation efficiency of this particle on tacrolimus is 14.5%, which was able to improve the skin penetration and therapeutic efficiency of this therapeutic agent [114]. Ren et al. prepared a dextran modified PLGA microsphere that delivered IL-1 receptor antagonist (IL-1RA). The microsphere can prolong the half-life of IL-1RA, allowing it to be released continuously. The results showed that IL-1ra-loaded dextran/PLGA microsphere might be a useful tool to combat periodontal disease [115]. Bazylińskaet al. prepared effective nanocarriers coated with PLGA, PLGA-PEG, or PLGA-FA by double emulsion evaporation process, which enabled co-encapsulation of cisplatin and verteporfin. The nanocarriers successfully delivered cargo to target cells and significantly enhanced the ability of drugs to kill cancer cells [116].

2.5. Amino Acid Derived Biopolymers

Amino acids have become promising biomaterials for their abundant source and diverse functional groups. Various polymerization methods are used to synthesize different types of amino acid derived biopolymers such as polyamides(PA)s, polyesters(PE)s, poly(ester-amide)s(PEA)s, polyurethanes(PU)s, and poly (depsipeptide)s (PDP)s [117]. Commonly used synthesis pathways are as follows: Direct polycondensation [118]; solution or activated polycondensation [119]; ring-opening polymerization [120]; interfacial polymerization [121]; melt polycondensation [122]; chemoenzymatic synthesis [123]. Poly(α-amino acid)s have the capability of readily self-assemble into discrete, stable, structures in solution. The positive charge of poly(beta-amino ester)s can bind to nucleic acids and be internalized into cells. At the same time, they can escape from the endolysosomal compartment and release nucleic acids into the appropriate cell compartment for gene delivery through a variety of targeted degradation mechanisms [68]. In addition, abundant functional groups provide multiple modification sites for amino acid derived biopolymers.

Various ligand-modified amino acid derived biopolymers were extensively studied in drug delivery (Table 4).

Table 4. Various responsive Amino acid derived biopolymers are used to deliver cargos.

Type	Ligands	Stimulus	Cargo	References
ssPBAE	HA	PH/redox	DOX/CXB	[124]
LPAE	-	Light	DNA	[125]
PBAE	PEG	PH	VP	[126]
PBLG	PEG	PH/Temperature	DOX	[127]
PBAE	-	PH	ATRA	[128]
SCA-PAE	HA	PH	siRNA	[129]

2.6. Alginates

Alginate (ALG) is a linear copolymer compound which has (1, 4)-linked-β-D- man-nuronic (M) and α-L-guluronic (G) acid units [130]. The composition and length of the M and G units determine the molecular and physicochemical properties of ALG. ALG is a widely used anionic biopolymer due to its easy availability, hydrophilicity, biodegradability and versatility. The hydroxyl groups and carboxyl groups of ALG can be modified easily by oxidation, acetylation, and esterification reactions [131]. The wide particle size distribution of ALG enables it create complexes with various other biomaterials by electrostatic interactions, chemical modification, or crosslinking [132]. The most important property of alginates is their ability to form ionic gel in the presence of polyvalent cations. So–gel is the most commonly used form of carrier for ALG. In recent years, the methods of producing hydrogels included ionic crosslinking, covalent crosslinking, phase transition, cell crosslinking, free radical polymerization, and click chemistry [130]. Alginate hydrogels have outstanding properties such as high-water content, nontoxicity, soft consistency, and biodegradability [133]. Meanwhile, alginate hydrogels can regulate the release of the drug according to the pH of the surrounding medium [134]. In addition, ALG can also be developed into microspheres and nanoparticles for drug delivery. Table 5 illustrates several alginate-based drug delivery systems.

Table 5. Various alginate-based vehicles used in drug delivery.

Carriers	Type	Cargo	References
ALG/Keratin	Hydrogels	Doxorubicin	[135]
ALG/HA/Folate	Hydrogels	OXA	[136]
ALG/CS/BSA	Microcapsule	DOX	[137]
ALG/PEG	Microspheres	Polystyrene	[138]
ALG/CS	Nanoparticles	Cur	[139]
ALG/Laponite	Nanohybrids	DOX	[140]

3. Liposomes

Liposomes are spherical vesicles composed of one or more layers of phospholipids which belong to amphiphilic molecules, hydrophilic drugs are encapsulated in a water core, and hydrophobic drugs are embedded in the lipid bilayer of the vesicle [141–143]. Liposomes as carriers have many advantages, including low toxicity, good biocompatibility, improved pharmacokinetics, and ease of synthesis [144–146]. The commonly used preparation methods are thin film hydration, reverse-phase evaporation, injection, dehydration-rehydration, and freeze-thaw. Liposomes are widely used in cancer treatment, viral infection, infectious disease, vaccines, and other medical research [147–150]. However,

unmodified liposomes are unstable in structure, thus are easily eliminated in the body's circulation, making drugs unable to effectively reach target organs and target sites [151–153]. Therefore, various ligand-targeting liposomes and stimulus-responding liposomes have been developed to improve the delivery and targeting performance of liposomes [154–159]. Table 6 shows that liposomes modified with different ligands to deliver different cargos.

Table 6. Various ligands modified liposomes to deliver different cargos.

Ligands	Stimulus	Cargo	References
H16 peptide	-	Alpha-galactosidase A	[160]
Ferritin receptors	-	Resveratrol	[161]
Lactoferrin	-	Doxorubicin	[162]
PEG and anti-EphA10 antibody	-	siRNA	[163]
Anti-CD44 aptamer	-	siRNA	[164]
DSPE–PEG-2000	Temperature	Doxorubicin	[165]
Peptide H7K(R2)2	PH	dDoxorubicin	[166]
Superparamagnetic magnetite	Magnetic Field	5-fluorouracil	[167]
Hyaluronic acid	Redox	Doxorubicin	[168]
Enzymatically cleavable peptide linkers GFLG	enzyme	pDNA	[169]

3.1. Ligand-Targeting Liposomes

Peptides as ligands have the advantages of small size, easy production, and high stability [170]. Peptides can be combined with liposomes through various covalent and non-covalent bonds, and are mainly divided into cell-penetrating peptides (CPP) and cell-targeting peptides (CTP) [171–173]. RGD sequences are the most widely used class of liposomal binding peptides, especially in tumor therapy [174]. Kang et al. developed a cyclic peptide c(RGDyC) modified liposomal delivery system to deliver the integrins αvβ3, which had a higher cellular uptake compared with liposomes without c(RGDyC) [175]. Belhadj et al. designed a Y-shaped multifunctional targeting material c(RGDyK)-pHA-PEG-DSPE to deliver DOX, which prolonged the survival time of mice [176]. The encapsulation rate of RGD-DXRL-PEG liposomes prepared by Chen et al. for doxorubicin was more than 98%, and the cellular doxorubicin uptake for RGD-DXRL-PEG was about 2.5-fold higher than that for DXRL-PEG (Figure 3) [177]. CPP typically contains 5 to 35 amino acid residues and is widely used in cancer treatment [178]. Ding et al. constructed CPP-modified pH-sensitive PEGylated liposomes (CPPL) which had high cell-penetrating and endosomal escape abilities [179]. Hayashi et al. developed H16 peptide-modified liposomes (H16-Lipo) which effectively delivered alpha-galactosidase A (GLA) to intracellular lysosomes and improved proliferation of GLA knockdown cells [160]. Some other types of peptides have also been used to modify liposomes. Chen et al. used peptide-20 modified liposome as a carrier for DOX delivery, and U87 cells had a high uptake rate of this liposome [177]. Jhaveri et al. used ferritin receptors modified liposomes to deliver resveratrol, which has a good effect on inhibiting tumor growth and improving the survival rate of mice [161]. Wei et al. developed a lactoferrin modified, polyethylene glycolated liposomes for doxorubicin delivery. The results of experiments in mice indicated that the liposome-loaded DOX has the potential to treat hepatocellular carcinoma [162].

Various immune liposomes can be obtained by attaching antibodies to the surface of liposomes using surface engineering techniques [180–182]. Gao et al. developed a liposome system modified with anti-EGFR Fab to deliver DOX and ribonucleotide reductase M2 siRNA, in vivo and in vitro experimental results showed that the vector system can improve the efficiency of gene therapy and had a certain therapeutic effect on hepatocellular carcinoma [183]. Saeed et al. prepared the immunoliposomes coupled to anti-MAGE A1

TCR-like single-chain antibody which can be specifically bound to and be internalized by positive melanoma cells [184]. Zang et al. prepared liposomes modified by PEG and anti-EphA10 antibody, the immunoliposome significantly improved the transfection efficiency of siRNA in MCF-7/ADR cells [163].
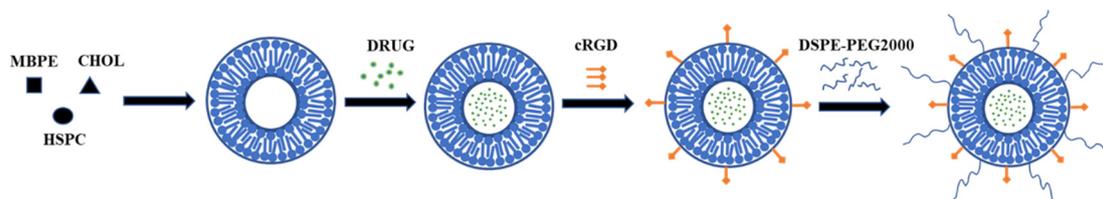

Figure 3. Schematic representation for preparation of RGD-DXRL-PEG.

An aptamer is a short synthetic single stranded DNA or RNA that can specifically bind to the target through hydrogen bonds, Van der Waals forces and electrostatic interactions [185,186]. Using aptamers as ligands has the characteristics of small volume, simple synthesis process, low toxicity, good stability, high affinity, and good targeting selectivity [187]. Alshaer et al. used anti-CD44 aptamer (APT1) modified liposome as a carrier system for siRNA delivery and achieved a good gene silencing effect in tumor cells [164]. Powell et al. used Aptamer A6modified liposome as a vector to deliver siRNA to breast cancer cells which enhanced cytotoxicity and antitumor efficacy [188]. Li et al. combined Aptamer AS1411 with PEGylated liposome surface to prepare a targeted carrier for siRNA delivery. Cell uptake experiment results showed that the accumulation of siRNA in tumor cells was greater than that in normal cells. Meanwhile, the carrier system showed significant silencing activity in tumor xenograft mice and inhibited the melanoma growth which indicated that the targeted delivery system of liposomes may have potential in the treatment of melanoma [189].

Molecules such as folate and sugars also serve as ligands for liposomes [190–192]. There are also studies devoted to the development of liposome carriers modified with various ligands, multivalent ligands have multiple binding groups and enhance the therapeutic efficacy of drugs [193]. Kang et al. prepared a dual ligand liposome drug delivery system modified with Pep-1 peptide and folate which showed higher cellular uptake and cytotoxicity in HeLa cells as compared to chimeric-ligand oriented liposomes [194]. Zong et al. prepared a dual ligand liposome drug delivery system modified with cell-penetrating peptide (TAT) and transferrin, which effectively delivered drugs to targeted tumor cells, the results of in vivo experiments also demonstrated that this drug delivery system could improve the survival time of brain tumor-bearing animals [195].

Abbreviations: HSPC, hydrogenated soybean phosphatidylcholine; CHOL, cholesterol; MBPE, maleimidobenzoylphosphatidylethanolamine; DSPE-PEG2000, N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl-sn-glycero-3- phosphoethanolamine sodium salt; DRUG, doxorubicin; DXRL-PEG, DXR-loaded PEGylated liposomes; RGD-DXRL-PEG, cRGD-modified DXRL-PEG.

3.2. Stimulus-Responding Liposomes

Internal physiological conditions and external stimuli were used to promote the release of drug delivery systems in specific locations and environments to alter pharmacokinetic characteristics [196,197]. Depending on the stimulus, scientists developed various liposome drug carrying systems such as temperature-responsive liposomes, pH-responsive liposomes, ultrasound responsive liposomes, magnetic-field responsive liposomes, redox-responsive liposomes, light-responsive liposomes, and enzyme-responsive liposomes. Needham et al. prepared a kind of temperature sensitive liposome using dipalmitoylphosphatidylcholine (DPPC), monopalmitoylphosphatidylcholine (MSPC), and distearoylphosphatidylethanolamine (DSPE)-PEG2000. The liposome is relatively stable at 37 °C. When the temperature reaches 41.5 °C, 31% of the drug can be released within one to two seconds

which was much higher than the unmodified liposome group [165]. Zhao et al. prepared a pH-responsive liposome drug delivery system using tumor-specific pH-responsive peptide H7K(R2)2 as a ligand. In vitro experiments proved that the drug delivery system effectively released drugs under acidic conditions, and in vivo experiments showed that the system had a good anti-tumor ability in C6 tumor-bearing mice [166]. Clares et al. used a reproducible thin film hiatus technique to prepare magnetic liposomes coated with 5-fluorouracil. Magnetic field caused the release of the drug and a good inhibition effect was observed in human colon cancer cells [167]. Sine et al. prepared a light-responsive liposome encapsulated with 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-A and calcein, laser irradiation (660 nm, 90 mW) can promote drug release which showed enhanced antitumor efficacy (Figure 4) [198]. Chi et al. prepared redox-responsive liposomes using hyaluronic acid as a compound. The drug can be effectively released when the liposome is exposed to reduced conditions. All animals treated with liposomal formulations survived in contrast to those animals treated with free-DOX, indicating the liposomal formulation have an effective tumor suppressive effect [168]. Song et al. synthesized enzymatic-responsive liposomes using the enzymatically cleavable peptide linkers GFLG (Gly-Phe-Leu-Gly) as the ligand system. After GFLG was degraded by endo-lysosomal enzyme, the encapsulated pDNA was released and the transfection efficiency was 100 times higher than that of the control group without GFPG modification [169].
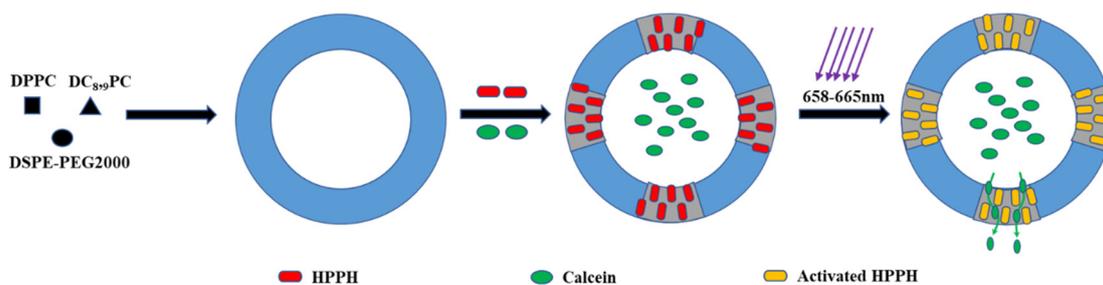

Figure 4. Design consideration of light-responsive liposomes.

Abbreviations: DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; $DC_{8,9}PC$, 1,2 bis(tricosa-10,12-diynoyl)-sn-glycero-3-phosphocholine; DSPE-PEG2000, 1,2-distearoyl -sn-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)-2000].

4. Gold Nanoparticles

Gold nanoparticles (AuNPs) have good stability and biocompatibility [199]. Quantum size effect and high surface area-to-volume ratio make AuNPs have high drug loading [200]. Meanwhile, gold nanoparticles are easy to modify and can improve the pharmacokinetics of many drugs which makes gold nanoparticles widely used in immune analysis, drug delivery, and detection of cancer cells and microorganisms [201–203]. For example, Ruan et al. synthesized the Angiopep-2-PEG modified AuNPs which could specifically deliver and release DOX in glioma and significantly expand the median survival time of glioma-bearing mice (Figure 5) [204]. The synthesis methods of gold nanoparticles include chemical synthesis and biological synthesis. The commonly used chemical methods include the turkevich method, the brust method, and digestive ripening method [205–207]. The chemosynthesis method has some limitations including low yield, difficulty in controlling particle shape, strict preparation conditions, and poor biocompatibility [208–211]. Therefore, more and more scientists are using friendly biosynthesis methods to synthesize gold nanoparticles.

