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REVIEW

Nano-Reagents in Acute Pancreatitis: Diagnostic, Therapeutic, and Theranostic Advances

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Abstract: This narrative review synthesizes the latest advances in nano-diagnostic and therapeutic reagents for acute pancreatitis (AP), based on peer-reviewed experimental and preclinical studies published in recent years. AP endangers life through self-digestion of pancreatic tissue and a cascading systemic inflammatory reaction. In clinical practice, the existing diagnostic and therapeutic tools are limited by low sensitivity and insufficient targeting, so it is difficult to achieve the ideal diagnosis and treatment effect of AP. However, the emerging nanotechnology is expected to overcome these drawbacks by offering highly specific delivery systems and ultrasensitive detection platforms. The studies included in this review are directly related to nanomedicine diagnosis, treatment, and diagnosis and treatment of AP, and are categorized by their functional implementation pathways to emphasize technological translational potential. For diagnosis, nano-sensors (optical, electrochemical) and contrast agents (MRI-responsive nanoparticles) enable early detection of biomarkers and precise imaging of pancreatic lesions. For treatment, nano-reagents address barriers like the blood-pancreatic barrier, low drug specificity, and insufficient intervention in the pathogenesis through multi-faceted strategies: targeted delivery systems, microenvironment-responsive release, and biological pathway regulation. Theranostic nano-reagents integrating diagnosis and therapy show promise for real-time monitoring and intervention. In the end, it emphasizes the need for further optimization of biocompatibility and clinical validation and provides insights for clinical strategy design.

Keywords: nanomedicine, acute pancreatitis, diagnosis, therapy, nano-reagent

Introduction

Acute Pancreatitis: Disease Burden and Clinical Challenges

Acute pancreatitis (AP) is a life-threatening self-digestive inflammatory disease of the pancreas caused by abnormal activation of pancreatic enzymes, which may trigger local tissue damage and systemic inflammatory responses, potentially culminating in multiple organ dysfunction syndrome (MODS). The global annual incidence of AP is approximately 34 cases per 100,000 population (0.034%), with a gradually increasing trend. AP predominantly affects middle-aged and elderly individuals, with similar incidence rates between males and females.[1,2] Common etiological factors include cholelithiasis, alcohol consumption, hyperlipidemia, endoscopic retrograde cholangiopancreatography (ERCP), diabetes mellitus, and unhealthy lifestyle habits such as smoking and overeating.[3–5] Developed countries (in North America and Europe), owing to their higher economic status and high-sugar, high-fat dietary habits, have a higher incidence rate than developing countries.[6]

Pathogenesis and Bottlenecks in Current Management

The pathogenesis of AP exhibits a multi-stage cascade pattern. In the initiation stage, pancreatic acinar cell injury is the core event. This can be caused by mechanical obstruction (like a blocked bile duct) leading to pancreatic fluid reflux and

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increased pressure within the pancreas; or by metabolic irritants (such as alcohol or fatty acids) directly harming the acinar cells.[7] These stimuli cause digestive enzymes from lysosomes (especially cathepsin B) to move into the vesicles that store trypsinogen. Cathepsin B then snips off the activation peptide from trypsinogen, transforming it from an inactive zymogen into active trypsin. Once trypsin is activated, it's like a spark igniting a wildfire, quickly setting off a chain reaction of protein breakdown, releasing even more enzymes, and pushing the condition into the next stage – the progression phase. In this phase, an inflammatory storm fully erupts: large numbers of neutrophils and macrophages flood the pancreatic tissue, while neutrophil extracellular traps (NETs) also form, further intensifying the damage and prompting the body to release various pro-inflammatory cytokines (like TNF-α, IL-6, IL-1β).[8] Microcirculatory disturbances and ischemia-reperfusion injury also make the ischemic necrosis of the pancreas much worse.[9] Finally, it enters the systemic effector phase: local inflammation evolves into a body-wide inflammatory response, potentially leading to acute kidney injury, acute respiratory distress syndrome (ARDS), and even multiple organ dysfunction syndrome (MODS).[10–14]

Clinically, AP presents as abrupt, unrelenting epigastric pain, typically coupled with nausea, vomiting, and abdominal distension. Key physical signs may include fever, abdominal tenderness (often with epigastric guarding and rebound tenderness), and Grey-Turner or Cullen signs.[15] Importantly, a subset of patients progresses to severe acute pancreatitis (SAP), defined by ongoing organ failure (>48 h), hypotension or shock, and significantly higher mortality.[16–18] At present, there are two main diagnostic bases for acute pancreatitis: First, circulating pancreatic enzymes (amylase or lipase) in the blood must rise to at least triple the laboratory's upper reference value. Second, cross-sectional imaging (such as contrast-enhanced CT, MRI, or transabdominal sonography) needs to reveal pancreatic enlargement and peripancreatic inflammatory changes.[19–23] However, a significant limitation persists: these traditional methods are not sensitive enough to reliably detect AP in its earliest stages.

The clinical management of AP has focused on cause-specific interventions and stratified treatment strategies. The primary objectives revolve around mitigating inflammation, preventing complications, and addressing the underlying causative factors.[18,24,25] While pharmacotherapy plays a pivotal role, significant limitations, including poor drug targeting, the development of drug resistance, and low specificity hamper its effectiveness.[26] Thus, the core challenges in AP management are: (1) achieving early and accurate diagnosis, with a particular focus on identifying early biomarkers; (2) overcoming the blood-pancreatic barrier (BPB) to facilitate effective pancreatic drug targeting; and (3) developing specific interventions that precisely target key pathogenic pathways, such as aberrant zymogen activation, inflammatory cascades, oxidative stress, and calcium overload.

Nanotechnology: Emerging Strategies for AP Diagnosis and Therapy

The National Science Foundation (NSF) and the National Nanotechnology Initiative (NNI) jointly recognize nanotechnology as the purposeful design, engineering, and manipulation of matter at the approximate scale of 1 to 100 nanometers.[27,28] This field looks at how size changes things. It uses these size-based changes to get special light reactions, strength, and chemical actions. This lets us build new kinds of structures, useful materials, and tiny systems.[29] Currently, nanotechnology, as an emerging and rapidly developing field, has been widely applied in various industries, especially in the interdisciplinary areas of materials science, biology, and medicine, where it demonstrates unique creativity.[30] In the medical domain, its applications primarily focus on two areas: first, it is used for diagnosing relevant diseases; second, it is utilized as a drug carrier to achieve targeted drug delivery. To achieve these goals, scientists design nanomaterials that can interact with the disease microenvironment. For instance, in cancer therapy, scientists use the high sensitivity and specificity of nanomaterials to identify biomarkers or imaging targets in the tumor microenvironment;[31] or develop new diagnostic or therapeutic agents. All of these are achieved through the special properties of nanomaterials (such as their large specific surface area and significant quantum effects) interacting with the unique microenvironment of tumors. This strategy helps to enhance the stability of the drugs, improve their water dispersibility, and reduce systemic adverse reactions.[32–35] In addition to oncology, nanotechnology has also shown significant translational potential in other inflammatory diseases. For instance, in inflammatory bowel disease (IBD), the MOF-818 nanozyme functions as an active gut microenvironment modulator. Oral administration alleviates IBD symptoms and oxidative damage by promoting beneficial bacteria (eg, *Roseburia intestinalis*) and improving gut microbiota composition.[36] Similarly, in viral hepatitis, a fluorescent immunosensing system utilizing Fe_3O_4 nanoparticles

and $CsPbBr_3$ perovskite nanocrystals has been developed for the rapid and ultrasensitive detection of HBsAg, demonstrating a 0.05 ng/mL limit of detection for early diagnosis.[37] These precedents highlight the potential of nanomedicine to solve various inflammatory diseases, and also provide a strong theoretical basis for its application in AP. Despite these advances, there are still many difficulties for nanomedicine to be used in the clinic. The approval process for new nanomaterials is complex, with regulatory agencies requiring rigorous assessment of their distribution in vivo over long periods of time, biocompatibility, and whether they elicit immune responses. Furthermore, clinical trials of nanotherapies have their own special challenges: standard methods for stable and reproducible production of nanoparticles are still in development, and trial results should be evaluated not only for therapeutic efficacy but also for nanomaterial-specific safety concerns, such as whether they accumulate in organs. These barriers underscore the need for interdisciplinary collaboration to bridge the gap between preclinical innovation and clinical adoption.[38,39] Overall, nano-reagents present a promising avenue for precision diagnosis and therapy of AP. This review categorizes the applications of nano-reagents in AP based on their distinct functional modes of action (Figure 1 and Table 1)

This review categorizes the applications of nano reagents in diagnosing and treating AP based on their distinct action modes, differing from studies that classify them by material type or pathogenesis or Microenvironment response.[108–111] It emphasizes the functional implementation pathways of nano diagnostic and therapeutic agents, providing references for technological translation and clinical diagnosis and treatment strategy design.

