

# A Mini-Review of Diagnostic and Therapeutic Nano-Tools for Pancreatitis

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**Abstract:** Pancreatitis is an inflammatory reaction of pancreatic tissue digestion, edema, bleeding and even necrosis caused by activation of pancreatin due to various causes. In particular, patients with severe acute pancreatitis (SAP) often suffer from secondary infection, peritonitis and shock, and have a high mortality rate. Chronic pancreatitis (CP) can cause permanent damage to the pancreas. Due to the innate characteristics, structure and location of the pancreas, there is no effective treatment, only relief of symptoms. Especially, AP is an unpredictable and potentially fatal disease, and the timely diagnosis and treatment remains a major challenge. With the rapid development of nanomedicine technology, many potential tools can be used to address this problem. In this review, we have introduced the pathophysiological processes of pancreatitis to understanding its etiology and severity. Most importantly, the current progress in the diagnosis and treatment tools of pancreatitis based on nanomedicine is summarized and prospected.

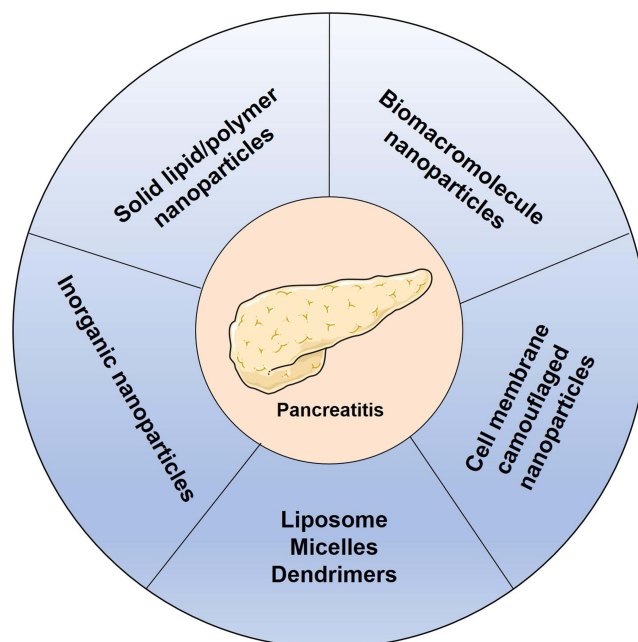
**Keywords:** pancreatitis, nanomedicine, diagnosis, therapy

## Introduction

Current pathology defines pancreatitis as a disease caused by the digestive action of trypsin, mainly divided into acute pancreatitis (AP) and chronic pancreatitis (CP), which is characterized by varying degrees of edema, bleeding, and acinar and associated pancreatic tissue necrosis.<sup>1-4</sup> The pathogenesis of AP have been extensively reported but remain unclear.<sup>5</sup> Gallstones, excessive alcohol intake, drug-induced injury, hypercalcemia, infection, genetics, and autoimmunity can all be listed as risk factors.<sup>6</sup>

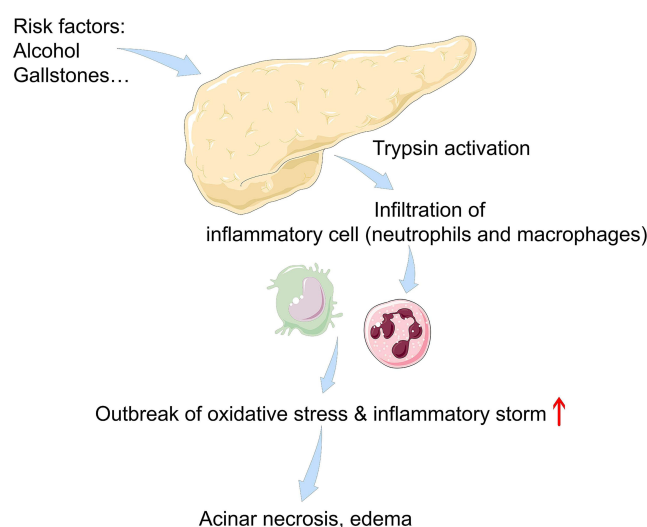
AP is characterized by mis-activation and release of trypsinogen that triggers the activation of other digestive enzymes, leading to self-digestion of pancreatic tissue (Figure 1). Mild acute pancreatitis (MAP) when limited inflammation and organ dysfunction are present.<sup>7</sup> However, when the inflammation expands to the surrounding organs, it evolves into severe acute pancreatitis (SAP), which not only leads to pancreatic necrosis, but also easily leads to multiple organ failure and sepsis. Despite the great advances in intensive care medicine over the past few decades, the mortality rate for patients with SAP is still about 30%.<sup>8</sup> As the glands are gradually replaced by fibrotic tissue, the glands and ducts atrophy and calcification of proteins in the interstitial tissue and glands and ducts leads to partial or complete obstruction, making pancreatitis prone to progressive progression.<sup>9</sup> According to statistics, up to 20% of patients with AP will develop to CP.<sup>10</sup> Notably, CP can lead to inflammation, fibrosis, and scarring, which can permanently damage pancreatic tissue and function.<sup>9</sup> Unfortunately, early diagnosis of CP is difficult due to the lack of typical blood, imaging, or functional biomarkers. Diagnostic tools available include risk factors, clinical history, imaging, and pancreatic function tests. In addition, no specific therapy has been identified to date. The current focus of treatment for CP is to improve quality of life by relieving symptoms. For example, quitting smoking and alcohol or taking non-opioid and

## Graphical Abstract



opioid pain relievers for pain. Surgery is performed when there are morphological problems such as catheter abnormalities.

Nanotechnology has been widely used in the field of biomedicine, which has made rapid progress in the prevention, diagnosis and treatment of diseases.<sup>11</sup> Nanomedicine focusing on the application of nanotechnology in diagnostics, therapeutics, and drug delivery systems throughout the biomedicine field.<sup>12–14</sup> Nanomedicine include nanoparticles, micelles, liposomes and other carriers with drug loading capability, as well as nano-scale drugs composed of some active substances themselves. Nanomedicine have smaller size and larger specific surface area, the ability to load drugs and the unique property that the surface can be modified with other structures.<sup>15</sup> It can be used to improve the effectiveness,



**Figure I** The molecular and cellular events in acute pancreatitis.

safety, physicochemical properties and pharmacokinetics or pharmacodynamics of drugs. Functionalized nanomedicines have the characteristics of improving the bioavailability of oral drugs in vivo, prolonging the half-life of injectable drugs by reducing immunogenicity, and realizing targeted drug delivery. The use of nanomedicines to treat diseases can reduce the frequency of drug administration, improve the pharmacological effects of drugs and minimize the side effects of drugs, thereby showing better clinical treatment effects and treatment compliance. In addition, nanomedicine can also actively or passively deliver drugs to the target site, which is conducive to the accumulation of drugs in inflammation or tumor microenvironment, so as to play a better therapeutic effect.<sup>16</sup>

This review summarizes the application research trends of nanomedicine in pancreatitis from two aspects of treatment and diagnosis, hoping to provide a reference for the research of new nanomedicine for pancreatitis.