Bacteria are important biological sources for the synthesis of AuNPs. The extracellular enzymes work as a reducing agent in the reduction of metals during the synthesis of microbial NPs and NADH-dependent reductase can carry out electron transfer from NADH, leading to reduction of metal ions [212,213]. Parastoo et al. prepared the gold nanoparticles with spherical, hexagonal, and octagonal shapes by reducing $HAuCl_4$ in

supernatant microbial of bacillus cereus culture [214]. Sharma et al. screened a marine bacterium from different sea cost in India to produce gold nanoparticles. The prepared gold nanoparticles were mostly spherical with a particle size of 10 nm [215]. Fungi also can be used to synthesize gold nanoparticles. Sanghi et al. synthesized intracellular gold nanoparticles with Phanerochaete chrysosporium and demonstrated that ligninase played an important role [216]. Molnár et al. synthesized gold nanoparticles of different sizes (between 6 nm and 40 nm) under controlled experimental conditions [217].
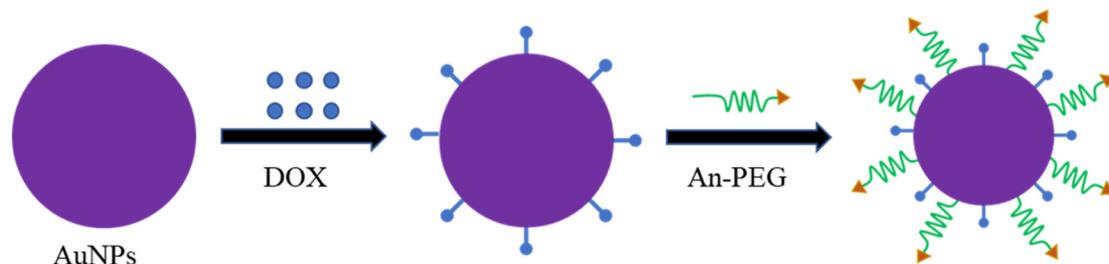

Figure 5. An-PEG modified gold nanoparticles are used to deliver DOX. Abbreviations: DOX, doxorubicin; An, Angiopep-2.

As a cheap biological material, plants were used to synthesize gold nanoparticles in recent years. Different plant species, different parts of the same plant species such as leaves, roots, stems, and fruits can be used as raw materials for the synthesis of gold nanoparticles [218]. Gopinath et al. synthesized spherical gold nanoparticles with particle size of 20 nm to 50 nm by aqueous leaf extract of terminalia arjuna [219]. Yu et al. used Citrus Maxima (C. Maxima) fruit extract to synthesize gold nanoparticles with an average particle size of 25.7 nm [220]. In addition, some studies have shown that gold nanoparticles can be synthesized from seaweed [221,222]. Table 7 shows the various biomaterials that can be used to synthesize gold nanoparticles.

Table 7. Characteristics of gold nanoparticles synthesized from different raw materials.

Name of Organism	Size (nm)	Shape	References
Bacteria			
Bacillus cereus	20–50	Spherical, hexagonal, octagonal	[214]
Brevibacterium casei	10–50	Spherical	[223]
Vibrio alginolyticus	50–100	Irregular	[224]
Paracoccus haeundaensis BC74171(T)	20.93 ± 3.46	Spherical	[225]
Fungi			
Macrophomina phaseolina	14–16	Spherical	[226]
Morchella esculenta	16.51	Spherical and hexagonal	[227]
endophytic Cladosporium species	5–10	Spherical	[228]
Ttichoderma sp. WL-Go	1–24	Spherical and pseudo-spherical	[229]
Plants			
Annona muricata	25.5	Spherical	[230]
Benincasa hispida	22.18 ± 2	Spherical	[231]
Capsicum annuum	19.97	Spherical	[232]
Turnera diffusa	24	Spherical	[233]

Table 7. *Cont.*

Name of Organism	Size (nm)	Shape	References
Algae			
Sargassum serratifolium	5.22	slightly spherical, triangles, pentagons, and narrow square	[234]
marine red algaAcanthophora spiciferaby	<20	Spherical	[235]
marine brown algae S. ilicifolium	20–25	Near-spherical	[236]
Chlorella sorokiniana Shihira & R.W	5–15	Spherical	[237]

The size and shape of gold nanoparticles can be tuned by controlling the synthesize conditions such as temperature, type of surfactant, and concentration of metal matrix in both chemical and biosynthetic methods [238]. The size and shape of gold nanoparticles strongly influence their toxicity, drug loading, and penetration properties, and then affect their biomedical applications. A study showed that 5 nm AuNPs in a concentration of more than 50 μM were associated with cytotoxic effects, while 15 nm AuNPs presented good biocompatibility [239]. Karol et al. studied the relationship between toxicity and shape of gold nanoparticles (rods, stars, and spheres). The results showed that star shape gold nanoparticles has the highest anticancer potential but has the slowest cellular uptake due to their big size, while the sphere shape gold nanoparticles exhibited the most safety, the fastest cellular uptake and weak anticancer potential [240]. A study about the size dependence of the antiviral activity of AuNPs demonstrated that small particles (2 nm) had no inhibitory effect for influenza virus, while medium-sized AuNPs (14 nm) inhibited the virus binding and infection [241].

5. Mesoporous Silica Nanoparticles

In 1992, the first ordered mesoporous silica (MCM type) was synthesized by the Mobile Research and Development Corporation [242,243]. Subsequently, many other types of mesoporous silica nanomaterials (MSNs) such as BSA type, HMM type, KIT type, KCC type, FSM type, and TUD type were synthesized using a variety of improved methods. Table 8 shows the specific example of the synthesis of various MSNs. Various distinctive properties of MSNs including substantial surface area, large pore size, low density, good adsorption and encapsulation capacity, controllable superficial charge, ease of modification, and high biocompatibility showed great potential in drug delivery applications [244–249]. The synthesis techniques of MSNs can be classified into sol–gel, as well as hydrothermal and green method (Table 9) [250].

Table 8. Synthesis of different series of MSNs.

Type	Silica Sources	Surfactant	References
MCM	Sodium silicate, Tetramethylammonium silicate, Tetraethyl orthosilicate	Quaternary ammonium surfactant	[242]
BSA	Sodium silicate	C_{18}TMACl	[251]
HMM	1,2-bis(trimethoxysilyl)ethane	$C_{18}H_{37}N(CH3)_3Cl$	[252]
KIT	Tetraethyl orthosilicate, Carboxyethylsilanetriol sodium salt	Pluronic F127	[253]
KCC	Tetraethyl orthosilicate	Cetylpyridinium bromide	[254]
FSM	Layered polysilicate kanemite	Quaternary ammonium surfactant	[255]
TUD	Tetraethyl orthosilicate	Tetraethyl ammonium hydroxide	[256]

Table 9. Three different synthesis methods of MSNs.

Method	Silica Sources	Surfactant	Catalyst	References
Sol–gel	Sodium silicate	Polyethylene glycol	Acetic acid	[257]
	Tetrethylorthosilicate	Cetyltrimethylammonium chloride	Triethanolamine	[258]
Hydrothermal	Tetrethylorthosilicate	Cetyltrimethylammonium bromide	Ammonia	[259]
	Tetrethylorthosilicate	Pluronic F-127	Chloride acid	[260]
Green	Banana Peel	Cetyltrimethylammonium bromide	NaOH	[261]
	Tetraethyl orthosilicate	C16-L-histidine, C16-L-poline and C16-L-tryptophan	HCl	[262]

Regardless of the synthesis method, studies have shown that selection of surfactant molecule, silica precursors, solvents, reaction temperature, stir speed, and pH of the media affect the shape, size, surface area, and pore size of MSNs [263,264], and these physical properties further affect the drug loading, toxicity, and uptake efficiency of the carriers [265–267]. Cho et al. found that compared with MSNs with a particle size of 100 nm or 200 nm, MSNs with a particle size of 50 nm had the fastest clearance rate in urine and bile [268]. Lu et al. prepared a series of MSNs with particle sizes of 30 nm, 50 nm, 110 nm, 170 nm, and 280 nm, the cellular uptake amount of 50 nm nanoparticles was much higher than other groups [269]. In addition, studies showed that rod-shaped MSNs internalize faster and higher on tumor cells than spherical MSNs [270]. Meanwhile, the pores of MSNS have a large surface area, and for different drugs, the release of drugs can be controlled by regulating the size of the pores [271]. Mellaerts et al. prepared four SBA-15 MSNs with pore size varying from 4.5 to 9.0 nm, and they found that the increase of the pore size from 4.5 to 6.4 nm significantly improved the release of itraconazole, while a further increase to 7.9 and 9.0 nm revealed a slight improvement in the release profile [272].

However, two challenges of MSNs may limit its broader application. The open pores of MSNs are ideal reservoirs for drugs, which adversely trigger a premature release of drugs before reach the target [266]. A simple way to minimize the leakage is the attachment of the drugs through a cleavable bond onto the inner surface of the particle [273]. Wong et al. connected doxorubicin (DOX) and zinc(II) phthalocyanine (ZnPc) to form a DOX-ZnPC complex using an acid cleavable hydrazone linker, and the resulted delivery system achieved drug release under acidic conditions [274]. Another method involved loading one drug inside the pores and attaching another drug at the outlet of the pores [273]. Willner et al. loaded the anticancer drug mitoxantrone into boric acid modified MSNs, the pores were capped with gossypol, then the capping units unlocked the pores and the drug is released under mild acidic conditions [275]. Another challenge is that unmodified MSNs lack the active targeting and slow-release ability; therefore, various responsive delivery systems were prepared through surface modification. Various ligands such as polyethylene glycol, folic acid, polyethylenimine, hyaluronic acid, phenyl, thiol, and sulfonate have been reported to modify MSNs [276–280]. After ligand modification, MSNs can realize the function of drug release under specific environment including pH, redox, enzyme, temperature, magnetic field, and light stimulation. Liu et al. designed and fabricated a biocompatible, enzyme-responsive drug delivery system based on MSNs for targeted drug delivery in vitro and in vivo. The system demonstrated sensitivity to MMP-2 for drug delivery, leading to cell apoptosis which displayed a good curative effect on the inhibition of tumor growth with minimal toxic side effects (Figure 6) [281]. Table 10 shows various stimulus-responsive-MSNs for controlled release.
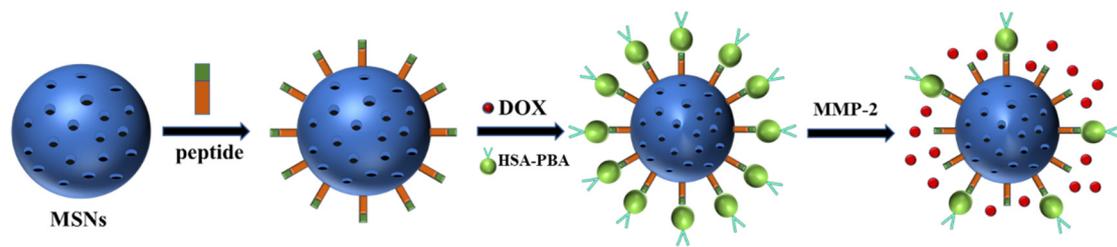
Figure 6. Design consideration of enzyme-responsive MSNs. Abbreviations: DOX, doxorubicin; HAS, human serum albumin; PBA, phenylboronic acid; MMP-2, matrix metalloproteinase-2.

Table 10. Various responsive MSNs are used to deliver cargos.

Ligands	Stimulus	Cargo	References
FA-PEG-COOH	Redox	Doxorubicin and Bcl-2	[282]
Disulfide bonds modifiedpolyethylene glycol	Redox	Rhodamine B	[283]
Galactose-modified trimethyl chitosan-cysteine	PH	Doxorubicin and vascular endothelial growth factor siRNA	[284]
Succinylated ε-polylysine	PH	Prednisolone	[285]
Peptide LVPRGSGGLVPRGSGGLVPRGSK-pentanoic acid (P)	Enzyme	Anticoagulant drug	[286]
Phenylboronic acid-human serum albumin	Enzyme	Doxorubicin	[281]
Superparamagnetic magnetite nanocrystal clusters	Magnetic Field	Small interfering RNA	[287]
PEI-Iron oxide	Magnetic Field	siRNA-PLK1	[288]
PEO-b-poly (N-isopropylacrylamide) based copolymeric micelles	Temperature	Ibuprofen	[289]
Poly(N-isopropylacrylamide)-co-(1-butyl-3-vinyl imidazolium bromide) (p-NIBIm)	Temperature	Cytochrome C	[290]
1-tetradecanol	Light	Doxorubicin	[291]
Ruthenium complex	Light	Safranin O	[292]

6. Carbon Nanotubes

The diameter of CNTs is in the order of nano and the length is in the order of micron, giving them a high aspect ratio and large surface area [293–296]. Due to their outstanding properties such as good adsorption ability, excellent chemical stability, high tensile strength, significant electrical, and thermal conductivity, CNTs have been used in a variety of biomedical fields, especially drug delivery and cancer treatment [297–299]. There are three main ways to manufacture CNTs, including arc discharge, chemical vapor deposition (CVD), and laser ablation [300]. Toxicity is often a concern in clinic applications. Several physical and chemical factors including purity of the material, morphology, and administration route are crucial for the toxicity of CNTs [301]. It has been reported that residual transition metal catalysts such as iron, cobalt or nickel contained in the pristine CNTs can catalyze the intracellular formation of free radicals and oxidative stress leading to cytotoxic effects [302]. Therefore, the purification of CNTs by exposing them to high temperatures or bathing sonication assisted acid oxidation reduced the remains of catalytic metals used in their synthesis, increasing their biocompatibility and decreasing the toxicity levels [303]. In addition, the modification of CNTs is also an effective method to reduce their toxicity [304].

CNTs tend to agglomerate uncontrollably due to Van der Waals forces among bundles and high surface energy, which hinders their dispersion in almost all organic and inorganic solvents [298]. Meanwhile, the morphology and chemical properties of CNTs are the main factors affecting their entry into target cells [305]. Chemical functionalization can modify CNTs' electronic properties, reduce agglomeration, and improve their solubility in different

solvents [306]. The main approaches for CNTs' functionalization can be divided into two main groups including covalent functionalization and non-covalent functionalization. The covalent functionalization mainly relies on covalent bond to connect carbon nanotubes to molecules. The non-covalent modification mainly relies on Van der Waals forces and electrostatic interaction to connect carbon nanotubes to molecules [307]. Antibodies, peptides, hyaluronic acid, oligonucleotides, polyethylene glycol, and other substances are often used to modify CNTs [308,309]. Mo et al. prepared a pH-responsive drug delivery system with SWCNTs as the core and CHI and HA as ligands (Figure 7) [310]. Table 11 provides detailed cases of various functionalized CNTs delivered to different cargoes.
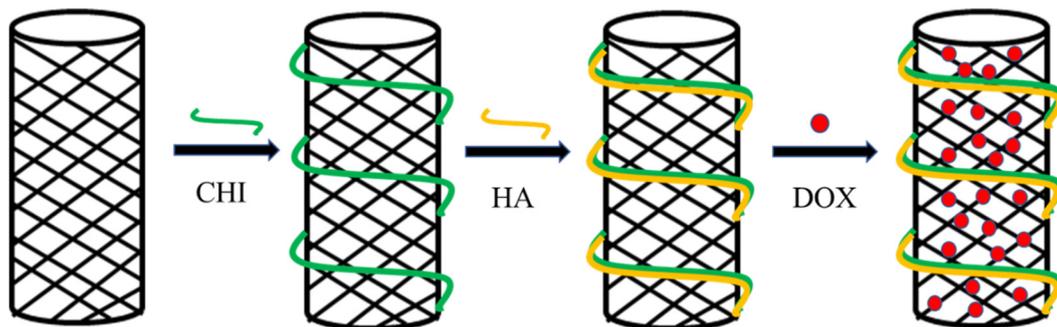
Figure 7. CHI- and HA-modified SWCNTs were used to deliver DOX. Abbreviations: CHI, chitosan; HA, hyaluronan; DOX, doxorubicin.

Table 11. Various ligand-modified SWNTs and WWNTs are used to deliver cargos.