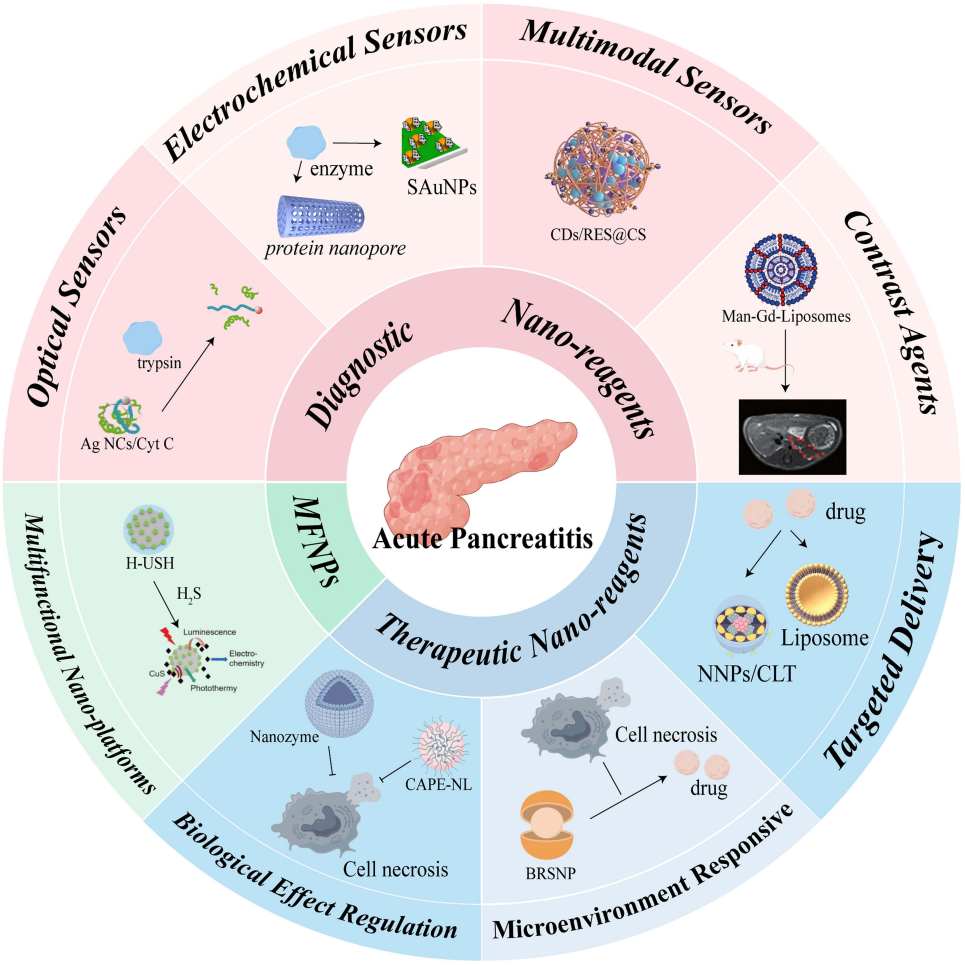

Figure 1 A schematic framework of diagnostic and therapeutic nano-reagents for AP: From mechanistic design to translational applications. In this panel, the *red dotted circle* in the pancreatic diagram highlights the focal lesion area affected by inflammation and autodigestion.

Abbreviations: Ag NCs/Cyt c, Ag Nanoclusters and Cytochrome c; SAuNPs, Starch-coated Gold Nanoparticles; CDs/RES@CS, Chitosan loading Carbon Dots and Resveratrol; Man-Gd-Liposomes, Gadolinium loaded Mannosylated Liposomes; MFNPs, Multifunctional Nano-platforms; H-USH, H-UCNP SiO_2@HKUST-1 (Highly doped Upconverting Nanoparticles-coupled Silica Microbeads coated with Metal-organic Frameworks); AP, Acute Pancreatitis.

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Table 1 Application of Nano-Reagents in Diagnosis and Therapy of AP

Application Direction	Category	Nano-Reagent Name	Application Effect/Mechanisms	References
Diagnosis	Optical Sensors	Pd(atz,ur) complex, AIE probes	Rapid trypsin detection, Rapid lipase/α-amylase fluorescent assay	[40–59]
		(S1, S2) BSA-rGO-AuNCs, G-CDs	Trypsin fluorescence detection, Highly sensitive lipase detection Chymotrypsin FRET-based sensing, Trypsin ratiometric fluorescence	
		dC_{12}-AgNCs/GO, GQDs-CMR2	Trypsin detection in urine, Lipase detection in serum	
		CNQD-AuNCs, Tween-GNPs	Trypsin detection in serum, Trypsin detection via color change	
		BSA-Au NCs, Au NBPs	Trypsin/α-Amylase detection, ROS detection for AP severity	
		Cyt c-TMB, Cu/Au NCs, SPN		
	Electrochemical Sensors	α-hemolysin NP, am7-CD	Label-free trypsin detection (1.4 ng/mL); electrochemical amplification;	[60–67]
		CPB, Starch-AuNPs-PANI	IL-6 voltammetric sensing (0.05 pg/mL); magnetic relaxation trypsin detection	
		Zr(IV)-ATRP, Au/GRD-UiO-66/Fc		
		EGr-MIP, Peptide-IONPs		
	Multimodal Sensors	Lanthanide-doped NPs, H-USH NPs, photothermal-colorimetric dual-mode platform	Triple-signal H_2S detection with >99% diagnostic accuracy; dual-mode trypsin detection via colorimetry and photothermal effect	[68–71]
	Nanoparticle-based Contrast Agents	Gd-DTPA-FA, M-Gd-NL	Lipase-activated MRI contrast; macrophage-targeted imaging; P-selectin-targeted dual-modal imaging for SAP diagnosis	[72–74]
		Gd-DTPA-Cy5.5-PsLmAb		
Treatment	Targeted Delivery Nano-reagents	DTM@KA NPs, BLN, MU, NNPs/CLT, CBP-AT-CC	Mitochondria-targeted KA delivery; Ca^{2+} overload scavenging; pancreatic fibrosis targeting	[75–86]
			macrophage/neutrophil biomimetic targeting;	
	Microenvironment-responsive Nano-reagents	HMPB, $COS@SiO_2$, BRSNP	pH-responsive PB degradation (survival rate 100%); pH-triggered COS release (Nrf2 activation);	[87–89]
			enzyme-triggered bilirubin release (NF-κB inhibition)	
	Biological Effect-regulating Nano-reagents	$Se@SiO_2$, CeO_2, Cu MOF, CAPE-NL, CA-NPs, PC@PLGA	ROS scavenging; Nrf2 activation/Ca^{2+} regulation; neutrophil clearance (50% infiltration reduction); NLRP3 inflammasome inhibition	[90–101]
	Others	H-MoS_2, Electrospun NF	Photothermal inhibition of inflammation (H-MoS_2: 50% reduction); postoperative hemostasis and anti-adhesion	[102,103]
Theranostics	Multifunctional Nano-platforms	Ce/Gd-CDs@CS NPs, SPIO liposomes, PB-upconversion NPs	MRI/fluorescence bimodal imaging with ROS scavenging; macrophage apoptosis visualization; H_2S sensing/imaging with lung injury mitigation	[104–107]

Abbreviations: Pd(atz,ur) complex=Pd-(2-aminothiazole)(urea) complex; AIE=aggregation-induced emission systems; am7-CD=Heptakis (6-deoxy-6-amino)-β-cyclodextrin; CPB=Carboxypeptidase B; PANI=Polyaniline Composite; Zr(IV)-ATRP=Zirconium (IV)-Mediated Atom Transfer Radical Polymerization; EGr-MIP=Expanded Graphene-Molecularly Imprinted Polymer; Peptide-IONPs=Peptide-Iron Oxide Nanoparticles; H-USH=Highly doped Upconverting Nanoparticles-SiO_2@HKUST-1; Gd-DTPA-FA =Gadolinium-Diethylenetriaminepentaacetic Acid-Folic Acid; M-Gd-NL=Mannose-coated Gadolinium Liposomes; Cy5.5-PsLmAb=Cyanine 5.5-Conjugated P-selectin Monoclonal Antibody; DTM@KA NPs=DTM-Loaded Kaempferol Nanoparticles; BLN=BAPTA-AM Liposome Nanoparticles; MU=Ulinastatin-Containing Macrophage Biomimetic Nanoparticles; NNPs/CLT=Neutrophil Membrane-Camouflaged Nanoparticles/Celastrol; CBP-AT-CC=Collagen-Binding Peptide-Alanine-Terminated Collagenase I; HMPB=Hollow Mesoporous Prussian Blue Nanoparticles; $COS@SiO_2$=Chitosan Oligosaccharide-SiO_2 Nanocomposite; BRSNP=Bilirubin-Loaded Silk Fibroin Nanoparticles; $Se@SiO_2$=Selenium@Silicon Dioxide; CeO_2=Cerium Dioxide; Cu MOF=Copper Metal-Organic Framework; CAPE-NL=Caffeic Acid Phenethyl Ester-Nanoliposome; PC@PLGA=Phosphatidylcholine@Poly Lactic-co-Glycolic Acid; H-MoS_2=Hydrogenated Molybdenum Disulfide; Electrospun NF=Electrospun Nanofibers; Ce/Gd-CDs@CS NPs=Cerium/Gadolinium-Carbon Dots-Chitosan Nanoparticles; SPIO Liposomes=Superparamagnetic Iron Oxide Liposomes.

Diagnostics Nano-Strategies

Nanomaterials possess high sensitivity and specificity. As sensors, they can more rapidly and efficiently detect and identify concentration changes of biomarkers in AP. As contrast agents, they enhance the contrast of lesions and reveal subtle abnormal imaging manifestations.[74] Consequently, the application of nanomaterials in AP diagnosis contributes to achieving earlier and more accurate diagnoses, thereby facilitating timely intervention to halt disease progression.

Nanosensors for Biomarker Detection

A serum lipase or amylase concentration exceeding the upper reference range by a factor of three or more is widely accepted as a pivotal biochemical marker for confirming AP.[3,112–114] Moreover, trypsin plays a pivotal part in the pathogenesis of AP: the abnormal activation of trypsinogen triggers pancreatic autodigestion and initiates an enzymatic cascade reaction, ultimately leading to tissue necrosis and inflammatory responses.[115,116] Therefore, detecting trypsin activity not only as a complementary indicator for confirming the presence of the disease but, more crucially, provides an effective means to assess the severity of pancreatic injury.[117]

Optical Sensors

In the clinical diagnosis of AP, optical sensors have emerged as research hotspots in nanomedicine due to their high sensitivity and specificity (Table 2).

Fluorescent Sensors

Fluorescent sensors enable quantitative detection of AP biomarkers via signal variations (quenching/recovery, ratiometric detection), with key technological pathways including: Attia and Al-Radadi's team introduces a new nano-optical sensor to diagnose α-amylase activity in AP using a binuclear Pd-(2-aminothiazole) (urea) complex, Pd(atz,ur) doped in a sol–gel matrix. The sensor pioneered redox quenching via α-amylase-generated 2-CNP. It achieves a limit of detection (LOD) of 7.4×10^{-10} mol/L for α-amylase (linear range 3–321 U/L). The method shows 96.88% sensitivity and 94.41% specificity in serum and urine samples, superior to traditional spectrophotometric methods, but its small sample size (n=20) limits statistical power and generalizability.[40] Jie Shi pioneered the development of an interface-controlled aggregation-induced emission (AIE) probe S1 by conjugating glutamic acid units to a BSA-rGO-AuNCs (TPE) core to introduce amino and carboxyl groups. S1 achieves an "AIE turn-on" dC_{12}-AgNCs/GOfluorescence response triggered by lipase-catalyzed ester bond hydrolysis with an LOD of 0.13 U/L for lipase (linear range 0–80 U/L, response time 7 minutes), but its very small sample size (n=12) significantly limits its statistical power and clinical generalizability.[41] Building on S1, probe S2 was designed for α-amylase specificity by covalently linking maltotriose units to the TPE core.