## Nanomedicine-Based Therapeutic Strategy of Pancreatitis

Nanotechnology has emerged as the most promising approach to pharmaceuticals. The term “nanomedicine” has been defined as regulators take a close look at nano-systems.<sup>17</sup> For example, Doxil (liposomal doxorubicin), Myocet (non-pegylated liposomal doxorubicin), Abraxane (Albumin-based paclitaxel nanoparticles), Genexol-PM (paclitaxel micelles), Marqibo (liposomal vincristine sulfate) are already approved.<sup>18</sup> Currently, commercial formulations for pancreatic disease (pancreatic cancer) are Abraxane and Onivyde (liposomal irinotecan).<sup>18</sup>

We know that delivering drugs to the pancreas has some difficulties. Both the pancreas-specific targeting ability and the ability to cross the blood-pancreatic barrier (BPB) need to be improved.<sup>19</sup> In addition, trypsin inhibitors are mostly peptides with short half-life, which affects the therapeutic effect of pancreatitis.<sup>20</sup> Finally, the harsh tissue microenvironment of patients also affects drug release and pharmacological activity.<sup>21</sup>

In theory, targeting can be achieved by passive or active targeting approach, which can increase many drugs targeted to the tissue to improve the therapeutic effect. For pancreatitis, passive targeting can be achieved through various abnormal biochemical signals (pH value, reactive oxygen species, abundant digestive enzymes, etc.) and tissue space with enhanced permeability.<sup>22</sup> Active targeting can be achieved by specifically targeting overexpressed receptors at the site of inflammation.<sup>23</sup> The following is a review of the development of early diagnosis and targeted therapy for pancreatitis based on nanomedicine from the perspective of different kinds of nanoparticles.

## Solid Lipid and Polymer Nanoparticles

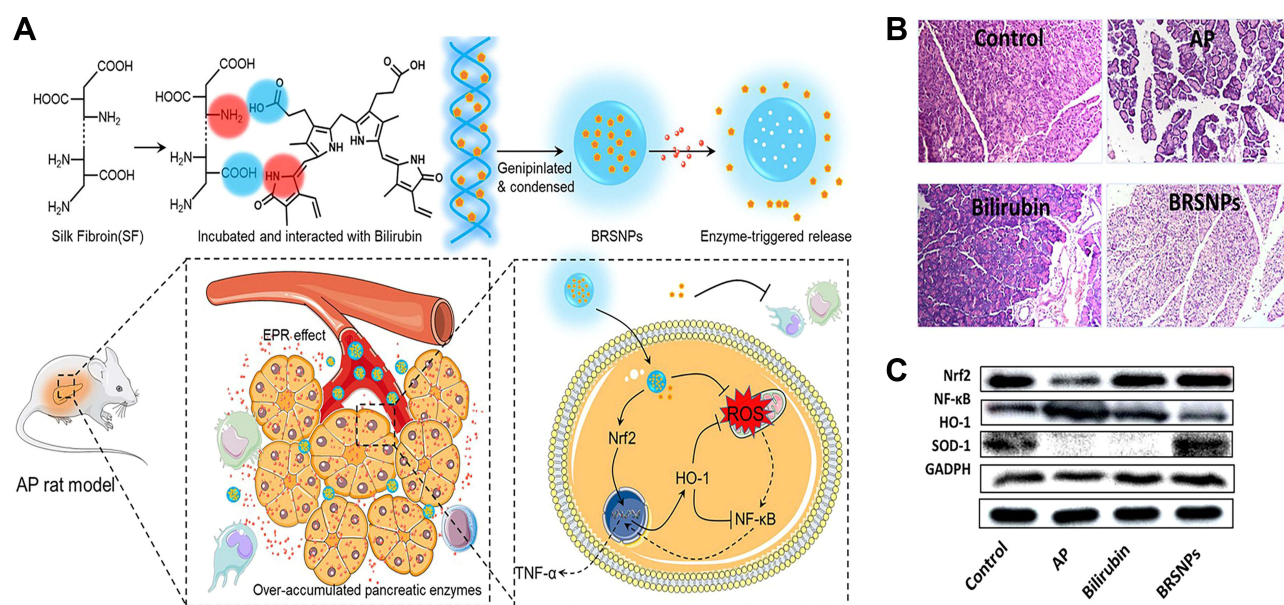
Lipid or polymeric nanoparticles are the most widely studied in the field of nanomedicine.<sup>24</sup> Not surprisingly, these materials have also been used as nanocarriers in the treatment of pancreatitis. For example, Cervin's group used lipid liquid crystal materials to load somatostatin, a peptide hormone with the potential to treat pancreatitis.<sup>25</sup> The nano-somatostatin can increase the effective half-life of this peptide from a few minutes to 1 hour, effectively eliminating its clinical application.

Moreover, polymeric nanoparticles with suitable and tunable particle size range have the effect of extravasation across leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS effect).<sup>26</sup> A growing number of studies exploit the ELVIS effect to enable passive targeting of nanoparticles to sites of inflammation and reduced systemic toxicity.<sup>27–30</sup> In pancreatitis, the nanoparticles with ELVIS effect has shown promise. For example, Yang et al developed a PLGA nanoparticles (CQ/pDNA/PLGA NPs), which co-loaded chloroquine diphosphate (CQ) and pDNA, to achieve targeted delivery to tumors and pancreatitis.<sup>31</sup> In this study, pDNA compacted by CQ was embedded into PLGA nanoparticles. The CQ/pDNA/PLGA NPs not only improved the transfection efficiency but also enhanced the targeting efficiency of CT26 transplanted tumor. More importantly, CQ/pDNA/PLGA NPs showed excellent targeting ability in *L*-arginine-induced AP model in mice. Impressively, after the first report on PLGA-based AP targeting, the same research group further reported a tamoxifen-loaded PLGA nanoparticles (TAM-NPs) in combination with CQ-loaded liposomes (CQ-LPs) in 2022.<sup>32</sup> The follow-up experiment proved that combination therapy achieved relief of AP and even SAP by upregulating IDO signaling pathways in bone marrow derived mesenchymal stem cells. The above two examples illustrated the ELVIS effect of PLGA NPs and their easy uptake by pancreatic macrophages and neutrophils, enabling this kind of delivery system with high therapeutic effect in AP. This property of being taken up by macrophages has also been applied in the precision therapy of pancreatic cancer.<sup>33</sup>