Type	Ligands	Cargo	Stimulus	References
SWCNTs	Polysaccharide chitosan-hyaluronic acid	Doxorubicin	pH	[310]
	Oligonucleotides	DNA/RNA	-	[311]
	Chitosan	Curcumin	pH	[312]
	Polyethylenimine with betaine	Survivin siRNA, Doxorubicin	pH	[313]
MWCNTs	Folic acid	Doxorubicin	Magnetic Field	[314]
	1-octadecanethiol-f-GNPs	Cisplatin	-	[315]
	Chitosan	Methotrexate	pH	[316]
	Distearyl phosphatidyl ethanolamine-PEG	-	Light	[317]

7. Conclusions and Perspectives

Viral vectors are the earliest and most widely used type of vectors. However, toxicity, immunogenicity, carcinogenicity, high cost, and other issues limit their broader application. The investigation of non-viral vectors such as f liposomes, polymer, gold nanoparticles, mesoporous silica nanoparticles, and carbon nanotubes in medical research is growing rapidly. In this contribution, the application of non-viral vectors in drug delivery and gene therapy is summarized. Non-viral vectors can prevent the premature degradation of nucleic acids, proteins or drugs, prolong therapeutic effect, and reduce side effects. In addition, ligand modifications make the vectors better connect with the cargo or with the target site of action, increase the loading capacity and uptake rate, as well as improve the sustained release and targeting properties of the delivery system. Polyethylene glycol, folic acid, hyaluronic acid, peptides, oligonucleotide sequences, and other ligands have been reported to modify various materials. Further research will be necessary to introduce new ligands and develop novel smart delivery systems. Furthermore, biomedical applications have high requirements for the physicochemical properties of the vectors, thus synthesizing

and purifying vector materials with suitable particle size, uniform morphology, and good biocompatibility are essential. Meanwhile, the residual toxic effects of catalysts, solvents, and other substances in a synthesis process cannot be ignored. Consequently, non-viral vector materials are constantly improving new synthetic methods especially green synthesis methods, which is also a key direction of future research.

Although many studies have pointed out that non-viral vectors are biocompatible, most of the results focus on the short-term toxicity in vivo, and the protocols used in some toxicity tests are not standardized, posing an important safety concern in clinical application. Therefore, standardizing the toxicological tests and determining the safe exposure limits are crucial. Despite these challenges, with the development of novel materials and new synthetic strategies, non-viral vectors are expected to be widely applied to enhance the performance of drug delivery and gene therapy in the near future.

References

1. Choi, J.W.; Lee, J.S.; Kim, S.W.; Yun, C.O. Evolution of oncolytic adenovirus for cancer treatment. *Adv. Drug Deliv. Rev.* **2012**, *64*, 720–729. [CrossRef]
2. Gao, X.; Tao, Y.; Lamas, V.; Huang, M.; Yeh, W.H.; Pan, B.; Hu, Y.J.; Hu, J.H.; Thompson, D.B.; Shu, Y.; et al. Treatment of autosomal dominant hearing loss by in vivo delivery of genome editing agents. *Nature* **2018**, *553*, 217–221. [CrossRef] [PubMed]
3. Rossidis, A.C.; Stratigis, J.D.; Chadwick, A.C.; Hartman, H.A.; Ahn, N.J.; Li, H.; Singh, K.; Coons, B.E.; Li, L.; Lv, W.; et al. In utero CRISPR-mediated therapeutic editing of metabolic genes. *Nat. Med.* **2018**, *24*, 1513–1518. [CrossRef]
4. Ryu, S.M.; Koo, T.; Kim, K.; Lim, K.; Baek, G.; Kim, S.T.; Kim, H.S.; Kim, D.E.; Lee, H.; Chung, E.; et al. Adenine base editing in mouse embryos and an adult mouse model of Duchenne muscular dystrophy. *Nat. Biotechnol.* **2018**, *36*, 536–539. [CrossRef]
5. Erdoğar, N.; Akkın, S.; Bilensoy, E. Nanocapsules for Drug Delivery: An Updated Review of the Last Decade. *Recent Pat. Drug Deliv. Formul.* **2018**, *12*, 252–266. [CrossRef]
6. Unsoy, G.; Gunduz, U. Smart Drug Delivery Systems in Cancer Therapy. *Curr. Drug Targets* **2018**, *19*, 202–212. [CrossRef]
7. Bono, N.; Ponti, F.; Mantovani, D.; Candiani, G. Non-Viral in Vitro Gene Delivery: It is Now Time to Set the Bar! *Pharmaceutics* **2020**, *12*, 183. [CrossRef]
8. Durymanov, M.; Reineke, J. Non-viral Delivery of Nucleic Acids: Insight into Mechanisms of Overcoming Intracellular Barriers. *Front. Pharmacol.* **2018**, *9*, 971. [CrossRef]
9. Schoch, K.M.; Miller, T.M. Antisense oligonucleotides: Translation from mouse models to human neurodegenerative diseases. *Neuron* **2017**, *94*, 1056–1070. [CrossRef] [PubMed]
10. Zhao, X.; Ye, Y.; Ge, S.; Sun, P.; Yu, P. Cellular and Molecular Targeted Drug Delivery in Central Nervous System Cancers: Advances in Targeting Strategies. *Curr. Top. Med. Chem.* **2020**, *20*, 2762–2776. [CrossRef]
11. Durymanov, M.O.; Rosenkranz, A.A.; Sobolev, A.S. Current Approaches for Improving Intratumoral Accumulation and Distribution of Nanomedicines. *Theranostics* **2015**, *5*, 1007–1020. [CrossRef]
12. Sun, B.; Hyun, H.; Li, L.T.; Wang, A.Z. Harnessing nanomedicine to overcome the immunosuppressive tumor microenvironment. *Acta Pharmacol. Sin.* **2020**, *41*, 970–985. [CrossRef]
13. Meng, Q.Y.; Hu, H.; Zhou, L.P.; Zhang, Y.X.; Yu, B.; Shen, Y.Q.; Cong, H.L. Logical design and application of prodrug platforms. *Polym. Chem.* **2019**, *10*, 306–324. [CrossRef]

14. He, B.; Sui, X.; Yu, B.; Wang, S.; Shen, Y.; Cong, H. Recent advances in drug delivery systems for enhancing drug penetration into tumors. *Drug Deliv.* **2020**, *27*, 1474–1490. [CrossRef] [PubMed]

15. Pezzoli, D.; Chiesa, R.; De Nardo, L.; Candiani, G. We still have a long way to go to effectively deliver genes! *J. Appl. Biomater. Funct. Mater.* **2012**, *10*, 82–91. [CrossRef] [PubMed]

16. Pezzoli, D.; Candiani, G. Non-viral gene delivery strategies for gene therapy: A "ménage à trois" among nucleic acids, materials, and the biological environment: Stimuli-responsive gene delivery vectors. *J. Nanopart. Res.* **2013**, *15*, 1523. [CrossRef]

17. Bennett, C.F.; Swayze, E.E. RNA targeting therapeutics: Molecular mechanisms of antisense oligonucleotides as a therapeutic platform. *Annu. Rev. Pharmacol. Toxicol.* **2010**, *50*, 259–293. [CrossRef]

18. Cavazzana-Calvo, M.; Thrasher, A.; Mavilio, F. The future of gene therapy. *Nature* **2004**, *427*, 779–781. [CrossRef]

19. Ashfaq, U.A.; Riaz, M.; Yasmeen, E.; Yousaf, M.Z. Recent Advances in Nanoparticle-Based Targeted Drug-Delivery Systems Against Cancer and Role of Tumor Microenvironment. *Crit. Rev. Ther. Drug Carr. Syst.* **2017**, *34*, 317–353. [CrossRef]

20. Liyanage, P.Y.; Hettiarachchi, S.D.; Zhou, Y.; Ouhtit, A.; Seven, E.S.; Oztan, C.Y.; Celik, E.; Leblanc, R.M. Nanoparticle-mediated targeted drug delivery for breast cancer treatment. *Biochim. Biophys. Acta Rev. Cancer* **2019**, *1871*, 419–433. [CrossRef]

21. De Jong, W.H.; Borm, P.J. Drug delivery and nanoparticles: Applications and hazards. *Int. J. Nanomed.* **2008**, *3*, 133–149. [CrossRef]

22. Yu, W.; Mookherjee, S.; Chaitankar, V.; Hiriyanna, S.; Kim, J.W.; Brooks, M.; Ataeijannati, Y.; Sun, X.; Dong, L.; Li, T.; et al. Nrl knockdown by AAV-delivered CRISPR/Cas9 prevents retinal degeneration in mice. *Nat. Commun.* **2017**, *8*, 14716. [CrossRef]

23. Shalem, O.; Sanjana, N.E.; Hartenian, E.; Shi, X.; Scott, D.A.; Mikkelson, T.; Heckl, D.; Ebert, B.L.; Root, D.E.; Doench, J.G.; et al. Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science* **2014**, *343*, 84–87. [CrossRef]

24. Humphreys, I.R.; Sebastian, S. Novel viral vectors in infectious diseases. *Immunology* **2018**, *153*, 1–9. [CrossRef] [PubMed]

25. Finer, M.; Glorioso, J. A brief account of viral vectors and their promise for gene therapy. *Gene Ther.* **2017**, *24*, 1–2. [CrossRef] [PubMed]

26. Lehrman, S. Virus treatment questioned after gene therapy death. *Nature* **1999**, *401*, 517–518. [CrossRef] [PubMed]

27. Thomas, C.E.; Ehrhardt, A.; Kay, M.A. Progress and problems with the use of viral vectors for gene therapy. *Nat. Rev. Genet.* **2003**, *4*, 346–358. [CrossRef]

28. Ahi, Y.S.; Bangari, D.S.; Mittal, S.K. Adenoviral vector immunity: Its implications and circumvention strategies. *Curr. Gene Ther.* **2011**, *11*, 307–320. [CrossRef]

29. Li, L.; Hu, S.; Chen, X. Non-viral delivery systems for CRISPR/Cas9-based genome editing: Challenges and opportunities. *Biomaterials* **2018**, *171*, 207–218. [CrossRef]

30. Zhang, Y.; Ren, T.; Gou, J.; Zhang, L.; Tao, X.; Tian, B.; Tian, P.; Yu, D.; Song, J.; Liu, X.; et al. Strategies for improving the payload of small molecular drugs in polymeric micelles. *J. Control. Release* **2017**, *261*, 352–366. [CrossRef]

31. Sung, Y.K.; Kim, S.W. Recent advances in the development of gene delivery systems. *Biomater. Res.* **2019**, *23*, 8. [CrossRef] [PubMed]

32. Li, L.; He, Z.Y.; Wei, X.W.; Gao, G.P.; Wei, Y.Q. Challenges in CRISPR/CAS9 Delivery: Potential Roles of Nonviral Vectors. *Hum. Gene Ther.* **2015**, *26*, 452–462. [CrossRef] [PubMed]

33. Wang, M.; Cheng, Y. The effect of fluorination on the transfection efficacy of surface-engineered dendrimers. *Biomaterials* **2014**, *35*, 6603–6613. [CrossRef] [PubMed]

34. Zinchenko, A. DNA conformational behavior and compaction in biomimetic systems, toward better understanding of DNA packaging in cell. *Adv. Colloid Interface Sci.* **2016**, *232*, 70–79. [CrossRef]

35. Jeong, G.W.; Nah, J.W. Evaluation of disulfide bond-conjugated LMWSC-g-bPEI as non-viral vector for low cytotoxicity and efficient gene delivery. *Carbohydr. Polym.* **2017**, *178*, 322–330. [CrossRef]

36. Vijayanathan, V.; Agostinelli, E.; Thomas, T.; Thomas, T.J. Innovative approaches to the use of polyamines for DNA nanoparticle preparation for gene therapy. *Amino Acids* **2014**, *46*, 499–509. [CrossRef]

37. Takahashi, Y.; Chen, Q.; Rajala, R.V.S.; Ma, J.X. MicroRNA-184 modulates canonical Wnt signaling through the regulation of frizzled-7 expression in the retina with ischemia-induced neovascularization. *FEBS Lett.* **2015**, *589*, 1143–1149. [CrossRef]

38. Sahay, G.; Querbes, W.; Alabi, C.; Eltoukhy, A.; Sarkar, S.; Zurenko, C.; Karagiannis, E.; Love, K.; Chen, D.; Zoncu, R.; et al. Efficiency of siRNA delivery by lipid nanoparticles is limited by endocytic recycling. *Nat. Biotechnol.* **2013**, *31*, 653–658. [CrossRef]

39. Zhi, D.; Bai, Y.; Yang, J.; Cui, S.; Zhao, Y.; Chen, H.; Zhang, S. A review on cationic lipids with different linkers for gene delivery. *Adv. Colloid Interface Sci.* **2018**, *253*, 117–140. [CrossRef]

40. Bazylińska, U. Rationally designed double emulsion process for co-encapsulation of hybrid cargo in stealth nanocarriers. *Colloids Surf. A Physicochem. Eng. Asp.* **2017**, *532*, 476–482. [CrossRef]

41. Hong, S.J.; Ahn, M.H.; Sangshetti, J.; Choung, P.H.; Arote, R.B. Sugar-based gene delivery systems, Current knowledge and new perspectives. *Carbohydr. Polym.* **2018**, *181*, 1180–1193. [CrossRef]

42. Wang, P.; Lin, L.; Guo, Z.; Chen, J.; Tian, H.; Chen, X.; Yang, H. Highly Fluorescent Gene Carrier Based on Ag-Au Alloy Nanoclusters. *Macromol. Biosci.* **2016**, *16*, 160–167. [CrossRef] [PubMed]

43. Chung Ang University Industry Academic Cooperation Foundation. *Composition for Gene Carrier Using a Triblock Co-Polyelectrolyte with Polyethylene Imine-Polylactic Acid-Polyethylene Glycol:KR20170025927[P]*; Chung Ang University Industry Academic Cooperation Foundation: Seoul, Korea, 5 September 2018.

44. Suzhou High-Tech Bioscience Co., Ltd. *Methoxypolyethylene Glycol-Polylactic Acid Block Copolymer and Preparation Method Thereof:US201414897504[P]*; Suzhou High-Tech Bioscience Co., Ltd.: Suzhou, China, 20 July 2017.

45. Dongguk University Industry-Academic Cooperation Foundation. *Amphiphilic Chitosan Derivative and Drug Carrier Containing the Same:KR20160016553[P]*; Dongguk University Industry-Academic Cooperation Foundation: Seoul, Korea, 22 August 2017.

46. Chung-Ang University Industry Academic Cooperation Foundation. *Method for Preparing Microspheres for Emboli, and Method for Preparing Microspheres to Which Drug-Containing Carrier Is Bound:EP20130833842[P]*; Chung-Ang University Industry Academic Cooperation Foundation: Seoul, Korea, 26 December 2018.

47. Haskoningdhv Nederland B.V. *Alginate Extraction Method:US201716085880[P]*; Haskoningdhv Nederland B.V.: Maastricht, The Netherlands, 28 March 2019.

48. Université de Strasbourg, Centre National de la Recherche Scientifique, ihu Strasbourg—Institut Hospitalo-Universitaire de Strasbourg. *Injectable Hybrid Alginate Hydrogels and Uses Thereof:WO2018EP75097[P]*; Institut Hospitalo-Universitaire de Strasbourg: Strasbourg, France, 21 March 2019.

49. Jiangsu Keygen Biotech Corp., Ltd.; Nanjing Core Tech Co., Ltd. *Decory Nucleic Acid Cationic Liposome Carrier and Preparation Method Thereof:US201515572845[P]*; Jiangsu Keygen Biotech Corp., Ltd.: Nanjing, China; Nanjing Core Tech Co., Ltd.: Nanjing, China, 17 May 2018.

50. Shanghai Pulmonary Hospital. *Human Lung Tissues—Active Targeting Immune Nanoliposome of Methylprednisolone and a Method for Producing the Same:US201515026219[P]*; Shanghai Pulmonary Hospital: Shanghai, China, 7 May 2019.

51. Biomics Biotechnologies CO., Ltd. *Lipidosome Preparation, Preparation Method and Application Thereof:AU20130380825[P]*; Biomics Biotechnologies CO., Ltd.: Nantong, China, 20 July 2017.

52. National Taiwan University of Science and Technology. *Biocompatible Confeito-Like Gold Nanoparticles, Method for Making the Same, and Their Biomedical Applications:US201113333868[P]*; National Taiwan University of Science and Technology: Taipei, Taiwan, 20 October 2015.

53. King Fahd University of Petroleum and Minerals. *Method for the Size Controlled Preparation of These Monodisperse Carboxylate Functionalized Gold Nanoparticles:US201816222748[P]*; King Fahd University of Petroleum and Minerals: Dhahran, Saudi Arabia, 18 April 2019.

54. Jeffrey, B.C.; Durfee, P.N.; Townson, J. *Mesoporous Silica Nanoparticles and Supported Lipid Bi-Layer Nanoparticles for Biomedical Applications: US201615757269[P]*; University of New Mexico: Albuquerque, NM, USA, 6 December 2018.