Table 2 Comparative Analysis of Fluorescent Sensor Technologies for AP Diagnosis

Category	Nano-Reagent Name	Target	Detection Mechanism	Ref.
Fluorescence Quenching-recovery strategies	Pd(atz,ur) complex	α-Amylase	2-CNP redox quenching (fluorescence quenching)	[40]
	TPE probe S1	Lipase	Aggregation-induced emission systems	[41]
	TPE probe S2	α-Amylase		[42]
	BSA-rGO-AuNCs	Lipase		[43]
	Green carbon dots (G-CDs)	Lipase	Surface passivation-enhanced fluorescence	[44]
	dC_{12}-AgNCs/GO	Chymotrypsin	Fluorescence resonance energy transfer systems	[45]
	Ag NCs-Cyt c	Trypsin		[46]
	Cu NCs-Cyt c	Trypsin		[47]
	CdTe QDs-Cyt c	Trypsin		[48]
	AuNPs-peptide probe	Chymotrypsin	Enzyme cleavage →fluorophore release from quencher	[49]
	Carbon NPs-fluorescein peptide	Trypsin		[50]
Ratiometric Fluorescence strategies	CNQD-AuNCs	Trypsin	Selective AuNCs quenching (CNQDs reference)	[51]
	LMOF-BR	H_2S	Single-excitation dual-emission (MOF reference)	[52]
	GQDs-CMR2/BSA	Trypsin	FRET systems →ratio change (F_{440}/F_{580})	[53]

Abbreviations: 2-CNP, 2-Carbon Nanoparticle (generated by α-amylase); TPE, Tetraphenylethylene; BSA-rGO-AuNCs, Bovine Serum Albumin-functionalized Reduced Graphene Oxide-Gold Nanoclusters; dC_{12}-AgNCs, Dodecyl-modified DNA-stabilized Silver Nanoclusters; Ag NCs-Cyt, Silver Nanoclusters-Cytochrome c; CdTe QDs, Cadmium Telluride Quantum Dots; CNQD, Carbon Nitride Quantum Dots; LMOF-BR, Luminescent Metal-Organic Framework with H_2S-Recognizing BR; GQDs-CMR2, Graphene Quantum Dots-Coumarin Derivative CMR2; FRET=Fluorescence Resonance Energy Transfer; F_{440}/F_{580}, Fluorescence emission peaks at 440 nm/580 nm.

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Enzymatic hydrolysis of α-1,4 glycosidic bonds induces hydrophobic TPE aggregation and fluorescence activation, achieving sensitive detection with an LOD of 0.14 U/L (linear range 0–45.5 U/L, response time 3 minutes) (Figure 2A).[42] The trypsin sensor based on protein-mediated gold nanoclusters modified reduced graphene oxide (BSA-rGO-AuNCs) also utilizes AIE. Trypsin-specific cleavage of BSA triggers AuNCs release from rGO and subsequent aggregation, leading to fluorescence recovery with an LOD for trypsin <100 ng/mL.[43] Similarly, green-emitting carbon dots (G-CDs) function as turn-on fluorescent nanoprobes for sensitive, selective serum lipase detection. G-CDs achieve an LOD of 0.01 mg/mL (response time 1 min) through surface state passivation upon binding to lipase, which significantly enhances the fluorescence signal.[44]

Metal nanoclusters (NCs) exhibit excellent fluorescence properties, serving as donors to construct fluorescence resonance energy transfer (FRET) systems.[118] This representative biosensor employs dC_{12}-AgNCs/GO, DNA-templated silver nanoclusters on graphene oxide, for chymotrypsin detection. Chymotrypsin cleavage of the peptide linker releases the AgNCs from the GO surface, which restores the FRET signal and enables quantification at an LOD of 3 ng/mL.[45] An analogous strategy utilizes oligonucleotide-templated AgNCs complexed with cytochrome c (Cyt c). Fluorescence quenching occurs due to electrostatic forces between anionic AgNCs and cationic Cyt c, serving as a biomolecular recognition mechanism. Upon trypsin-mediated hydrolysis of Cyt c, the AgNCs are liberated and their fluorescence is recovered, affording an LOD of 58.7 ng/mL. This study demonstrates a clever and well-characterized sensing mechanism with high potential for reproducibility in controlled settings, but its complete lack of human sample testing means its statistical power and clinical relevance cannot be assessed.[46] Extending this concept to copper

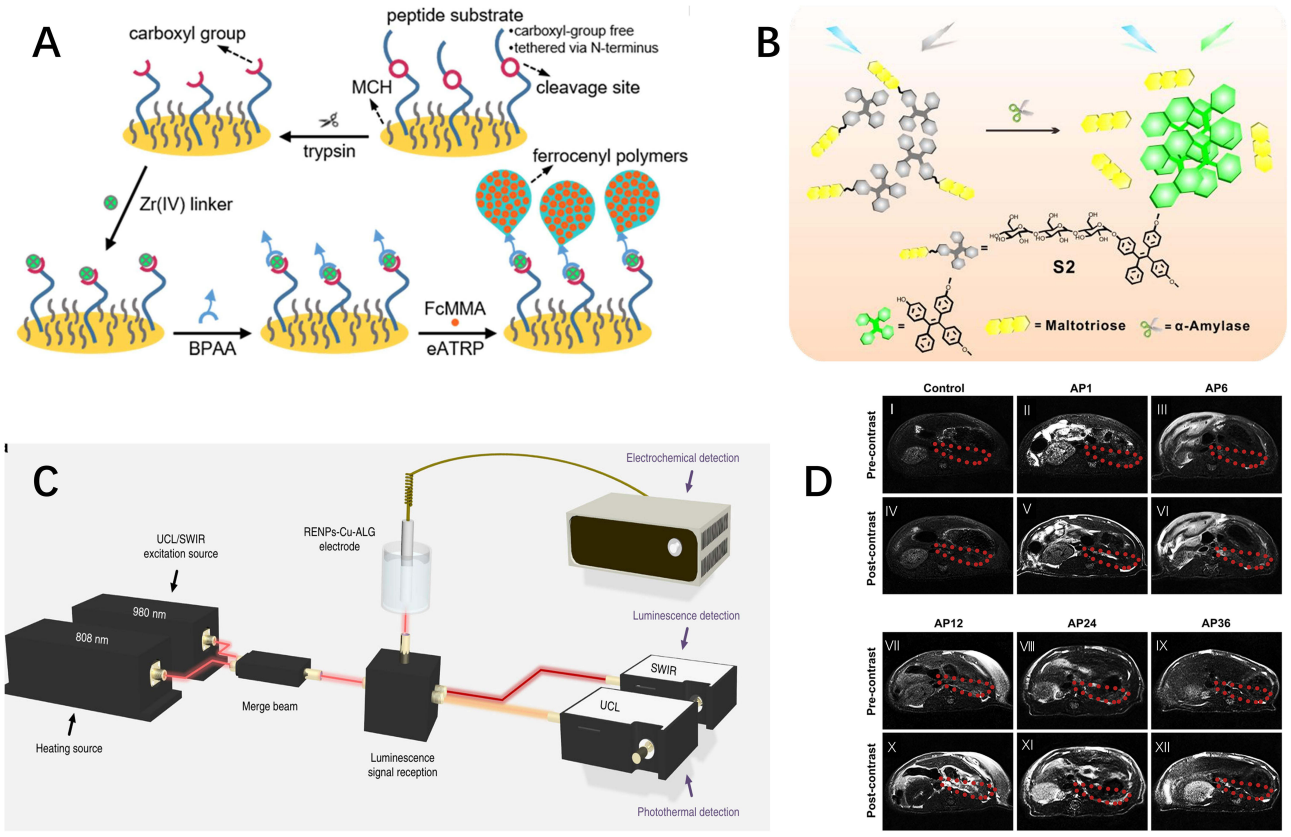

Figure 2 (**A**) Working principle of probe S2 in α-amylase activity assay. Reproduced with permission from reference.[64] Copyright 2018, American Chemical Society. (**B**) Working principle of the electrochemical trypsin activity biosensor. Reproduced with permission from reference.[42] Copyright 2020, Elsevier. (**C**) Three-channel electrochemical platform (RENPs-Cu-ALG-gel electrode). Reproduced with permission from reference.[71] Copyright 2019, Nature Communications. (**D**) In vivo MR imaging of AP using a lipase-responsive nanoprobe (Gd-DTPA-FA). T1-weighted magnetic resonance images of the upper abdomen in SD rats. The images show the upper abdomen of rats across six experimental groups: Control, AP1, AP6, AP12, AP24, and AP36, where "APn" indicates the time point (n hours) after AP induction. Each group contains paired *pre-contrast* (top row: subpanels I, II, III, VII, VIII, IX) and *post-contrast* (bottom row: subpanels IV, V, VI, X, XI, XII) scans, showing progressive and significant signal enhancement within the pancreatic region (demarcated by red dashed circles). Reproduced with permission from reference.[72] Copyright 2013, Elsevier.

nanoclusters, the CuNCs–Cyt c assembly enables, for the first time, room-temperature phosphorescence detection of trypsin, achieving an LOD of 2 ng/mL.[47] Moreover, Cyt c can be replaced by CdTe quantum dots (QDs) to construct a FRET pair. Trypsin-induced degradation of Cyt c disrupts the complex, leading to fluorescence recovery of the QDs with an LOD of 0.42 nM.[48]

In contrast to NCs as fluorescent donors, conventional metal nanoparticles (NPs) act as fluorescence quenchers, requiring external fluorophore labeling while relying on fluorescence quenching/recovery for signal transduction.[119–121] For example, a fluorophore-labeled peptide is chemically coupled and immobilized to AuNPs to construct an "AuNPs-peptide probe", which remains in a low-fluorescence state. When chymotrypsin cleaves the specific site on the peptide, the fluorophore is released from the AuNP surface, escaping the quenching range and leading to significant fluorescence recovery.[49] Carbon nanoparticles (CNPs) follow the same mechanism: CNPs quench the fluorescence of fluorescein-labeled peptides, and trypsin addition cleaves the peptide chain, releasing the dye moiety and significantly increasing fluorescence intensity.[50] This approach reduces the detection limit and shortens the detection time, making it suitable for point-of-care testing (POCT).

