Review
Mesoporous Silica Nanoparticle-Based Drug Delivery Systems for the Treatment of Pancreatic Cancer: A Systematic Literature Overview

Etienne J. Slapak 1,2,3,*, Mouad el Mandili 1,2, Maarten F. Bijlsma 2,3 and C. Arnold Spek 1

1 Center of Experimental and Molecular Medicine, Cancer Center Amsterdam, University of Amsterdam, Amsterdam UMC, 1105 AZ Amsterdam, The Netherlands; m.elmandili@amsterdamumc.nl (M.e.M.); c.a.spek@amsterdamumc.nl (C.A.S.)
2 Laboratory for Experimental Oncology and Radiobiology, Cancer Center Amsterdam, University of Amsterdam, Amsterdam UMC, 1105 AZ Amsterdam, The Netherlands; m.f.bijlsma@amsterdamumc.nl
3 Oncode Institute, 1105 AZ Amsterdam, The Netherlands
* Correspondence: e.j.slapak@amsterdamumc.nl

Abstract: Pancreatic cancer is a devastating disease with the worst outcome of any human cancer. Despite significant improvements in cancer treatment in general, little progress has been made in pancreatic cancer (PDAC), resulting in an overall 5-year survival rate of less than 10%. This dismal prognosis can be attributed to the limited clinical efficacy of systemic chemotherapy due to its high toxicity and consequent dose reductions. Targeted delivery of chemotherapeutic drugs to PDAC cells without affecting healthy non-tumor cells will largely reduce collateral toxicity leading to reduced morbidity and an increased number of PDAC patients eligible for chemotherapy treatment. To achieve targeted delivery in PDAC, several strategies have been explored over the last years, and especially the use of mesoporous silica nanoparticles (MSNs) seem an attractive approach. MSNs show high biocompatibility, are relatively easy to surface modify, and the porous structure of MSNs enables high drug-loading capacity. In the current systematic review, we explore the suitability of MSN-based targeted therapies in the setting of PDAC. We provide an extensive overview of MSN-formulations employed in preclinical PDAC models and conclude that MSN-based tumor-targeting strategies may indeed hold therapeutic potential for PDAC, although true clinical translation has lagged behind.

Keywords: MSN; PDAC; targeted therapy; drug delivery; antitumor; modification

1. Introduction
1.1. Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC), a neoplasm of the ductal cells in the exocrine pancreas, accounts for around 85% of pancreatic cancer diagnoses [1–3]. In 2020 the incidence rate (496,000 cases) for PDAC was almost equal to the number of deaths (446,000), making PDAC the seventh leading cause of cancer-related death in both sexes worldwide [4]. Median survival rates of PDAC are low at 11–15 months for resectable pancreatic cancer, 6–10 months for locally advanced cancer, and only 3–5 months for metastatic disease [5]. The average 5-year overall survival is 10% [6].

Treatment of PDAC depends on its disease stage and comprises surgical resection, radiation therapy, chemotherapy, and supportive care. Surgical resection is the only treatment with curative potential [7]. Based on disease stage, PDAC patients are divided into three groups; resectable/borderline resectable (10–20% of cases), non-resectable/locally advanced (around 30% of cases), and metastatic (around 60% of patients). Resectable/borderline resectable patients may receive neoadjuvant chemotherapy in combination with radiotherapy or adjuvant chemotherapy after surgical resection [8–10]. Gemcitabine monotherapy,
which has been the golden standard for adjuvant treatment of the latter patients, has recently been replaced with fluorouracil, leucovorin, oxaliplatin, and irinotecan combination therapy (FOLFIRINOX) for patients with good post-operative performance status. The PRODIGE-24 trial showed significantly increased disease-free survival and increased median overall survival (OS) of around 20 months for FOLFIRINOX-treated patients [9]. In non-resectable/locally advanced diseases, nab-paclitaxel or FOLFIRINOX chemotherapy is the standard treatment option. Although a small percentage of patients do become eligible for surgery, most patients show limited response and remain ineligible for surgical resection [11].

Systemic chemotherapy is also the standard treatment option in metastatic disease. Gemcitabine monotherapy, the golden standard for many years, has been replaced by FOLFIRINOX as a first-line treatment option, based on improved progression-free survival (PFS) and OS reported in the ACCORD-11 phase III trial [12]. In addition to FOLFIRINOX, the MPACT phase III clinical trial also demonstrated improved PFS and OS of nab-paclitaxel/gemcitabine combination therapy compared to gemcitabine monotherapy in metastatic disease [13]. However, it is important to note that FOLFIRINOX is only recommended for patients with good performance status due to its significant treatment-associated toxicity [14]. In older patients, or those with a lower performance status, the administration of nab-paclitaxel/gemcitabine combination therapy is preferred over FOLFIRINOX due to its lower cytotoxicity profile. In patients with poor performance status, gemcitabine-based therapy remains the only treatment option available, but many patients refrain from treatment in this stage due to the limited benefit and high toxicity [11].

The limited effect of current treatment modalities on the survival in PDAC may be explained by several factors, including poor delivery of chemotherapeutic agents and high toxicity profiles of existing drugs [15]. Of note, PDAC is characterized by a desmoplastic reaction, and PDAC tissue frequently consists of over 80% non-tumor cells, and typically a minority of the tumor mass is made up of tumor cells [16]. The physical barrier posed by the stroma results in poor delivery of chemotherapeutic agents to the tumor cells, thereby severely hampering treatment efficacy [17]. As a consequence of poor drug delivery, patients must receive high drug doses to reach effective levels in the tumor, but the efficacy of such treatments is hampered by systemic toxicity with subsequent dose limitations and early cessation of therapy. Indeed, of the patients receiving gemcitabine or nab-paclitaxel/gemcitabine combination therapy, around 60% and 70%, respectively, have to discontinue treatment [18]. Of note, treatment-associated toxicities result in supportive care costs that surpass the cost of first-line treatment in FOLFIRINOX and nab-paclitaxel/gemcitabine combination therapy [18].

1.2. Targeted Delivery

To prevent toxicity-dependent dose-limitations, targeted delivery of chemotherapeutic drugs to cancer cells without affecting healthy non-tumor cells is an attractive therapeutic avenue to pursue. Such an approach would not only largely reduce morbidity but may also increase the number of patients eligible for chemotherapy treatment and increase efficacy by boosting local drug concentrations in the tumor. Proof of concept for targeted therapy was obtained by coupling paclitaxel to albumin nanoparticles (nab-paclitaxel), which increased the intratumoral activity of paclitaxel compared to free paclitaxel in preclinical models [19]. After a Phase III trial in which nab-paclitaxel (with gemcitabine) was associated with significantly better survival rates than gemcitabine alone, nab-paclitaxel was approved by the FDA for the treatment of PDAC [13]. Targeting nab-paclitaxel to the tumor site was hypothesized to depend on the binding of the albumin-moiety to the protein Secreted Protein Acidic and Rich in Cysteine (SPARC/osteonectin/BM40) overexpressed by fibroblasts in the stromal compartment [20]. However, subsequent preclinical work showed that nab-paclitaxel delivery and antitumor activity is independent of SPARC [21,22], implying that the increased efficacy of nab-paclitaxel hinges on improved bioavailability rather than specific targeting. Nevertheless, as already outlined above,
nab-paclitaxel remains widely used as the first-line treatment in the setting of PDAC due to its relatively favorable toxicity profiles.

Several alternative targeted delivery strategies have been explored in PDAC over the last decades. These strategies employ—amongst others—liposomes [23–26], poly(lactic-co-glycolic acid) (PLGA)-based polymeric nanoparticles [27–29], solid lipid nanoparticles [30–32], and mesoporous silica nanoparticles (MSNs) of which especially the use of MSNs seems an attractive approach. MSNs are nanoscale silica-based particles with a porous structure as implied by their name. This porous structure enables high drug-loading capacity and time-dependent drug release. Additional advantages of MSNs include the tunable particle and pore sizes, high biocompatibility, the possibility of functionalizing the inner core and outer surface, and the possibility of controlled release through the use of a gatekeeper system [33,34]. The use of a gatekeeper system allows the targeted delivery and spatial-temporal release of, for instance, chemotherapeutics or RNAi (siRNAs or shRNAs) from MSNs specifically (in)to PDAC cells and can be achieved by internal and external stimuli, such as pH gradients, enzymes, light or magnetic field [34–36]. In this review, we explore the suitability of MSN-based targeted therapies in the setting of PDAC by providing a systematic literature overview.

