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REVIEW

Peptides in the Diagnosis and Treatment of Pancreatic Cancer and Other Pancreatic Diseases from Basic Research to Clinical Translation

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Abstract: Peptides have emerged as pivotal agents in biomedicine due to their exceptional physicochemical properties, including high binding affinity, minimal immunogenicity, and precise target specificity. This review critically examines recent advancements in peptide-based strategies for pancreatic disorders, encompassing inflammatory conditions (e.g. pancreatitis), metabolic dysfunctions (e.g. diabetes), and notably, pancreatic cancer. We delineate the evolution of peptide therapeutics, emphasizing rational drug design approaches such as backbone cyclization and N-methylation to enhance metabolic stability, complemented by computational methodologies like molecular docking and AI-driven affinity maturation to optimize target engagement. The discussion highlights key innovations, including peptide probes for early diagnostic detection and peptide-drug conjugates for targeted intervention, while evaluating their efficacy in preclinical models and assessing their biosafety profiles. Furthermore, we survey current clinical trials aimed at translating these engineered peptides into clinical applications. Concluding with a perspective on precision medicine, we outline future trajectories necessitating advanced AI-integrated design frameworks and robust clinical validation to accelerate the bench-to-bedside translation of peptide technologies.

Keywords: peptides, pancreatic diseases, diagnosis and therapy, clinical translation

Introduction

Pancreatic pathologies, encompassing pancreatic cancer (PC), acute pancreatitis (AP), chronic pancreatitis (CP), and diabetes mellitus (DM), exact a profound toll due to their alarming morbidity and mortality profiles.[1] AP frequently precipitates multiple organ dysfunction syndrome and life-threatening sequelae, claiming 15% to 20% of affected lives.[2,3] CP is characterized by the relentless, irreversible erosion of pancreatic architecture, culminating in exocrine and endocrine failure while increasing the risk of PC.[4,5] PC remains a formidable adversary, notorious for its elusiveness in early detection, rapid progression, and therapeutic recalcitrance, with only 13% of patients surviving five years post-diagnosis.[6,7] DM is associated with a range of systemic complications, ranging from nephropathy and ischemic heart disease to stroke and peripheral vascular disease.[8,9] A pivotal clinical impasse persists: the absence of diagnostic and therapeutic modalities that simultaneously offer high specificity, sensitivity, and minimal adverse effects. Consequently, the discovery of potent strategies for intervention stands as a paramount imperative in pancreatic research.

The molecular and clinical landscapes of these diseases are defined by distinct aberrations that drive their progression. In PC, oncogenic KRAS mutations act as a master switch, fueling uncontrolled proliferation and fostering a dense, fibrotic microenvironment that impedes drug delivery and promotes chemoresistance.[10] Similarly, CP is driven by a self-

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perpetuating cycle of inflammation and fibrosis within the pancreatic stroma, yet targeted therapies to halt this scarring remain conspicuously absent.[11,12] In DM, pervasive insulin resistance disrupts metabolic homeostasis, leading to widespread tissue damage.[13] Current therapeutic options are often limited by these complexities; conventional chemotherapy in PC frequently fails due to intrinsic resistance mechanisms,[14,15] while the management of CP lacks precision tools to address its underlying fibrotic drivers.[16] These limitations underscore the urgent rationale for developing novel, peptide-based interventions.

However, a critical bottleneck in translating these novel interventions into clinical success stems from the limited predictive power of current preclinical models. Rodent models of pancreatitis and pancreatic cancer, including genetically engineered mice and xenografts, often fail to fully recapitulate the desmoplastic stroma, immune microenvironment, and metabolic complexity characteristic of human disease.[17] Similarly, reductionist in vitro assays, while indispensable for mechanistic dissection, cannot faithfully recapitulate the systemic pharmacokinetics, organ crosstalk, or chronic toxicity profiles that decisively influence therapeutic efficacy and safety in patients.[18] This well-recognized disconnect is evidenced by the high attrition rate of candidate therapeutics that demonstrate robust activity in animal studies yet ultimately fail due to lack of efficacy or unacceptable toxicity in clinical trials.