## Biomacromolecule Nanoparticles

Compared with artificial lipids and synthetic polymers, biological macromolecules (such as proteins, nucleic acids, etc.) have obvious advantages in terms of biocompatibility and safety.<sup>34</sup> In addition, some proteins have clear sensitivity to up-regulated amylase, proteases and lipases in pancreatitis lesions, and can be used as responsive drug carriers to achieve effective passive targeting of pancreatitis lesions.<sup>35</sup> As shown in Figure 2, Zhao et al developed a primary three-dimensional (3D) structure similar to DNA double helix with bilirubin using silk fibroin as a carrier with the help of multiple intermolecular forces (hydrogen bonds, hydrophobic forces), and collapsed into nanoparticles (BRSNPs).<sup>36</sup> In vivo imaging experiments showed that BRSNPs were more efficiently enriched in pancreatic tissue, enabling passive targeting. In acinar cells model and *L*-arginine-induced rat AP model, BRSNPs can release bilirubin under the action of excessive pancreatic enzymes (trypsin) at the AP site. Bilirubin not only directly inhibited cellular mitochondrial ROS generation, but also activated the Nrf2 pathway, increased HO-1, and then inhibited the pro-inflammatory NF- $\kappa$ B signaling pathway. BRSNPs effectively reduced the levels of various serum biomarkers, including amylase, alanine aminotransferase, aspartate aminotransferase, creatinine, urea nitrogen, etc. It alleviated the oxidative stress state and lipid oxidation of pancreatic tissues, inhibited edema and fibrosis, and finally achieved better AP relief effect than somatostatin or free bilirubin positive treatment group.

In addition, endogenous macromolecules are also ideal carriers. It is known that although carbon monoxide (CO) has anti-inflammatory and antioxidant activities, its potential therapeutic ability for AP is limited in its use in inflammation-related diseases due to disadvantages of toxicity and non-specific distribution.<sup>37</sup> However, a blessing in disguise, exploiting the natural binding ability of hemoglobin to CO, Maruyama et al developed a CO-bound hemoglobin vesicles (CO-HbV).<sup>38</sup> The authors established a choline-deficient ethionine-supplemented diet-induced SAP mice model. Compared with saline or HbV treatment, CO-HbV obviously attenuated the death of SAP mice. By inhibiting systemic proinflammatory cytokine production, neutrophil infiltration, and oxidative stress status, CO-HbV significantly suppresses AP severity. Notably, the SAP mice also developed secondary multiple organ damage. Interestingly, CO-HbV may be due to inhibition of neutrophil infiltration and oxidative stress damage, as well as moderating multiple organ failure.



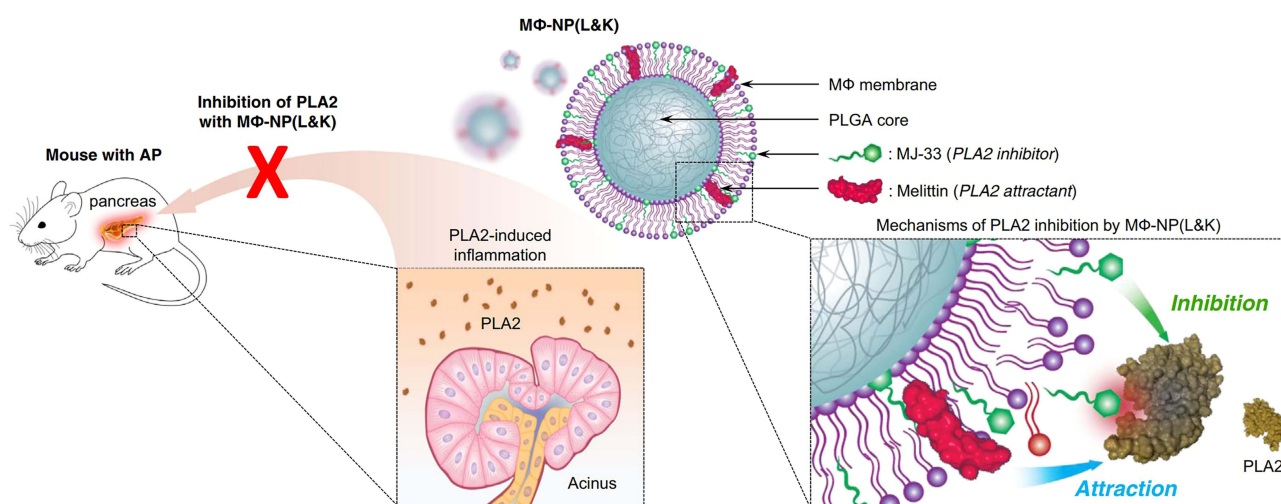
**Figure 2** (A) Schematic diagram of preparation, targeting and mechanism of bilirubin nanomedicine (BRSNPs). (B) H&E staining sections of pancreatic tissue after BRSNPs treatment. (C) BRSNPs activated Nrf2 signaling pathway, up-regulated SOD-1, and ultimately inhibited the expression level of HO-1 and NF- $\kappa$ B. Reproduced from Yao Q, Jiang X, Zhai YY, et al. Protective effects and mechanisms of bilirubin nanomedicine against acute pancreatitis. *J Control Release*. 2020;322:312–325. Copyright 2020, with permission from Elsevier.<sup>36</sup>



In addition to macromolecules such as proteins, nucleic acid is also a qualified carrier construction material.<sup>39–41</sup> For example, tetrahedral framework nucleic acids, so-called tFNAs, is reported as an emerging class of nanoparticles.<sup>42</sup> In briefly, tFNAs are self-assembled from four single-stranded DNA (ssDNA) with a three-dimensional cage-like structure.<sup>43,44</sup> Recent literature indicated that tFNAs can regulate cell behaviors such as cell proliferation, migration, and autophagy.<sup>45</sup> The tFNAs have also been shown to have excellent anti-inflammatory and anti-apoptotic effects and have been used to treat a variety of diseases: including acute kidney injury,<sup>46</sup> periodontitis,<sup>47,48</sup> diabetes,<sup>49,50</sup> and Sjögren's syndrome.<sup>51</sup> Surprisingly, Yunfeng Lin's team found that tFNAs can inhibit SAP by inhibiting the expression of inflammatory factors in tissues and blood, and at the same time regulating the expression of anti-apoptotic proteins. In addition, tFNA can also inhibit the typical inflammatory manifestations through lymphocyte infiltration, thereby protecting multiple organs such as pancreas, lung, liver and kidney.<sup>52</sup>