2. Materials and Methods

To explore the potential promise of MSNs for the management of PDAC, a systematic literature search was performed in MEDLINE/PubMed, Web of Science Core Collection, and the EMBASE database. The combination of search terms ‘PDAC’, ‘pancreatic’ or ‘pancreatic ductal adenocarcinoma’ with ‘MSN’, ‘mesoporous’, or ‘silica’ was used to retrieve all papers that focus on MSNs in PDAC until November 30th, 2021. The exact search can be found below. All retrieved papers were screened by title and abstract for eligibility. Review papers, conference manuscripts, papers without full-text, papers not written in English or of poor quality, and papers that did not focus on MSNs or PDAC cytotoxicity were excluded. PubMed search query: (“pancreatic cancer” AND MSN) OR (“pancreatic cancer” AND mesoporous) OR (“pancreatic cancer” AND silica) OR (PDAC AND MSN) OR (PDAC AND Mesoporous) OR (PDAC AND silica) OR (pancreatic ductal adenocarcinoma AND MSN) OR (pancreatic ductal adenocarcinoma and silica) OR (pancreatic ductal adenocarcinoma AND mesoporous) OR (pancreatic ductal adenocarcinoma AND MSN)Web of Science Core Collection search query: ((((((ALL = (“pancreatic cancer” AND silica)) OR ALL = (“pancreatic cancer” AND mesoporous)) OR ALL = (“pancreatic cancer” AND MSN)) OR ALL = (PDAC AND silica)) OR ALL = (PDAC AND mesoporous)) OR ALL = (PDAC AND MSN)) OR ALL = (“pancreatic ductal adenocarcinoma” AND silica)) OR ALL = (“pancreatic ductal adenocarcinoma” AND mesoporous)) OR ALL = (“pancreatic ductal adenocarcinoma” AND MSN)EMBASE database search query: pancreatic cancer’ AND msn OR (‘pancreatic cancer’ AND mesoporous) OR (‘pancreatic cancer’ AND MSN) OR (‘pdac’ AND mdn) OR (‘pdac’ AND mesoporous) OR (‘pdac’ AND silica) OR (‘pancreatic ductal adenocarcinoma’ AND MSN) OR (‘pancreatic ductal adenocarcinoma’ AND silica) OR (‘pancreatic ductal adenocarcinoma’ AND mesoporous).

3. Results

A total of 457 papers were retrieved from the different databases (Figure 1). After removing duplicates, 140 eligible papers were identified that were thoroughly screened for experimental data on MSNs in PDAC. This resulted in the inclusion of 42 papers in this systematic review (Table 1). As outlined below, MSN-based targeted therapies may use classical MSNs or may exploit hybrid MSN-based strategies comprised of MSNs combined with a liposomal, gold, or magnetic iron oxide component. Both these systems are mainly used for cytotoxicity experiments but are also under consideration for imaging purposes. A schematic representation of the MSN-based nanoparticles and their applications can be seen in Figure 2.
Figure 1. Flowchart explaining the systematic literature search. All retrieved papers were screened, and duplicates were removed, followed by exclusion based on title and abstract, full text, or quality.

Figure 2. Diagram summarizing loading strategies of different molecules (siRNA/DNA, oxygen, sonosensitizer (e.g., IR780), anticancer drugs (e.g., gemcitabine, cisplatin, curcumin, irinotecan, paclitaxel, palbociclib, and oxaliplatin), anti-stroma drugs (e.g., TGF-β inhibitor), antifibrotic drugs (e.g., pirfenidone), photosensitizers (e.g., ZnPcOBP and methylene blue), methods to prolong half-life, increase specificity and cellular uptake (passive targeting molecules (e.g., polyethyleneimine), PDAC targeting molecules/proteins (e.g., folic acid, transferrin, urokinase plasminogen activator, V7 peptides, cyclosporine A, IGF1, c(RGDfE), and CCKBR aptamer), stroma targeting molecules (e.g., iRGD), gatekeeper with pH sensitive linkers (e.g., chitosan, disulfide bonds, and poly(D,L-lactide-co-glycolide) (PLGA)), gatekeepers with protease linkers (e.g., ADAM9-responsive linker capped with avidin, thermoresponsive gatekeeper (e.g., aliphatic azo group capped with β-cyclodextrin), antibodies (e.g., tMUC-antibody, GPC1-antibody, Cetuximab, anti-claudin 4, and anti-mesothelin), and hybrid MSNs.
Table 1. MSN-based Therapies for Improved Drug Delivery in PDAC.

| MSN       | Modification | Aim of Modification | Experimental Model | Drug/ Treatment | Main Outcome | Ref.   |
|-----------|--------------|---------------------|--------------------|-----------------|--------------|--------|
| MSN PEG   | PEG PEI      | ↑ Biodistribution   | PDAC cells         | Paclitaxel      | ↑ cellular uptake compared to unmodified MSN | [37]   |
|           |              | ↑ Uptake            |                    |                 | ↑ cytotoxicity compared to free drug |        |
| MSN       | FC-Chain     | Oxygen Delivery     | PDAC cells         | Sonodynamic Therapy | ↓ cell proliferation of multi-treatment MSNs compared to single treatment MSNs | [38] * |
|           |              |                     | Subc. Mouse        |                 | ↓ tumor volume compared to untreated, single-treatment MSNs |        |
|           |              |                     |                    |                 | ↑ improved survival compared to untreated, single-treatment MSNs |        |
| MSN       | Folate       | ↑ Uptake            | Subc. mouse        | Camptothecin    | ↑ tumor volume compared to untreated, free drug and unmodified MSNs | [39]   |
| MSN       | PEG LY364947 | TGF-β inhibition   | PDAC cells         | LY364947 (TGFβ inhibitor) | ↓ pericytes coverage compared to free TGF-β inhibitor | [40] * |
|           | PEI          | ↑ Biodistribution   | Orth. mouse        |                 | ↑ delivery Gemcitabine-loaded-liposomes compared to single-treatment MSNs |        |
|           |              | ↑ Uptake            | Subc. mouse        |                 | ↓ tumor volume compared to untreated, free drug and unmodified MSNs |        |
| MSN       | ACVA β-cyclodextrin | Cargo Release Gatekeeper | PDAC cells | Doxycycline | ↑ Thermoresponsive release of cargo | [41]   |
|           |              |                     |                    |                 | ↑ cytotoxicity compared to untreated and empty MSN |        |
| MSN       | PEG          | ↑ Biodistribution   | PDAC cells         | Curcumin        | ↑ curcumin formulation | [42]   |
| MSN       | Gemcitabine  | Gatekeeper          | PDAC cells         | Pirfenidone/Gemcitabine | ↓ expression stromal components | [43] * |
|           |              |                     | Subc. Mouse        |                 | ↓ IC50 compared to free drug |        |
|           |              |                     |                    |                 | ↓ tumor volume compared to untreated and free drug |        |
|           |              |                     |                    |                 | ↑ survival compared to untreated and free drug |        |
|           |              |                     |                    |                 | No adverse effects major organs after three weeks of treatment |        |
| MSN       | Cetuximab Imidazole | ↑ Uptake Gatekeeper | PDAC cells | ZnPcOBP (Photodynamic Therapy) | ↑ cellular uptake compared to unmodified MSN | [44] * |
|           | PEG PLGA     | ↑ Biodistribution   |                    |                 | ↑ cytotoxicity compared to empty and unmodified MSN |        |
| MSN       | Chitosan     | Cargo Release       | PDAC cells         | N6L (Nuceolin antagonist) | pH-sensitive cargo release | [45]   |
| MSN       | Transferrin Chitosan PEG | ↑ Uptake Cargo Release | PDAC cells | Gemcitabine | ↑ cytotoxicity compared to unmodified MSN | [46]   |
|           |              | Cargo Release       |                    |                 | pH-sensitive cargo release |        |
| MSN       | Transferrin  | ↑ Uptake            | PDAC cells         | Curcumin        | ↑ cellular uptake compared to unmodified MSN | [47]   |
|           | PEG          | ↑ Biodistribution   | Subc. mouse        |                 | ↑ tumor growth and metastasis compared to free drug and unmodified MSN |        |
Table 1. Cont.