In recent years, peptides have emerged as promising candidates in this field, distinguished by their unique biochemical versatility and therapeutic potential. Capable of reproducible synthesis and precise chemical modification based on amino acid composition, peptides exhibit high binding affinity, low immunogenicity, and exceptional target specificity.[19] These attributes position them as ideal candidates for overcoming the hurdles of pancreatic disease management. The therapeutic promise of peptides is manifested through diverse strategic applications aimed at curbing tumor growth and arresting disease progression. Targeted therapy, utilizing peptides to home in on malignant cells while sparing healthy tissue, is gaining traction as a sophisticated alternative to the blunt instrument of conventional chemotherapy.[20] Peptides operate through a multifaceted mechanism of action: they can serve as direct cytotoxic agents or function as precision-guided delivery vehicles for chemotherapeutics and radioisotopes in oncology; concurrently, they demonstrate significant potential in mitigating pancreatitis and diabetes via anti-inflammatory, immunomodulatory, and islet β-cell protective roles.[21–23]

This review systematically delineates the four core dimensions of peptides in pancreatic cancer and other pancreatic diseases—the research and development trajectory, diagnostic applications, therapeutic strategies, and clinical translation—and incorporates a dedicated discussion section that critically examines current limitations and future directions. In contrast to earlier reviews that have either concentrated on a single facet or provided only a compilation of existing data, we highlight the latest advances of recent years, underscoring the trend of interdisciplinary convergence. In particular, we adopt the deep integration of artificial intelligence and clinical practice as a central theme—specifically, leveraging deep generative models and reinforcement learning in peptide drug design to refine lead compound screening. Building on this foundation, we explicitly bridge the gap between fundamental research and clinical translation for peptide-based drugs. This review not only provides a comprehensive and forward-looking roadmap for translating peptide tools into precision diagnosis and treatment of pancreatic diseases; furthermore, its novelty lies in constructing a trinity perspective of "AI-peptide-clinic," which revealing the significant potential of AI in the process from molecular design to clinical transformation, thereby charting a course for the future development of mature, stable, and safe innovative peptide drugs and theranostic systems.

Development of Peptide-Based Drugs

The trajectory of peptide therapeutics has evolved from natural discovery to sophisticated application, yet this narrative is here distilled to highlight milestones specifically catalyzing advancements in pancreatic disease management. While the broader field has expanded through chemical synthesis and technological optimization, our focus remains strictly on developments pivotal to pancreatic pharmacology. Figure 1 schematically illustrates this targeted evolution.

Exploration and Origins (1920s–1960s)

This era was defined by the seminal isolation of insulin from bovine and porcine pancreata in 1922, a breakthrough that not only inaugurated the age of peptide therapeutics but also established the foundational paradigm for treating