55. The Regents of The University of California. *Mesoporous Silica Nanoparticles with Lipid Bilayer Coating for Cargo Delivery:US201715798287[P]*; The University of California: Oakland, CA, USA, 4 December 2018.

56. Molecular Rebar Design, LLC. *Payload Molecule Delivery Using Functionalized Discrete Carbon Nanotubes:AU20150218735[P]*; Molecular Rebar Design, LLC.: Austin, TX, USA, 22 September 2016.

57. Smith, B.R.; Ghosn, E. *The Board of Trustees of The Leland Stanford Junior University. Carbon Nanotubes for Imaging and Drug Delivery:US201314020794[P]*; The Leland Stanford Junior University: Stanford, CA, USA, 20 March 2014.

58. Abed, O.S.A.; Chaw, C.; Williams, L.; Elkordy, A.A. Lysozyme and DNase I loaded poly (D, L lactide-co-caprolactone) nanocapsules as an oral delivery system. *Sci. Rep.* **2018**, *8*, 13158. [CrossRef]

59. Boca, S.; Gulei, D.; Zimta, A.A.; Onaciu, A.; Magdo, L.; Tigu, A.B.; Ionescu, C.; Irimie, A.; Buiga, R.; Berindan-Neagoe, I. Nanoscale delivery systems for microRNAs in cancer therapy. *Cell. Mol. Life Sci.* **2020**, *77*, 1059–1086. [CrossRef] [PubMed]

60. Bolhassani, A.; Javanzad, S.; Saleh, T.; Hashemi, M.; Aghasadeghi, M.R.; Sadat, S.M. Polymeric nanoparticles: Potent vectors for vaccine delivery targeting cancer and infectious diseases. *Hum. Vaccines Immunother.* **2014**, *10*, 321–332. [CrossRef]

61. Yang, J.; Zhang, Q.; Chang, H.; Cheng, Y. Surface-engineered dendrimers in gene delivery. *Chem. Rev.* **2015**, *115*, 5274–5300. [CrossRef]

62. Lostalé-Seijo, I.; Montenegro, J. Synthetic materials at the forefront of gene delivery. *Nat. Rev. Chem.* **2018**, *2*, 258–277. [CrossRef]

63. Teixeira, H.F.; Bruxel, F.; Fraga, M.; Schuh, R.S.; Zorzi, G.K.; Matte, U.; Fattal, E. Cationic nanoemulsions as nucleic acids delivery systems. *Int. J. Pharm.* **2017**, *534*, 356–367. [CrossRef] [PubMed]

64. Ding, X.; Wang, W.; Wang, Y.; Bao, X.; Wang, Y.; Wang, C.; Chen, J.; Zhang, F.; Zhou, J. Versatile reticular polyethylenimine derivative-mediated targeted drug and gene codelivery for tumor therapy. *Mol. Pharm.* **2014**, *11*, 3307–3321. [CrossRef]

65. Casettari, L.; Vllasaliu, D.; Lam, J.K.; Soliman, M.; Illum, L. Biomedical applications of amino acid-modified chitosans: A review. *Biomaterials* **2012**, *33*, 7565–7583. [CrossRef]

66. Tian, W.D.; Ma, Y.Q. Theoretical and computational studies of dendrimers as delivery vectors. *Chem. Soc. Rev.* **2013**, *42*, 705–727. [CrossRef]

67. Ghasemi, R.; Abdollahi, M.; Zadeh, E.E.; Khodabakhshi, K.; Badeli, A.; Bagheri, H.; Hosseinkhani, S. mPEG-PLA and PLA-PEG-PLA nanoparticles as new carriers for delivery of recombinant human Growth Hormone (rhGH). *Sci. Rep.* **2018**, *8*, 9854. [CrossRef] [PubMed]

68. Karlsson, J.; Rhodes, K.R.; Green, J.J.; Tzeng, S.Y. Poly(beta-amino ester)s as gene delivery vehicles: Challenges and opportunities. *Expert Opin. Drug Deliv.* **2020**, *17*, 1395–1410. [CrossRef] [PubMed]

69. Sherje, A.P.; Jadhav, M.; Dravyakar, B.R.; Kadam, D. Dendrimers: A versatile nanocarrier for drug delivery and targeting. *Int. J. Pharm.* **2018**, *548*, 707–720. [CrossRef] [PubMed]

70. Sung, Y.K.; Kim, S.W. Recent advances in polymeric drug delivery systems. *Biomater. Res.* **2020**, *24*, 12. [CrossRef]

71. Amreddy, N.; Babu, A.; Muralidharan, R.; Munshi, A.; Ramesh, R. Polymeric Nanoparticle-Mediated Gene Delivery for Lung Cancer Treatment. *Top. Curr. Chem.* **2017**, *375*, 35. [CrossRef]

72. Sharma, A.K.; Gothwal, A.; Kesharwani, P.; Alsaab, H.; Iyer, A.K.; Gupta, U. Dendrimer nanoarchitectures for cancer diagnosis and anticancer drug delivery. *Drug Discov. Today* **2017**, *22*, 314–326. [CrossRef] [PubMed]

73. Wang, X.; Shao, N.; Zhang, Q.; Cheng, Y. Mitochondrial targeting dendrimer allows efficient and safe gene delivery. *J. Mater. Chem. B* **2014**, *2*, 2546–2553. [CrossRef]

74. Mendes, L.P.; Pan, J.; Torchilin, V.P. Dendrimers as Nanocarriers for Nucleic Acid and Drug Delivery in Cancer Therapy. *Molecules* **2017**, *22*, 1401. [CrossRef]

75. Guan, L.; Huang, S.; Chen, Z.; Li, Y.; Liu, K.; Liu, Y.; Du, L. Low Cytotoxicity Fluorescent PAMAM Dendrimer as Gene Carriers for Monitoring the Delivery of siRNA. *J. Nanopart. Res.* **2015**, *17*, 385. [CrossRef]

76. Mastorakos, P.; Kambhampati, S.P.; Mishra, M.K.; Wu, T.; Song, E.; Hanes, J.; Kannan, R.M. Hydroxyl PAMAM dendrimer-based gene vectors for transgene delivery to human retinal pigment epithelial cells. *Nanoscale* **2015**, *7*, 3845–3856. [CrossRef]

77. Liaw, K.; Reddy, R.; Sharma, A.; Li, J.; Chang, M.; Sharma, R.; Salazar, S.; Kannan, S.; Kannan, R.M. Targeted systemic dendrimer delivery of CSF-1R inhibitor to tumor-associated macrophages improves outcomes in orthotopic glioblastoma. *Bioeng. Transl. Med.* **2020**, *6*, e10205.

78. Qadir, A.; Gao, Y.; Suryaji, P.; Tian, Y.; Lin, X.; Dang, K.; Jiang, S.; Li, Y.; Miao, Z.; Qian, A. Non-Viral Delivery System and Targeted Bone Disease Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 565. [CrossRef]

79. Liu, S.; Huang, W.; Jin, M.J.; Fan, B.; Xia, G.M.; Gao, Z.G. Inhibition of murine breast cancer growth and metastasis by survivin-targeted siRNA using disulfide cross-linked linear PEI. *Eur. J. Pharm. Sci.* **2016**, *82*, 171–182. [CrossRef]

80. Thomas, T.J.; Tajmir-Riahi, H.A.; Pillai, C.K.S. Biodegradable Polymers for Gene Delivery. *Molecules* **2019**, *24*, 3744. [CrossRef]

81. Boussif, O.; Lezoualc'h, F.; Zanta, M.A.; Mergny, M.D.; Scherman, D.; Demeneix, B.; Behr, J.P. A versatile vector for gene and oligonucleotide transfer into cells in culture and in vivo: Polyethylenimine. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 7297–7301. [CrossRef]

82. Hall, A.; Lächelt, U.; Bartek, J.; Wagner, E.; Moghimi, S.M. Polyplex Evolution: Understanding Biology, Optimizing Performance. *Mol. Ther.* **2017**, *25*, 1476–1490. [CrossRef]

83. Zhou, Y.; Yu, F.; Zhang, F.; Chen, G.; Wang, K.; Sun, M.; Li, J.; Oupický, D. Cyclam-Modified PEI for Combined VEGF siRNA Silencing and CXCR4 Inhibition To Treat Metastatic Breast Cancer. *Biomacromolecules* **2018**, *19*, 392–401. [CrossRef] [PubMed]

84. Huang, Q.; Li, S.; Ding, Y.F.; Yin, H.; Wang, L.H.; Wang, R. Macrocycle-wrapped polyethylenimine for gene delivery with reduced cytotoxicity. *Biomater. Sci.* **2018**, *6*, 1031–1039. [CrossRef] [PubMed]

85. Jiang, H.L.; Islam, M.A.; Xing, L.; Firdous, J.; Cao, W.; He, Y.J.; Zhu, Y.; Cho, K.H.; Li, H.S.; Cho, C.S. Degradable Polyethylenimine-Based Gene Carriers for Cancer Therapy. *Top. Curr. Chem.* **2017**, *375*, 34. [CrossRef] [PubMed]

86. Zakeri, A.; Kouhbanani, M.A.J.; Beheshtkhoo, N.; Beigi, V.; Mousavi, S.M.; Hashemi, S.A.R.; Karimi Zade, A.; Amani, A.M.; Savardashtaki, A.; Mirzaei, E.; et al. Polyethylenimine-based nanocarriers in co-delivery of drug and gene: A developing horizon. *Nano Rev. Exp.* **2018**, *9*, 1488497. [CrossRef] [PubMed]

87. Patnaik, S.; Gupta, K.C. Novel polyethylenimine-derived nanoparticles for in vivo gene delivery. *Expert Opin. Drug Deliv.* **2013**, *10*, 215–228. [CrossRef]

88. Mattheolabakis, G.; Ling, D.; Ahmad, G.; Amiji, M. Enhanced Anti-Tumor Efficacy of Lipid-Modified Platinum Derivatives in Combination with Survivin Silencing siRNA in Resistant Non-Small Cell Lung Cancer. *Pharm. Res.* **2016**, *33*, 2943–2953. [CrossRef] [PubMed]

89. Liu, S.; Zhou, D.; Yang, J.; Zhou, H.; Chen, J.; Guo, T. Bioreducible Zinc(II)-Coordinative Polyethylenimine with Low Molecular Weight for Robust Gene Delivery of Primary and Stem Cells. *J. Am. Chem. Soc.* **2017**, *139*, 5102–5109. [CrossRef] [PubMed]

90. Taranejoo, S.; Chandrasekaran, R.; Cheng, W.; Hourigan, K. Bioreducible PEI-functionalized glycol chitosan: A novel gene vector with reduced cytotoxicity and improved transfection efficiency. *Carbohydr. Polym.* **2016**, *153*, 160–168. [CrossRef] [PubMed]

91. Davoodi, P.; Srinivasan, M.P.; Wang, C.H. Synthesis of intracellular reduction-sensitive amphiphilic polyethyleneimine and poly(ε-caprolactone) graft copolymer for on-demand release of doxorubicin and p53 plasmid DNA. *Acta Biomater.* **2016**, *39*, 79–93. [CrossRef] [PubMed]

92. Zhang, J.H.; Yang, H.Z.; Zhang, J.; Liu, Y.H.; He, X.; Xiao, Y.P.; Yu, X.Q. Biodegradable Gene Carriers Containing Rigid Aromatic Linkage with Enhanced DNA Binding and Cell Uptake. *Polymers* **2018**, *10*, 1080. [CrossRef]

93. Motiei, M.; Kashanian, S.; Lucia, L.A.; Khazaei, M. Intrinsic parameters for the synthesis and tuned properties of amphiphilic chitosan drug delivery nanocarriers. *J. Control. Release* **2017**, *260*, 213–225. [CrossRef] [PubMed]

94. Nicolle, L.; Casper, J.; Willimann, M.; Journot, C.M.A.; Detampel, P.; Einfalt, T.; Grisch-Chan, H.M.; Thöny, B.; Gerber-Lemaire, S.; Huwyler, J. Development of Covalent Chitosan-Polyethylenimine Derivatives as Gene Delivery Vehicle: Synthesis, Characterization, and Evaluation. *Int. J. Mol. Sci.* **2021**, *8*, 3828. [CrossRef]

95. Woraphatphadung, T.; Sajomsang, W.; Rojanarata, T.; Ngawhirunpat, T.; Tonglairoum, P.; Opanasopit, P. Development of Chitosan-Based pH-Sensitive Polymeric Micelles Containing Curcumin for Colon-Targeted Drug Delivery. *AAPS Pharm. Sci. Technol.* **2018**, *19*, 991–1000. [CrossRef]

96. Meng, Q.; Sun, Y.; Cong, H.; Hu, H.; Xu, F.J. An overview of chitosan and its application in infectious diseases. *Drug Deliv. Transl. Res.* **2021**, *11*, 1340–1351. [CrossRef] [PubMed]

97. Bravo-Anaya, L.M.; Soltero, J.F.; Rinaudo, M. DNA/chitosan electrostatic complex. *Int. J. Biol. Macromol.* **2016**, *88*, 345–353. [CrossRef] [PubMed]

98. Amaduzzi, F.; Bomboi, F.; Bonincontro, A.; Bordi, F.; Casciardi, S.; Chronopoulou, L.; Diociaiuti, M.; Mura, F.; Palocci, C.; Sennato, S. Chitosan-DNA complexes: Charge inversion and DNA condensation. *Colloids Surf. B Biointerfaces* **2014**, *114*, 1–10. [CrossRef] [PubMed]

99. Oliveira, A.V.; Marcelo, A.; da Costa, A.M.; Silva, G.A. Evaluation of cystamine-modified hyaluronic acid/chitosan polyplex as retinal gene vector. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2016**, *58*, 264–272. [CrossRef] [PubMed]

100. Oliveira, A.V.; Silva, G.A.; Chung, D.C. Enhancement of chitosan-mediated gene delivery through combination with phiC31 integrase. *Acta Biomater.* **2015**, *17*, 89–97. [CrossRef] [PubMed]

101. Kamra, M.; Moitra, P.; Ponnalagu, D.; Karande, A.A.; Bhattacharya, S. New Water-Soluble Oxyamino Chitosans as Biocompatible Vectors for Efficacious Anticancer Therapy via Co-Delivery of Gene and Drug. *ACS Appl. Mater. Interfaces* **2019**, *11*, 37442–37460. [CrossRef]

102. Chen, S.; Deng, J.; Zhang, L.M. Cationic nanoparticles self-assembled from amphiphilic chitosan derivatives containing poly(amidoamine) dendrons and deoxycholic acid as a vector for co-delivery of doxorubicin and gene. *Carbohydr. Polym.* **2021**, *258*, 117706. [CrossRef]

103. Lee, Y.H.; Park, H.I.; Chang, W.S.; Choi, J.S. Triphenylphosphonium-conjugated glycol chitosan microspheres for mitochondria-targeted drug delivery. *Int. J. Biol. Macromol.* **2021**, *167*, 35–45. [CrossRef]

104. Babii, O.; Wang, Z.; Liu, G.; Martinez, E.C.; van Drunen, L.; van den Hurk, S.; Chen, L. Low molecular weight chitosan nanoparticles for CpG oligodeoxynucleotides delivery: Impact of molecular weight, degree of deacetylation, and mannosylation on intracellular uptake and cytokine induction. *Int. J. Biol. Macromol.* **2020**, *159*, 46–56. [CrossRef]

105. Masjedi, A.; Ahmadi, A.; Atyabi, F.; Farhadi, S.; Irandoust, M.; Khazaei-Poul, Y.; Chaleshtari, M.G.; Fathabad, M.E.; Baghaei, M.; Haghnavaz, N.; et al. Silencing of IL-6 and STAT3 by siRNA loaded hyaluronate-N,N,N-trimethyl chitosan nanoparticles potently reduces cancer cell progression. *Int. J. Biol. Macromol.* **2020**, *149*, 487–500. [CrossRef]

106. Singhvi, M.S.; Zinjarde, S.S.; Gokhale, D.V. Polylactic acid: Synthesis and biomedical applications. *J. Appl. Microbiol.* **2019**, *127*, 1612–1626. [CrossRef] [PubMed]