| Modification | Aim of Modification | Experimental Model | Drug/Treatment | Main Outcome | Ref. |
|--------------|---------------------|--------------------|----------------|--------------|------|
| tMUC-antibody PEG PEI | ↑ Uptake ↑ Biodistribution ↑ Uptake | PDAC cells Genetic mouse | Gemcitabine-/cisplatin prodrug | ↑ cellular uptake compared to unmodified MSN ↑ cytotoxicity double-loaded MSNs compared to a single drug and mixed ↓ tumor volume and weight compared to control, free drug and unmodified MSN No adverse effects major organs | [48] * |
| Cetuximab PEG | ↑ Uptake ↑ Biodistribution | PDAC cells Orth. mouse | Zinc phthalocyanine | ↑ cellular uptake compared to free drug and unmodified MSN ↓ tumor volume | [49] |
| ADAM9-linker Biotin-avidin Cargo Release Gatekeeper | | PDAC and white blood cells | Paclitaxel | ↑ cytotoxicity in PDAC compared to white blood cells | [50] |
| L-arginine CO₂ adsorption/release | | PDAC cells Subc. mouse | Sonodynamic Therapy | ↑ cytotoxicity compared to single-treatment ↓ tumor volume compared to single-treatment | [52] |
| GPC1-antibody | ↑ Uptake | PDAC cells | Gemcitabine/Ferulic Acid | ↑ cytotoxicity compared to unmodified MSNs | [53] |
| Chitosan UPA Cargo Release Cargo Release | | PDAC cells | Gemcitabine | pH-specific cargo release | [54] |
| Quantum Dots Cargo Loading | | PDAC cells | Doxorubicin/Camptothecin | ↑ cytotoxicity multidrug-loaded MSNs compared to single drug-loaded MSNs | [56] |
| MSN | | PDAC cells | Paclitaxel | ↑ tumor shrinkage compared to free drug, MSN-loaded and combination therapy ↓ primary tumor growth and metastasis | [57] |
| Lipo-MSN | | PDAC cells Orth. mouse | Paclitaxel/Gemcitabine | Synergy of paclitaxel and gemcitabine upon co-delivery ↑ tumor shrinkage compared to free drug, MSN-loaded and combination therapy ↓ primary tumor growth and metastasis | [58] |
| Lipo-MSN PEG | ↑ Biodistribution | PDAC cells Subc. mouse Orth. mouse | Palbociclib/Hydroxy-chloroquine | ↑ cytotoxicity co-delivery compared to free and single drug MSNs ↓ tumor size co-delivery compared to free drug and single drug MSNs ↓ tumor size co-delivery compared to free drug and single drug MSNs | [59] |
| Lipo-MSN | | Orth. mouse | Irinotecan | ↑ tumor size and improved survival compared to free drug and Onivyde ↓ liver, GIT, and bone marrow toxicity | [60] |
| MSN          | Modification | Aim of Modification | Experimental Model | Drug/Treatment | Main Outcome                                                                 | Ref.       |
|--------------|--------------|---------------------|--------------------|----------------|-------------------------------------------------------------------------------|-----------|
| Lipo-MSN     | iRGD         | ↑ Uptake            | Orth. mouse        | Irinotecan     | ↑ cellular uptake compared to unmodified Lipo-MSN                             | [62]      |
| Lipo-MSN     | PEG          | ↑ Biodistribution   | Orth. mouse        | Oxaliplatin/ fDACHPt | ↓ tumor weight and metastasis, improved survival compared to free drug        | [63]      |
| Lipo-MSN     | PEG          | ↑ Biodistribution   | Orth. mouse        | Irinotecan     | ↑ tumor weight and metastasis compared to free drug                           | [64] *    |
| Lipo-MSN     | PEG          | ↑ Biodistribution   | Orth. mouse        | Irinotecan     | ↓ tumor weight and metastasis compared to free drug                           | [65]      |
| Lipo-MSN     | PEG          | ↑ Biodistribution   | Orth. mouse        | Irinotecan     | ↑ tumor weight and metastasis compared to free drug                           | [66] *    |
| Lipo-MSN     | Cyclosporine A | ↑ Uptake            | PDAC cells         | Bortezomib/ IR-820 (Photothermal Therapy) | ↑ cellular uptake compared to unmodified Lipo-MSN                             | [67]      |
| Lipo-MSN     | PEG          | ↑ Biodistribution   | Subc. mouse        | Oxaliplatin/ Indoximod | ↑ survival compared to free drug, single-drug Lipo-MSNs                      | [68]      |
| Gold-MSN     | IGF-1        | ↑ Uptake            | PDAC cells         | Gemcitabine/ Perfluorohexane | ↑ cytotoxicity compared to untreated, free drug, unmodified MSNs             | [69] *    |
| Gold-MSN     | Transferrin   | ↑ Uptake            | PDAC cells         | Gemcitabine    | ↑ cellular uptake compared to unmodified Gold-MSN                             | [70] *    |
| Gold-MSN     | V7-peptide   | ↑ Uptake Cargo      | PDAC cells         | Gemcitabine    | ↑ cytotoxicity Gold-modified MSNs compared to unmodified                       | [71]      |
| Gold-MSN     | Chitosan     |                     |                    |                | ↑ cytotoxicity compared to free drug and empty MSNs                          | [72]      |
Table 1. Cont.

| MSN              | Modification | Aim of Modification | Experimental Model | Drug/Treatment       | Main Outcome                                                                 | Ref.  |
|------------------|--------------|---------------------|--------------------|----------------------|-------------------------------------------------------------------------------|-------|
| Iron-MSN         |              |                     | PDAC cells         | Camptothecin         | ↑ cytotoxicity compared to free drug, empty MSN, and unmodified MSN           | [73] *|
|                  |              |                     | Orth. mouse        |                      | ↓ tumor volume compared to untreated and free drug                           |       |
|                  |              |                     |                    |                      | No adverse effects major organs                                              |       |
| Iron-MSN Dicarboxylic acid | Cargo Release | PDAC cells         | Cisplatin          |                      | ↑ cytotoxicity compared to free drug                                          | [74]  |
|                  |              |                     |                    |                      | ↓ cytotoxicity nonmalignant human pancreatic duct cells                      |       |
| Iron-MSN         |              |                     | PDAC cells         | Gemcitabine/Losartan | ↑ cytotoxicity compared to free drug                                          | [75] *|
|                  |              |                     | Subc. Mouse        |                      | ↓ tumor weight and volume compared to monotherapy                            |       |
|                  |              |                     |                    |                      | No adverse effects major organs                                              |       |
| Iron-MSN c(RGDfE) PEG | ↑ Uptake Biodistribution | PDAC cells         | Gemcitabine        |                      | ↑ uptake compared to unmodified Iron-MSNs                                     | [77]  |
| Iron-MSN CCKBR aptamer G16 PEG citrate | ↑ Uptake Biodistribution | PDAC cells         | FdUMP/dFdCMP       |                      | ↓ proliferation compared to free drug and empty MSNs                         | [78]  |
|                  |              |                     | Orth. mouse        |                      | ↓ thymidylate synthase levels compared to unmodified MSNs                    |       |

*= in vitro, • = in vivo, Orth. = Orthotopic, Subc. = Subcutaneous, Intraperi. = Intrapertitoneal, ↑ = increased, ↓ = decreased, * indicates particularly relevant publication.
3.1. Cytotoxicity of Classical MSNs in PDAC

The last decade has seen a rise in the number of studies exploring MSNs in PDAC [37–57]. Building on experience with MSNs in other tumor types [79–81], MSNs are preferentially surface modified to increase biodistribution and/or tumor uptake. Pioneering studies showed that surface modification by conjugation with polyethyleneimine (PEI) [37], folic acid [82], or monoclonal antibodies targeting anti-claudin4 and anti-mesothelin [83] indeed improved nanoparticle uptake by PDAC cells, whereas modification with polyethylene glycol (PEG) was shown to enhance biodistribution and circulation time in experimental animal models [40,42]. More recent studies use alternative surface modifications to target chemotherapeutics to PDAC tumors, and MSNs have been conjugated with transferrin [46,47,83], urokinase plasminogen activator [54], anti-GPC1, anti-tMUC1 [48], or V7 [84] peptides for this purpose. As envisioned, cellular uptake was increased using tumor-targeting moieties compared to controls lacking a modification both in vitro [46,47,83] and in vivo [48,54,84]. A recent study confirmed the importance of tumor-targeting surface modifications [84]. Utilizing V7 peptide-conjugated MSNs in an orthotopic PDAC model, MacCuaig and colleagues showed that active targeting of MSNs (i.e., including surface modifications to increase tumor cell uptake) outperforms passive targeting (i.e., no tumor targeting modifications on the MSNs) irrespective of nanoparticle size [84]. However, it is important to note that improved uptake and cytotoxicity in vitro does not always translate to similar findings in vivo, as PEGylated MSNs showed higher tumor uptake compared to PEG-transferrin-modified MSNs in one study [47]. More importantly, drug-loaded anti-tMUC1-conjugated MSNs outperformed MSNs lacking the anti-tMUC1 moiety in reducing tumor volume and weight in a syngeneic mouse model in which human tMUC expressing PDAC cells were implanted [48].

In addition to targeting MSNs to tumor cells, MSNs may also be surface modified to only release their cargo in the proximity of tumor cells. To this end, several so-called gatekeeper systems have been developed that prevent drug release in the circulation and/or at healthy, non-tumor-bearing organ sites. The addition of pH-sensitive gatekeepers such as chitosan, disulfide bonds, and poly(D,L-lactide-co-glycolide) showed pH-specific cargo release in vitro [45,46] and in tissue-mimicking phantoms [54,84]. The reduction in tumor weight and volume upon administration to PDAC bearing mice suggests that pH-based gatekeepers also hold promise for in vivo settings [43]. Unfortunately, no in vitro or in vivo experiments have been performed to compare the cytotoxicity of MSNs with and without a pH-sensitive gatekeeper to prove its superior sensitivity for the tumor microenvironment compared to healthy tissue. MSNs may also achieve specific drug release in the vicinity of tumor cells capped and locked by protease linkers that are specifically cleaved by tumor-enriched proteases. Indeed, conjugating MSNs with an ADAM9-responsive peptide linker more efficiently killed PDAC cells than white blood cells in vitro [50].