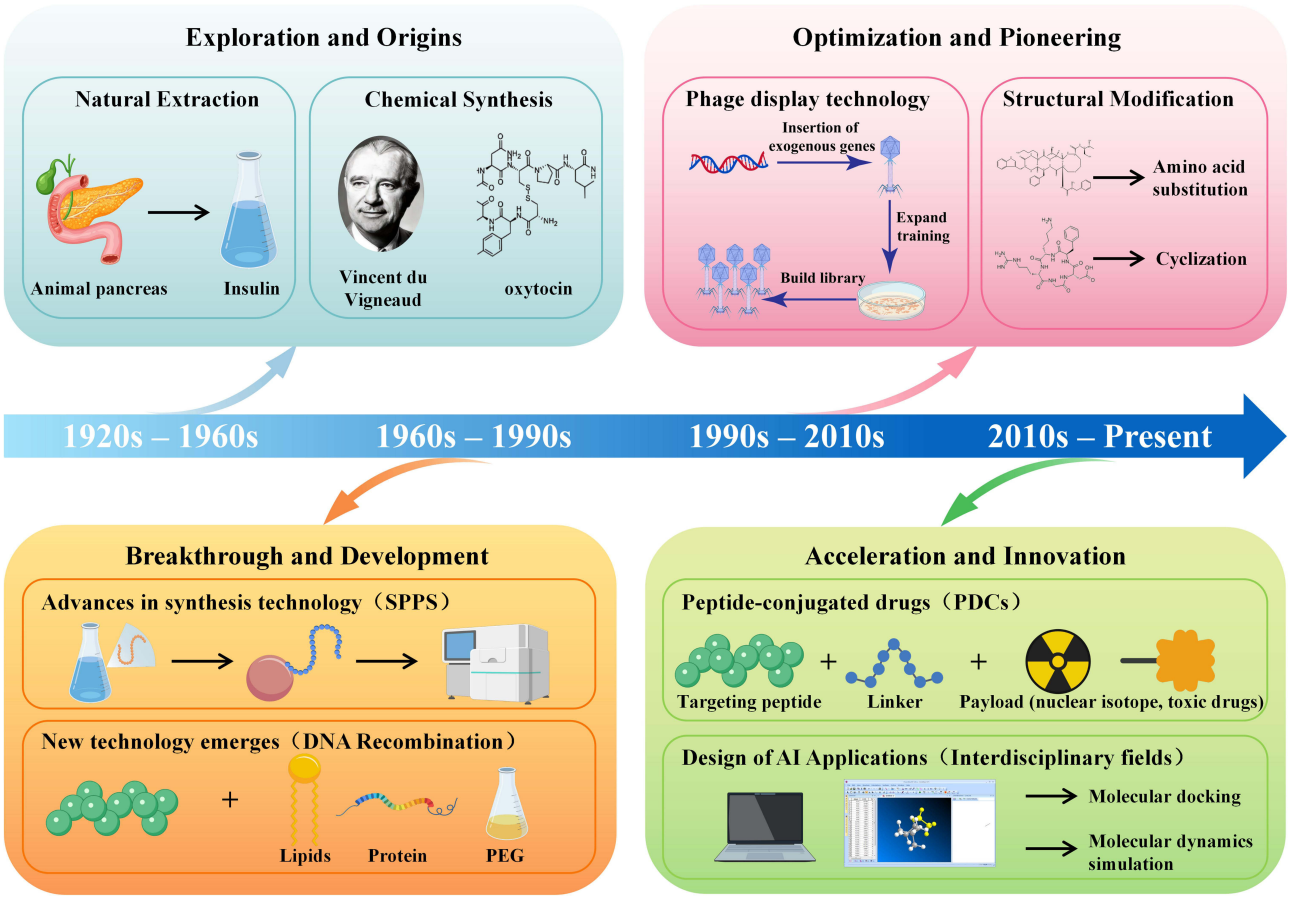

Figure 1 Development of peptide-based drugs. This timeline delineates the four pivotal eras in the maturation of peptide drugs: the Exploratory Origin (1920s–1960s), marked by the isolation of natural insulin and the synthesis of oxytocin; the Breakthrough Development phase (1960s–1990s), driven by solid-phase synthesis and DNA technologies; the Optimization epoch (1990s–2010s), characterized by phage display methodologies; and the current era of Accelerated Innovation (2010s-present), featuring PDCs and AI. Collectively, this trajectory underscores the paradigm shift from reliance on natural products to the establishment of peptides as a cornerstone of modern research and development.

diabetes.[24] Although subsequent achievements, such as the Nobel-winning chemical synthesis of oxytocin and vasopressin by du Vigneaud's team in 1954, demonstrated the feasibility of synthetic peptides,[25,26] the primary impetus for pancreatic research remained rooted in the therapeutic potential first unlocked by insulin.

Breakthrough and Development (1960s–1990s)

Advancements in synthesis technologies, particularly Robert Bruce Merrifield's invention of solid-phase peptide synthesis (SPPS), revolutionized the production landscape by enabling automated, large-scale assembly.[27] For pancreatic applications, this period was further transformed by the advent of recombinant DNA technology in the 1980s. Strategies involving conjugation with lipids, proteins, or polyethylene glycol (PEG) were employed to augment molecular weight, thereby mitigating renal clearance and prolonging plasma circulation—critical modifications for enhancing the efficacy of peptide interventions in pancreatic disorders.[28]

Optimization and Pioneering (1990s–2010s)

Research efforts subsequently shifted toward overcoming intrinsic pharmacokinetic barriers, such as instability and short half-life, which had previously limited peptide utility in pancreatic therapy.[29] The advent of display technologies, notably phage display, enabled the discovery of peptides with superior drug-like profiles from vast libraries.[30] Rigorous structural engineering strategies, including the incorporation of D-amino acids,[31] unnatural amino acids,[32] N-terminal capping, deamination,[33,34] terminal extensions,[35] and disulfide bond mimetics,[36,37] significantly enhanced stability. These

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refinements were instrumental in developing agents relevant to pancreatic function and regulation, such as desmopressin and terlipressin.[38,39] Notably, backbone cyclization strategies, including head-to-tail and side-chain-to-side-chain cyclization, were introduced to further reduce susceptibility to pancreatic enzymes. By restricting conformational flexibility, these macrocyclic structures exhibit markedly improved metabolic stability against pancreatic proteases, an approach that has garnered significant attention in peptide drug design for pancreatic diseases.[40–42] In parallel, the incorporation of N-methylated amino acids gained traction as a complementary modification. The N-methyl groups introduce steric hindrance and constrain the peptide backbone, thereby impeding protease access to the scissile bond and significantly reducing proteolytic cleavage.[43,44]