In addition to utilizing fluorescence quenching and recovery, ratiometric fluorescence detection can also be employed for AP diagnosis. For the carbon nitride quantum dots (CNQD)-AuNCs composite material, trypsin induces quenching of AuNCs fluorescence while CNQDs fluorescence remains unchanged. This method achieves a trypsin LOD of 1.5 ng/mL, a linear range of 10–400 ng/mL, and is suitable for urine testing.[51] Yang's team designed a luminescent metal-organic framework-based ratiometric fluorescent nanoprobe (LMOF-BR) specifically for sensitive and selective detection of hydrogen sulfide (H_2S) in AP. The nanoprobe uses synthesized LMOF for detecting H_2S in AP. It uses LMOF for a stable signal, while BR both recognizes H_2S and produces the output signal. The probe works with one light source but gives two fluorescence signals, making it resistant to interference.[52] Besides, a ratiometric fluorescent probe comprising graphene quantum dots (GQDs) and a coumarin derivative (CMR2) has been developed. Bovine serum albumin (BSA) serves as a bridge between GQDs (donor) and CMR2 (acceptor), establishing a FRET configuration. Trypsin-catalyzed hydrolysis of BSA alters the F_{440}/F_{580} emission ratio, permitting trypsin quantification with an LOD of 0.7 μg/mL.[53]

Colorimetric Sensors

Beyond fluorescence strategies, colorimetric sensors have achieved continuous breakthroughs in the diagnosis of AP by optical sensors. Yan Tang and Wei Zhang's team addressed the technical bottleneck lipase detection by designing Tween 20/80-functionalized gold nanoparticles (Tween 20-GNPs and Tween 80-GNPs) as colorimetric probes. Their mechanism relies on lipase-catalyzed hydrolysis of the ester bonds within the surfactant layer triggers rapid GNPs aggregation in high-salt media, producing a red-to-blue color transition that circumvents lipid–water interface constraints.[54,55] Luo engineered a multicolor trypsin sensor by integrating two nanomaterial systems: the peroxidase-like activity of bovine serum albumin-capped gold nanoclusters (BSA–Au NCs) with the selective etching of gold nanobipyramids (Au NBPs). Trypsin-mediated hydrolysis of the BSA ligand enhances the nanozyme activity of BSA-Au NBPs, accelerating the oxidation of TMB to TMB^+. Under acidic conditions, the generated TMB^+ etches Au NBPs, inducing a pronounced longitudinal plasmon shift and a visible color transition occurred, shifting from brown-red to blue-gray. The sensor exhibits a linear range of 0.1–100 μg/mL and an LOD of 0.045 μg/mL, and has been successfully applied to discriminate serum samples from healthy individuals and AP patients.[56] Zhang's group utilized Cyt c as the enzyme substrate and TMB as the chromogenic substrate in their system. Intact Cyt c displays negligible catalytic activity, whereas peptides generated by trypsin-catalyzed hydrolysis rapidly catalyze TMB oxidation to yield a blue product. A linear relationship exists between absorbance at 652 nm and trypsin concentration, with an LOD of 4.5 ng/mL.[57]

Chemiluminescent Sensors

Chemiluminescent sensors, as a subset of optical sensors, play a vital role in the diagnosis of AP. In the field of rapid diagnosis for AP, chemiluminescent sensors have emerged prominently due to their high sensitivity and the advantage of requiring no external light excitation. A chemiluminescent system constructed from starch-stabilized Cu/Au nanoclusters (Cu/Au NCs) achieves precise detection of α-amylase by utilizing the property that α-amylase-catalyzed hydrolysis of

starch induces NC aggregation and decreases peroxidase activity. This method demonstrates excellent linearity over the concentration range of 0.05–8 U/mL, achieving an LOD of 0.006 U/mL, featuring short detection time and stable signal duration.[58] Another study developed a semiconducting polymer nanoplatform (SPN), whose chemiluminescent intensity is positively correlated with reactive oxygen species (ROS) levels. When tested on mice with AP, the SPN's glow clearly showed how much stress and damage the pancreas had. This helped them know exactly how severe the pancreatitis was.[59]

Even though these remarkable optical sensors (like fluorescent, colorimetric, and chemiluminescent ones) are very sensitive for AP signs in the lab, their clinical translation faces challenges that could lead to false-positive or false-negative results. First, endogenous substances in complex biological samples (eg, serum, whole blood), such as proteins or pigments, can cause light scattering or background fluorescence interference, compromising signal specificity. Second, the stability of many probes (eg, metal nanoclusters) may be compromised in the unique inflammatory microenvironment of AP, leading to signal drift. Furthermore, for enzyme activity assays, non-specific enzyme elevation in certain disease states (eg, renal dysfunction) could potentially yield false-positive signals. Therefore, future research must validate the specificity and robustness of these sensors in more realistic clinical samples and disease models.

Electrochemical Sensors

Electrochemical nanosensors have become indispensable tools for early-stage AP diagnostics driven by their superior sensitivity, cost-effectiveness, and ease of miniaturization. According to the underlying transduction mechanism, current advances can be systematically categorized into four paradigms: nanopore single-molecule sensing, impedance/conductive-film detection, electrochemical cascade amplification, and magneto-electrical conversion platforms.[122] The following will present representative studies in each category:

Nanopore Single-Molecule Sensing

Zhou immobilized a lysine-containing peptide at the nanopore orifice; tryptic cleavage generated fragment translocation events with an ultralow LOD of 1.4 ng/mL in serum without any fluorescent label.[60] Li incorporated amino-modified β-cyclodextrin (am7β-CD) inside the pore to selectively trap BAEE hydrolysis products, markedly suppressing substrate background and enhancing specificity, but its complete lack of human sample validation and unspecified biological replication limit its current statistical power and clinical translatability.[61] An analogous strategy was extended to H-USH (CPB): a peptide bearing basic residues was tethered within a nanochannel, and CPB-mediated hydrolysis produced an instantaneous current increase, affording an LOD of 0.01 U/mL within 10s.[61] While these approaches excel in sensitivity and sample economy, their throughput remains limited; future integration with microfluidic nanopore arrays is anticipated to enable multiplexed profiling.

Impedance/Conductive-Film Sensing

Enzyme-triggered modulation of conductive networks translates protease activity into measurable resistance changes. Mandal embedded starch-coated AuNPs into a polyaniline film; α-amylase hydrolysis released the AuNPs, producing a real-time resistance drop suitable for rapid serum α-amylase quantification.[63] The device architecture is simple and POCT-compatible, yet further optimization of antifouling coatings is required to mitigate non-specific interference in complex matrices. The device architecture is simple and POCT-compatible, yet further optimization of antifouling coatings is required to mitigate non-specific interference in complex matrices.

Electrochemical Cascade Amplification

A "cleavage-coordination-polymerization" cascade can exponentially amplify trace protease signals. Hu's team engineered a peptide–electrode interface: tryptic cleavage exposed carboxyl groups, which were bridged by Zr(IV) to anchor ATRP initiators; subsequent electrochemically triggered eATRP yielded ferrocene (Fc) polymers, amplifying the current by 3–4 orders of magnitude and enabling sub-femtomolar trypsin detection (Figure 2B).[64]

Magneto-Electrical/Multi-Modal Conversion

Translating biorecognition events into magnetic signals circumvents interference from electroactive species. Wang

adopted a sandwich electrochemical format: capture antibody-IL-6-UiO-66/Fc amplifiers on an Au/GRD substrate converted IL-6 concentration into Fc current, achieving an LOD of 0.2 pg/mL.[65] IL-6 can also be detected by voltammetry. Chen further employed defect-engineered graphene nanoribbons (EGr) as the transducer, coupled with a molecularly imprinted polymer (MIP) layer for IL-6 recognition; defect-enhanced electron transfer yielded an LOD of 0.05 pg/mL by voltammetry.[66] Gandhi constructed an "IONP-peptide-IONP" magnetic network; tryptic scission dispersed the iron oxide nanoparticles (IONPs), producing a decrease in magnetic particle spectroscopy (MPS) signal with an LOD <1 nM.[67] Magneto-electrical platforms exhibit excellent matrix tolerance and are amenable to wearable or microfluidic integration for continuous monitoring.

These studies show electrochemical nanosensors offer rapid, sensitive protease detection for early pancreatitis diagnosis. Future work may focus on multiplexed sensors for simultaneous enzyme profiling. While electrochemical sensors offer advantages in miniaturization and sensitivity, they also present limitations in practical applications. Electrode surfaces are susceptible to biofouling in complex biofluids, where non-specific adsorption of proteins or cells can impede electron transfer, leading to reduced sensitivity (false negatives) or baseline drift. Additionally, other electroactive species present in serum (eg, ascorbic acid, uric acid) may generate interfering currents, posing a risk of false positives. Although impedance-based and magneto-electrical sensor designs aim to circumvent these interferences, their long-term stability and batch-to-batch reproducibility require further validation in larger clinical cohorts.

Multimodal Sensor

Integrating two or more orthogonal signal channels, multimodal sensors effectively mitigate the false-positive/false-negative limitations inherent to single-signal assays and have thus become a pivotal direction for accurate AP diagnosis. This section will systematically review the representative work of the recent period.