As opposed to tumor intrinsic properties, external cues can also be applied to remove the gatekeeper from MSNs thereby inducing drug release. Removing a thermo-responsive gatekeeper using an alternating magnetic field (AMF) led to rapid drug release and efficient PDAC cell death whereas no cell death was observed in the absence of AMF [41]. Alternatively, external stimuli may be applied to activate MSNs to induce cell death. Photonic stimulation of MSNs loaded with the photosensitizer ZnPcOBP caused a high phototoxic effect compared to free ZnPcOBP on PDAC cells in vitro. This effect was further enhanced by surface modification with Cetuximab, a monoclonal antibody that targets the Epidermal Growth Factor Receptor [44]. Of note, the observed photokilling of ZnPcOBP-loaded Cetuximab-conjugated MSNs correlated with (epidermal growth factor receptor (EGFR) expression levels in the PDAC cells. Similarly, the delivery of oxygen and the sonosensitizer IR780 by MSNs to the hypoxic tumor environment reduced tumor volume and improved survival in experimental animals upon sonodynamic therapy [38]. This method, however, relies on ultrasound irradiation and the presence of EGFR on tumor cells, which might not be translatable to real-world clinical routines and possibilities. Despite the substantial number of in vitro studies with MSNs in PDAC, only several
papers study the potential of MSNs in preclinical animal models. To target, the stromal compartment, MSNs coated with PEI/PEG/LY364947 (a small molecule TGF-β inhibitor) were administered to tumor-bearing mice [40]. Of note, the number of pericytes in the stroma surrounding the tumor cells was reduced and subsequent treatment with PEGylated gemcitabine-loaded liposomes efficiently reduced tumor weight as compared to control mice that were only treated with gemcitabine-loaded liposomes [40]. Importantly, combination therapy of PEI/PEG/LY364947 coated MSNs with gemcitabine-loaded liposomes did not induce cytotoxicity (i.e., body weight loss or nephrotoxicity) as opposed to free gemcitabine. Of note, this promising study was already published in 2013, and no follow-up has yet been reported. Gao and co-workers employed MSNs loaded with the antifibrotic drug pirfenidone that were subsequently capped with gemcitabine to simultaneously target the stromal and tumor compartment combined with ultrasound destruction [43]. This intriguing approach almost completely halted tumor growth for three weeks and prolonged survival compared to both free gemcitabine and pirfenidone [43]. However, half of the mice succumbed to the disease after seven weeks, indicating that the observed tumor growth inhibition was an early response not sustained over time. In addition, although the increased cytotoxicity of the MSNs was not accompanied by any toxicity after three weeks of treatment, ultrasound destruction is well-known to induce damage to healthy tissues, limiting the applicability in clinical trials. One possibility to circumvent this caveat would be to monitor biological tissue damage using, for example, the IMWPE-PNN method [as described in Bei Liu et al. [85]]. The combination of cisplatin and gemcitabine is associated with high toxicity, yet recent clinical trials imply an added benefit of including cisplatin in existing PDAC treatment regimens [86,87]. Based on this notion, a very recent study designed MSNs with cisplatin and gemcitabine prodrugs to the inner and outer surface, respectively. Systemic administration of these MSNs to two genetic tumor-bearing mouse models significantly suppressed tumor growth and eliminated the off-target toxicities of the highly toxic chemotherapy combination. By mimicking advanced stages of PDAC in vivo over a study course of three months, they were able to show therapeutic effect by a decrease in pancreas weight, attributed by a reduction of the tumor mass. [48]. In vivo study designs like these might improve the clinical translation.

In addition to conventional chemotherapeutics, MSNs also open up new avenues for drugs whose clinical potential is hampered by their hydrophobicity and consequent biodistribution. The clinical efficacy of curcumin, a candidate anticancer drug [88] that potentiates the effect of gemcitabine [89,90], is limited by its poor solubility. Loading curcumin into MSNs was found to inhibit tumor growth and minimize distant metastasis in a subcutaneous xenograft model [47]. Of note, subsequent administration of gemcitabine potentiates the effect of curcumin-loaded MSNs in vitro, but in vivo validation is lacking [47].

Overall, a picture emerges in which classical MSNs are attractive vehicles to deliver drugs to PDAC tumors. Different surface modifications have shown promising characteristics in preclinical PDAC models, and several MSN formulations warrant follow-up in future clinical studies.

3.2. Liposome-Coated MSNs

Amongst all nanomedicine platforms, liposomes—spherical vesicles composed of a lipid bilayer—are most used and several FDA-approved liposome formulations (most notably liposomal irinotecan, Onivyde, in the setting of PDAC) are used in the clinic. Based on the favorable characteristics of liposomes, several papers describe the coating of MSNs with a lipid bilayer to improve stability after systemic administration, thereby overcoming one of the major limitations of MSNs in vivo. The majority of lipid membrane-enhanced MSNs lack a targeted delivery moiety [58–61,63–66,68], however iRGD- [62] and cyclosporine A-conjugated [67] liposome-coated MSNs have been designed to improve tumor targeting and cellular uptake. Non-targeted irinotecan-loaded liposome-coated MSNs consistently outperform irinotecan-loaded liposomes, including FDA-approved
Onivyde, in terms of drug delivery, cytotoxicity, survival as well by reducing bone marrow, gastrointestinal and liver toxicity [64,66]. Indeed, compared to free drug and Onyvide, the liposome-coated MSNs amounted to a 79- and 8.7-fold increase in tumor drug content, respectively. In line, irinotecan-loaded liposomes significantly increased survival compared to Onyvide in an orthotopic PDAC model [66]. Modifying the liposome-coated MSNs with a tumor-homing and penetrating iRGD-peptide enhanced survival even further and resulted in reduced metastasis [62]. The significant improvement of irinotecan-loaded liposome-coated MSNs over the last five years resulting in their superiority over Onyvide, poses it as an interesting candidate for progressing to clinical testing. Further research showed that combining different drugs in lipid-modified MSNs greatly improves tumor reduction compared to free drugs or corresponding monotherapies. Indeed, gemcitabine/paclitaxel-loaded MSNs outperform gemcitabine-loaded MSN monotherapy and combination therapy of free gemcitabine and nab-paclitaxel [58]. Moreover, co-administration of palbociclib- and hydroxychloroquine-loaded MSNs [59], or indoximod- and oxaliplatin-loaded MSNs [68] reduced PDAC growth more efficiently compared to mono MSN therapy or free drug combinations. Besides, the co-delivery of chemotherapeutic-loaded liposome-coated MSNs can also be adjusted to facilitate photothermal and photodynamic-induced cancer cell apoptosis [67]. The increased uptake dependent on cyclosporine A conjugation improved the apoptotic effects of bortezomib in combination with the cytotoxic effects of the near infrared (NIR) dye IR-820 upon NIR irradiation in a subcutaneous PDAC model [67]. In conclusion, liposome-coated MSNs confer great versatility and show great promise in preclinical research, notably by outperforming the FDA-approved classical liposomal formulation Onivyde upon loading with irinotecan.

3.3. Gold-MSN Hybrid Nanocarriers

Gold-MSN hybrid nanocarriers are typically employed for imaging purposes (see below for details), but they may also be used to potentiate treatment response. By extending the lifetime of highly toxic singlet oxygen species necessary for photosensitization, the cytotoxic potential of the involved photosensitizer molecules is increased [91]. Indeed, the conjugation of gold-nanoparticles to MSNs loaded with the photosensitizer methylene blue decreased PANC-1 cell viability following photodynamic therapy (PDT) compared to MB-loaded MSNs lacking a gold nanoparticle tethered to the outer layer in vitro [71]. The superior efficacy of gold-MSNs has been confirmed in preclinical animal models by two research groups [69,70]. Both studies employing gold-MSNs in vivo used conjugated MSNs, with IGF1 [69] or transferrin [70], to increase their cellular uptake. In a patient-derived xenograft PDAC mouse model, gemcitabine-loaded IGF1-conjugated gold-MSNs reduced tumor growth by around 70% [69]. Combining the gold-MSNs with photothermal therapy further enhanced efficacy leading to complete eradication of the xenograft and an astounding survival rate of 100% [69]. Next to their remarkable antitumor efficacy, the gold-MSNs did not seem to induce any cytotoxicity off-target. Albeit promising, intratumoral injection for photoablation limits the therapeutic efficacy to the primary tumor, leaving metastatic foci unharmed. Moreover, such a treatment would be hard to implement in the clinic and would require incorporation in local ablation modalities. In line with these intriguing data, gemcitabine-loaded transferrin-conjugated gold-MNs also greatly enhanced chemosensitivity of PDAC cells and induced effective regression of human pancreatic cancer xenografts in mice by the combination of photothermal- and chemotherapy [70]. The impressive antitumor efficacy was in part attributed to an increased penetration of gemcitabine after photothermal therapy. However, it is important to note that photothermal ablation is not readily translatable to human PDAC due to the tissue absorption of laser light causing a decrease in intensity of approximately 10-fold every 2 cm deeper [92]. Consequently, it would be necessary to address whether MSN-based therapies involving photothermal ablation by laser light can be applied in a clinical setting. Additionally, it would be interesting to assess if loading gold-MSNs with drugs with a
higher cytotoxic activity towards PDAC cells, such as nab-paclitaxel, may even further reduce tumor growth.