Acceleration and Innovation (2010s–Present)

The contemporary landscape is defined by rapid advancement and paradigm-shifting innovation, propelled by the convergence of cutting-edge technologies and interdisciplinary methodologies. Through the strategic conjugation of targeting peptides with cytotoxic payloads, small-molecule therapeutics, or radionuclides via specialized linkers, investigators have achieved precise targeting of disease sites, thereby amplifying therapeutic efficacy while mitigating systemic toxicity. This approach has positioned peptide-drug conjugates (PDCs) as a transformative force in tumor diagnosis and therapy.[45] Concurrently, the deployment of artificial intelligence algorithms has expedited the screening of therapeutic peptide sequences and empowered computational modeling to forecast peptide–target interactions and binding affinities, highlighting the pivotal role of cross-disciplinary strategies in advancing drug development and precision medicine.[46,47]

Application of Peptides in the Diagnosis of Pancreatic Diseases

Currently, pancreatic diseases, particularly PC, are often associated with poor clinical prognosis due to difficulties in early diagnosis and the lack of highly specific biomarkers. The development of highly specific diagnostic methods is therefore imperative. Peptide molecules, with their exceptional targeting specificity, high designability and engineering potential, excellent biocompatibility, and high tissue penetration,[48] offer a powerful tool to address this challenge. The applications of peptides in the diagnosis of pancreatic diseases are shown in Figure 2.

Targeted Peptide Probes

Current diagnostic modalities for PC, including endoscopic ultrasound, magnetic resonance imaging, and the tumor marker carbohydrate antigen 19–9 (CA19-9), are insufficient for early-stage diagnosis. This limitation results in 80–85% of PC patients presenting with metastatic disease at the time of diagnosis, rendering them ineligible for surgical resection.[49,50] Research has shown that peptide-based imaging probes have emerged as a viable tool for achieving enhanced tumor permeability and specificity. Many researchers select peptides as potential tumor ligands due to their smaller size, versatility and lower cost of chemical modification, and the fact that tumor-targeting peptides can be obtained from natural products, biological screening libraries, or synthetic peptide arrays.[51] Consequently, peptide-based probes are increasingly being employed for the early diagnosis of PC in recent years.

The ANXA2-Targeted Near-Infrared Fluorescent Probe Cy7-YW7

Through bioinformatics analysis and other methods, researchers have identified annexin A2 (ANXA2) as a novel biomarker for pancreatic ductal adenocarcinoma (PDAC), as elevated ANXA2 expression is significantly correlated with poorer overall survival (OS) and disease-free survival (DFS) in PDAC patients.[52] Building on this finding, researchers utilized phage display technology to screen for and identify YW7, a heptapeptide targeting the ANXA2 protein.[53] They subsequently developed a molecular fluorescence imaging probe, Cy7-YW7, and validated its targeting specificity through both in vitro and in vivo experiments. The results suggest its potential as a probe to enhance diagnostic efficacy in PDAC.[54] The primary novelty of this study resides in the screening of an ANXA2-targeting heptapeptide via phage display and the development of a novel near-infrared fluorescence (NIRF) probe, Cy7-YW7. However, its validation was performed solely in mouse models, and crucially, pharmacokinetic properties—including biodistribution and half-life—were not assessed; consequently, the full extent of its target specificity and potential off-