Multimodal Detection of Trypsin

Guo engineered a photothermal-colorimetric dual-mode platform leveraging the localized surface plasmon resonance (LSPR) of Au NPs. Competitive protection of Au NPs by bovine serum albumin (BSA) versus trypsin-catalyzed hydrolysis simultaneously triggers a color change and a photothermal response. By smartphone-assisted RGB analysis and infrared thermometry, LODs of 1.2 μg/mL (colorimetric) and 6 μg/mL (photothermal) are achieved. Clinical samples are processed within 1 h, with 92.3% concordance to ELISA, offering a portable solution for POCT.[68]

Multimodal Detection of H_2S

Significant progress has been made in multimodal sensing technologies based on H_2S detection. Wei's team developed lanthanide-doped nanoprobes that break through the limitations of wavelength-dependent light absorption in whole blood by converting fluorescence signals into temperature signals, enabling reliable H_2S detection and precise serum diagnosis of AP.[69] On this basis, a three-signal detection platform integrating luminescence, photothermal, and electrochemical signals was further constructed. The core of this platform is H-USH nanoparticles, which have a metal-organic framework coating. It can accurately measure how much hydrogen sulfide (H_2S) there is, using three different signals. When used, a 980 nm laser controls the particles, and an 808 nm laser makes them give off signals. In an AP mouse model, this three-signal method showed changes in blood H_2S levels much more clearly than single or dual signal methods. ROC curve analysis demonstrated a diagnostic accuracy of >99.0%, While the study demonstrates innovative triple-signal detection with high AUC values, the small sample size (n=5 per group) and lack of detailed power analysis or replication data may limit statistical robustness and generalizability (Figure 2C).[70,71]

Perspectives on Multimodal microRNA Detection

MicroRNAs, as gene expression regulatory molecules, exhibit significant expression changes in diseases such as cancer and inflammation. Detection of microRNA expression levels in serum enables early and precise diagnosis of these diseases.[123,124] Recently, scientists have been actively exploring strategies for faster and more efficient detection of AP-specific microRNAs, aiming to leverage their unique expression profiles for early diagnosis of AP. For instance, a dual-engine DNA Walker-driven electrochemiluminescence (ECL) biosensor was used to detect miRNA-24-3p; this platform

achieved an ultralow LOD of ~60 aM and a wide dynamic range (10^{-15} M to 10^{-6} M), with excellent specificity against homologous miRNAs (eg, miRNA-21, miRNA-155) and good stability in serum (recovery rate: 96.79–104.08%, RSD: 0.81–2.56%), supporting its potential for clinical translation. However, it requires specialized ECL detection equipment and involves multi-step electrode modification, which limits its applicability in resource-limited settings.[125] A study based on a cysteine-catalyzed oxidation colorimetric method was conducted to detect miRNA-21; this approach allows naked-eye readout (color change from red to blue), has a low LOD of 4 fM, and enhances specificity via dual recognition (padlock probe cyclization + exonuclease digestion). Nevertheless, it relies on rolling circle amplification (RCA), which requires a relatively long incubation time (~90 min for RCA), and the stability of AuNPs in the color reaction is susceptible to environmental factors (eg, salt concentration).[126] Another study was carried out based on primer exchange reaction (PER) combined with the fluorescence characteristics of AgNCs to detect miRNA-31; this label-free method avoids cumbersome fluorescent labeling, has a low LOD of 47 fM, and uses low-toxicity AgNCs. However, it needs a long total incubation time (120 min) and its specificity is highly dependent on probe design to avoid cross-reactivity with homologous miRNA family members.[127]

While metal-based sensors have demonstrated superior sensitivity for AP biomarker detection, their potential hazards cannot be overlooked. For metal nanoclusters (Au NCs[43] Ag NCs[45] Cu NCs[47]), physiological conditions in AP may trigger the release of toxic metal ions: Ag^+ can induce intracellular oxidative stress and membrane disruption,[128] Cu^{2+} may accumulate in the liver/kidneys to mediate Fenton reaction-related ROS overproduction, and even biocompatible Au NCs could elicit mild immune responses (eg, reticuloendothelial system phagocytosis) in metal-hypersensitive patients.[129] Metal oxide-based sensors (eg, IONPs[67]) face similar risks: IONP dissolution in inflamed tissues releases Fe^{2+}/Fe^{3+}, which exacerbates pancreatic oxidative stress and inflammatory cascades.[130] Lanthanide-doped nanomaterials (eg, Eu^{3+}/Tb^{3+}-doped probes for H_2S detection[65]) pose unique challenges, including slow in vivo clearance leading to RES accumulation (inducing chronic inflammation/fibrosis) and potential thermal damage to vulnerable pancreatic tissues if their photothermal effect is not precisely controlled.[131] Additionally, rare earth metals (eg, Gd) may accumulate in bones and brains, raising long-term neurotoxicity and nephrotoxicity concerns, especially in patients with impaired renal function.[132] To mitigate these risks, future designs should prioritize surface modification with biocompatible polymers (eg, PVP),[133] use of biodegradable metal cores (eg, controlled-degradation iron-based materials), and strict regulation of metal ion content/photothermal intensity to ensure safety while maintaining diagnostic performance.

Nanoparticle-Based Contrast Agents

CT, MRI, and transabdominal ultrasound are the primary imaging modalities for pancreatic disorders.[134] Nevertheless, conventional small-molecule contrast agents suffer from rapid blood clearance and fail to provide simultaneous functional information. Nanoparticle-based contrast agents (NPCAs) offer tailorable surfaces, prolonged circulation, and multimodal payloads, providing new opportunities for early detection and severity stratification of AP.[135,136] The following is a detailed introduction:

Zhang self-assembled gadolinium-DTPA-fatty acid nanoparticles (Gd-DTPA-FA) whose ester bonds are selectively hydrolyzed by pancreatic lipase. Upon hydrolysis, the hydrophobic core converts into hydrophilic Gd-DTPA, increasing the longitudinal relaxivity (r_1) from 3.8 to 12.4 mM^{-1} s^{-1} and generating a "dark-to-bright" T_1-weighted signal. In AP rats, pancreatic hyperintensity was observed within 1 h post-injection and continued to rise for 36 h, preceding serum amylase elevation (Figure 2D).[72] While this microenvironment-specific activation minimizes background enhancement, inter-individual variability in lipase activity may compromise signal uniformity, necessitating larger-cohort validation. Tian covalently functionalized gadolinium liposomes with mannose (M-Gd-NL) to actively target macrophage mannose receptors. Compared with enzyme-activated probes, M-Gd-NL achieved a 2.1-fold difference in signal-to-noise ratio (SNR) between mild and severe AP models, enabling imaging-based disease stratification. However, reliance on macrophage infiltration may yield false negatives in early mild AP with limited inflammatory influx; complementary biomarkers should therefore be integrated.[73] Besides, Long engineered Gd-DTPA-Cy5.5-PsLmAb nanoparticles in which a P-selectin monoclonal antibody (PsLmAb) targets P-selectin overexpressed on AP endothelium. Gd provides high-sensitivity T_1-MRI contrast, while Cy5.5 enables near-infrared fluorescence (NIRF) imaging. In SAP mice, the pancreas exhibited pronounced T_1 hyperintensity ($\Delta SNR = 3.6$) and NIRF enhancement ($\Delta F/F_0 = 4.2$), allowing early dual-modal

diagnosis of SAP. The probe was efficiently cleared via the hepatobiliary route within 24 h without detectable Gd deposition, yet long-term toxicity assessments remain indispensable.[74]

While these nanoprobes demonstrate promising targeting and activation properties, a critical appraisal of their preclinical validation is warranted. For instance, studies on mannose-coated gadolinium liposomes[73] and P-selectin-targeted dual-modal probes[74] employed sample sizes of n=6–7 per group, which is common but at the lower limit for robust statistical power in imaging studies. Although some studies, like the lipase-responsive Gd-DTPA-FA nanoparticle,[72] utilized G*Power analysis to justify a sample size of n≥8, the majority did not report a priori power calculations, potentially limiting the detection of smaller effect sizes. Reproducibility is supported by detailed synthesis and modeling protocols; however, the predominant reliance on single animal models (eg, L-arginine-induced AP in SD rats) and a general lack of independent, multi-laboratory validation necessitate caution when extrapolating these promising results.

Therapeutic Nano-Strategies

The drug therapeutic effect of AP is limited by the blood-pancreatic barrier (BPB), which is both restrictive and poorly selective.[83] In recent years, research on nanomedicine in AP has been continuously progressing and is expected to become an effective solution for addressing the challenges in AP treatment.[137] The following will introduce the application progress of nano-reagents in AP treatment from three different modes of action: Targeted delivery nano-reagents, Microenvironmental response nano-reagents, and Biological effect regulating nano-reagents.

Targeted Delivery Nano-Reagents

Nano-reagents, as a drug delivery carrier in nanotechnology, have gained significant attention. Compared with common drug reagents, nano-reagents possess a surface area and quantum effect.[138,139] They achieve precise accumulation in the pancreatic inflammation area through the physical properties of high vascular permeability in the inflamed region (ie, ELVIS effect)[140,141] and biological modification via ligand-receptor specificity or biomimetic membrane camouflage.[142] This boosts drug levels at the target site while curtailing systemic exposure.[143,144]

Passive Targeting

As the core carrier of nanodrug delivery systems, liposomes play a critical role in enhancing drug targeting efficiency, reducing toxic side effects, and overcoming physiological barriers by virtue of their excellent biocompatibility, high drug loading capacity, and modifiability.[145,146] Wen's team designed DTM@KA NPs by encapsulating Kaempferol (KA) in liposomes composed of DSPE-TK-PEG2000. These nano-reagents enhance the bioavailability of KA and improve mitochondrial and redox homeostasis, thereby inhibiting inflammation and apoptosis.[75] Chegini also focused on the delivery of traditional Chinese medicine via nano-reagents. They conducted a randomized controlled trial of nano-curcumin therapy for mild-to-moderate AP. They found that nano-curcumin could shorten the length of stay in the gastrointestinal ward and reduce the need for analgesics, providing clinical evidence for the application of nanotechnology in the clinical treatment of AP.[76] FU's team prepared liposome nanoparticles (BLN) loaded with BAPTA-AM, a cell-permeable chelator. Both in vitro and in vivo experiments demonstrated that BLN could rapidly and effectively remove intracellular Ca^{2+} overload, inhibit inflammatory responses, and increase the survival rate of rats, illustrating the effectiveness of nanotechnology in addressing key pathogenic mechanisms of AP. (Figure 3A).[77] Based on the modifiability of liposomes, precise targeting of AP lesions can be achieved, and the progression of the disease course can be slowed down: Fisetin-loaded lipid-polymer hybrid nanoparticles (FST-LPHNPs) enhance encapsulation efficiency and drug loading through lipid-polymer hybrid structures.[78] Hyaluronic acid-conjugated cationic liposomes (HA-P-LP) enable gene-targeted delivery via surface modification, regulating the necroptosis pathway.[79] To address pancreatic fibrosis, dual-drug nanoparticles were developed featuring collagen-binding peptide (CBP) for targeted delivery and collagenase I (AT-CC) for extracellular matrix remodeling. These constructs degrade excess collagen via enzymatic activity, enhancing permeability through fibrotic tissue. Subsequently, ATRA and TM are transported across the modified matrix to exert a combined inhibitory effect on collagen synthesis and fibril stabilization.[80] These studies collectively demonstrate that liposomes, as multifunctional nanocarriers, play a critical role in AP therapy.