### 3.4. Magnetic Iron Oxide-MSN Hybrid Nanocarriers

A relatively recently developed hybrid MSN nanocarrier system combined MSNs with an iron oxide component [73–78]. These hybrid MSNs allow simultaneous MRI contrast imaging and drug delivery, thereby enabling the visualization of therapy efficacy in a non-invasive manner. Although the number of papers describing theranostic magnetic iron oxide-MSNs is limited, they seem to hold promise in the setting of PDAC. Indeed, tumor microenvironment-triggered release of poorly water-soluble camptothecin molecules from magnetic iron oxide-MSNs reduced tumor growth in vivo [73]. This study, however, was limited to 13 days, and, therefore, long-term efficacy must be demonstrated in future research. The safety and biocompatible nature of the magnetic iron oxide-MSNs was confirmed by histological analysis, and no overt signs of toxicity were observed in other organs. As described above, in PDAC, MSNs may be employed in a ‘two-hit’ approach in which the first hit targets the stroma to then improve tumor delivery of drugs carried by the MSNs (second hit). Based upon this notion, Li and colleagues treated tumor-bearing mice with magnetic iron oxide-MSNs loaded with losartan that inhibits type I collagen and hyaluronic acid present in PDAC stroma. Mono treatment of losartan-loaded magnetic iron oxide-MSNs marginally reduced tumor volume, but subsequent treatment with gemcitabine-loaded magnetic Iron Oxide-MSNs very efficiently diminished tumor growth by over 70%. Notably, monotherapy with gemcitabine-loaded magnetic iron oxide-MSNs was less effective and reduced tumor growth by around 40% [75]. Unfortunately, the endpoint was after only three weeks, limiting the observation of long-term effects. Similar to surface modifications described above, magnetic iron oxide hybrid MSNs may also be further modified to increase specificity or efficacy. As the first example of such an approach, Sun and colleagues showed that adding a c(RGDfE) moiety improved the cellular uptake by PDAC cells [77]. Whether this modification or alternative modifications used for targeting purposes in classical MSNs, also improves efficacy in preclinical PDAC animal models need to be established. Preclinical assessment needs to be improved by extending the treatment and follow-up period of in vivo experiments. Furthermore, the wide variety of magnetic iron oxide molecules used in hybrid-MSNs complicate the ability to compare studies and address superiority, future standardization experiments might be particularly useful for this type of MSNs.

### 4. Conclusions

The preclinical studies discussed in this systematic review suggest that MSN-based tumor-targeting strategies may hold therapeutic potential for PDAC. Indeed, MSNs-based therapies show antitumor activity in PDAC mouse models and seem to reduce adverse toxicity. Several issues need to be kept in mind before MSNs can move forward to clinical development in PDAC management. The MSNs employed in the (preclinical) studies are rather variable with respect to their synthesis and surface modifications, and no direct comparisons have been made between these MSNs. Indeed, the MSN formulations have been tested in different preclinical models with varying drug concentrations, controls, endpoints, and treatment modalities. Hence, it will be pivotal to compare different MSN formulations head-to-head in similar models with predefined endpoints. Only when such studies have been performed will we be able to select the most promising MSN-based strategy to test in clinical studies. Unfortunately, clinical translation remains slow. Even though the safety of MSNs has been widely demonstrated in clinical trials, it has taken over more than two decades for gold-MSNs to reach clinical trials [93]. This slow progression may be explained by the over-interpretation of results combined with the majority of papers not passing the critical assessment of their translatable applicability. Additionally, multiple MSN-based nanoplatorms showing pre-clinical promise are not followed up or improved over time, raising the question of whether follow-up was not performed or
whether it yielded less than encouraging results. Another important limitation of several of the discussed studies is the lack of proper controls to address potential side effects of the MSN formulations. To conclude that MSN-loaded drugs confer reduced cytotoxicity, it is pivotal to include relevant control cells in vitro and proper toxicity readouts in vivo. As most chemotherapeutics show bone marrow toxicity induces neuropathy and diarrhea, preclinical mouse models should be designed to assess these common side effects. In vitro, one should consider including blood, neuronal, or (gut) epithelial cells to assess the effect of the MSNs on the relevant cell types. Irrespective of these latter considerations, MSN-based targeted therapies seem to hold promise for treating PDAC, a disease that is in dire need of improved therapeutic options.

**Author Contributions:** Conceptualization, E.J.S. and C.A.S.; methodology, E.J.S.; validation, E.J.S. and M.e.M.; data curation, E.J.S. and M.e.M.; writing—original draft preparation, E.J.S. and C.A.S.; writing—review and editing, E.J.S., C.A.S. and M.F.B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by a grant from the Dutch Cancer Foundation (KWF) via grant UVA 2017-11174. The funders have not participated in the study design, data collection, data analysis, interpretation, or writing of the report.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** M.F.B. has received funding from Celgene and Lead Pharma and has acted as a consultant to Servier. These parties were not involved in writing this manuscript. All other authors declare no conflicts of interest.

**References**

1. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 2015, 136, E359–E386. [CrossRef] [PubMed]

2. Hidalgo, M.; Casciriu, S.; Kleeff, J.; Labianca, R.; Lohr, J.M.; Neoptolemos, J.; Real, F.X.; Van Laethem, J.L.; Heinemann, V. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology* 2015, 15, 8–18. [CrossRef]

3. Ilic, M.; Ilic, I. Epidemiology of pancreatic cancer. *World J. Gastroenterol.* 2016, 22, 9694–9705. [CrossRef] [PubMed]

4. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 2021, 71, 209–249. [CrossRef] [PubMed]

5. Alderson, D.; Johnson, C.D.; Neoptolemos, J.P.; Ainley, C.C.; Bennett, M.K. Guidelines for the management of patients with pancreatic cancer, periampullary and ampullary carcinomas. *Gut* 2005, 54 (Suppl. 5), 1–16.

6. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA Cancer J. Clin.* 2021, 71, 7–33. [CrossRef]

7. Millikan, K.W.; Deziel, D.J.; Silverstein, J.C.; Kanjo, T.M.; Christein, J.D.; Doolas, A.; Prinz, R.A. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. *Am. Surg.* 1999, 65, 618–623, discussion 623–614. [PubMed]

8. Neoptolemos, J.P.; Dunn, J.A.; Stocken, D.D.; Almond, J.; Link, K.; Beger, H.; Bassi, C.; Falconi, M.; Pederzoli, P.; Dervenis, C.; et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: A randomised controlled trial. *Lancet* 2001, 358, 1576–1585. [CrossRef]

9. Conroy, T.; Hammel, P.; Hebbel, M.; Ben Abdelghani, M.; Wei, A.C.; Raoul, J.-L.; Choné, L.; Francois, E.; Artru, P.; Biagi, J.J.; et al. FOLFIRINOX and Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N. Engl. J. Med.* 2018, 379, Z095–2046. [CrossRef]

10. Versteijne, E.; Suker, M.; Groothuis, K.; Ackermans-Vogelaar, J.M.; Besselink, M.G.; Bosma, B.A.; Buijsen, J.; Busch, O.R.; Creemers, G.M.; van Dam, R.M.; et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J. Clin. Oncol.* 2020, 38, 1763–1773. [PubMed] [CrossRef]

11. Mizrahi, J.D.; Surana, R.; Valle, J.W.; Shroff, R.T. Pancreatic cancer. *Lancet* 2020, 395, 2008–2020. [CrossRef]

12. Conroy, T.; Desseigne, F.; Ychou, M.; Bouche, O.; Guimbaud, R.; Becouarn, Y.; Adenis, A.; Raoul, J.L.; Gourgou-Bourgade, S.; de la Fouchardiere, C.; et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.* 2011, 364, 1817–1825. [CrossRef] [PubMed]

13. Von Hoff, D.D.; Ervin, T.; Arena, F.P.; Chiorean, E.G.; Infante, J.; Moore, M.; Seay, T.; Tjulandin, S.A.; Ma, W.W.; Saleh, M.N.; et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl. J. Med.* 2013, 369, 1691–1703. [CrossRef] [PubMed]
14. Kamisawa, T.; Wood, L.D.; Itoi, T.; Takaori, K. Pancreatic cancer. *Lancet* 2016, 388, 73–85. [CrossRef]

15. Singh, D.; Upadhyay, G.; Srivastava, R.K.; Shankar, S. Recent advances in pancreatic cancer: Biology, treatment, and prevention. *Biochim. Biophys. Acta* 2015, 1856, 13–27. [CrossRef]

16. Zhan, H.X.; Zhou, B.; Cheng, Y.G.; Xu, J.W.; Wang, L.; Zhang, G.Y.; Hu, S.Y. Crosstalk between stromal cells and cancer cells in pancreatic cancer: New insights into stromal biology. *Cancer Lett.* 2017, 392, 83–93. [CrossRef]

17. Hidalgo, M. Pancreatic cancer. *N. Engl. J. Med.* 2010, 362, 1605–1617. [CrossRef]

18. McBride, A.; Bonafeade, M.; Cai, Q.; Princic, N.; Tran, O.; Pelletier, C.; Parisi, M.; Patel, M. Comparison of treatment patterns and economic outcomes among metastatic pancreatic cancer patients initiated on nab-paclitaxel plus gemcitabine versus FOLFIRINOX. *Expert Rev. Clin. Pharm.* 2017, 10, 1133–1160. [CrossRef]

19. Desai, N.; Trieu, V.; Yao, Z.; Louie, L.; Ci, S.; Yang, A.; Tao, C.; De, T.; Beals, B.; Dykes, D.; et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin. Cancer Res.* 2016, 12, 1317–1324. [CrossRef]