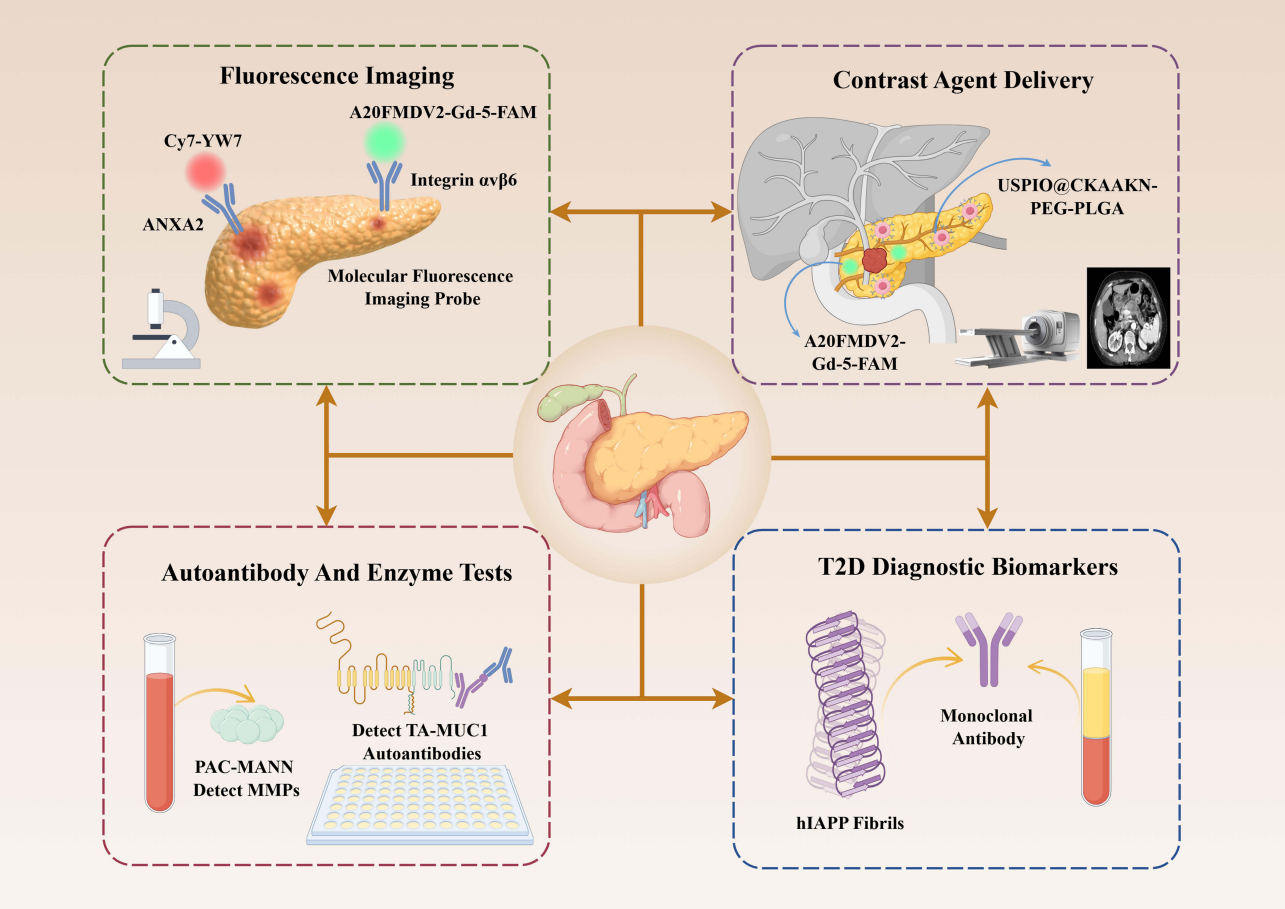

Figure 2 Application of peptides in the diagnosis of pancreatic diseases. This schematic elucidates two critical avenues for peptide-mediated diagnosis of pancreatic disorders: firstly, the deployment of imaging probes targeting oncogenic biomarkers (e.g., ANXA2) alongside liquid biopsy strategies via protease detection; and secondly, the utilization of diagnostic antibodies directed against hIAPP amyloid fibrils in T2D. By capitalizing on their exceptional specificity, superior tissue penetration, and modular engineering potential, peptides facilitate early-stage detection, with particular efficacy in PC.

target toxicity remains undetermined. Therefore, future development of the Cy7-YW7 probe should include comprehensive biodistribution studies to exclude off-target toxicity and ensure true targeting specificity.

Peptide Probes for the Specific Delivery of MRI Contrast Agents

To enable targeted delivery of the magnetic resonance imaging (MRI) contrast agent ultrasmall superparamagnetic iron oxide (USPIO)[55] and improve the early diagnostic efficacy for PDAC, researchers developed magnetic polymer nanoparticles based on poly (lactic-co-glycolic acid) (PLGA) (USPIO@CKAAKN-PEG-PLGA). These peptide-modified targeted nanoparticles, prepared via amidation reaction and emulsion solvent evaporation methods, demonstrated specific targeting capability for PC cells in in vitro experiments. Biosafety assessments were also conducted, confirming their favorable safety profile.[56] The innovation of this study lies in the combination of a targeting peptide with a PLGA-PEG nanocarrier to achieve precise targeting, potentially via the Wnt signaling pathway, resulting in the development of a highly specific, low-toxicity molecular imaging probe.