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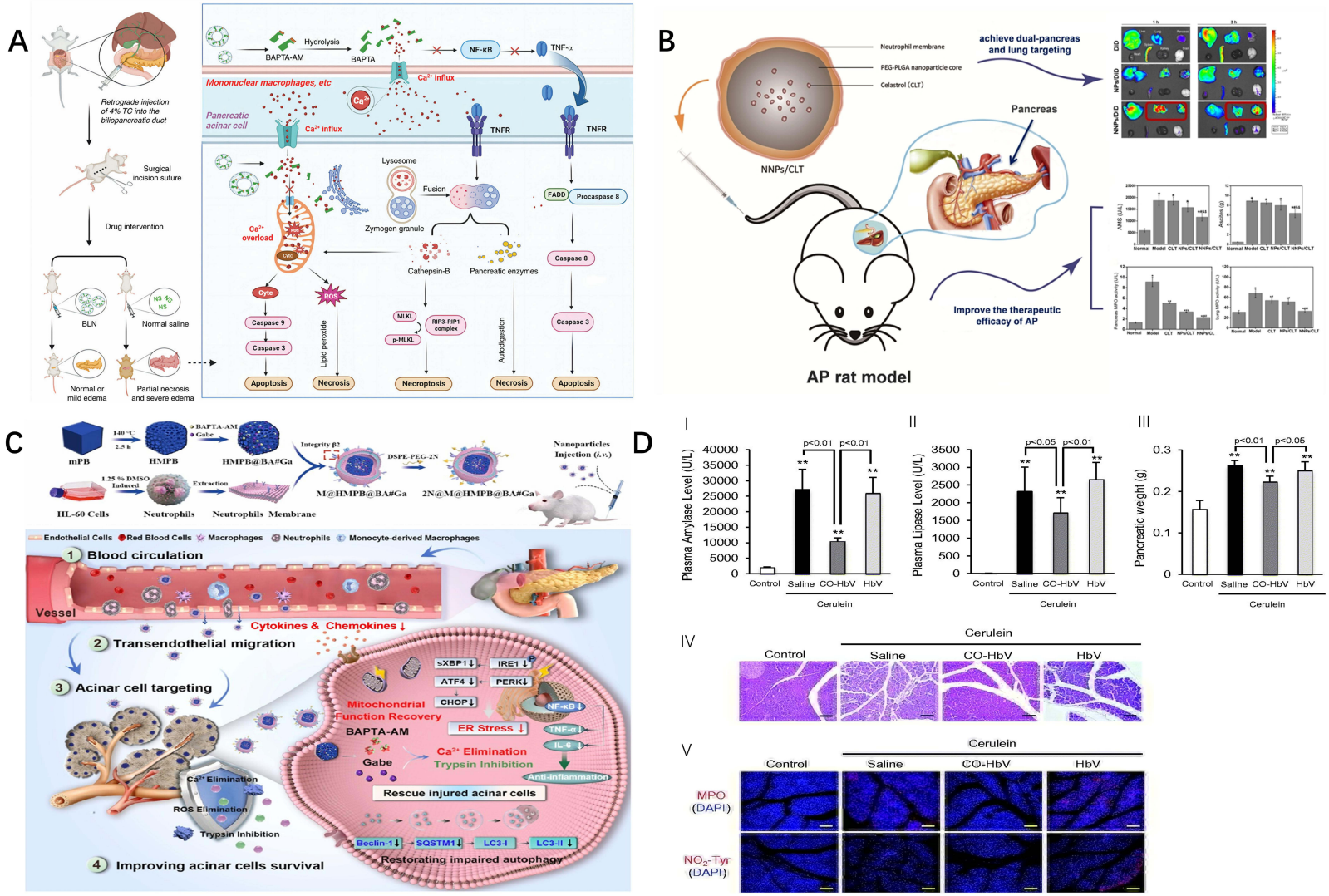

Figure 3 (**A**) The putative mechanism underlying BLN-mediated pancreatic cytoprotection in rat AP, specifically through counteracting pathological intracellular calcium accumulation. Reproduced with permission from reference.[77] Copyright 2024, International Journal of Molecular Medicine. (**B**) Neutrophil membrane-camouflaged nanocarriers delivering Celastrol to AP. In this panel, *p < 0.05 versus sham group, $^{\#}$p < 0.05 versus model group, $^{\&}$p < 0.05 versus CLT solution group, and $^{\$}$p < 0.05 versus NPs/CLT group. Data represent mean ± S.D. Reproduced with permission from reference.[84] Copyright 2019, American Chemical Society. (**C**) HMPB nanoparticle fabrication and therapeutic action in murine AP (sodium taurocholate-induced). In this panel, *arrows* indicate the action process of nanoparticles (eg, blood circulation, acinar cell targeting, etc.) and the regulatory direction of intracellular signals/substances. Reproduced with permission from reference.[87] Copyright 2024, Nature Communications. (**D**) Therapeutic evaluation of CO-HbV nanoparticles in murine acute pancreatitis. (I–III) Quantification of key disease indicators: (I) plasma amylase (acinar injury marker), (II) plasma lipase (pancreatic enzyme), and (III) pancreas/body weight ratio (edema index). (IV) Representative H&E-stained pancreatic tissue sections. (V) Immunofluorescence staining for neutrophil marker MPO (upper, red) and oxidative stress marker nitrotyrosine (lower, red); nuclei are DAPI-stained (blue). Scale bars: 100 μm. Data in a-c are mean ± S.D. (n=6). p < 0.01 vs untreated AP model.

Additionally, Chuang's team developed a curcumin-loaded nano-emulsion (TLNS) that passively targets intestinal M cells and is subsequently internalized, significantly enhancing drug dissolution and oral bioavailability, thus offering an experimental basis for non-invasive administration.[81] A separate study investigated the influence of particle size on pancreatic accumulation at different AP stages and found that 150 nm IR780-loaded mesoporous silica nanoparticles exhibited the highest pancreatic distribution, with greater accumulation in mild AP than in severe AP, indicating that the effect of nanoparticle size is disease-stage dependent.[82]

Active Targeting

Currently, active targeting strategies for nano-reagents are mostly based on cell membrane-coated biomimetic systems and ligand modification.[147–150] The macrophage cell membrane was used as the shell of the mixture of PEG-PLGA and ulinastatin to prepare a kind of macrophage biomimetic nanoparticle (MU), which remains stable and biocompatible in vitro and in vivo, and effectively suppresses pro-inflammatory mediators while preserving cell viability in experimental AP.[83] To create NNPs/CLT, Zhou developed celastrol-loaded PEG-PLGA nanoparticles camouflaged by neutrophil cell membranes. NNPs/CLT selectively accumulate in the inflamed pancreas, markedly reducing serum amylase, IL-6, TNF-α, and pancreatic/lung MPO activity while alleviating pancreatic edema and lung injury (Figure 3B).[84] Li's team designed cysteine-modified PEG nanoparticles that target methylprednisolone to L-type amino acid transporter 1. The nano-system significantly improves internalization by pancreatic acinar cells while markedly suppressing inflammatory cascades in acinar cells within a rat AP model.[85] Wang's team developed a trypsin-responsive biomimetic nanosystem that achieves precise intervention through a dual active targeting strategy: mesoporous silica nanoparticles (MSNs) coated with mesenchymal stem cell membranes and surface-modified with pancreatic acinar cell (PACs) targeting ligands. Dual active targeting achieved 4.7-fold pancreatic accumulation; upon AP onset, trypsin cleaves arginine amide bonds to release BAPTA-AM, eliminating Ca^{2+} overload and blocking necrotic signaling, raising mouse survival from 50% to 91.6%.[86]

To sum up, these studies demonstrate the innovative application of biomimetic and targeted nano-reagents in AP treatment. By coating nano-reagents with macrophage or neutrophil cell membranes, the resulting biomimetic systems (MU, NNPs/CLT) exhibit enhanced inflammatory site-targeting capabilities, enabling selective accumulation at AP. Meanwhile, amino acid transporter-targeted nano-reagents (cysteine-modified PEG) improve drug uptake efficiency in acinar cells, directly intervening in inflammatory responses. Or combine the two methods. These approaches not only leverage the natural targeting properties of cell membranes but also optimize drug delivery via molecular modification, providing multi-faceted strategies for precise AP treatment.

Microenvironmental Response Nano-Reagents

AP is characterized by a complex pathogenesis. Most scholars agree that AP arises from autophagy in acinar cells, which induces microcirculatory disorders, mitochondrial failure, calcium mishandling, and endoplasmic reticulum proteotoxic stress. These collective pathophysiological changes alter the pancreatic microenvironment. Consequently, numerous scientists have focused on harnessing microenvironment-specific signals in AP (including pH, enzymes, ROS, and Ca^{2+}) to trigger drug release or functional activation, aiming for "precise lesion-site activation with minimal exposure in normal tissues".[151,152]

Prussian blue (PB) and porous silica (SiO_2) exhibit pH responsiveness.[153–155] When exposed to an acidic environment, the structure of hollow mesoporous PB degrades rapidly, while in an alkaline environment, the pore structure of porous SiO_2 expands. Both mechanisms enable targeted drug release. Wang designed neutrophil membrane-enveloped hollow mesoporous Prussian blue nanoparticles (HMPB), where the hollow mesoporous architecture accelerates PB degradation. This nano reagent overcomes challenges such as the poor water solubility of the hydrophobic calcium chelator BA and the short half-life of the trypsin inhibitor Ga. In AP mouse models, this approach increased the survival rate from 58.3% in the control group to 100% (Figure 3C).[87] Mei developed a nanocomposite (COS@SiO_2) that slowly releases chitosan oligosaccharides (COS) by leveraging the pH responsiveness of SiO_2, which can maintain a high concentration of COS. COS activates the Nrf2 signaling pathway and inhibits NLRP3 inflammasome assembly and

suppresses NF-κB activation, thereby blocking oxidative stress and the inflammatory cascade and significantly reducing the pathological damage of pancreatic and lung tissues.[88]

Another study took the properties of many enzymes present in AP lesions and the property that silk fibroin can be degraded by multiple proteolytic enzymes. Silk fibroin was used to encapsulate bilirubin, constructing a type of nanoparticle (BRSNP). When BRSNP enters AP lesions, bilirubin is released through an enzyme degradation reaction, effectively overcoming the inherent limitations of hydrophobicity and cytotoxic potential. The results of the study indicate that BRSNPs confer cytoprotection to pancreatic acinar cells by concurrently suppressing NF-κB-mediated inflammation while activating the Nrf2/HO-1 antioxidant axis.[89]