107. Zhou, M.; Lai, W.; Li, G.; Wang, F.; Liu, W.; Liao, J.; Yang, H.; Liu, Y.; Zhang, Q.; Tang, Q.; et al. Platelet Membrane-Coated and VAR2CSA Malaria Protein-Functionalized Nanoparticles for Targeted Treatment of Primary and Metastatic Cancer. *ACS Appl. Mater. Interfaces* **2021**, *13*, 25635–25648. [CrossRef] [PubMed]

108. Tyler, B.; Gullotti, D.; Mangraviti, A.; Utsuki, T.; Brem, H. Polylactic acid (PLA) controlled delivery carriers for biomedical applications. *Adv. Drug Deliv. Rev.* **2016**, *107*, 163–175. [CrossRef] [PubMed]

109. Li, G.; Zhao, M.; Xu, F.; Yang, B.; Li, X.; Meng, X.; Teng, L.; Sun, F.; Li, Y. Synthesis and Biological Application of Polylactic Acid. *Molecules* **2020**, *25*, 5023. [CrossRef]

110. Ali, M.; Walboomers, X.F.; Jansen, J.A.; Yang, F. Influence of formulation parameters on encapsulation of doxycycline in PLGA microspheres prepared by double emulsion technique for the treatment of periodontitis. *J. Drug Deliv. Sci. Technol.* **2019**, *52*, 263–271. [CrossRef]

111. Kamel, R.; Abbas, H.; Shaffie, N.M. Development and evaluation of PLA-coated co-micellar nanosystem of Resveratrol for the intra-articular treatment of arthritis. *Int. J. Pharm.* **2019**, *569*, 118560. [CrossRef]

112. Lai, X.; Geng, X.; Li, M.; Tang, M.; Liu, Q.; Yang, M.; Shen, L.; Zhu, Y.; Wang, S. Glutathione-responsive PLGA nanocomplex for dual delivery of doxorubicin and curcumin to overcome tumor multidrug resistance. *Nanomedicine* **2021**, *16*, 1411–1427. [CrossRef]

113. Zhou, J.; Zhai, Y.; Xu, J.; Zhou, T.; Cen, L. Microfluidic preparation of PLGA composite microspheres with mesoporous silica nanoparticles for finely manipulated drug release. *Int. J. Pharm.* **2021**, *593*, 120173. [CrossRef] [PubMed]

114. Zabihi, F.; Graff, P.; Schumacher, F.; Kleuser, B.; Hedtrich, S.; Haag, R. Synthesis of poly(lactide-co-glycerol) as a biodegradable and biocompatible polymer with high loading capacity for dermal drug delivery. *Nanoscale* **2018**, *10*, 16848–16856. [CrossRef] [PubMed]

115. Ren, B.; Lu, J.; Li, M.; Zou, X.; Liu, Y.; Wang, C.; Wang, L. Anti-inflammatory effect of IL-1ra-loaded dextran/PLGA microspheres on Porphyromonas gingivalis lipopolysaccharide-stimulated macrophages in vitro and in vivo in a rat model of periodontitis. *Biomed. Pharmacother.* **2021**, *134*, 111171. [CrossRef]

116. Bazylińska, U.; Kulbacka, J.; Chodaczek, G. Nanoemulsion Structural Design in Co-Encapsulation of Hybrid Multifunctional Agents: Influence of the Smart PLGA Polymers on the Nanosystem-Enhanced Delivery and Electro-Photodynamic Treatment. *Pharmaceutics* **2019**, *11*, 405. [CrossRef]

117. Gupta, S.S.; Mishra, V.; Mukherjee, M.D.; Saini, P.; Ranjan, K.R. Amino acid derived biopolymers: Recent advances and biomedical applications. *Int. J. Biol. Macromol.* **2021**, *188*, 542–567. [CrossRef]

118. Feng, J.H.; He, F.Y.; Yang, Z.Z.; Yao, J.S. Differential study of the biological degradation of polyamide-imides based on the amino acids. *Polym. Degrad. Stab.* **2016**, *129*, 231–238. [CrossRef]

119. Yamanouchi, D.; Wu, J.; Lazar, A.N.; Kent, K.C.; Chu, C.C.; Liu, B. Biodegradable arginine-based poly(ester-amide)s as non-viral gene delivery reagents. *Biomaterials* **2008**, *29*, 3269–3277. [CrossRef] [PubMed]

120. Pounder, R.J.; Dove, A.P. Towards poly(ester) nanoparticles: Recent advances in the synthesis of functional poly(ester)s by ring-opening polymerization. *Polym. Chem.* **2010**, *1*, 260–271. [CrossRef]

121. Karimi, P.; Rizkalla, A.S.; Mequanint, K. Versatile Biodegradable Poly(ester amide)s Derived from α-Amino Acids for Vascular Tissue Engineering. *Materials* **2010**, *3*, 2346. [CrossRef]

122. Patrick, A.J.M.; Paul, P.K.C.; Khoshdel, E.; Wilson, P.; Kempe, K.; Haddleton, D.M. High Tg poly(ester amide)s by melt polycondensation of monomers from renewable resources; citric acid, D-glucono-δ-lactone and amino acids: A DSC study. *Eur. Polym. J.* **2017**, *94*, 11–19.

123. Nitta, S.; Komatsu, A.; Ishii, T.; Iwamoto, H.; Numata, K. Synthesis of peptides with narrow molecular weight distributions via exopeptidase-catalyzed aminolysis of hydrophobic amino-acid alkyl esters. *Polym. J.* **2016**, *48*, 955–961. [CrossRef]

124. Zhang, S.; Guo, N.; Wan, G.; Zhang, T.; Li, C.; Wang, Y.; Wang, Y.; Liu, Y. pH and redox dual-responsive nanoparticles based on disulfide-containing poly(β-amino ester) for combining chemotherapy and COX-2 inhibitor to overcome drug resistance in breast cancer. *J. Nanobiotechnol.* **2019**, *17*, 109. [CrossRef]

125. Duan, S.; Cao, D.; Li, X.; Zhu, H.; Lan, M.; Tan, Z.; Song, Z.; Zhu, R.; Yin, L.; Chen, Y. Topology-assisted, photo-strengthened DNA/siRNA delivery mediated by branched poly(β-amino ester)s via synchronized intracellular kinetics. *Biomater. Sci.* **2020**, *8*, 290–301. [CrossRef]

126. Shamul, J.G.; Shah, S.R.; Kim, J.; Schiapparelli, P.; Vazquez-Ramos, C.A.; Lee, B.J.; Patel, K.K.; Shin, A.; Quinones-Hinojosa, A.; Green, J.J. Verteporfin-Loaded Anisotropic Poly(Beta-Amino Ester)-Based Micelles Demonstrate Brain Cancer-Selective Cytotoxicity and Enhanced Pharmacokinetics. *Int. J. Nanomed.* **2019**, *14*, 10047–10060. [CrossRef]

127. Yu, H.; Ingram, N.; Rowley, J.V.; Green, D.C.; Thornton, P.D. Meticulous Doxorubicin Release from pH-Responsive Nanoparticles Entrapped within an Injectable Thermo responsive Depot. *Chemistry* **2020**, *26*, 13352–13358. [CrossRef]

128. Karimi, N.; Mansouri, K.; Soleiman-Beigi, M.; Fattahi, A. All-Trans Retinoic Acid Grafted Poly Beta-Amino Ester Nanoparticles: A Novel Anti-angiogenic Drug Delivery System. *Adv. Pharm. Bull.* **2020**, *10*, 221–232. [CrossRef] [PubMed]

129. Wang, M.Z.; Niu, J.; Ma, H.J.; Dad, H.A.; Shao, H.T.; Yuan, T.J.; Peng, L.H. Transdermal siRNA delivery by pH-switchable micelles with targeting effect suppress skin melanoma progression. *J. Control. Release* **2020**, *322*, 95–107. [CrossRef] [PubMed]

130. Wagle, S.R.; Kovacevic, B.; Walker, D.; Ionescu, C.M.; Shah, U.; Stojanovic, G.; Kojic, S.; Mooranian, A.; Al-Salami, H. Alginate-based drug oral targeting using bio-micro/nano encapsulation technologies. *Expert Opin. Drug Deliv.* **2020**, *17*, 1361–1376. [CrossRef] [PubMed]

131. Pawar, S.N.; Edgar, K.J. Alginate derivatization: A review of chemistry, properties and applications. *Biomaterials* **2012**, *33*, 3279–3305. [CrossRef]

132. Hariyadi, D.M.; Islam, N. Current Status of Alginate in Drug Delivery. *Adv. Pharmacol. Pharm. Sci.* **2020**, *2020*, 8886095. [CrossRef]

133. Abraham, E.; Weber, D.E.; Sharon, S.; Lapidot, S.; Shoseyov, O. Multifunctional Cellulosic Scaffolds from Modified Cellulose Nanocrystals. *ACS Appl. Mater. Interfaces* **2017**, *9*, 2010–2015. [CrossRef]

134. Danafar, H.; Davaran, S.; Rostamizadeh, K.; Valizadeh, H.; Hamidi, M. Biodegradable m-PEG/PCL Core-Shell Micelles: Preparation and Characterization as a Sustained Release Formulation for Curcumin. *Adv. Pharm. Bull.* **2014**, *4*, 501–510.

135. Hosseinifar, T.; Sheybani, S.; Abdouss, M.; Najafabadi, S.A.H.; Ardestani, M.S. Pressure responsive nanogel base on Alginate-Cyclodextrin with enhanced apoptosis mechanism for colon cancer delivery. *J. Biomed. Mater. Res. A* **2018**, *106*, 349–359. [CrossRef]

136. Shad, P.M.; Karizi, S.Z.; Javan, R.S.; Mirzaie, A.; Noorbazargan, H.; Akbarzadeh, I.; Rezaie, H. Folate conjugated hyaluronic acid coated alginate nanogels encapsulated oxaliplatin enhance antitumor and apoptosis efficacy on colorectal cancer cells (HT29 cell line). *Toxicol. In Vitro* **2020**, *65*, 104756. [CrossRef]

137. Shen, H.; Li, F.; Wang, D.; Yang, Z.; Yao, C.; Ye, Y.; Wang, X. Chitosan-alginate BSA-gel-capsules for local chemotherapy against drug-resistant breast cancer. *Drug Des. Dev. Ther.* **2018**, *12*, 921–934. [CrossRef]

138. Kang, S.M.; Lee, G.W.; Huh, Y.S. Centrifugal Force-Driven Modular Micronozzle System: Generation of Engineered Alginate Microspheres. *Sci. Rep.* **2019**, *9*, 12776. [CrossRef]

139. Song, W.; Su, X.; Gregory, D.A.; Li, W.; Cai, Z.; Zhao, X. Magnetic Alginate/Chitosan Nanoparticles for Targeted Delivery of Curcumin into Human Breast Cancer Cells. *Nanomaterials* **2018**, *8*, 907. [CrossRef]

140. Gonçalves, M.; Figueira, P.; Maciel, D.; Rodrigues, J.; Qu, X.; Liu, C.; Tomás, H.; Li, Y. pH-sensitive Laponite(®)/doxorubicin/alginate nanohybrids with improved anticancer efficacy. *Acta Biomater.* **2014**, *10*, 300–307. [CrossRef]

141. Nisini, R.; Poerio, N.; Mariotti, S.; De Santis, F.; Fraziano, M. The Multirole of Liposomes in Therapy and Prevention of Infectious Diseases. *Front. Immunol.* **2018**, *9*, 155. [CrossRef]

142. El-Hammadi, M.M.; Arias, J.L. An update on liposomes in drug delivery, a patent review (2014–2018). *Expert Opin. Ther. Pat.* **2019**, *29*, 891–907. [CrossRef]

143. Torchilin, V.P. Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.* **2005**, *4*, 145–160. [CrossRef]

144. Bozzuto, G.; Molinari, A. Liposomes as nanomedical devices. *Int. J. Nanomed.* **2015**, *10*, 975–999. [CrossRef]

145. Yan, W.; Leung, S.S.; To, K.K. Updates on the use of liposomes for active tumor targeting in cancer therapy. *Nanomedicine* **2020**, *15*, 303–318. [CrossRef]

146. Torchilin, V. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. *Eur. J. Pharm. Biopharm.* **2009**, *71*, 431–444. [CrossRef]

147. Bangham, A.D.; Horne, R.W. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. *J. Mol. Biol.* **1964**, *8*, 660–668. [CrossRef]

148. Mandpe, P.; Prabhakar, B.; Shende, P. Role of Liposomes-Based Stem Cell for Multimodal Cancer Therapy. *Stem Cell Rev. Rep.* **2020**, *16*, 103–117. [CrossRef]

149. Bulbake, U.; Doppalapudi, S.; Kommineni, N.; Khan, W. Liposomal Formulations in Clinical Use, An Updated Review. *Pharmaceutics* **2017**, *9*, 12. [CrossRef]

150. Xu, Y.; Yao, Y.; Wang, L.; Chen, H.; Tan, N. Hyaluronic Acid Coated Liposomes Co-Delivery of Natural Cyclic Peptide RA-XII and Mitochondrial Targeted Photosensitizer for Highly Selective Precise Combined Treatment of Colon Cancer. *Int. J. Nanomed.* **2021**, *16*, 4929–4942. [CrossRef]

151. Lorenzer, C.; Dirin, M.; Winkler, A.M.; Baumann, V.; Winkler, J. Going beyond the liver, progress and challenges of targeted delivery of siRNA therapeutics. *J. Control. Release* **2015**, *203*, 1–15. [CrossRef] [PubMed]

152. Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S.; Joo, S.W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: Classification, preparation, and applications. *Nanoscale Res. Lett.* **2013**, *8*, 102. [CrossRef]

153. Perche, F.; Torchilin, V.P. Recent trends in multifunctional liposomal nanocarriers for enhanced tumor targeting. *J. Drug Deliv.* **2013**, *2013*, 705265. [CrossRef]

154. Eloy, J.O.; Petrilli, R.; Trevizan, L.N.F.; Chorilli, M. Immunoliposomes, A review on functionalization strategies and targets for drug delivery. *Colloids Surf. B Biointerfaces* **2017**, *159*, 454–467. [CrossRef] [PubMed]

155. Ta, T.; Porter, T.M. Thermosensitive liposomes for localized delivery and triggered release of chemotherapy. *J. Control. Release* **2013**, *169*, 112–125. [CrossRef] [PubMed]

156. Lee, Y.; Thompson, D.H. Stimuli-responsive liposomes for drug delivery. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2017**, *9*, 1450. [CrossRef]

157. Riaz, M.K.; Riaz, M.A.; Zhang, X.; Lin, C.; Wong, K.H.; Chen, X.; Zhang, G.; Lu, A.; Yang, Z. Surface Functionalization and Targeting Strategies of Liposomes in Solid Tumor Therapy, A Review. *Int. J. Mol. Sci.* **2018**, *19*, 195. [CrossRef]

158. Yang, T.; Sui, X.; Yu, B.; Shen, Y.; Cong, H. Recent Advances in the Rational Drug Design Based on Multi-target Ligands. *Curr. Med. Chem.* **2020**, *27*, 4720–4740. [CrossRef]

159. Gao, Y.G.; Alam, U.; Ding, A.X.; Tang, Q.; Tan, Z.L.; Shi, Y.D.; Lu, Z.L.; Qian, A.R. AneN3-based lipid with naphthalimide moiety for enhanced gene transfection efficiency. *Bioorg. Chem.* **2018**, *79*, 334–340. [CrossRef]

160. Hayashi, T.; Shinagawa, M.; Kawano, T.; Iwasaki, T. Drug delivery using polyhistidine peptide-modified liposomes that target endogenous lysosome. *Biochem. Biophys. Res. Commun.* **2018**, *501*, 648–653. [CrossRef]

161. Jhaveri, A.; Deshpande, P.; Pattni, B.; Torchilin, V. Transferrin-targeted, resveratrol-loaded liposomes for the treatment of glioblastoma. *J. Control. Release* **2018**, *277*, 89–101. [CrossRef] [PubMed]

162. Wei, M.; Guo, X.; Tu, L.; Zou, Q.; Li, Q.; Tang, C.; Chen, B.; Xu, Y.; Wu, C. Lactoferrin-modified PEGylated liposomes loaded with doxorubicin for targeting delivery to hepatocellular carcinoma. *Int. J. Nanomed.* **2015**, *10*, 5123–5137.