Genetically Engineered MUC1 Glycopeptide Nanoprobes

To Addressing the lack of specificity in early diagnostic markers for PC, and aiming to improve diagnostic specificity, researchers focused on detecting autoantibodies against tumor-associated mucin-1 (TA-MUC1).[57] Based on this, they designed engineered glycopeptide nanoprobes for the detection of TA-MUC1 autoantibodies. The glycopeptide was designed and optimized based on the X-ray crystal structure of TA-MUC1[58] and used to construct the nanoprobe. The glycopeptide was validated through a series of binding assays, and the detection performance was verified via dot blot

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analysis. A subsequent retrospective clinical study demonstrated its potential as an independent diagnostic marker.[59] The innovation of this research is the development of a multivalent nanoprobe that enhances detection sensitivity, leading to a highly specific and sensitive glycopeptide nanoprobe. However, a limitation is the small sample size of the retrospective clinical study, indicating the need for further validation with larger clinical cohorts.

A Dual-Modal Peptide Probe That Targets Overexpressed Integrin αvβ6

Integrin αvβ6 is highly expressed in various tumors, particularly PDAC, while being nearly absent in normal tissues, making it an ideal target.[60] Targeting this, researchers designed a nanoprobe designated A20FMDV2-Gd-5-FAM. A20FMDV2, a peptide derived from foot-and-mouth disease virus, serves as the ligand for targeting αvβ6, enabling early diagnosis of αvβ6-high PC. Following synthesis, the probe's stability and performance were evaluated using a series of characterization methods, including dynamic light scattering.[61] Both in vivo and in vitro experiments demonstrated its excellent targeting specificity for integrin αvβ6 and its capability for dual-modal imaging. Furthermore, assessments of blood biochemical parameters and H&E staining of tissue sections confirmed its good biosafety.[62] The innovation of this study is the integration of a targeting peptide with an MRI contrast agent to design a dual-modal molecular probe possessing good stability, excellent targeting ability, and dual-modal imaging capacity, resulting in a highly specific, low-toxicity molecular imaging probe. However, a limitation is the insufficient assessment of the long-term toxicity associated with gadolinium (Gd) retention in vivo.

Protease-Cleaved Nanosensors Based on High-Throughput Screening of Peptide Probes

In cancer detection based on liquid biopsy, proteases represent an underutilized class of proteins directly implicated in tumor progression.[63] Building on this, researchers discovered that PDAC is particularly adept at secreting matrix metalloproteinases (MMPs), which degrade extracellular matrix components such as collagen and elastin to facilitate cancer cell migration across tissues. Consequently, these proteases inevitably enter the bloodstream and circulatory system, providing detectable targets for researchers.[64–66] Based on this rationale, researchers designed a high-throughput screening platform utilizing peptide probes to develop protease-cleaved nanosensors (PAC-MANN) for the early diagnosis of PDAC. The peptide probes were designed and screened using a charge change protease (CCP) assay platform, and key enzymes were validated using protease inhibitors. Subsequently, the screened probes were conjugated to magnetic nanoparticles to construct the PAC-MANN sensor, and its clinical utility was evaluated using patient samples. The results from retrospective studies demonstrated its high specificity and sensitivity for the early diagnosis of PDAC.[67] The innovation of this study lies in the development of the PAC-MANN nanosensor, which requires only 8 μL of serum for detection, offering operational simplicity, rapid analysis, and high specificity and sensitivity. However, a limitation is the relatively small sample size from patients with pancreatitis and pancreatic premalignant lesions, necessitating further validation with larger cohorts. Additionally, its specificity for other cancer types has not yet been verified.

Diagnostic Biomarkers

Current diagnostic approaches for diabetes commonly rely on measuring fasting blood glucose or glycated hemoglobin. However, these parameters are susceptible to short-term fluctuations that can compromise accuracy.[68,69] Research has established that in type 2 DM (T2D), aberrant aggregation of human islet amyloid polypeptide (hIAPP) forms fibrils that disrupt pancreatic β-cell function and induce inflammatory responses,[70] yet existing therapeutic interventions fail to effectively target this pathological process. In response to the pathological of cytotoxic hIAPP fibrils in pancreatic β-cells in T2D,[71] researchers have developed monoclonal antibodies (mAbs) specifically targeting hIAPP fibrils, offering novel strategies for early diagnosis and therapeutic intervention. The research team utilized an engineered nuclear binding protein (mNUCB1) to stabilize hIAPP fibrils as an immunogen, and through mouse immunization and hybridoma screening, obtained two candidate antibodies (07G10 and 10H04). These antibodies were subsequently validated through both in vivo and in vitro experiments. Notably, these antibodies enabled detection of hIAPP fibrils in serum via ELISA, showing elevated signals prior to disease onset in T2D mouse models, suggesting their potential as early diagnostic biomarkers.[72] The innovation of this research lies in the first successful development of hIAPP fibril-specific antibodies,