## Cell Membrane Camouflaged Nanoparticles

As mentioned above, bio-macromolecular nanoparticles have shown good application effects, which suggested that biomimetic nanoparticles have unique advantages.<sup>53,54</sup> Cell membrane camouflaged nanoparticles (CMCNPs) are a kind of “Trojan”-like strategy, which is a hot research direction of biomimetic nanomedicine in recent years.<sup>55</sup> Briefly, the partial or complete membrane of specific cells is extracted and wrapped on the surface of various nanoparticles, so that the nanoparticles inherit some specific functions derived from cells, such as biological activity, homing effect, etc.<sup>55</sup> Numerous literatures have reported that CMCNPs can be used as excellent therapeutic drug carriers, diagnostic reagent carriers, etc., through the natural homing effect of specific cell membranes on the corresponding lesions, to achieve precise treatment of diseases.<sup>56–58</sup> We know that pancreatitis is a serious inflammatory disease, and there are a large number of inflammatory cells infiltrating the lesions, such as neutrophils and macrophages.<sup>59</sup> In view of this, Li Deng's group developed a neutrophil membrane-covered PEG-PLGA nanoparticles (NNPs).<sup>60</sup> This study found that NNPs can more effectively penetrate the BPB and specifically distribute into pancreatic tissue compared with NPs without cell membrane. Compared with free celastrol (CLT) and NNPs/CLT treatment groups, NNPs/CLT significantly down-regulated serum amylase and myeloperoxidase levels in AP rats. In addition, the use of NNPs also attenuated the systemic toxicity of CLT. Not only that, in vitro imaging experiments also demonstrated that NNPs can be enriched in the lung tissue of AP mice, which is due to a large number of neutrophil infiltration during AP-induced lung injury. Similarly, it has been reported that silk fibroin nanoparticles can precisely deliver the antioxidant ferulic acid to the pancreas after being coated with neutrophil membranes.<sup>61</sup>



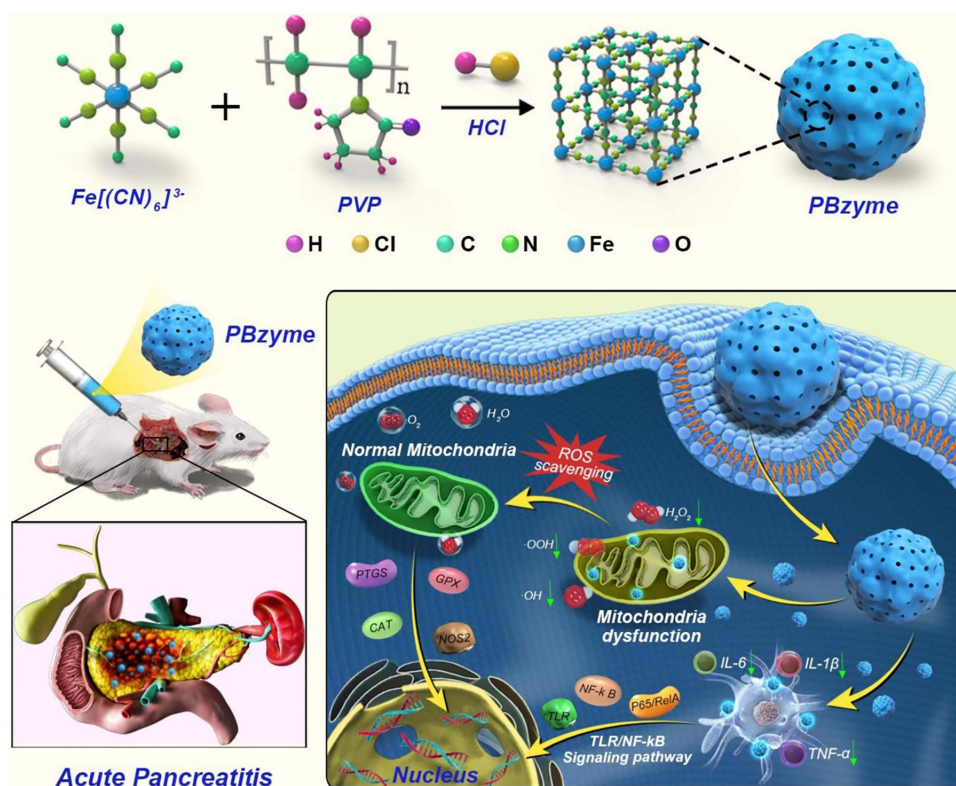
**Figure 3** Macrophage membrane camouflaged PLGA nanoparticles, called as MΦ-NP(L&K), co-loading attractant (Melittin) and inhibitor (MJ-33) of PLA2 to achieve targeted therapy of AP mice. Reproduced from Zhang Q, Zhou J, Zhou J, Fang RH, Gao W, Zhang L. Lure-and-kill macrophage nanoparticles alleviate the severity of experimental acute pancreatitis. *Nat Commun.* 2021;12:4136. Copyright 2021, the Authors. Springer Nature. Creative Commons CC BY.<sup>65</sup>

Meanwhile, macrophage infiltration is also a common and important pathological process of pancreatitis.<sup>62</sup> Macrophages appear to be a negative factor in the progression of pancreatitis because of excessive recruitment and release of proinflammatory factors.<sup>63,64</sup> As in Figure 3, Liangfang Zhang's group used autologous macrophage membrane to coating PLGA nanoparticles, supplemented with phospholipase A2 (PLA2) attractant (Melittin) and inhibitor (MJ-33), and prepared a kind of "Lure-and-Kill" macrophage-like nanoparticles (MΦ-NP(L&K)).<sup>65</sup> The MΦ-NP(L&K) can significantly reduce the expression levels of serum markers (including PLA2, IL-6, TNF- $\alpha$ , IL-1 $\beta$ ) in the MAP mouse model, relieve the edema of pancreatic tissue, and reduce the number of necrotic pancreatic acinar cells. Significantly decreased, reducing the degree of infiltration of CD45-positive lymphocytes in pancreatic tissue. On SAP mice, MΦ-NP (L&K) also achieved excellent therapeutic effect. Moreover, M-NP(L&K) has also been confirmed to have good biocompatibility in vitro and in vivo, which is also the unique advantage of this type of CMCNPs.