Biological Effect Regulating Nano-Reagents

In addition, nano-reagents can also block the pathological process of AP at the biomolecular level by directly regulating the function of inflammatory cells, signaling pathways, or upstream events of the pathways.[156–158]

Immune Cell Regulatory Type

In the rapidly evolving field of nanomedicine research, nano-reagents that target immune cells and regulate their polarization and function have gradually emerged as a research frontier for intervening in inflammatory homeostasis imbalance in diseases.[159,160] Three recent studies highlight distinct strategies targeting macrophages and neutrophils through biomimetic design, metabolic reprogramming, and programmed cell removal, collectively showcasing the versatility of nano-reagents in resolving AP. Taguchi report a P-selectin-targeted nanotherapeutic, CO-bound hemoglobin vesicles (CO-HbV), that exploits platelet-derived vesicle homing to accumulate in inflamed pancreatic tissues, inducing M1-to-M2 macrophage phenotypic switching to resolve inflammation. Mechanistically, CO-HbV suppresses HMGB1/TLR-4 signaling, thereby reducing pro-inflammatory mediators (TNF-α, IL-6, IL-1β) while increasing the anti-inflammatory cytokine IL-10. In cerulein-induced AP mice, this platform diminishes neutrophil infiltration (via reduced MPO activity), mitigates oxidative stress (lower nitrotyrosine levels), and alleviates acute lung injury. (Figure 3D)[161] Chen employed mannose-conjugated chitosan lipid nanocapsules with emodin (M-CS-E-LNC) to target macrophage mannose receptors. M-CS-E-LNC induces lipid metabolic reprogramming by upregulating carnitine palmitoyltransferase 1 (CPT1), a key enzyme in mitochondrial fatty acid oxidation. This shift promotes M2 polarization, enhances anti-inflammatory IL-10 secretion, and suppresses M1-driven cytokines. In LPS-induced SAP mice, the nanocapsules accumulate in pancreatic and gastrointestinal tissues, reducing serum amylase, pancreatic edema, and neutrophil accumulation.[162] Song engineered a biomimetic hybrid nanoparticle, designated PC@PLGA, by cloaking a PLGA core with platelet-derived extracellular vesicles (PEVs) and calreticulin (CRT)-displaying membranes. PEVs enable PSGL-1-dependent targeting of activated neutrophils, while surface-displayed CRT mimics "aged" cell signals to induce macrophage-mediated programmed cell removal (PrCR) via LRP1/SIRPα pathways independent of apoptosis. In cerulein/LPS-induced SAP, PC@PLGA labels activated neutrophils for phagocytosis, reducing their pancreatic infiltration by 50% and suppressing HMGB1/TLR-4-driven inflammation. This non-apoptotic clearance mechanism mitigates pancreatic edema, necrosis, and systemic cytokine storms, with therapeutic efficacy comparable to healthy controls.[163]

Signal Pathway Intervention Type

AP involves dysregulated signaling networks, including oxidative stress mediated by the Nrf2 pathway,[164] inflammatory cascades (NF-κB, NLRP3 pathways),[165,166] and apoptotic dysregulation (ASK1/MAPK, Bcl-2/Bax pathways).[167] Nano-reagents delivery systems, leveraging advantages in targeted delivery and biocompatibility, enable precise intervention in these key molecular pathways.[168] Shahin developed caffeic acid phenethyl ester nanoliposomes (CAPE-NL), which enhance antioxidant defense by activating the Nrf2 pathway elevating glutathione (GSH), glutathione reductase (GR) activity, and reducing malondialdehyde (MDA). At the same time, suppressing the NF-κB pathway to decrease pro-inflammatory cytokines like TNF-α. CAPE-NL also regulates apoptosis by balancing Bcl-2/Bax expression and reducing cleaved caspase-3 levels.[90] Abozaid reported cinnamic acid nanoparticles (CA-NPs) that restore redox homeostasis by normalizing the GSH/GSSG ratio, inhibit excessive activation of the NLRP3 inflammasome, NF-κB, and ASK1/MAPK pathways to dampen inflammation, and mitigate caspase-3-mediated pancreatic acinar cell apoptosis.[91] In summary, both

nano-reagents demonstrate a comprehensive intervention network targeting AP's core pathogenic pathways, ie, the antioxidant-anti-inflammatory-anti-apoptotic signaling axis, highlighting the unique advantages of nano-reagents in precisely regulating signaling pathways for molecular-level AP treatment and their promising clinical translational potential.

Nanozymes

Nanozymes, defined as nanomaterials possessing enzyme-like catalytic activity, are broadly classified into metal-based, carbon-based, metal-oxide-based, and composite types.[169,170] These materials have garnered significant interest for AP therapy due to their ability to mimic natural enzymes such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD), thereby targeting upstream events in key AP-related pathways (notably oxidative stress and inflammation). Given substantial progress in AP models, this section critically reviews: selenium-based nanozymes, metal-centric nanozymes, and tetrahedral framework nucleic acids (tFNAs), followed by future perspectives.

Selenium-Based Nanozymes

Selenium-based nanomaterials ($Se@SiO_2$ Ns and Se-NPs) exhibit potent antioxidant and anti-inflammatory activities. They scavenge excessive ROS by mimicking glutathione peroxidase (GPx) activity and activate the Nrf2/ ARE pathway to effectively treat AP. $Se@SiO_2$ Ns enhance selenium catalytic efficiency through a porous structure, promoting Nrf2 nuclear translocation to upregulate antioxidant enzymes, significantly reducing MDA levels and restoring GSH content in pancreatic tissues.[163] Se-NPs, synthesized via green extraction from plant extracts, feature natural surface functional groups that confer low toxicity and passive targeting to the inflamed pancreas. In addition to activating the Nrf2 pathway, they inhibit the TLR4/MyD88/NF-κB inflammatory axis, reducing the release of IL-6 and TNF-α, while regulating the Bax/Bcl-2 apoptotic protein balance to decrease acinar cell apoptosis by 43%.[93]

Metal-Centric Nanozymes

Metal-centric nanozymes are characterized by catalytic activity originating directly from metallic elements in elemental, ionic, or coordinated states. This diverse class demonstrates multiple mechanisms in AP therapy.

Rare earth nanozymes, such as yttrium oxide (NY) and cerium oxide (NC), focus on epigenetic regulation and mitochondrial protection. NY inhibits NF-κB transcriptional activity by downregulating histone H3K14Ac modification, while NC efficiently scavenges superoxide anions through Ce^{3+}/Ce^{4+} valence cycling, resulting in a 60% increase in mitochondrial membrane potential recovery.[94–97]

Transition metal compound nanozymes also show remarkable efficacy; molybdenum diselenide ($MoSe_2$-Gd NPs) and ultrasmall iridium nanoparticles (IrNP-PVP) are characterized by multi-enzymatic synergy (four-enzyme mimicry/ dienzyme cascade) and size-dependent targeting, with the former constructing a complete ROS scavenging network and the latter achieving deep pancreatic penetration at a 1.55 nm particle size to alleviate endoplasmic reticulum stress.[98,99]

Metal-organic framework (MOF) nanozymes constitute another significant category. Copper-based MOFs (Cu-MOFs) feature CuN_2Cl_2 coordination centers that confer both SOD- and CAT-mimetic activities, enabling cascaded ROS elimination via Cu^{2+}/Cu^{+} redox cycling. Cu-MOF inhibits TLR4/MyD88 interaction, reducing NF-κB p65 nuclear translocation by 55%, and activates PINK1/PARK2-mediated mitophagy to clear damaged mitochondria and limit necroptosis. In vivo, it lowers serum amylase and lipase by 60% and 55%, improves pancreatic injury by 60%, preferentially accumulates in the inflamed pancreas via retention (EPR), and is safely cleared within 24 h. [100] Prussian blue (PB), as a typical MOF material, has attracted extensive attention in the field of enzyme mimicry due to its excellent redox activity and electrochemical stability.[171–173] Xie prepared the PB-based nanozyme (PBzyme) via polyvinylpyrrolidone (PVP) modification and demonstrated at the cellular level that it inhibits inflammatory responses and scavenges ROS by suppressing the TLR/NF-κB signaling pathway, effectively alleviating oxidative stress and inflammatory damage in AP models.[174]

Tetrahedral Framework Nucleic Acids (tFNAs)

TFNAs represent another promising approach. tFNAs inhibit the TLR4/MyD88/NF-κB signaling pathway, reducing the release of IL-6 and TNF-α, and modulating apoptotic proteins to disrupt the detrimental "inflammation-apoptosis" cycle in acinar cells. In taurocholate-induced SAP models, tFNAs significantly alleviate pancreatic edema, necrosis, and inflammatory cell infiltration in remote organs such as the lung, liver, and kidney, with efficacy closely linked to inhibiting NF-κB p65 nuclear translocation and downregulating adhesion molecule ICAM1 expression.[101]

Despite progress, clinical translation of nanozyme-based AP therapy is hindered by limited preclinical models and passive delivery, long-term biosafety concerns (metal ion leaching), and challenges in scalable manufacturing. Future work should prioritize stimuli-responsive designs, active targeting, standardized safety protocols, and nanozyme–drug combination strategies.

Photodynamic Therapy and Postoperative Adjuncts with Nano-Reagents

Additionally, nanotechnology-based photodynamic therapy (PDT) is an almost non-invasive treatment approach that utilizes photosensitizers, specific wavelength light sources, and oxygen. With both precision and low systemic toxic side effects, PDT has brought hope for the treatment of various diseases.[102,175,176] Morphology-regulated molybdenum disulfide (MoS_2) nanoreactors achieve inflammatory suppression in SAP via PDT. The hollow-structured H-MoS_2, with the highest electric field intensity and light absorption efficiency, can reduce serum amylase/lipase levels to one-third of those in SAP models and decrease the apoptosis rate of pancreatic acinar cells by 50% under 808 nm laser irradiation.[103] Paying attention to postoperative complications of AP is equally important. Shanto invented a dual-layer nanofibrous membrane loaded with mitomycin C and thrombin, constructing a composite structure via electrospinning technology—an inner layer with high hydrophilicity (gelatin/alginate) and an outer layer for mechanical support (polycaprolactone, PCL). This membrane not only achieves strong tissue adhesion and biodegradability through cross-linking modification but also exerts multiple effects postoperatively: hemostasis (reducing clotting time by 40% in vitro), inhibition of tissue adhesion, and promotion of wound healing. In vivo experiments confirmed its efficacy in preventing pancreatic leakage caused by suture rupture.[177]

The therapeutic efficacy of nano-reagents is compelling in these preclinical studies, yet their experimental design presents common translational challenges. Sample sizes typically range from n=5 to n=10 per group, which, while conventional, may be underpowered for assessing complex outcomes like survival. The use of G*Power for sample size estimation is a strength in some studies but is not a universal practice. Reproducibility is facilitated by comprehensive descriptions of nanoparticle formulation, drug loading, and animal modeling. A significant limitation, however, is the nearly exclusive use of a single AP induction method and animal strain per study, which does not fully recapitulate the heterogeneity of human AP and may limit the generalizability of the findings.