20. Mantoni, T.S.; Schendel, R.R.; Rodel, F.; Niedobitek, G.; Al-Assar, O.; Masamune, A.; Brunner, T.B. Stromal SPARC expression and patient survival after chemotherapy for non-resectable pancreatic adenocarcinoma. *Cancer Biol Ther* 2008, 7, 1806–1815. [CrossRef]

21. Kim, H.; Samuel, S.; Lopez-Casas, P.; Grizzle, W.; Hidalgo, M.; Kovar, J.; Oelschlager, D.; Zinn, K.; Warram, J.; Buchsbaum, D. SPARC-Independent Delivery of Nab-Paclitaxel without Depleting Tumor Stroma in Patient-Derived Pancreatic Cancer Xenografts. *Mol. Cancer* 2016, 15, 680–688. [CrossRef] [PubMed]

22. Neesse, A.; Frese, K.K.; Chan, D.S.; Bapiro, T.E.; Howat, W.J.; Richards, F.M.; Ellenrieder, V.; Jodrell, D.I.; Tuveson, D.A. SPARC independent drug delivery and antitumour effects of na-paclitaxel in genetically engineered mice. *Gut* 2014, 63, 974–983. [CrossRef] [PubMed]

23. Wang-Gillam, A.; Li, C.-P.; Bodoky, G.; Dean, A.; Shan, Y.-S.; Jameson, G.; Macarulla, T.; Lee, K.-H.; Cunningham, D.; Blanc, J.E.; et al. Nanoliposomal irinotecan with fluorouracil and folic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. *Lancet* 2016, 387, 545–557. [CrossRef]

24. Lohr, J.M.; Haas, S.L.; Bechstein, W.O.; Bodoky, G.; Cwiertka, K.; Fischbach, W.; Folsch, U.R.; Jager, D.; Osinsky, D.; Prausova, J.; et al. Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: A randomized controlled phase II trial. *Ann. Oncol.* 2012, 23, 1214–1222. [CrossRef] [PubMed]

25. Rao, D.D.; Luo, X.; Wang, Z.; Jay, C.M.; Brunicardi, F.C.; Maltese, W.; Manning, L.; Senzer, N.; Nemunaitis, J. KRAS mutant allele-specific expression knockdown in pancreatic cancer model with systemically delivered bi-shRNA KRAS lipoplex. *PloS ONE* 2018, 13, e0193644. [CrossRef]

26. Mao, Y.; Li, X.; Chen, G.; Wang, S. Thermosensitive Hydrogel System With Paclitaxel Liposomes Used in Localized Drug Delivery System for In Situ Treatment of Tumor: Better Antitumor Efficacy and Lower Toxicity. *J. Pharm Sci.* 2016, 105, 194–204. [CrossRef]

27. Matsumoto, S.; Nakata, K.; Sagara, A.; Guan, W.; Ikenaga, N.; Ohuchida, K.; Nakamura, M. Efficient pre-treatment for pancreatic cancer using chloroquine-loaded nanoparticles targeting pancreatic stellate cells. *Oncol. Lett.* 2021, 22, 633. [CrossRef]

28. Cai, H.; Wang, R.; Guo, X.; Song, M.; Yan, F.; Ji, B.; Liu, Y. Combining Gemcitabine-Loaded Macrophage-like Nanoparticles and Erlotinib for Pancreatic Cancer Therapy. *Mol. Pharm.* 2021, 18, 2495–2506. [CrossRef]

29. Jung, J.Y.; Ryu, H.J.; Lee, S.H.; Kim, D.Y.; Kim, M.J.; Lee, E.J.; Ryu, Y.M.; Kim, S.Y.; Kim, K.P.; Choi, E.Y.; et al. siRNA Nanoparticle Targeting PD-L1 Activates Tumor Immunity and Abrogates Pancreatic Cancer Growth in Humanized Preclinical Model. *Cells* 2021, 10, 2734. [CrossRef]

30. Thakkar, A.; Chenreddy, S.; Wang, J.; Prabhu, S. Ferulic acid combined with aspirin demonstrates chemopreventive potential towards pancreatic cancer when delivered using chitosan-coated solid-lipid nanoparticles. *Cell Biosci.* 2021, 11, 46. [CrossRef]

31. Thakkar, A.; Desai, P.; Chenreddy, S.; Modi, J.; Thio, A.; Khamas, W.; Ann, D.; Wang, J.; Prabhu, S. Novel nano-drug combination therapeutic regimen demonstrates significant efficacy in the transgenic mouse model of pancreatic ductal adenocarcinoma. *Am. J. Cancer Res.* 2018, 8, 2005–2019. [PubMed]

32. Ferreira, R.G.; Narvaez, L.E.M.; Espindola, K.M.M.; Rosario, A.C.R.S.; Lima, W.G.N.; Monteiro, M.C. Can Nimesulide Nanoparticles Be a Therapeutic Strategy for the Inhibition of the KRAS/PTEN Signaling Pathway in Pancreatic Cancer? *Front. Oncol.* 2021, 11, 2647. [CrossRef] [PubMed]

33. Porta, F.; Lamers, G.E.; Morrhayim, J.; Chatzopoulou, A.; Schaaf, M.; den Dulk, H.; Backendorf, C.; Zink, J.I.; Kros, A. Folic acid-modified mesoporous silica nanoparticles for cellular and nuclear targeted drug delivery. *Adv. Healthc. Mater.* 2013, 2, 281–286. [CrossRef] [PubMed]

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

35. Knežević, N.Z.; Jean-Olivier, D. Targeted Treatment of Cancer with Nanotherapeutics Based on Mesoporous Silica Nanoparticles. *ChemPlusChem* 2015, 80, 26–36. [CrossRef]

36. Mekaru, H.; Lu, J.; Tamanoi, F. Development of mesoporous silica-based nanoparticles with controlled release capability for cancer therapy. *Adv. Drug Deliv. Rev.* 2015, 95, 40–49. [CrossRef]

37. Xia, T.; Kovochich, M.; Liong, M.; Meng, H.; Kabehie, S.; George, S.; Zink, J.I.; Nel, A.E. Polyethyleneimine coating enhances the cellular uptake of mesoporous silica nanoparticles and allows safe delivery of siRNA and DNA constructs. *ACS Nano* 2009, 3, 3273–3286. [CrossRef]
38. Chen, J.; Luo, H.; Liu, Y.; Zhang, W.; Li, H.; Luo, T.; Zhang, K.; Zhao, Y.; Liu, J. Oxygen-Self-Produced Nanoplatform for Relieving Hypoxia and Breaking Resistance to Sonodynamic Treatment of Pancreatic Cancer. *ACS Nano* 2017, 11, 12849–12862. [CrossRef]

39. Lu, J.; Li, Z.; Zink, J.J.; Tamanoi, F. In vivo tumor suppression efficacy of mesoporous silica nanoparticles-based drug-delivery system: Enhanced efficacy by folate modification. *Nanomedicine* 2012, 8, 212–220. [CrossRef]

40. Meng, H.; Zhao, Y.; Dong, J.; Xue, M.; Lin, Y.S.; Ji, Z.; Mai, W.X.; Zhang, H.; Chang, C.H.; Brinker, C.J.; et al. Two-wave nanotherapy to target the stroma and optimize gemcitabine delivery to a human pancreatic cancer model in mice. *ACS Nano* 2013, 7, 10048–10065. [CrossRef]

41. Chen, W.; Cheng, C.A.; Zink, J.J. Spatial, Temporal, and Dose Control of Drug Delivery using Noninvasive Magnetic Stimulation. *ACS Nano* 2019, 13, 1292–1308. [CrossRef] [PubMed]

42. Seeta Rama Raju, G.; Pavitra, E.; Nagaraju, G.P.; Ramesh, K.; El-Rayes, B.F.; Yu, J.S. Imaging and curcumin delivery in pancreatic cancer cell lines using PEGylated alpha-Gd2(MO4)3 mesoporous particles. *Dalton Trans.* 2014, 43, 3330–3338. [CrossRef] [PubMed]

43. Gao, F.; Wu, F.; Niu, S.; Sun, T.; Li, F.; Bai, Y.; Jin, L.; Lin, L.; Shi, Q.; Zhu, L.M.; et al. Biodegradable, pH-Sensitive Hollow Mesoporous Organosilica Nanoparticle (HMON) with Controlled Release of Pirfenidone and Ultrasound-Target-Microbubble-Destruction (UTMD) for Pancreatic Cancer Treatment. *Theranostics* 2019, 9, 6002–6018. [CrossRef] [PubMed]

44. Er, Ö.; Colak, S.G.; Oacakoglu, K.; Ince, M.; Bresoli-Obach, R.; Mora, M.; Sagristà, M.L.; Yurt, F.; Nonell, S. Selective Photokilling of Human Pancreatic Cancer Cells Using Cetuximab-Targeted Mesoporous Silica Nanoparticles for Delivery of Zinc Phthalocyanine. *Molecules* 2018, 23, 2749. [CrossRef]