## Inorganic Nanoparticles

For inflammatory diseases, exogenous materials with antioxidant capacity that mimic endogenous enzymes.<sup>66</sup> Inorganic nanoparticles are generally smaller in particle size and narrower in size distribution than polymer/lipid nanoparticles, and their surface chemistry is also well suited for ligand conjugation. Therefore, artificial enzymes are the best candidates for treating dysregulated redox homeostasis.<sup>67–69</sup>

Hu et al reported that a polyvinylpyrrolidone-stabilized MoSe<sub>2</sub> nanoparticle (MoSe<sub>2</sub>-PVP NPs) could be easily prepared.<sup>70</sup> The MoSe<sub>2</sub>-PVP NPs effectively simulates various natural enzymes, and eliminates free radicals such as  $\bullet$ OH,  $\bullet$ O<sub>2</sub><sup>-</sup> and 3-ethylbenzothiazoline-6-sulfonic acid. MoSe<sub>2</sub>-PVP NPs significantly increased the survival probability of cells in H<sub>2</sub>O<sub>2</sub> and had a significant protective effect on AP animal models.<sup>70</sup> Another example, Prussian blue, as an ancient dye, is a clinical antidote for radioactive element poisoning such as thallium. Prussian blue nanoparticles (PB



**Figure 4** Prussian blue nanoparticles prepared by PVP stabilized  $\text{Fe}[(\text{CN})_6]^{3-}$ . This artificial nano-enzyme, called the PBzyme, can restore mitochondrial homeostasis by scavenging ROS, reduce pro-inflammatory cytokines IL-6, IL-1 $\beta$  and TNF- $\alpha$ , and inhibit TLR/NF- $\kappa$ B signaling pathway, ultimately achieving the remission of acute pancreatitis. Reproduced from Xie X, Zhao J, Gao W, et al. Prussian blue nanozyme-mediated nanoscavenger ameliorates acute pancreatitis via inhibiting TLRs/NF-kappaB signaling pathway. *Theranostics*. 2021;11:3213–3228. This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>). See <http://ivyspring.com/terms> for full terms and conditions.<sup>76</sup>

NPs) have stable chemical structure and excellent physical, chemical, optical and magnetic properties. Meanwhile, PB NPs can simulate a variety of antioxidant enzyme activities, which has attracted great attention in the treatment of inflammatory diseases in recent years.<sup>71–75</sup> As shown in Figure 4, Zheng et al developed a PB NPs (PBzyme) that can act as a nano-enzyme to remove a variety of ROS and pro-inflammatory factors including  $\bullet\text{OH}$ ,  $\bullet\text{OOH}$ , and  $\text{H}_2\text{O}_2$ . It reduces necrosis, nucleic acid damage, and peroxidation by downregulating TLR-related NF- $\kappa\text{B}$  signaling pathway

Similarly, the rare earth element nanoparticles also have ROS scavenging properties.<sup>77,78</sup> The nanoceria (NC) developed by Chandraiah Godugu's group can remove excess superoxide anion and hydrogen peroxide in cells by mimicking SOD and catalase activities, thereby alleviating oxidative stress and restoring mitochondrial membrane potential. Furthermore, NC could reduce the expression level of p65-NF- $\kappa\text{B}$  and the acetylation of histone H3 in AP mice.<sup>79</sup> Using the same strategy, in 2019, the same team also reported that yttrium oxide nanoparticles not only inhibited the infiltration of inflammatory cells around damaged pancreatic acinar cells, but also attenuated endoplasmic reticulum stress and the expression of molecular chaperones. Finally, an effective treatment for caerulein-stimulated SAP was achieved.<sup>80</sup>

In addition to the above-mentioned metallic inorganic nanoparticles, non-metallic inorganic nanoparticles represented by selenium can also achieve the purpose of alleviating pancreatitis. Abdel-Hakeem's team restored endocrine and exocrine functions in the pancreas of AP mice using only selenium nanoparticles (10–45 nm) with antioxidant properties.<sup>81</sup>

On the other hand, non-metallic nanoparticles represented by porous silica have excellent drug loading capacity. Chitosan oligosaccharides (COS) has been proved to be an antioxidant, but due to its non-specific distribution, it is difficult to exert sufficient effects in vivo.<sup>82</sup> Zeng et al used porous  $\text{SiO}_2$  material to load COS. The complex ( $\text{COS}@\text{SiO}_2$ ) can slowly release COS in pancreatic tissues with acidosis caused by SAP. Accurate release of COS inhibited NF- $\kappa\text{B}$  and NLRP3 inflammasome expression by activating Nrf2 pathway, and reduced systemic inflammatory response and oxidative stress indicators in tissues, ultimately alleviating pancreatic and subsequent lung pathological damage in SAP mice.<sup>83</sup>