Theranostic Nano-Strategies

In the field of integrated nano-theranostics for AP, multifunctional nano-reagents have exhibited remarkable diagnostic and therapeutic potential. Chitosan-based inflammation-responsive nano-reagents (CDs/RES@CS NPs) employ Ce/Gd bimetal-doped carbon dots (Ce/Gd-CDs) for reactive oxygen species (ROS) scavenging, coupled with resveratrol (RES) to promote macrophage polarization toward the anti-inflammatory M2 phenotype, and enable therapeutic monitoring via Gd^{3+} mediated MRI—significantly alleviating inflammatory responses in both in vitro and in vivo models.[104] Superparamagnetic iron oxide (SPIO)-loaded liposomes encapsulated with clodronate inhibit proinflammatory cytokine (TNF-α, IL-6) release through macrophage apoptosis induction while leveraging SPIO-induced T2-weighted MRI signal attenuation to visualize real-time inflammatory dynamics in liver/kidney injuries, offering an integrated "therapy-imaging" solution for organ protection in severe SAP.[105,106] Prussian blue-modified upconversion nanoprobes enable ultrasensitive serum H_2S detection (linear range 0–150 μM, detection limit 50 nM) and in vivo fluorescence/MRI bimodal imaging via PB's specific H_2S responsiveness. In combination with the H_2S synthase inhibitor DL-PAG, these probes synergistically mitigate AP-related lung injury. The purely inorganic nature and clinical safety of PB endow this system with translational potential for early AP diagnosis and complication intervention.[107]

Experiments exemplify how functional integration of nano-reagents has enabled breakthroughs in pathological intervention (ROS scavenging, macrophage polarization regulation) and real-time diagnostic monitoring, paving the way for precision theranostics of inflammatory diseases. Such diagnosis-guided, feedback-responsive theranostic strategies establish a virtuous cycle: early biomarker detection facilitates targeted nano-intervention, while dynamic imaging provides immediate therapeutic efficacy feedback—ultimately enabling adaptive AP management. Notwithstanding these preclinical successes, challenges remain in enhancing pancreatic targeting specificity, microenvironmental adaptability, and long-term biosafety. Drawing from closed-loop theranostic strategies validated in oncology and other inflammatory disorders, future AP research should prioritize rational nanoplatform design with multi-stimuli responsiveness and artificial intelligence integration for real-time precision decision-making.[178–180] This closed-loop paradigm represents a frontier for achieving individualized and efficacious AP therapy.

Conclusion and Prospect

This review has systematically categorized the functional applications of nano-reagents in the diagnosis and treatment of acute pancreatitis (AP), emphasizing their modes of action to provide a framework for clinical translation. While significant preclinical progress has been achieved, moving from concept to clinical reality requires overcoming several specific, unresolved challenges. Future research must strategically address these bottlenecks through deep interdisciplinary integration. Specifically, we identify the following critical directions and propose corresponding solutions to accelerate clinical translation:

Key Future Research Directions: From Concept to Integration

From Single-Analyte Diagnostics to Comprehensive Biomarker Profiling

While nano-sensors and contrast agents have indeed "enabled early detection of biomarkers and precise imaging of pancreatic lesions" as discussed, current diagnostic nanoprobes predominantly target single markers. Examples include Pd(atz,ur) complexes for amylase,[40] G-CDs for lipase,[44] or specific dual-engine DNA Walker biosensors for individual miRNAs like miRNA-24-3p.[125] However, accurate AP diagnosis and severity stratification often rely on a composite panel of indicators. A critical unmet need is the development of integrated nanosystems for the simultaneous, real-time detection of multiple AP-related biomarkers. Future efforts should focus on "lab-on-a-chip" platforms that integrate multiplexed nanosensors (eg, multi-color quantum dots or FRET-based nano-arrays). Such platforms could simultaneously quantify key enzymes (amylase, lipase, trypsin) and critical inflammatory cytokines (eg, TNF-α, IL-6) from a single biological sample, providing a comprehensive "AP signature" for rapid diagnosis and prognostic assessment.

From Unimodal Interventions to Multi-Pronged Therapeutic Strategies

The pathogenesis of AP involves a complex and "cascading systemic inflammatory reaction" and "self-digestion of pancreatic tissue" as highlighted in the Abstract. While nano-reagents have begun to "address barriers like the blood-pancreatic barrier, low drug specificity, and insufficient intervention in the pathogenesis through multi-faceted strategies", many existing nanotherapeutics still predominantly target single pathways. For instance, Se@SiO_2 nanoparticles focus on ROS scavenging,[92] and CAPE-NL primarily targets NF-κB inhibition.[90] The efficacy of such unimodal interventions is often limited in severe AP (SAP), where autodigestion, overwhelming inflammation, and oxidative stress intricately coexist.[87] The therapeutic efficacy of such unimodal interventions is often limited in halting the multifaceted progression of severe AP. Thus, the next generation of therapeutic nano-reagents should therefore be conceived as "poly-pharmacological platforms", drawing inspiration from successful preclinical models: Cu-MOF@PLGA core-shell nanoparticles. A Cu-MOF core can mimic SOD/CAT dual enzymes, demonstrating significant reduction in pancreatic MDA levels.[100] Concurrently, the PLGA shell co-delivers inhibitors like aprotinin (a trypsin inhibitor) and PDTC (an NF-κB inhibitor), leading to a substantial suppression of TNF-α/IL-6 release.[90] This multi-pronged design directly aims to disrupt AP's complex vicious cycle.

Real-Time Dynamic Feedback in Theranostics for Adaptive Management

Despite this recognized potential of theranostic strategies, most current systems primarily provide static information (Gd-DTPA-FA[72]) rather than dynamic feedback directly indicative of therapeutic action or disease progression. Thus, a significant gap lies in the scarcity of "smart" theranostic nano-reagents capable of reporting on their own therapeutic effect in real-time. Research should be directed towards creating "activatable" theranostic systems. For example, a nanoplatform could maintain a quenched fluorescence signal until its therapeutic payload is released upon encountering the high protease activity in the AP microenvironment; the subsequent fluorescence activation would not only confirm targeted drug delivery but also serve as a real-time proxy for enzymatic activity and therapeutic engagement at the lesion site.

Critical Challenges and Pathways for Clinical Translation

Despite remarkable preclinical achievements, the clinical translation of AP nanomedicines confronts multifaceted obstacles encompassing safety, clinical validation, and production.

Regarding safety, some metal-based nanomaterials pose long-term accumulation risks due to an incomplete understanding of their pharmacokinetics and biodegradability. This necessitates systematic toxicological studies and long-term follow-up in clinically relevant disease models (eg, SAP-induced alterations in PK/retention), and the development of inherently safer biomimetic/degradable materials and in silico optimization.[181,182]

For clinical validation, Current animal models often fail to reflect the complexity of AP subtypes, hindering direct extrapolation of efficacy and safety to humans.[183] This gap can only be addressed through multi-center, large-sample clinical trials with personalized research plans tailored to specific AP patient cohorts.

In terms of production, Complex synthesis, difficulties in achieving mass production, and prominent batch-to-batch quality inconsistencies impede clinical supply.[184] Future efforts must focus on high-throughput preparation technologies, standardized production processes, and AI-driven optimization to ensure scalable yield and stringent quality control.

Promising Translational Pathways and Future Roadmap

Among the diverse nano-reagents discussed, lipid-based systems (eg, liposomes) and certain inorganic nanomaterials (eg, porous silica) currently hold the greatest near-term potential for clinical translation for AP. Liposomes benefit from superior biocompatibility, biodegradability, and a well-established clinical track record. Their success in FDA-approved nanomedicines (eg, Doxil,®[185] Onivyde®[186]) for delivering chemotherapeutic agents provides a clear regulatory pathway for their repurposing in AP, evidenced by their use in delivering therapeutic agents like kaempferol[75] and BAPTA-AM[77] in AP models. Certain Inorganic Nanomaterials, particularly porous silica nanoparticles (eg, COS@SiO_2[88]), offer high drug loading capacity and tunable structures. More importantly, candidates like C-dots[187] a fluorescent silica nanoparticle, have already entered human trials (NCT02106598) under FDA oversight, marking a critical breakthrough for inorganic nanoreagents.

Looking forward, a structured, phased roadmap is essential to guide the transition from bench to bedside: In the short term (next 3–5 years), priority should be given to finalizing robust preclinical safety and efficacy data for the most promising candidates (like polymer-based multi-pronged systems) in advanced animal models. Concurrently, developing standardized manufacturing protocols is crucial. This should be followed by early-phase (I/II) human trials within approximately 5–8 years, initially focusing on severe AP patient cohorts where unmet need is highest. In the mid-to-long term (8–15 years and beyond), larger Phase III trials and post-marketing surveillance will be essential for broader adoption. Critically, integration with AI-guided precision medicine should be pursued throughout this roadmap. AI can accelerate nanomaterial design (eg, predicting in vivo behavior), optimize trial design via patient stratification based on AP endotypes identified through multi-omics data, and eventually enable dynamic treatment adjustment by analyzing real-time diagnostic data from theranostic nano-reagents, truly realizing personalized AP management.

Finally, bridging the gap between promising preclinical data and clinical application requires addressing methodological standardization. Future research must prioritize robust statistical design, independent replication, and testing in multiple, clinically relevant animal models to firmly establish efficacy and reproducibility before clinical translation.

Ethics Statement

Ethical review and approval were not required for this submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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