163. Zang, X.; Ding, H.; Zhao, X.; Li, X.; Du, Z.; Hu, H.; Qiao, M.; Chen, D.; Deng, Y.; Zhao, X. Anti-EphA10 antibody-conjugated pH-sensitive liposomes for specific intracellular delivery of siRNA. *Int. J. Nanomed.* **2016**, *11*, 3951–3967. [CrossRef] [PubMed]

164. Alshaer, W.; Hillaireau, H.; Vergnaud, J.; Mura, S.; Deloménie, C.; Sauvage, F.; Ismail, S.; Fattal, E. Aptamer-guided siRNA-loaded nanomedicines for systemic gene silencing in CD-44 expressing murine triple-negative breast cancer model. *J. Control. Release* **2018**, *271*, 98–106. [CrossRef] [PubMed]

165. Needham, D.; Park, J.Y.; Wright, A.M.; Tong, J. Materials characterization of the low temperature sensitive liposome (LTSL): Effects of the lipid composition (lysolipid and DSPE-PEG2000) on the thermal transition and release of doxorubicin. *Faraday Discuss.* **2013**, *161*, 515–534, discussion 563–589. [CrossRef]

166. Zhao, Y.; Ren, W.; Zhong, T.; Zhang, S.; Huang, D.; Guo, Y.; Yao, X.; Wang, C.; Zhang, W.Q.; Zhang, X.; et al. Tumor-specific pH-responsive peptide-modified pH-sensitive liposomes containing doxorubicin for enhancing glioma targeting and anti-tumor activity. *J. Control. Release* **2016**, *222*, 56–66. [CrossRef]

167. Clares, B.; Biedma-Ortiz, R.A.; Sáez-Fernández, E.; Prados, J.C.; Melguizo, C.; Cabeza, L.; Ortiz, R.; Arias, J.L. Nano-engineering of 5-fluorouracil-loaded magnetoliposomes for combined hyperthermia and chemotherapy against colon cancer. *Eur. J. Pharm. Biopharm.* **2013**, *85*, 329–338. [CrossRef] [PubMed]

168. Chi, Y.; Yin, X.; Sun, K.; Feng, S.; Liu, J.; Chen, D.; Guo, C.; Wu, Z. Redox-sensitive and hyaluronic acid functionalized liposomes for cytoplasmic drug delivery to osteosarcoma in animal models. *J. Control. Release* **2017**, *261*, 113–125. [CrossRef] [PubMed]

169. Song, S.J.; Lee, S.; Lee, Y.; Choi, J.S. Enzyme-responsive destabilization of stabilized plasmid-lipid nanoparticles as an efficient gene delivery. *Eur. J. Pharm. Sci.* **2016**, *91*, 20–30. [CrossRef]

170. Zylberberg, C.; Gaskill, K.; Pasley, S.; Matosevic, S. Engineering liposomal nanoparticles for targeted gene therapy. *Gene Ther.* **2017**, *24*, 441–452. [CrossRef]

171. Koren, E.; Torchilin, V.P. Cell-penetrating peptides, breaking through to the other side. *Trends Mol. Med.* **2012**, *18*, 385–393. [CrossRef] [PubMed]

172. Munyendo, W.L.; Lv, H.; Benza-Ingoula, H.; Baraza, L.D.; Zhou, J. Cell penetrating peptides in the delivery of biopharmaceuticals. *Biomolecules* **2012**, *2*, 187–202. [CrossRef] [PubMed]

173. McClorey, G.; Banerjee, S. Cell-Penetrating Peptides to Enhance Delivery of Oligonucleotide-Based Therapeutics. *Biomedicines* **2018**, *6*, 51. [CrossRef] [PubMed]

174. Park, J.; Singha, K.; Son, S.; Kim, J.; Namgung, R.; Yun, C.O.; Kim, W.J. A review of RGD-functionalized nonviral gene delivery vectors for cancer therapy. *Cancer Gene Ther.* **2012**, *19*, 741–748. [CrossRef] [PubMed]

175. Kang, W.; Svirskis, D.; Sarojini, V.; McGregor, A.L.; Bevitt, J.; Wu, Z. Cyclic-RGDyC functionalized liposomes for dual-targeting of tumor vasculature and cancer cells in glioblastoma, An in vitro boron neutron capture therapy study. *Oncotarget* **2017**, *8*, 36614–36627. [CrossRef]

176. Belhadj, Z.; Ying, M.; Cao, X.; Hu, X.; Zhan, C.; Wei, X.; Gao, J.; Wang, X.; Yan, Z.; Lu, W. Design of Y-shaped targeting material for liposome-based multifunctional glioblastoma-targeted drug delivery. *J. Control. Release* **2017**, *255*, 132–141. [CrossRef]

177. Chen, Z.; Deng, J.; Zhao, Y.; Tao, T. Cyclic RGD peptide-modified liposomal drug delivery system, enhanced cellular uptake in vitro and improved pharmacokinetics in rats. *Int. J. Nanomed.* **2012**, *7*, 3803–3811. [CrossRef]

178. Nakase, I.; Akita, H.; Kogure, K.; Gräslund, A.; Langel, U.; Harashima, H.; Futaki, S. Efficient intracellular delivery of nucleic acid pharmaceuticals using cell-penetrating peptides. *Acc. Chem. Res.* **2012**, *45*, 1132–1139. [CrossRef]

179. Ding, Y.; Sun, D.; Wang, G.L.; Yang, H.G.; Xu, H.F.; Chen, J.H.; Xie, Y.; Wang, Z.Q. An efficient PEGylated liposomal nanocarrier containing cell-penetrating peptide and pH-sensitive hydrazone bond for enhancing tumor-targeted drug delivery. *Int. J. Nanomed.* **2015**, *10*, 6199–6214.

180. Al-Ahmady, Z.S.; Chaloin, O.; Kostarelos, K. Monoclonal antibody-targeted.; temperature-sensitive liposomes, in vivo tumor chemotherapeutics in combination with mild hyperthermia. *J. Control. Release* **2014**, *196*, 332–343. [CrossRef] [PubMed]

181. Petrilli, R.; Eloy, J.O.; Lee, R.J.; Lopez, R.F.V. Preparation of Immunoliposomes by Direct Coupling of Antibodies Based on a Thioether Bond. *Methods Mol. Biol.* **2018**, *1674*, 229–237.

182. Lu, L.; Ding, Y.; Zhang, Y.; Ho, R.J.; Zhao, Y.; Zhang, T.; Guo, C. Antibody-modified liposomes for tumor-targeting delivery of timosaponin AIII. *Int. J. Nanomed.* **2018**, *13*, 1927–1944. [CrossRef] [PubMed]

183. Gao, J.; Chen, H.; Yu, Y.; Song, J.; Song, H.; Su, X.; Li, W.; Tong, X.; Qian, W.; Wang, H.; et al. Inhibition of hepatocellular carcinoma growth using immunoliposomes for co-delivery of adriamycin and ribonucleotide reductase M2 siRNA. *Biomaterials* **2013**, *34*, 10084–10098. [CrossRef]

184. Saeed, M.; van Brakel, M.; Zalba, S.; Schooten, E.; Rens, J.A.; Koning, G.A.; Debets, R.; Hagen, T.L.T. Targeting melanoma with immunoliposomes coupled to anti-MAGE A1 TCR-like single-chain antibody. *Int. J. Nanomed.* **2016**, *11*, 955–975. [CrossRef] [PubMed]

185. Moosavian, S.A.; Sahebkar, A. Aptamer-functionalized liposomes for targeted cancer therapy. *Cancer Lett.* **2019**, *448*, 144–154. [CrossRef]

186. Prakash, J.S.; Rajamanickam, K. Aptamers and their significant role in cancer therapy and diagnosis. *Biomedicines* **2015**, *3*, 248–269. [CrossRef]

187. Torchilin, V.P. Passive and active drug targeting: Drug delivery to tumors as an example. *Drug Deliv.* **2010**, *197*, 3–53.

188. Powell, D.; Chandra, S.; Dodson, K.; Shaheen, F.; Wiltz, K.; Ireland, S.; Syed, M.; Dash, S.; Wiese, T.; Mandal, T.; et al. Aptamer-functionalized hybrid nanoparticle for the treatment of breast cancer. *Eur. J. Pharm. Biopharm.* **2017**, *114*, 108–118. [CrossRef]

189. Li, L.; Hou, J.; Liu, X.; Guo, Y.; Wu, Y.; Zhang, L.; Yang, Z. Nucleolin-targeting liposomes guided by aptamer AS1411 for the delivery of siRNA for the treatment of malignant melanomas. *Biomaterials* **2014**, *35*, 3840–3850. [CrossRef] [PubMed]

190. Palchetti, S.; Digiacomo, L.; Pozzi, D.; Chiozzi, R.Z.; Capriotti, A.L.; Laganà, A.; Coppola, R.; Caputo, D.; Sharifzadeh, M.; Mahmoudi, M.; et al. Effect of Glucose on Liposome-Plasma Protein Interactions, Relevance for the Physiological Response of Clinically Approved Liposomal Formulations. *Adv. Biosyst.* **2019**, *3*, e1800221. [CrossRef]

191. Soe, Z.C.; Thapa, R.K.; Ou, W.; Gautam, M.; Nguyen, H.T.; Jin, S.G.; Ku, S.K.; Oh, K.T.; Choi, H.G.; Yong, C.S.; et al. Folate receptor-mediated celastrol and irinotecan combination delivery using liposomes for effective chemotherapy. *Colloids Surf. B Biointerfaces* **2018**, *170*, 718–728. [CrossRef] [PubMed]

192. Sakashita, M.; Mochizuki, S.; Sakurai, K. Hepatocyte-targeting gene delivery using a lipoplex composed of galactose-modified aromatic lipid synthesized with click chemistry. *Bioorg. Med. Chem.* **2014**, *22*, 5212–5219. [CrossRef]

193. Kraft, J.C.; Freeling, J.P.; Wang, Z.; Ho, R.J. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *J. Pharm. Sci.* **2014**, *103*, 29–52. [CrossRef] [PubMed]

194. Kang, M.H.; Yoo, H.J.; Kwon, Y.H.; Yoon, H.Y.; Lee, S.G.; Kim, S.R.; Yeom, D.W.; Kang, M.J.; Choi, Y.W. Design of Multifunctional Liposomal Nanocarriers for Folate Receptor-Specific Intracellular Drug Delivery. *Mol. Pharm.* **2015**, *12*, 4200–4213. [CrossRef]

195. Zong, T.; Mei, L.; Gao, H.; Cai, W.; Zhu, P.; Shi, K.; Chen, J.; Wang, Y.; Gao, F.; He, Q. Synergistic dual-ligand doxorubicin liposomes improve targeting and therapeutic efficacy of brain glioma in animals. *Mol. Pharm.* **2014**, *11*, 2346–2357. [CrossRef]

196. Lu, Y.; Sun, W.; Gu, Z. Stimuli-responsive nanomaterials for therapeutic protein delivery. *J. Control. Release* **2014**, *194*, 1–19. [CrossRef]

197. Lou, J.; Carr, A.J.; Watson, A.J.; Mattern-Schain, S.I.; Best, M.D. Calcium-Responsive Liposomes via a Synthetic Lipid Switch. *Chemistry* **2018**, *24*, 3599–3607. [CrossRef]

198. Sine, J.; Urban, C.; Thayer, D.; Charron, H.; Valim, N.; Tata, D.B.; Schiff, R.; Blumenthal, R.; Joshi, A.; Puri, A. Photo activation of HPPH encapsulated in "Pocket" liposomes triggers multiple drug release and tumor cell killing in mouse breast cancer xenografts. *Int. J. Nanomed.* **2014**, *10*, 125–145.

199. Rosarin, F.S.; Mirunalini, S. Nobel Metallic Nanoparticles with Novel Biomedical Properties. *J. Bioanal. Biomed.* **2011**, *3*, 85–91. [CrossRef]

200. Daniel, M.C.; Astruc, D. Gold nanoparticles: Assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chem. Rev.* **2004**, *104*, 293–346. [CrossRef]

201. Singh, P.; Mijakovic, I. Advances in gold nanoparticle technology as a tool for diagnostics and treatment of cancer. *Expert Rev. Mol. Diagn.* **2021**, *21*, 627–630. [CrossRef]
202. Petrushev, B.; Boca, S.; Simon, T.; Berce, C.; Frinc, I.; Dima, D.; Selicean, S.; Gafencu, G.A.; Tanase, A.; Zdrenghea, M.; et al. Gold nanoparticles enhance the effect of tyrosine kinase inhibitors in acute myeloid leukemia therapy. *Int. J. Nanomed.* **2016**, *11*, 641–660.
203. Hyeon-Ho, J.; Eunjin, C.; Elizabeth, E.; Tung-Chun, L. Recent advances in gold nanoparticles for biomedical applications: From hybrid structures to multi-functionality. *J. Mater. Chem. B* **2019**, *7*, 3480–3496.
204. Ruan, S.; Yuan, M.; Zhang, L.; Hu, G.; Chen, J.; Cun, X.; Zhang, Q.; Yang, Y.; He, Q.; Gao, H. Tumor microenvironment sensitive doxorubicin delivery and release to glioma using angiopep-2 decorated gold nanoparticles. *Biomaterials* **2015**, *37*, 425–435. [CrossRef]
205. Turkevich, J.; Cooper, P.H.J. A study of the nucleation and growth process in the synthesis of colloidal gold. *Discuss. Faraday Soc.* **1951**, *55*, 55–75. [CrossRef]
206. Brust, M.; Walker, M.; Bethell, D.; Schiffrin, D.J.; Whyman, R. Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid-liquid system. *J. Chem. Soc. Chem. Commun.* **1994**, *7*, 5–7. [CrossRef]
207. Sahu, P.; Prasad, B.L. Time and temperature effects on the digestive ripening of gold nanoparticles: Is there a crossover from digestive ripening to Ostwald ripening? *Langmuir* **2014**, *30*, 10143–10150. [CrossRef]
208. Dong, J.; Carpinone, P.L.; Pyrgiotakis, G.; Demokritou, P.; Moudgil, B.M. Synthesis of Precision Gold Nanoparticles Using Turkevich Method. *KONA Powder Part. J.* **2020**, *37*, 224–232. [CrossRef] [PubMed]
209. Shimpi, J.R.; Sidhaye, D.S.; Prasad, B.L.V. Digestive Ripening: A Fine Chemical Machining Process on the Nanoscale. *Langmuir* **2017**, *33*, 9491–9507. [CrossRef] [PubMed]
210. Herizchi, R.; Abbasi, E.; Milani, M.; Akbarzadeh, A. Current methods for synthesis of gold nanoparticles. *Artif. Cells Nanomed. Biotechnol.* **2016**, *44*, 596–602. [CrossRef] [PubMed]
211. Chen, Y.S.; Hung, Y.C.; Liau, I.; Huang, G.S. Assessment of the In Vivo Toxicity of Gold Nanoparticles. *Nanoscale Res. Lett.* **2009**, *4*, 858–864. [CrossRef]
212. Subbaiya, R.; Saravanan, M.; Priya, A.R.; Shankar, K.R.; Selvam, M.; Ovais, M.; Balajee, R.; Barabadi, H. Biomimetic synthesis of silver nanoparticles from Streptomyces atrovirens and their potential anticancer activity against human breast cancer cells. *IET Nanobiotechnol.* **2017**, *11*, 965–972. [CrossRef]
213. Bose, D.; Chatterjee, S. Biogenic synthesis of silver nanoparticles using guava (Psidium guajava) leaf extract and its antibacterial activity against Pseudomonas aeruginosa. *Appl. Nanosci.* **2016**, *6*, 895–901. [CrossRef]
214. Pourali, P.; Badiee, S.H.; Manafi, S.; Noorani, T.; Rezaei, A.; Yahyaei, B. Biosynthesis of gold nanoparticles by two bacterial and fungal strains, Bacillus cereus and Fusarium oxysporum, and assessment and comparison of their nanotoxicity in vitro by direct and indirect assays. *Electron. J. Biotechnol.* **2017**, *29*, 86–93. [CrossRef]
215. Sharma, N.; Pinnaka, A.K.; Raje, M.; Fnu, A.; Bhattacharyya, M.S.; Choudhury, A.R. Exploitation of marine bacteria for production of gold nanoparticles. *Microb. Cell Fact.* **2012**, *11*, 86. [CrossRef]
216. Sanghi, R.; Verma, P.; Puri, S. Enzymatic formation of gold nanoparticles using phanerochaete chrysosporium. *Adv. Chem. Eng. Sci.* **2011**, *1*, 154–162. [CrossRef]
217. Molnár, Z.; Bódai, V.; Szakacs, G.; Erdélyi, B.; Fogarassy, Z.; Sáfrán, G.; Varga, T.; Kónya, Z.; Tóth-Szeles, E.; Szűcs, R.; et al. Green synthesis of gold nanoparticles by thermophilic filamentous fungi. *Sci. Rep.* **2018**, *8*, 3943. [CrossRef]
218. Amina, S.J.; Guo, B. A Review on the Synthesis and Functionalization of Gold Nanoparticles as a Drug Delivery Vehicle. *Int. J. Nanomed.* **2020**, *15*, 9823–9857. [CrossRef]
219. Gopinath, K.; Venkatesh, K.S.; Ilangovan, R.; Sankaranarayanan, K.; Arumugam, A. Green synthesis of gold nanoparticles from leaf extract of terminalia arjuna, for the enhanced mitotic cell division and pollen germination activity. *Ind. Crops Prod.* **2013**, *50*, 737–742. [CrossRef]
220. Yu, J.; Xu, D.; Guan, H.N.; Wang, C.; Huang, L.K.; Chi, D.F. Facile one-step green synthesis of gold nanoparticles using Citrus maxima aqueous extracts and its catalytic activity. *Mater. Lett.* **2016**, *166*, 110–112. [CrossRef]
221. Naveena, B.E.; Prakash, S. Biological synthesis of gold nanoparticles using marine algae gracilaria corticata and its application as a potent antimicrobial and antioxidant agent. *Asian J. Pharm. Clin. Res.* **2013**, *6*, 179–182.
222. Swaminathan, S.; Subbiah, M.; Damodarkumar, S.; Dhamotharan, R.; Bhuvaneshwari, S. Synthesis and characterization of gold nanoparticles from alga acanthophora specifera (VAHL) boergesen. *Int. J. Nano Sci. Nanotechnol.* **2011**, *2*, 85–94.
223. Kalishwaralal, K.; Deepak, V.; Pandian, S.R.K.; Kottaisamy, M.; Kanth, S.B.; Kartikeyan, B.; Gurunathan, S. Biosynthesis of silver and gold nanoparticles using Brevibacterium casei. *Colloids Surf. B Biointerfaces* **2010**, *77*, 257–262. [CrossRef] [PubMed]
224. Rajeshkumar, S.; Sri, R.B.; Venkat, K.; Soumya, M.; Lakshmi, T.; Haribalan, P. Biosynthesis of gold nanoparticles using marine microbe (Vibrio alginolyticus) and its anticancer and antioxidant analysis. *J. King Saud Univ. Sci.* **2021**, *33*, 101260.
225. Patil, M.P.; Kang, M.J.; Niyonizigiye, I.; Singh, A.; Kim, J.O.; Seo, Y.B.; Kim, G.D. Extracellular synthesis of gold nanoparticles using the marine bacterium Paracoccus haeundaensis BC74171T and evaluation of their antioxidant activity and antiproliferative effect on normal and cancer cell lines. *Colloids Surf. B Biointerfaces* **2019**, *183*, 110455. [CrossRef]
226. Sreedharan, S.M.; Gupta, S.; Saxena, A.K.; Singh, R. Macrophomina phaseolina: Microbased biorefinery for gold nanoparticle production. *Ann. Microbiol.* **2019**, *69*, 435–445. [CrossRef]