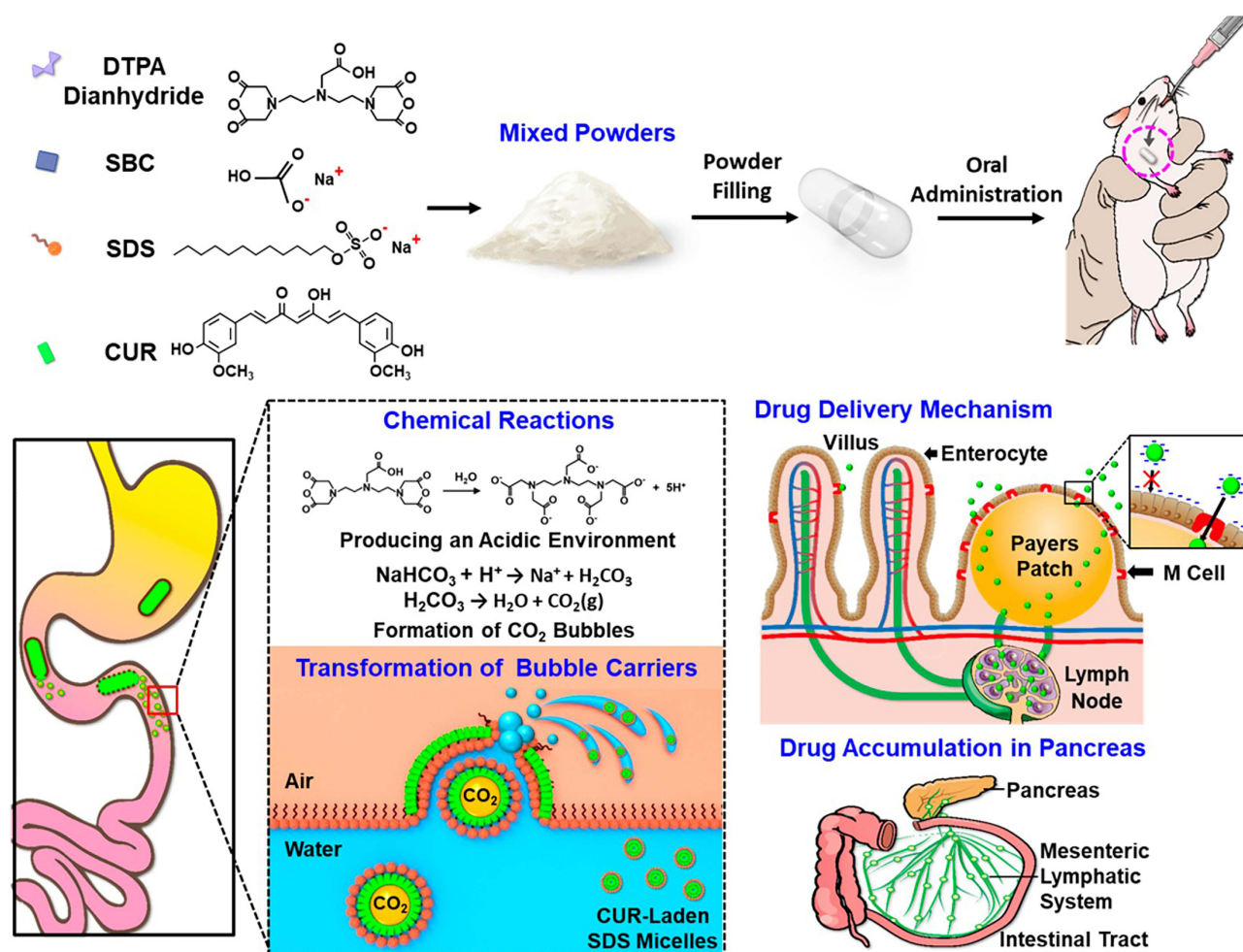
But it has also been reported that intravenous injections of commonly used inorganic nanoparticles can speed up the spread of breast cancer cells to other sites, promoting the emergence of new tumors.<sup>84</sup> This will be a barrier to the clinical application of inorganic nanoparticles.

## Liposome, Micelles and Dendrimers

Liposomes, micelles, and dendrimers have also been reported as novel drug carriers for the treatment of pancreatitis. Hsing-wen Sung's research group developed a “transformer”-like nanocarrier system (TLNS). It has been confirmed in vitro that TLNS can undergo structural changes in the intestinal environment and form nanoscale micelles with curcumin (CUR) in the process.<sup>85</sup> The mechanisms for AP-specific therapy through CUR-loaded micelles is shown (Figure 5). The pancreas of rats treated with TLNS produced about 12 times of CUR signal than that of rats treated with free CUR, possibly improving AP recovery. These results suggest that TLNS can significantly increase drug dissolution in the gut, making oral administration a more effective treatment route for pancreatitis.

Active targeting mediated by specific ligands is more efficient than passive targeting that relies on morphological changes.<sup>23</sup> However, the development of targeted therapies has been hampered by limited treatment options and the lack of molecule-targeted ligands or non-serum-based biomarkers. Kimberly Kelly et al used computation-guided phage display technology to screen five polypeptide ligands selectively for activated pancreatic stellate cells, acinus cells, macrophages, and extracellular matrix in a CP model induced by caerulein.<sup>86</sup> PEG-DOPC-based liposomes were modified by five ligands to form targeted liposomes, and an optimal target unit (MDLSLKP) was selected by investigating the pharmacokinetic parameters in vivo. The enrichment of optimal liposomes in the inflammatory pancreas increased to 1.3 times compared with the control group. They also observed that apigenin (Api) loaded targeted liposomes (Api-ECM Lip) improved the survival of acinar structures. Api-ECM Lip reduced the expression of collagen and fibronectin in pancreatic tissues of mice with CP by 37% and 33%, respectively. Surprisingly, Api-ECM Lip also alleviated Api-induced hepatic oxidative stress. In another similar study, nano-scale liposomal delivery of caffeic acid





**Figure 5** Transformer-like shape-changeable drug-loading system in situ loading curcumin for AP. Oral capsules consist of proton donor DTPA dianhydride, sodium bicarbonate, SDS and curcumin (CUR). When carbon dioxide is released in an acidic environment, the formed bubbles will form CUR-loaded SDS micelles in situ when they cross the water interface composed of SDS and CUR. The micelles can be taken up by M cells in the gut, enter the payer's patch, accumulate in the mesenteric lymph nodes, and then precisely introduced into the pancreatic tissue through the mesenteric-lymphatic system. Reproduced from Chuang EY, Lin KJ, Huang TY, et al. An intestinal "transformers"-like nanocarrier system for enhancing the oral bioavailability of poorly water-soluble drugs. *ACS Nano*. 2018;12:6389–6397. doi:10.1021/acsnano.8b00470.<sup>85</sup>

phenethyl ester, using passive targeting effect, enriched in inflammatory sites, reduced oxidative stress storm by regulating Nrf-2 and NF- $\kappa$ B signaling pathways, alleviated AP in rats.<sup>87</sup>

In addition, some dendrimers with polyhydroxyl groups have been shown to have antioxidant activity,<sup>88,89</sup> suggesting their application in the treatment of pancreatitis. As previously reported, two generation 5 (G5) polyamidoamine (PAMAM) dendrimers with hydroxyl or carboxyl, G4.5-COOH and G5-OH were synthesized. In a caerulein-induced AP mouse model, their protective effects were investigated.<sup>90</sup> G4.5-COOH and G5-OH not only significantly reduced inflammatory storms in the AP mice, but also distinctly inhibited the expression of LPS-induced mouse peritoneal inflammatory macrophages. They also significantly reduced the WBC and monocytes. The in vivo protective effect of G4.5-COOH on AP was better than that of G5-OH. Finally, authors demonstrated that the anti-inflammatory mechanism of G4.5-COOH and G5-OH may be the inhibition of NF- $\kappa$ B nuclear translocation in macrophages.

To make a long story short, the nanoscale therapeutic strategies for pancreatitis are summarized in Table 1.