which not only provide tools for investigating T2D pathological mechanisms but also open new avenues for disease intervention through targeted clearance of toxic fibrils and inhibition of inflammatory responses. However, a limitation is that validation has been primarily confined to mouse models and limited human tissue samples, necessitation expansion to larger clinical cohorts. Further studies are required to validate its clinical translational potential, particularly regarding its applicability as a non-invasive diagnostic biomarker and its possible integration into combination therapeutic strategies.

Application of Peptides in the Treatment of Pancreatic Diseases

The current clinical management of pancreatic diseases, including PC and AP, is hampered by significant challenges such as pronounced side effects associated with pharmacotherapy, poor post-treatment management, and a paucity of therapeutic options that offer both high specificity and low toxicity.[73,74] Peptides, characterized by their high affinity and specificity coupled with a short half-life, present viable therapeutic agents for pancreatic diseases. Figure 3 depicts the applications of peptides in the treatment of pancreatic diseases.

Targeted Peptide Therapy

Currently, effective pharmacotherapeutic options for PC and AP are lacking, and a major limitation of monotherapy is poor specificity accompanied by significant adverse effects. This therapeutic gap has led to the emergence of targeted

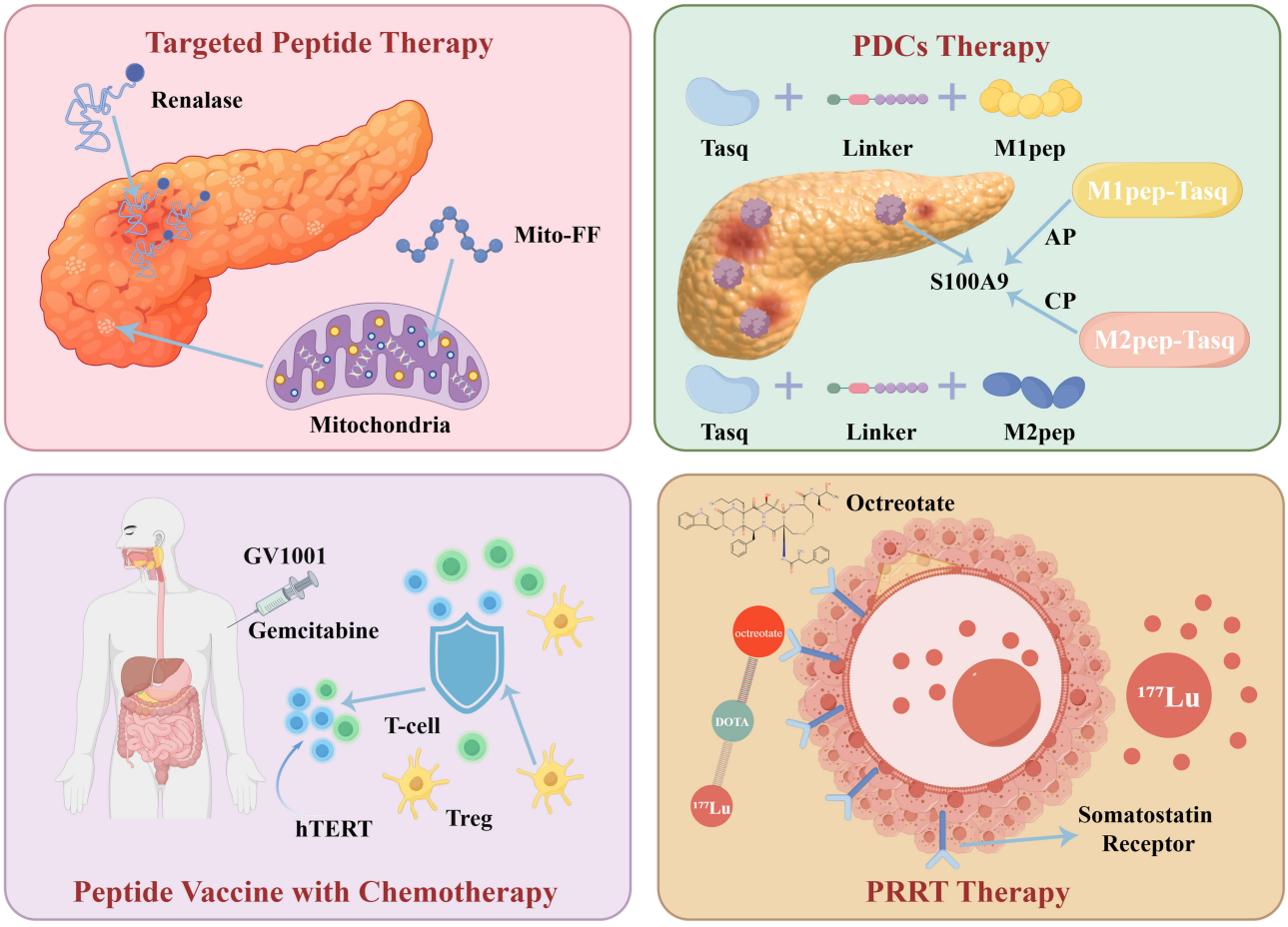

Figure 3 Application of peptides in the treatment of pancreatic diseases. This illustration categorizes four principal modalities for peptide-based intervention in pancreatic conditions: targeted therapy, PDCs, Peptide Vaccine-Chemotherapy Combinations, and PRRT. The figure emphasizes cutting-edge advancements in precision delivery systems—exemplified by M1/M2 macrophage-targeting PDCs and mitochondria-specific self-assembling peptides—as well as synergistic approaches in combination immunotherapy.

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peptide therapy. As an emerging precision treatment strategy, therapeutic peptides exhibit high specificity, enabling them to selectively recognize and bind disease-associated markers,[19] thereby achieving therapeutic efficacy.

Peptides Derived from the Renalase Active Site RP220