227. Acay, H. Utilization of Morchella esculenta-mediated green synthesis golden nanoparticles in biomedicine applications. *Prep. Biochem. Biotechnol.* **2021**, *51*, 127–136. [CrossRef] [PubMed]

228. Munawer, U.; Raghavendra, V.B.; Ningaraju, S.; Krishna, K.L.; Ghosh, A.R.; Melappa, G.; Pugazhendhi, A. Biofabrication of gold nanoparticles mediated by the endophytic Cladosporium species: Photodegradation, in vitro anticancer activity and in vivo antitumor studies. *Int. J. Pharm.* **2020**, *588*, 119729. [CrossRef]

229. Qu, Y.; Li, X.; Lian, S.; Dai, C.; Jv, Z.; Zhao, B.; Zhou, H. Biosynthesis of gold nanoparticles using fungus Trichoderma sp. WL-Go and their catalysis in degradation of aromatic pollutants. *IET Nanobiotechnol.* **2019**, *13*, 12–17. [CrossRef] [PubMed]

230. Folorunso, A.; Akintelu, S.; Oyebamiji, A.K.; Ajayi, S.; Abiola, B.; Abdusalam, I.; Morakinyo, A. Biosynthesis, characterization and antimicrobial activity of gold nanoparticles from leaf extracts of Annona muricata. *J. Nanostruct. Chem.* **2019**, *9*, 111–117. [CrossRef]

231. Al Saqr, A.; Khafagy, E.S.; Alalaiwe, A.; Aldawsari, M.F.; Alshahrani, S.M.; Anwer, M.K.; Khan, S.; Lila, A.S.A.; Arab, H.H.; Hegazy, W.A.H. Synthesis of Gold Nanoparticles by Using Green Machinery: Characterization and In Vitro Toxicity. *Nanomaterials* **2021**, *11*, 808. [CrossRef]

232. Qais, F.A.; Ahmad, I.; Altaf, M.; Alotaibi, S.H. Biofabrication of Gold Nanoparticles Using Capsicum annuum Extract and Its Antiquorum Sensing and Antibiofilm Activity against Bacterial Pathogens. *ACS Omega* **2021**, *6*, 16670–16682. [CrossRef]

233. Martha, R.B.; Fernando, R.; Veronica, S.; Mercedes, G.L.; Jorge, S.J.; Luis, H.A.; Carlos, A. Green synthesis of gold nanoparticles using Turnera diffusa Willd enhanced antimicrobial properties and immune response in Longfin yellowtail leukocytes. *Aquac. Res.* **2021**, *52*, 3391–3402.

234. Kim, B.; Song, W.C.; Park, S.Y.; Park, G. Green Synthesis of Silver and Gold Nanoparticles via Sargassum serratifolium Extract for Catalytic Reduction of Organic Dyes. *Catalysts* **2021**, *11*, 347. [CrossRef]

235. Babu, B.; Palanisamy, S.; Vinosha, M.; Anjali, R.; Kumar, P.; Pandi, B.; Tabarsa, M.; You, S.; Prabhu, N.M. Bioengineered gold nanoparticles from marine seaweed Acanthophora spicifera for pharmaceutical uses: Antioxidant, antibacterial, and anticancer activities. *Bioprocess Biosyst. Eng.* **2020**, *43*, 2231–2242. [CrossRef]

236. Xavier, H.F.M.; Nadar, V.M.; Patel, P.; Umapathy, D.; Joseph, A.V.; Manivannan, S.; Santhiyagu, P.; Pandi, B.; Muthusamy, G.; Rathinam, Y.; et al. Selective antibacterial and apoptosis-inducing effects of hybrid gold nanoparticles—A green approach. *J. Drug Deliv. Sci. Technol.* **2020**, *59*, 101890. [CrossRef]

237. Gürsoy, N.; Öztürk, B.Y.; Dağ, İ. Synthesis of intracellular and extracellular gold nanoparticles with a green machine and its antifungal activity. *Turk. J. Biol.* **2021**, *45*, 196–213. [CrossRef]

238. Singla, R.; Guliani, A.; Kumari, A.; Yadav, S. Toxicity issues and applications in medicine. *Met. Nanopart.* **2016**, 41–80. [CrossRef]

239. Coradeghini, R.; Gioria, S.; García, C.P.; Nativo, P.; Franchini, F.; Gilliland, D.; Ponti, J.; Rossi, F. Size-dependent toxicity and cell interaction mechanisms of gold nanoparticles on mouse fibroblasts. *Toxicol. Lett.* **2013**, *217*, 205–216. [CrossRef] [PubMed]

240. Steckiewicz, K.P.; Barcinska, E.; Malankowska, A.; Zauszkiewicz-Pawlak, A.; Nowaczyk, G.; Zaleska-Medynska, A.; Inkielewicz-Stepniak, I. Impact of gold nanoparticles shape on their cytotoxicity against human osteoblast and osteosarcoma in in vitro model. Evaluation of the safety of use and anti-cancer potential. *J. Mater. Sci. Mater. Med.* **2019**, *30*, 22. [CrossRef]

241. Papp, I.; Sieben, C.; Ludwig, K.; Roskamp, M.; Böttcher, C.; Schlecht, S.; Herrmann, A.; Haag, R. Inhibition of influenza virus infection by multivalent sialic-acid-functionalized gold nanoparticles. *Small* **2010**, *6*, 2900–2906. [CrossRef] [PubMed]

242. Beck, J.S.; Vartuli, J.C.; Roth, W.J.; Leonowicz, M.E.; Kresge, C.T.; Schmitt, K.D.; Chu, C.T.W.; Olson, D.H.; Sheppard, E.W.; McCullen, S.B.; et al. A new family of mesoporous molecular sieves prepared with liquid crystal templates. *J. Am. Chem. Soc.* **1992**, *114*, 10834–10843. [CrossRef]

243. Kresge, C.T.; Leonowicz, M.E.; Roth, W.J.; Vartuli, J.C.; Beck, J.S. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature* **1992**, *359*, 710–712. [CrossRef]

244. Cheng, Y.J.; Luo, G.F.; Zhu, J.Y.; Xu, X.D.; Zeng, X.; Cheng, D.B.; Li, Y.M.; Wu, Y.; Zhang, X.Z.; Zhuo, R.X.; et al. Enzyme-induced and tumor-targeted drug delivery system based on multifunctional mesoporous silica nanoparticles. *ACS Appl. Mater. Interfaces* **2015**, *7*, 9078–9087. [CrossRef] [PubMed]

245. Bagheri, E.; Ansari, L.; Abnous, K.; Taghdisi, S.M.; Charbgoo, F.; Ramezani, M.; Alibolandi, M. Silica based hybrid materials for drug delivery and bioimaging. *J. Control. Release* **2018**, *277*, 57–76. [CrossRef]

246. Bitar, A.; Ahmad, N.M.; Fessi, H.; Elaissari, A. Silica-based nanoparticles for biomedical applications. *Drug Discov. Today* **2012**, *17*, 1147–1154. [CrossRef] [PubMed]

247. Fijneman, A.J.; Högblom, J.; Palmlöf, M.; With, G.; Persson, M.; Friedrich, H. Multiscale Colloidal Assembly of Silica Nanoparticles into Microspheres with Tunable Mesopores. *Adv. Funct. Mater.* **2020**, *30*, 2002725–2002732. [CrossRef]

248. Thi, T.T.H.; Cao, V.D.; Nguyen, T.N.Q.; Hoang, D.T.; Ngo, V.C.; Nguyen, D.H. Functionalized mesoporous silica nanoparticles and biomedical applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *99*, 631–656.

249. Watermann, A.; Brieger, J. Mesoporous Silica Nanoparticles as Drug Delivery Vehicles in Cancer. *Nanomaterials* **2017**, *7*, 189. [CrossRef]

250. Mohamed Isa, E.D.; Ahmad, H.; Rahman, M.B.A.; Gill, M.R. Progress in Mesoporous Silica Nanoparticles as Drug Delivery Agents for Cancer Treatment. *Pharmaceutics* **2021**, *13*, 152. [CrossRef] [PubMed]

251. Chao, M.C.; Wang, D.S.; Lin, H.P.; Mou, C.Y. Control of single crystal morphology of SBA-1 mesoporous silica. *J. Mater. Chem.* **2003**, *13*, 2853–2854. [CrossRef]

252. Inagaki, S.; Guan, S.Y.; Fukushima, Y.; Ohsuna, T.; Terasaki, O. Novel Mesoporous Materials with a Uniform Distribution of Organic Groups and Inorganic Oxide in Their Frameworks. *J. Am. Chem. Soc.* **1999**, *121*, 9611–9614. [CrossRef]
253. Deka, J.R.; Lin, Y.H.; Kao, H.M. Ordered cubic mesoporous silica KIT-5 functionalized with carboxylic acid groups for dye removal. *RSC Adv.* **2014**, *4*, 49061–49069. [CrossRef]
254. Polshettiwar, V.; Cha, D.; Zhang, X.; Basset, J.M. High-surface-area silica nanospheres (KCC-1) with a fibrous morphology. *Angew. Chem. Int. Ed. Eng.* **2010**, *49*, 9652–9656. [CrossRef]
255. Tozuka, Y.; Wongmekiat, A.; Kimura, K.; Moribe, K.; Yamamura, S.; Yamamoto, K. Effect of pore size of FSM-16 on the entrapment of flurbiprofen in mesoporous structures. *Chem. Pharm. Bull.* **2005**, *53*, 974–977. [CrossRef]
256. Saleh, K.A.; Aldulmani, S.A.A.; Awwad, N.S.; Ibrahium, H.A.; Asiri, T.H.; Hamdy, M.S. Utilization of lithium incorporated mesoporous silica for preventing necrosis and increase apoptosis in different cancer cells. *BMC Chem.* **2019**, *13*, 8. [CrossRef] [PubMed]
257. Hwang, J.; Lee, J.H.; Chun, J. Facile approach for the synthesis of spherical mesoporous silica nanoparticles from sodium silicate. *Mater. Lett.* **2021**, *283*, 128765. [CrossRef]
258. Lv, X.; Zhang, L.; Xing, F.; Lin, H. Controlled synthesis of monodispersed mesoporous silica nanoparticles: Particle size tuning and formation mechanism investigation. *Microporous Mesoporous Mater.* **2016**, *225*, 238–244. [CrossRef]
259. Song, T.; Zhao, H.; Hu, Y.; Sun, N.; Zhang, H. Facile assembly of mesoporous silica nanoparticles with hierarchical pore structure for CO_2 capture. *Chin. Chem. Lett.* **2019**, *30*, 2347–2350. [CrossRef]
260. Soares, D.C.F.; Soares, L.M.; de Goes, A.M.; Melo, E.M.; de Barros, A.L.B.; Bicalho, T.C.A.S.; Leao, N.M.; Tebaldi, M.L. Mesoporous SBA-16 silica nanoparticles as a potential vaccine adjuvant against Paracoccidioides brasiliensis. *Microporous Mesoporous Mater.* **2020**, *291*, 109676. [CrossRef]
261. Mohamad, D.F.; Osman, N.S.; Nazri, M.K.H.M.; Mazlan, A.A.; Hanafi, M.F.; Esa, Y.A.M.; Rafi, M.I.I.M.; Zailani, M.N.; Rahman, N.N.; Rahman, A.H.A.; et al. Synthesis of Mesoporous Silica Nanoparticle from Banana Peel Ash for Removal of Phenol and Methyl Orange in Aqueous Solution. *Mater. Today Proc.* **2019**, *19*, 1119–1125. [CrossRef]
262. Li, H.; Wu, X.; Yang, B.; Li, J.; Xu, L.; Liu, H.; Li, S.; Xu, J.; Yang, M.; Wei, M. Evaluation of biomimetically synthesized mesoporous silica nanoparticles as drug carriers: Structure, wettability, degradation, biocompatibility and brain distribution. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *94*, 453–464. [CrossRef] [PubMed]
263. Naik, S.P.; Elangovan, S.P.; Tatsuya, O.; Sokolov, I. Morphology control of mesoporous silica particles. *J. Phys. Chem. C* **2007**, *111*, 11168–11173. [CrossRef]
264. Frickenstein, A.N.; Hagood, J.M.; Britten, C.N.; Abbott, B.S.; McNally, M.W.; Vopat, C.A.; Patterson, E.G.; MacCuaig, W.M.; Jain, A.; Walters, K.B.; et al. Mesoporous Silica Nanoparticles: Properties and Strategies for Enhancing Clinical Effect. *Pharmaceutics* **2021**, *13*, 570. [CrossRef]
265. Tang, F.; Li, L.; Chen, D. Mesoporous silica nanoparticles: Synthesis, biocompatibility and drug delivery. *Adv. Mater.* **2012**, *24*, 1504–1534. [CrossRef]
266. Küçüktürkmen, B.; Rosenholm, J.M. Mesoporous Silica Nanoparticles as Carriers for Biomolecules in Cancer Therapy. *Adv. Exp. Med. Biol.* **2021**, *1295*, 99–120.
267. He, Q.; Zhang, Z.; Gao, Y.; Shi, J.; Li, Y. Intracellular localization and cytotoxicity of spherical mesoporous silica nano- and microparticles. *Small* **2009**, *5*, 2722–2729. [CrossRef] [PubMed]
268. Cho, M.; Cho, W.S.; Choi, M.; Kim, S.J.; Han, B.S.; Kim, S.H.; Kim, H.O.; Sheen, Y.Y.; Jeong, J. The impact of size on tissue distribution and elimination by single intravenous injection of silica nanoparticles. *Toxicol. Lett.* **2009**, *189*, 177–183. [CrossRef] [PubMed]
269. Lu, F.; Wu, S.H.; Hung, Y.; Mou, C.Y. Size effect on cell uptake in well-suspended, uniform mesoporous silica nanoparticles. *Small* **2009**, *5*, 1408–1413. [CrossRef] [PubMed]
270. Huang, X.; Li, L.; Liu, T.; Hao, N.; Liu, H.; Chen, D.; Tang, F. The shape effect of mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo. *ACS Nano* **2011**, *5*, 5390–5399. [CrossRef] [PubMed]
271. Lin, Y.S.; Haynes, C.L. Impacts of mesoporous silica nanoparticle size, pore ordering, and pore integrity on hemolytic activity. *J. Am. Chem. Soc.* **2010**, *132*, 4834–4842. [CrossRef] [PubMed]
272. Mellaerts, R.; Aerts, C.A.; Van Humbeeck, J.; Augustijns, P.; Van den Mooter, G.; Martens, J.A. Enhanced release of itraconazole from ordered mesoporous SBA-15 silica materials. *Chem. Commun.* **2007**, *13*, 1375–1377. [CrossRef]
273. Pontón, I.; Del Rio, A.M.; Gómez, M.G.; Sánchez-García, D. Preparation and Applications of Organo-Silica Hybrid Mesoporous Silica Nanoparticles for the Co-Delivery of Drugs and Nucleic Acids. *Nanomaterials* **2020**, *10*, 2466. [CrossRef]
274. Wong, R.C.H.; Ng, D.K.P.; Fong, W.P.; Lo, P.C. Encapsulating pH-responsive doxorubicin-phthalocyanine conjugates in mesoporous silica nanoparticles for combined photodynamic therapy and controlled chemotherapy. *Chem. Eur. J.* **2017**, *23*, 16505–16515. [CrossRef]
275. Heleg-Shabtai, V.; Aizen, R.; Sharon, E.; Sohn, Y.S.; Trifonov, A.; Enkin, N.; Freage, L.; Nechushtai, R.; Willner, I. Gossypol-Capped Mitoxantrone-Loaded Mesoporous SiO2 NPs for the Cooperative Controlled Release of Two Anti-Cancer Drugs. *ACS Appl. Mater. Interfaces* **2016**, *8*, 14414–14422. [CrossRef]
276. Croissant, J.G.; Fatieiev, Y.; Khashab, N.M. Degradability and Clearance of Silicon, Organosilica, Silsesquioxane, Silica Mixed Oxide, and Mesoporous Silica Nanoparticles. *Adv. Mater.* **2017**, *29*, 1604634. [CrossRef] [PubMed]