45. Poostforooshan, J.; Belbekhouche, S.; Shaban, M.; Alphonse, V.; Habert, D.; Bousserrhine, N.; Courty, J.; Weber, A.P. Aerosol-Assisted Synthesis of Tailor-Made Hollow Mesoporous Silicon Microspheres for Controlled Release of Antibacterial and Anticancer Agents. *ACS Appl. Mater. Interfaces* 2020, 12, 6885–6898. [CrossRef] [PubMed]

46. Saini, K.; Bandypadhyayya, R. Transferrin-Conjugated Polymer-Coated Mesoporous Silica Nanoparticles Loaded with Gemcitabine for Killing Pancreatic Cancer Cells. *ACS Appl. Nano Mater.* 2020, 3, 229–240. [CrossRef]

47. RS, P.; Mal, A.; Valvi, S.K.; Srivastava, R.; De, A.; Bandypadhyayya, R. Noninvasive Preclinical Evaluation of Targeted Nanoparticles for the Delivery of Curcumin in Treating Pancreatic Cancer. *ACS Appl. Bio. Mater.* 2020, 3, 4643–4654. [CrossRef]

48. Tarannum, M.; Hessain, A.M.; Holmes, B.; Yan, S.; Mukherjee, P.; Vivero-Escoto, J.L. Advanced Nanoengineering Approach for Target-Specific, Spatiotemporal, and Ratiometric Delivery of Gemcitabine-Cisplatin Combination for Improved Therapeutic Outcome in Pancreatic Cancer. *Small* 2021, e2104449. [CrossRef] [PubMed]

49. Er, O.; Tuncel, A.; Oacakoglu, K.; Ince, M.; Kolatan, E.H.; Yilmaz, O.; Aktaş, S.; Yurt, F. Radiolabeling, In Vitro Cell Uptake, and In Vivo Photodynamic Therapy Potential of Targeted Mesoporous Silica Nanoparticles Containing Zinc Phthalocyanine. *Mol. Pharm.* 2020, 17, 2648–2659. [CrossRef]

50. Slapak, E.J.; Kong, L.; El Mandilli, M.; Nieuwland, R.; Kros, A.; Bijlsma, M.F.; Spek, C.A. ADAM9-Responsive Mesoporous Silica Nanoparticles for Targeted Drug Delivery in Pancreatic Cancer. *Cancers* 2021, 13, 3321. [CrossRef]

51. Fu, Q.; Hargrove, D.; Lu, X. Improving paclitaxel pharmacokinetics by using tumor-specific mesoporous silica nanoparticles with intraperitoneal administration. *Nanomed. Nanotechnol. Biol. Med.* 2016, 12, 1951–1959. [CrossRef]

52. Zhang, K.; Xu, H.; Chen, H.; Jia, X.; Zheng, S.; Cai, X.; Wang, R.; Mou, J.; Zheng, Y.; Shi, J. CO2 bubbling-based ‘Nanobomb’ System for Targetedly Suppressing Panc-1 Pancreatic Tumor via Low Intensity Ultrasound-activated Inertial Cavitation. *Theranostics* 2015, 5, 1291–1302. [CrossRef] [PubMed]

53. Estevão, B.M.; Comparetti, E.J.; Rissi, N.C.; Zucolotto, V. Anti-GPI-CD1-modified mesoporous silica nanoparticles as nanocarriers for combination therapy and targeting of PANC-1 cells. *Mater. Adv.* 2021, 2, 5224–5235. [CrossRef]

54. Gurka, M.K.; Fender, D.; Chuong, P.; Fouts, B.L.; Sobolov, A.; McNally, M.W.; Mezera, M.; Woo, S.Y.; McNally, L.R. Identification of pancreatic tumors in vivo with ligand-targeted, pH-responsive mesoporous silica nanoparticles by multispectral optoacoustic tomography. *J. Control. Release* 2016, 231, 60–67. [CrossRef] [PubMed]

55. Cong, V.T.; Tilley, R.D.; Sharbeen, G.; Phillips, P.A.; Gaus, K.; Gooding, J.J. How to exploit different endocytosis pathways to allow selective delivery of anticancer drugs to cancer cells over healthy cells. *Chem. Sci.* 2021, 12, 15407–15417. [CrossRef]

56. Muhammad, F.; Guo, M.; Wang, A.; Zhao, J.; Qi, W.; Guo, Y.; Zhu, G. Responsive delivery of drug cocktail via mesoporous silica nanolamps. *J. Colloid Interface Sci.* 2014, 434, 1–8. [CrossRef] [PubMed]

57. Lu, J.; Liong, M.; Sherman, S.; Xia, T.; Kovochich, M.; Nel, A.E.; Zink, J.I.; Tamanoi, F. Mesoporous Silica Nanoparticles for Cancer Therapy: Energy-Dependent Cellular Uptake and Delivery of Paclitaxel to Cancer Cells. *Nanobiotechnology* 2007, 3, 89–95. [CrossRef]

58. Meng, H.; Wang, M.; Liu, H.; Liu, X.; Sittu, A.; Wu, B.; Ji, Z.; Chang, C.H.; Nel, A.E. Use of a lipid-coated mesoporous silica nanoparticle platform for synergistic gemcitabine and paclitaxel delivery to human pancreatic cancer in mice. *ACS Nano* 2015, 9, 3540–3557. [CrossRef] [PubMed]

59. Ji, Y.; Liu, X.; Li, J.; Xie, X.; Huang, M.; Jiang, J.; Liao, Y.P.; Donahue, T.; Meng, H. Use of ratiometrically designed nanocarrier targeting CDK4/6 and autophagy pathways for effective pancreatic cancer treatment. *Nat. Commun.* 2020, 11, 4249. [CrossRef]

60. Feng, Z.; Meng, H. Efficient nano-enabled therapy for gastrointestinal cancer using silicasome delivery technology. *Sci. China Chem.* 2021, 64, 1946–1957. [CrossRef]
61. Zheng, Y.; Fahrenholtz, C.D.; Hackett, C.L.; Ding, S.; Day, C.S.; Dhall, R.; Marrs, G.S.; Gross, M.D.; Singh, R.; Bierbach, U. Large-Pore Functionalized Mesoporous Silica Nanoparticles as Drug Delivery Vector for a Highly Cytotoxic Hybrid Platinum-Acridine Anticancer Agent. *Chemistry 2017*, 23, 3386–3397. [CrossRef] [PubMed]

62. Liu, X.; Lin, P.; Perrett, J.; Lin, J.; Liao, Y.P.; Chang, C.H.; Jiang, J.; Wu, N.; Donahue, T.; Wainberg, Z.; et al. Tumor-penetrating peptide enhances transcytosis of silicasome-based chemotherapy for pancreatic cancer. *J. Clin. Investig. 2017*, 127, 2007–2018. [CrossRef] [PubMed]

63. Liu, X.; Jiang, J.; Chang, C.H.; Liao, Y.P.; Lodico, J.J.; Tang, I.; Zheng, E.; Qiu, W.; Lin, M.; Wang, X.; et al. Development of Facile and Versatile Platinum Drug Delivering Silicasome Nanocarriers for Efficient Pancreatic Cancer Chemo-Immunotherapy. *Small 2021*, 17, e2005993. [CrossRef]

64. Liu, X.; Jiang, J.; Liao, Y.P.; Tang, I.; Zheng, E.; Qiu, W.; Lin, M.; Wang, X.; Ji, Y.; Mei, K.C.; et al. Combination Chemo-Immunotherapy for Pancreatic Cancer Using the Immunogenic Effects of an Irinotecan Silicasome Nanocarrier Plus Anti-PD-1. *Adv. Sci. 2021*, 8, 2002147. [CrossRef] [PubMed]

65. Liu, X.; Situ, A.; Kang, Y.; Villabroza, K.R.; Liao, Y.; Chang, C.H.; Donahue, T.; Nel, A.E.; Meng, H. Irinotecan Delivery by Lipid-Coated Mesoporous Silica Nanoparticles Shows Improved Efficacy and Safety over Liposomes for Pancreatic Cancer. *ACS Nano 2016*, 10, 2702–2715. [CrossRef]

66. Liu, X.; Jiang, J.; Chan, R.; Ji, Y.; Lu, J.; Liao, Y.P.; Okene, M.; Lin, J.; Lin, P.; Chang, C.H.; et al. Improved Efficacy and Reduced Toxicity Using a Custom-Designed Irinotecan-Delivering Silicasome for Orthotopic Colon Cancer. *ACS Nano 2019*, 13, 38–53. [CrossRef]

67. Thapa, R.K.; Nguyen, H.T.; Gautam, M.; Shrestha, A.; Lee, E.S.; Ku, S.K.; Choi, H.G.; Yong, C.S.; Kim, J.O. Hydrophobic binding peptide-conjugated hybrid lipid-mesoporous silica nanoparticles for effective chemo-photothermal therapy of pancreatic cancer. *Drug Deliv. 2017*, 24, 1690–1702. [CrossRef]

68. Lu, J.; Liu, J.; Liao, Y.P.; Salazar, F.; Sun, B.; Jiang, W.; Chang, C.H.; Jiang, J.; Wang, X.; Wu, A.M.; et al. Nano-enabled pancreas cancer immunotherapy using immunogenic cell death and reversing immunosuppression. *Nat. Commun. 2017*, 8, 1811. [CrossRef]