## Nanomedicine-Based Diagnosis Strategy of Pancreatitis

Current diagnosis of pancreatitis is based on disease symptoms, which is poorly defined and more empirical.<sup>2</sup> The nanomedicine based on nanotechnology approach provides a new option for the diagnosis of pancreatitis. Given the



**Table I** Reported Nanotechnology-Based Therapeutic Strategy for Experimental Pancreatitis

Category	Purpose	Materials	Drug	Animal Models	Target	Therapeutic Mechanism	Ref.
Solid lipid/polymer nanoparticles	Nanocarrier	Lipid liquid crystal PLGA	Somatostatin Chloroquine diphosphate (CQ) and pDNA	AP <i>L</i> -arginine-induced AP	– Passive targeting (ELVIS effect)	Extending plasma half-lives of drug CQ show synergistic anti-inflammatory effect with the therapeutic gene	[25] [31]
	Nanocarrier	PLGA/liposome	CQ and tamoxifen (TAM)	Caerulein-induced AP and LPS-induce SAP	Passive targeting	CQ/TAM combination and MSCs synergistically up-regulated IDO signaling pathway	[32]
Biomacromolecule nanoparticles	Nanocarrier	Silk fibroin	Bilirubin	<i>L</i> -arginine-induced AP	Passive targeting (enzyme response)	Protect acinar cells by regulating NF- $\kappa$ B and Nrf2/HO-1 pathways	[36]
	Nanocarrier	Hemoglobin	Carbon monoxide	Choline-deficient ethionine (CDE) diet-induced AP	Bionic targeting	Anti-inflammatory and antioxidation	[38]
	Nanomedicine	Tetrahedral framework nucleic acids	–	2% Sodium taurocholate-induced AP	–	Inhibiting the cytokines in tissues and blood	[52]
Cell membrane camouflaged nanoparticles	Nanocarrier	Neutrophil membrane-coated PEG-PLGA nanoparticles	Celastrol	3% Sodium taurocholate-induce AP	Bionic targeting (Homing)	Down-regulated serum amylase and myeloperoxidase levels	[60]
	Nanocarrier	Neutrophil membrane-coated silk fibroin nanoparticles	Ferulic acid	Not mentioned	Bionic targeting (Homing)	Anti-inflammatory and antioxidation	[61]
	Nanocarrier	Macrophage membrane-coated PLGA nanoparticles	Melittin and MJ-33	Caerulein-induced AP	Bionic targeting (Homing)	While Melittin induces PLA2, MJ-33 inhibits PLA2 activity (PLA2 exacerbates AP)	[65]

(Continued)

**Table 1** (Continued).

Category	Purpose	Materials	Drug	Animal Models	Target	Therapeutic Mechanism	Ref.
Inorganic nanoparticles	Nanomedicine	MoSe <sub>2</sub> -PVP nanoparticles	–	Caerulein-induced AP	–	Effectively mimicked various enzymes and scavenged free radicals	[70]
	Nanomedicine	Prussian blue nanoparticles	–	Caerulein-induced AP	–	Simulate a variety of antioxidant enzyme and inhibit TLRs/NF-κB signaling pathway	[76]
	Nanomedicine	Nanoceria	–	Caerulein-induced AP	–	Reduced NF-κB expression and histone H3 acetylation by mimicking SOD and catalase	[77]
	Nanomedicine	Yttrium oxide nanoparticles	–	Caerulein-induced AP	–	Regulation of the Nrf2/NF-κB pathway to restore mitochondrial and ER homeostasis	[80]
	Nanomedicine	Selenium nanoparticles	–	L-arginine-induced AP	Passive targeting	Anti-inflammatory, antioxidant, and pro-apoptotic actions	[81]
	Nanocarrier	Porous SiO <sub>2</sub>	Chitosan oligosaccharides	Caerulein-induced AP; L-arginine-induced SAP	Passive targeting	Regulating the Nrf2 signaling pathway in AP or SAP mice	[83]
Others	Nanocarrier	Sodium dodecyl sulfate (SDS)-based micelles	Curcumin	L-arginine-induced AP	Passive targeting	Curcumin specifically accumulates AP site through the mesenteric lymphatic system	[85]
	Nanocarrier	Liposome	Apigenin	Caerulein-induced CP	Active targeting (specific peptide as the target unit)	Increased nanoparticle accumulate in inflamed pancreas	[86]
	Nanocarrier	Liposome	Caffeic acid phenethyl ester	L-ornithine	Passive targeting	Modulates Nrf2 and NF-κB Signaling in AP rat	[87]
	Nanomedicine	PAMAM dendrimers with different surface modification groups	–	Caerulein-induced AP	Passive targeting	PAMAM dendrimers reduced the WBC and monocytes, inhibited cytokines and the NF-κB in macrophages	[90]

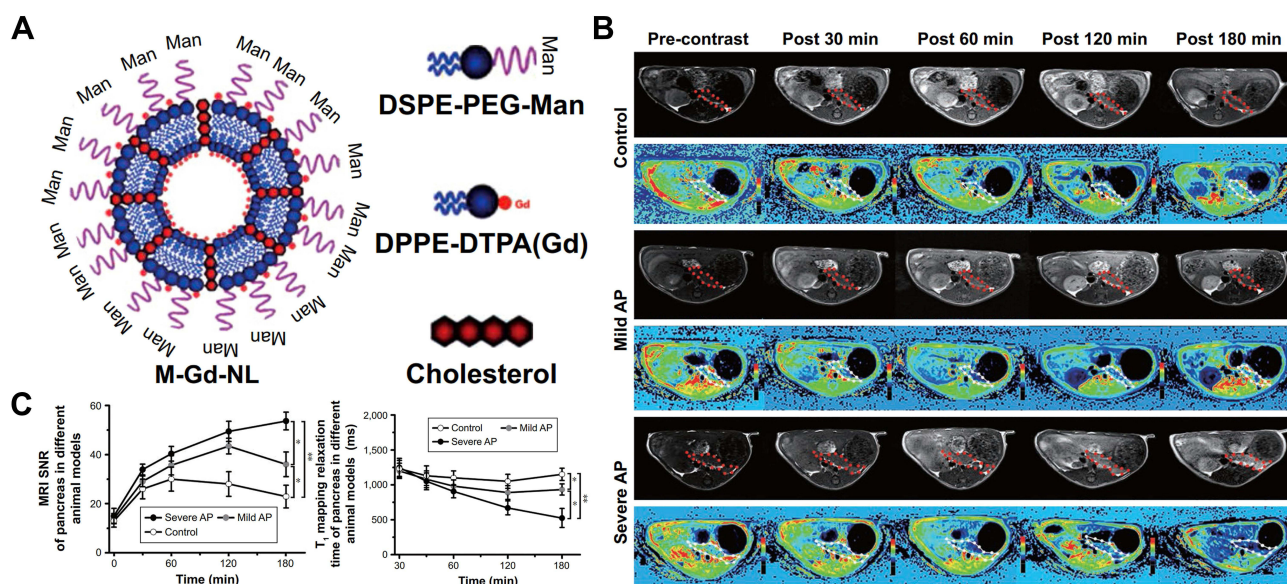
physiological function of the pancreas, amylase is a major class of serum biomarkers for pancreatitis. A novel synthetic nano-sensor binuclear Pd complex has been reported to be able to sensitively detect  $\alpha$ -amylase in serum and urine.<sup>91</sup> The detection limit of this method was ( $7.4 \times 10^{-10}$  mol/L) even lower than the  $\alpha$ -amylase concentration (3–321 U/L) in different samples from patients with pancreatitis. This method greatly improved the sensitivity (96.88%) and specificity (94.41%) of  $\alpha$ -amylase in the early diagnosis of pancreatitis.