277. Ma, X.; Zhao, Y.; Ng, K.W.; Zhao, Y. Integrated Hollow Mesoporous Silica Nanoparticles for Target Drug/siRNA Co-Delivery. *Chem. Eur. J.* **2013**, *19*, 15593–15603. [CrossRef] [PubMed]

278. Meng, H.; Liong, M.; Xia, T.; Li, Z.; Ji, Z.; Zink, J.I.; Nel, A.E. Engineered design of mesoporous silica nanoparticles to deliver doxorubicin and P-glycoprotein siRNA to overcome drug resistance in a cancer cell line. *ACS Nano* **2010**, *4*, 4539–4550. [CrossRef] [PubMed]

279. Shahin, S.A.; Wang, R.; Simargi, S.I.; Contreras, A.; Echavarria, L.P.; Qu, L.; Wen, W.; Dellinger, T.; Unternaehrer, J.; Tamanoi, F.; et al. Hyaluronic acid conjugated nanoparticle delivery of siRNA against TWIST reduces tumor burden and enhances sensitivity to cisplatin in ovarian cancer. *Nanomedicine* **2018**, *4*, 1381–1394. [CrossRef] [PubMed]

280. Deaconu, M.; Nicu, I.; Tincu, R.; Brezoiu, A.M.; Mitran, R.A.; Vasile, E.; Matei, C.; Berger, D. Tailored doxycycline delivery from MCM-41-type silica carriers. *Chem. Pap.* **2018**, *72*, 1869–1880. [CrossRef]

281. Liu, J.; Zhang, B.; Luo, Z.; Ding, X.; Li, J.; Dai, L.; Zhou, J.; Zhao, X.; Ye, J.; Cai, K. Enzyme responsive mesoporous silica nanoparticles for targeted tumor therapy in vitro and in vivo. *Nanoscale* **2015**, *7*, 3614–3626. [CrossRef]

282. Zhou, X.; Chen, L.; Nie, W.; Wang, W.; Qin, M.; Mo, X.; Wang, H.; He, C. Dual-Responsive Mesoporous Silica Nanoparticles Mediated Codelivery of Doxorubicin and Bcl-2 SiRNA for Targeted Treatment of Breast Cancer. *J. Phys. Chem. C* **2016**, *120*, 22375–22387. [CrossRef]

283. Wang, Y.; Han, N.; Zhao, Q.; Bai, L.; Li, J.; Jiang, T.; Wang, S. Redox-responsive mesoporous silica as carriers for controlled drug delivery: A comparative study based on silica and PEG gatekeepers. *Eur. J. Pharm. Sci.* **2015**, *72*, 12–20. [CrossRef]

284. Han, L.; Tang, C.; Yin, C. Dual-targeting and pH/redox-responsive multi-layered nanocomplexes for smart co-delivery of doxorubicin and siRNA. *Biomaterials* **2015**, *60*, 42–52. [CrossRef]

285. Nguyen, C.T.; Webb, R.I.; Lambert, L.K.; Strounina, E.; Lee, E.C.; Parat, M.O.; McGuckin, M.A.; Popat, A.; Cabot, P.J.; Ross, B.P. Bifunctional Succinylated ε-Polylysine-Coated Mesoporous Silica Nanoparticles for pH-Responsive and Intracellular Drug Delivery Targeting the Colon. *ACS Appl. Mater. Interfaces* **2017**, *9*, 9470–9483. [CrossRef]

286. Bhat, R.; Ribes, À.; Mas, N.; Aznar, E.; Sancenón, F.; Marcos, M.D.; Murguía, J.R.; Venkataraman, A.; Martínez-Máñez, R. Thrombin-Responsive Gated Silica Mesoporous Nanoparticles As Coagulation Regulators. *Langmuir* **2016**, *32*, 1195–1200. [CrossRef] [PubMed]

287. Xiong, L.; Bi, J.; Tang, Y.; Qiao, S.Z. Magnetic Core-Shell Silica Nanoparticles with Large Radial Mesopores for siRNA Delivery. *Small* **2016**, *12*, 4735–4742. [CrossRef] [PubMed]

288. Hartono, S.B.; Yu, M.; Gu, W.; Yang, J.; Strounina, E.; Wang, X.; Qiao, S.; Yu, C. Synthesis of multi-functional large pore mesoporous silica nanoparticles as gene carriers. *Nanotechnology* **2014**, *25*, 055701. [CrossRef] [PubMed]

289. Bathfield, M.; Reboul, J.; Cacciaguerra, T.; Lacroix-Desmazes, P.; Gérardin, C. Thermosensitive and Drug-Loaded Ordered Mesoporous Silica: A Direct and Effective Synthesis Using PEO-b-PNIPAM Block Copolymers. *Chem. Mater.* **2016**, *28*, 3374–3384. [CrossRef]

290. Eltohamy, M.; Seo, J.W.; Hwang, J.Y.; Jang, W.C.; Kim, H.W.; Shin, U.S. Ionic and thermo-switchable polymer-masked mesoporous silica drug-nanocarrier: High drug loading capacity at 10 °C and fast drug release completion at 40 °C. *Colloids Surf. B BioInterfaces* **2016**, *144*, 229–237. [CrossRef] [PubMed]

291. Liu, J.; Detrembleur, C.; De Pauw-Gillet, M.C.; Mornet, S.; Jérôme, C.; Duguet, E. Gold nanorods coated with mesoporous silica shell as drug delivery system for remote near infrared light-activated release and potential phototherapy. *Small* **2015**, *11*, 2323–2332. [CrossRef]

292. Salinas, Y.; Brüggemann, O.; Monkowius, U.; Teasdale, I. Visible Light Photocleavable Ruthenium-Based Molecular Gates to Reversibly Control Release from Mesoporous Silica Nanoparticles. *Nanomaterials* **2020**, *10*, 1030. [CrossRef]

293. Iijima, S. Helical microtubules of graphitic carbon. *Nature* **1991**, *354*, 56. [CrossRef]

294. Baughman, R.H.; Zakhidov, A.A.; de Heer, W.A. Carbon nanotubes–the route toward applications. *Science* **2002**, *297*, 787–792. [CrossRef]

295. Lay, C.L.; Liu, H.Q.; Tan, H.R.; Liu, Y. Delivery of paclitaxel by physically loading onto poly(ethylene glycol) (PEG)-graft-carbon nanotubes for potent cancer therapeutics. *Nanotechnology* **2010**, *21*, 065101. [CrossRef]

296. Costa, P.M.; Bourgognon, M.; Wang, J.T.; Al-Jamal, K.T. Functionalised carbon nanotubes: From intracellular uptake and cell-related toxicity to systemic brain delivery. *J. Control. Release* **2016**, *241*, 200–219. [CrossRef]

297. Liu, X.; Tao, H.; Yang, K.; Zhang, S.; Lee, S.T.; Liu, Z. Optimization of surface chemistry on single-walled carbon nanotubes for in vivo photothermal ablation of tumors. *Biomaterials* **2011**, *32*, 144–151. [CrossRef]

298. Dizaji, B.F.; Khoshbakht, S.; Farboudi, A.; Azarbaijan, M.H.; Irani, M. Far-reaching advances in the role of carbon nanotubes in cancer therapy. *Life Sci.* **2020**, *257*, 118059. [CrossRef]

299. Saeednia, L.; Yao, L.; Cluff, K.; Asmatulu, R. Sustained Releasing of Methotrexate from Injectable and Thermosensitive Chitosan-Carbon Nanotube Hybrid Hydrogels Effectively Controls Tumor Cell Growth. *ACS Omega* **2019**, *4*, 4040–4048. [CrossRef]

300. Karimi, M.; Solati, N.; Amiri, M.; Mirshekari, H.; Mohamed, E.; Taheri, M.; Hashemkhani, M.; Saeidi, A.; Estiar, M.A.; Kiani, P.; et al. Carbon nanotubes part I: Preparation of a novel and versatile drug-delivery vehicle. *Expert Opin. Drug Deliv.* **2015**, *12*, 1071–1087. [CrossRef]

301. Salas-Trevino, D.; Saucedo-Cardenas, O.; de Jesus Loera-Arias, M.; De Casas-Ortiz, E.G.; Rodriguez-Rocha, H.; Garcia-Garcia, A.; Montes-de-Oca-Luna, R.; Soto-Dominguez, A. Carbon nanotubes: An alternative for platinum-based drugs delivery systems. *J. BU ON* **2018**, *23*, 541–549.

302. Hassan, H.A.F.M.; Diebold, S.S.; Smyth, L.A.; Walters, A.A.; Lombardi, G.; Al-Jamal, K.T. Application of carbon nanotubes in cancer vaccines: Achievements, challenges and chances. *J. Control. Release* **2019**, *297*, 79–90. [CrossRef]

303. Tsukahara, T.; Matsuda, Y.; Usui, Y.; Haniu, H. Highly purified, multi-wall carbon nanotubes induce light-chain3B expression in human lung cells. *Biochem. Biophys. Res. Commun.* **2013**, *440*, 348–453. [CrossRef]

304. Dumortier, H.; Lacotte, S.; Pastorin, G.; Marega, R.; Wu, W.; Bonifazi, D.; Briand, J.P.; Prato, M.; Muller, S.; Bianco, A. Functional-ized carbon nanotubes are non-cytotoxic and preserve the functionality of primary immune cells. *Nano Lett.* **2006**, *6*, 1522–1528. [CrossRef]

305. Kang, B.; Chang, S.; Dai, Y.; Yu, D.; Chen, D. Cell response to carbon nanotubes: Size-dependent intracellular uptake mechanism and subcellular fate. *Small* **2010**, *6*, 2362–2366. [CrossRef]

306. Bekyarova, E.; Ni, Y.; Malarkey, E.B.; Montana, V.; McWilliams, J.L.; Haddon, R.C.; Parpura, V. Applications of Carbon Nanotubes in Biotechnology and Biomedicine. *J. Biomed. Nanotechnol.* **2005**, *1*, 3–17. [CrossRef]

307. Martincic, M.; Tobias, G. Filled carbon nanotubes in biomedicalimaging and drug delivery. *Expert Opin. Drug Deliv.* **2014**, *12*, 563–581. [CrossRef]

308. Comparetti, E.J.; Pedrosa, V.A.; Kaneno, R. Carbon Nanotube as a Tool for Fighting Cancer. *Bioconjug. Chem.* **2018**, *29*, 709–718. [CrossRef] [PubMed]

309. Son, K.H.; Hong, J.H.; Lee, J.W. Carbon nanotubes as cancer therapeutic carriers and mediators. *Int. J. Nanomed.* **2016**, *11*, 5163–5185. [CrossRef]

310. Mo, Y.; Wang, H.; Liu, J.; Lan, Y.; Guo, R.; Zhang, Y.; Xue, W.; Zhang, Y. Controlled release and targeted delivery to cancer cells of doxorubicin from polysaccharide-functionalised single-walled carbon nanotubes. *J. Mater. Chem. B* **2015**, *3*, 1846–1855. [CrossRef]

311. Alidori, S.; Asqiriba, K.; Londero, P.; Bergkvist, M.; Leona, M.; Scheinberg, D.A.; McDevitt, M.R. Deploying RNA and DNA with Functionalized Carbon Nanotubes. *J. Phys. Chem. C Nanomater. Interfaces* **2013**, *117*, 5982–5992. [CrossRef]

312. Singh, N.; Sachdev, A.; Gopinath, P. Polysaccharide Functionalized Single Walled Carbon Nanotubes as Nanocarriers for Delivery of Curcumin in Lung Cancer Cells. *J. Nanosci. Nanotechnol.* **2018**, *18*, 1534–1541. [CrossRef]

313. Cao, Y.; Huang, H.Y.; Chen, L.Q.; Du, H.H.; Cui, J.H.; Zhang, L.W.; Lee, B.J.; Cao, Q.R. Enhanced Lysosomal Escape of pH-Responsive Polyethylenimine-Betaine Functionalized Carbon Nanotube for the Codelivery of Survivin Small Interfering RNA and Doxorubicin. *ACS Appl. Mater. Interfaces* **2019**, *11*, 9763–9776. [CrossRef] [PubMed]

314. Lu, Y.J.; Wei, K.C.; Ma, C.C.; Yang, S.Y.; Chen, J.P. Dual targeted delivery of doxorubicin to cancer cells using folate-conjugated magnetic multi-walled carbon nanotubes. *Colloids Surf. B Biointerfaces* **2012**, *89*, 1–9. [CrossRef] [PubMed]

315. Li, J.; Yap, S.Q.; Yoong, S.L.; Nayak, T.R.; Chandra, G.W.; Ang, W.H.; Panczyk, T.; Ramaprabhu, S.; Vashist, S.K.; Sheu, F.S.; et al. Carbon nanotube bottles for incorporation, release and enhanced cytotoxic effect of cisplatin. *Carbon* **2019**, *50*, 1625–1634. [CrossRef]

316. Cirillo, G.; Vittorio, O.; Kunhardt, D.; Valli, E.; Voli, F.; Farfalla, A.; Curcio, M.; Spizzirri, U.G.; Hampel, S. Combining Carbon Nanotubes and Chitosan for the Vectorization of Methotrexate to Lung Cancer Cells. *Materials* **2019**, *12*, 2889. [CrossRef]

317. Eldridge, B.N.; Bernish, B.W.; Fahrenholtz, C.D.; Singh, R. Photothermal therapy of glioblastoma multiforme using multiwalled carbon nanotubes optimized for diffusion in extracellular space. *ACS Biomater. Sci. Eng.* **2016**, *2*, 963–976. [CrossRef]