69. Xing, L.; Li, X.; Xing, Z.; Li, F.; Shen, M.; Wang, H.; Shi, X.; Du, L. Silica/gold nanoplateform combined with a thermosensitive gel for imaging-guided interventional therapy in PDX of pancreatic cancer. *Chem. Eng. J. 2020*, 382, 122949. [CrossRef]

70. Zhao, R.; Han, X.; Li, Y.; Wang, H.; Ji, T.; Zhao, Y.; Nie, G. Photothermal Effect Enhanced Cascade-Targeting Strategy for Improved Pancreatic Cancer Therapy by Gold Nanoshell@Mesoporous Silica Nanorod. *ACS Nano 2017*, 11, 8103–8113. [CrossRef]

71. Roy, I. Gold Nanoparticle-Enhanced Photodynamic Therapy from Photosensitiser-Entrapped Ormosil Nanoparticles. *J. NanoSci. Nanotechnol. 2019*, 19, 6942–6948. [CrossRef] [PubMed]

72. Zeiderman, M.R.; Morgan, D.E.; Christein, J.D.; Grizzle, W.E.; McMasters, K.M.; McNally, L.R. Acidic pH-targeted chitosan capped mesoporous silica coated gold nanorods facilitate detection of pancreatic tumors via multispectral optoacoustic tomography. *ACS Biomater Sci. Eng. 2016*, 2, 1108–1120. [CrossRef] [PubMed]

73. Ren, S.; Yang, J.; Ma, L.; Li, X.; Wu, W.; Liu, C.; He, J.; Miao, L. Ternary-Responsive Drug Delivery with Activatable Dual Mode Contrast-Enhanced in Vivo Imaging. *ACS Appl. Mater. Interfaces 2018*, 10, 31947–31958. [CrossRef] [PubMed]

74. Ferreira, B.; Martel, F.; Silva, C.; Santos, T.M.; Daniel-da-Silva, A.L. Nanostructured functionalized magnetic platforms for the sustained delivery of cisplatin: Synthesis, characterization and in vitro cytotoxicity evaluation. *J. Inorg BioChem. 2020*, 213, 111258. [CrossRef] [PubMed]

75. Li, Y.; Tang, Y.; Chen, S.; Liu, Y.; Wang, S.; Tian, Y.; Wang, C.; Teng, Z.; Lu, G. Sequential therapy for pancreatic cancer by losartan- and gemcitabine-loaded magnetic mesoporous spheres. *Adv. Sci. 2019*, 6, 19690–19698. [CrossRef] [PubMed]

76. Wang, A.; Qi, W.; Wang, N.; Zhao, J.; Muhammad, F.; Cai, K.; Ren, H.; Sun, F.; Chen, L.; Guo, Y.; et al. A smart nanoporous theranostic platform for simultaneous enhanced MRI and drug delivery. *Microporous Mesoporous Mater. 2013*, 180, 1–7. [CrossRef]

77. Sun, J.; Kim, D.H.; Guo, Y.; Teng, Z.; Li, Y.; Zheng, L.; Zhang, Z.; Larson, A.C.; Lu, G. A c(RGDfE) conjugated multi-functional nanomedicine delivery system for targeted pancreatic cancer therapy. *J. Mater. Chem. B 2015*, 3, 1049–1058. [CrossRef]

78. Loc, W.S.; Linton, S.S.; Wilczynski, Z.R.; Matters, G.L.; McGovern, C.O.; Abraham, T.; Fox, T.; Gigliotti, C.M.; Tang, X.; Tabakovic, A.; et al. Effective encapsulation and biological activity of phosphorylated chemotherapeutics in calcium phosphosilicate nanoparticles for the treatment of pancreatic cancer. *Nanomedicine 2017*, 13, 2313–2324. [CrossRef]

79. Zhang, J.; Yuan, Z.F.; Wang, Y.; Chen, W.H.; Luo, G.F.; Cheng, S.X.; Zhuo, R.X.; Zhang, X.Z. Multifunctional envelope-type mesoporous silica nanoparticles for tumor-triggered targeting drug delivery. *J. Am. Chem. Soc. 2013*, 135, 5068–5073. [CrossRef]

80. Morelli, C.; Maris, P.; Sisci, D.; Perrotta, E.; Brunelli, E.; Perrotta, I.; Panno, M.L.; Tagarelli, A.; Versace, C.; Casula, M.F.; et al. PEG-templated mesoporous silica nanoparticles exclusively target cancer cells. *Nanoscale 2011*, 3, 3198–3207. [CrossRef] [PubMed]

81. Lebret, V.; Raehm, L.; Durand, J.O.; Smalhi, M.; Werts, M.H.; Blanchard-Desce, M.; Methy-Gonnod, D.; Dubernet, C. Folic acid-targeted mesoporous silica nanoparticles for two-photon fluorescence. *J. Biomed. Nanotechnol. 2010*, 6, 176–180. [CrossRef] [PubMed]

82. Yin, F.; Zhang, B.; Zeng, S.; Lin, G.; Tian, J.; Yang, C.; Wang, K.; Xu, G.; Yong, K.T. Folic acid-conjugated organically modified silica nanoparticles for enhanced targeted delivery in cancer cells and tumor in vivo. *J. Mater. Chem. B 2015*, 3, 6081–6093. [CrossRef]

83. Kumar, R.; Roy, I.; Ohulchanskyy, T.Y.; Goswami, L.N.; Bonou, A.C.; Bergey, E.J.; Trampusch, K.M.; Maitra, A.; Prasad, P.N. Covalently dye-linked, surface-controlled, and bioconjugated organically modified silica nanoparticles as targeted probes for optical imaging. *ACS Nano 2008*, 2, 449–456. [CrossRef] [PubMed]
84. MacCuaig, W.M.; Fouts, B.L.; McNally, M.W.; Grizzle, W.E.; Chuong, P.; Samykutty, A.; Mukherjee, P.; Li, M.; Jasinski, J.B.; Behkam, B.; et al. Active Targeting Significantly Outperforms Nanoparticle Size in Facilitating Tumor-Specific Uptake in Orthotopic Pancreatic Cancer. *ACS Appl. Mater. Interfaces* 2021, 13, 49614–49630. [CrossRef] [PubMed]

85. Liu, B.; Zhang, X.; Zou, X.; Cao, J.; Peng, Z. Biological Tissue Damage Monitoring Method Based on IMWPE and PNN during HIFU Treatment. *Information* 2021, 12, 404. [CrossRef]

86. Jameson, G.S.; Borazanci, E.; Babiker, H.M.; Poplin, E.; Niewiarowska, A.A.; Gordon, M.S.; Barrett, M.T.; Rosenthal, A.; Stoll-D’Astice, A.; Crowley, J.; et al. Response Rate Following Albumin-Bound Paclitaxel Plus Gemcitabine Plus Cisplatin Treatment Among Patients with Advanced Pancreatic Cancer: A Phase 1b/2 Pilot Clinical Trial. *JAMA Oncol.* 2019, 6, 125–132. [CrossRef]

87. Reni, M.; Zanon, S.; Balzano, G.; Passoni, P.; Pircher, C.; Chiaravalli, M.; Fugazza, C.; Ceranulo, D.; Nicoletti, R.; Arcidiacono, P.G.; et al. A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma. *Eur. J. Cancer* 2018, 102, 95–102. [CrossRef]

88. Giordano, A.; Tommonaro, G. Curcumin and Cancer. *Nutrients* 2019, 11, 2376. [CrossRef] [PubMed]

89. Bisht, S.; Mizuma, M.; Feldmann, G.; Ottenhof, N.A.; Hong, S.M.; Pramanik, D.; Chenna, V.; Karikari, C.; Sharma, R.; Goggins, M.G.; et al. Systemic administration of polymeric nanoparticle-encapsulated curcumin (NanoCurc) blocks tumor growth and metastases in preclinical models of pancreatic cancer. *Mol. Cancer* 2010, 9, 2255–2264. [CrossRef]

90. Khan, S.; Setua, S.; Kumari, S.; Dan, N.; Massey, A.; Hafeez, B.B.; Yallapu, M.M.; Stiles, Z.E.; Alabkaa, A.; Yue, J.; et al. Superparamagnetic iron oxide nanoparticles of curcumin enhance gemcitabine therapeutic response in pancreatic cancer. *Biomaterials* 2019, 208, 83–97. [CrossRef] [PubMed]

91. Khaing Oo, M.K.; Yang, Y.; Hu, Y.; Gomez, M.; Du, H.; Wang, H. Gold Nanoparticle-Enhanced and Size-Dependent Generation of Reactive Oxygen Species from Protoporphyrin IX. *ACS Nano* 2012, 6, 1939–1947. [CrossRef] [PubMed]

92. Hudson, D.E.; Hudson, D.O.; Wininger, J.M.; Richardson, B.D. Penetration of laser light at 808 and 980 nm in bovine tissue samples. *Photomed Laser Surg.* 2013, 31, 163–168. [CrossRef] [PubMed]

93. Janjua, T.I.; Cao, Y.; Yu, C.; Popat, A. Clinical translation of silica nanoparticles. *Nat. Rev. Mater.* 2021, 1–3. [CrossRef] [PubMed]