Compared with serum biomarkers, in vivo imaging can provide more information for the clinical diagnosis, and magnetic resonance imaging (MRI) is a technique for pancreatitis.<sup>92</sup> Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) is a common contrast agent for MRI. Although the MRI imaging effect is closely related to the concentration of Gd-DTPA in the lesion, Gd-DTPA lacks the ability to target pancreatic tissue. Some abnormally elevated markers or immune cells in local lesions of pancreatitis provide targets to this problem. As shown in Figure 6, in the case of a large number of macrophages infiltrating in the AP lesion, a mannose-coated nanoliposome containing Gd-DTPA (M-Gd-NL) was previously reported, which was easily phagocytosed by the focal macrophages, thus enhancing the imaging effect of AP. Moreover, since the degree of macrophage infiltration of MAP and SAP is different, the use of M-Gd-NL can further distinguish the severity of AP.<sup>93</sup> Similarly, the locally overexpressed lipase in AP is another target. A previous study synthesized Gd-DTPA fatty acid nanoparticles (Gd-DTPA-FA).<sup>94</sup> Gd-DTPA-FA can be disassembled under the action of excess lipase and release the Gd-DTPA. In the *L*-arginine-induced AP rat model, Gd-DTPA-FA significantly increased  $T_1$ -weighted MRI signal intensity from 1 to 36 hours.

Furthermore, a near-infrared fluorescence and MRI dual-model nanoprobe has been reported recently to realize early visual diagnosis of SAP.<sup>95</sup> Deng et al prepared a dual-mode nanoprobe (Gd-DTPA-Cy5.5-PsLmAb) by coupling Cy5.5 (a near-infrared fluorescent dye) and P-selectin mAb on DTPA. Take advantage of P-selectin significantly upregulated at the SAP site, this nanoparticles have high spatial resolution and sensitivity in the early stage of SAP animal models. This is important to provide SAP patients with accurate treatment as soon as possible, thereby reducing their mortality.

## Factors Affecting the Distribution of Nanomedicines in Pancreatitis Mice

The key to solving the current limitations of the treatment of pancreatitis is the targeting efficiency of nanoparticles, but few literatures have explored the factors affecting the distribution of nanoparticles in animal pancreatitis model.<sup>96</sup> As we



**Figure 6** Mannose-modified gadolinium-containing nanoliposomes enhance local MRI imaging of AP. **(A)** M-Gd-NL is composed of DSPE-PEG-Man, DPPE-DTPA(Gd), and cholesterol stabilizes its structure. **(B)** MRI imaging of M-Gd-NL within 180 minutes of in vivo injection in mice with AP of different severity. **(C)** The comparison of MRI SNR signal and  $T_1$  mapping relaxation time shows that M-Gd-NL can both diagnose MAP and SAP, but the imaging effect of SAP is the best.<sup>93</sup> All comparisons were performed between the two groups by one-way analysis of variance with Newman-Keuls posttest. Data are expressed as mean  $\pm$  SD (n=5). \*P<0.05; \*\*P<0.01. Reproduced from Tian B, Liu R, Chen S, et al. Mannose-coated gadolinium liposomes for improved magnetic resonance imaging in acute pancreatitis. *Int J Nanomedicine*. 2017;12:1127–1141. Copyright 2017, Dove Medical Press.<sup>93</sup>

all known, inflammation-related diseases often involve ELVIS effects.<sup>97</sup> Due to changes in vascular permeability during AP progression, the ELVIS effects may change during progression of AP. Previous studies have explored the effect of nanoparticles size on their behavior in different stages of AP.<sup>21</sup> After intravenous administration of mesopore silica nanoparticles (MSN) at 60, 150 or 300 nm for 4 h in rats with MAP or SAP. The presence of MSN<sub>150</sub> in the pancreas was significantly greater than that of MSN<sub>60</sub> or MSN<sub>300</sub> in both MAP and SAP. The content of MSN<sub>150</sub> in pancreas, intestine and ascites of SAP rats was lower than that of MAP rats, indicating that the targeting performance of MSN in SAP rats was decreased. This may be related to more blood loss and slower blood flow in SAP rats. Such findings can guide us to pay attention to engineering principles when developing therapeutic nanoparticles in pancreatitis.

## Conclusion and Prospect

Pancreatitis is an inflammatory disease, especially SAP, which can be life-threatening in severe cases. Without timely diagnosis, CP will seriously affect pancreatic function and induce pancreatic cancer, diabetes and other pancreatic diseases. With the development of pathology, its pathogenesis has been confirmed to be related to premature activation of trypsinogen, calcium overload, pancreatic microcirculation disturbance, NF- $\kappa$ B pathway activation, leukocyte infiltration, and autophagy damage.

The rapid development of nanomedicine, which focus on targeted delivery and increase local drug accumulation, provides new opportunities for the treatment of pancreatitis. As the most common platforms, lipid and polymer nanoparticles tend to accumulate at sites of inflammation due to their appropriate particle size and ELVIS effect. Camouflaged by inflammatory cell membranes, the nanoparticles can be endowed with the ability to target APs. Therapeutic biomaterials such as antioxidant PAMAM and metallic nanoparticles have also been used to treat acute pancreatitis. We believe that, in accordance with the basic principles of design engineering (such as particle size distribution range, etc.), we should try to integrate the advantages of the above different carriers and propose a nanocarrier with advantages. On the other hand, nanomedicine in the diagnosis of pancreatitis mainly focuses on hypersensitivity detection of serum markers and imaging of pancreatic tissues, while existing studies are limited to amylase and lipase abnormal signals. Therefore, the efforts of researchers related to proteomics, genomics and other emerging disciplines will provide positive help for the development of specific markers for pancreatitis.

Finally, although there are numerous nanomedicine-based strategies for pancreatitis treatment, many experiments have only been carried out in simple animal models, which are insufficient for clinical studies. We believe that the support of pathology and statisticians will also help us to achieve multi-center, large scale clinical trials.

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## Disclosure

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

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