There are currently no specific pharmacotherapies for AP, and the inflammatory response constitutes a critical determinant of disease severity.[75] In addressing this inflammatory response, researchers identified that the active site RP220, a conserved 20-amino acid region of renalase,[76] may retain its anti-inflammatory and pro-survival properties. Furthermore, small peptide fragments are more amenable to production than the full-length renalase protein. Subsequently, investigators validated the therapeutic efficacy of RP10, a peptide containing the RP220 sequence, in two clinically relevant AP models (post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) and severe cerulein-induced pancreatitis). In vivo studies demonstrated that administration of RP10, which encompasses the RP220 site, significantly attenuated inflammation and tissue damage in both AP models by inhibiting bone marrow-derived inflammatory cell infiltration.[77] The innovation of this study lies in its first demonstration that a peptide containing the core renalase active site RP220 can exert therapeutic effects independently. Concurrently, it validated the efficacy of both prophylactic and therapeutic administration regimens in two clinically relevant models. This research has provided a novel candidate molecule, the renalase-derived peptide RP10, for the development of the first specific pharmacotherapy for AP.

Mitochondria-Targeting Self-Assembling Peptides

Compared with conventional chemotherapeutic approaches, mitochondria-targeted therapy is recognized as an emerging and prominent therapeutic modality,[78] demonstrating the potential for synergistic anticancer effects through its unique mechanism of action. Building upon this concept, researchers developed a novel therapeutic strategy for treating PC utilizing a mitochondria-targeting self-assembling peptide designated Mito-FF. Following mitochondrial localization, Mito-FF exploits organelle-localized induced self-assembly (OLISA)[79] to trigger its self-assembly into fibrous structures, thereby disrupting mitochondrial function. Subsequent in vitro experiments demonstrated its concentration-dependent cytotoxic effects against various PC cell lines, with relatively low toxicity towards normal cells. In vivo studies further confirmed its ability to significantly inhibit tumour growth and upregulate the expression of apoptosis markers.[80] The innovation of this study lies in its integration of a targeting peptide with mitochondrial targeting, offering a novel approach and strategy for the treatment of PC. However, a limitation is the lack of assessment of long-term accumulation toxicity; therefore, further safety evaluations are needed.

Targeted Peptide–Drug Combination Therapy

PDCs, as the next generation of targeted therapeutic agents following antibody–drug conjugates (ADCs), are rapidly emerging as a research focus in the field of precision medicine.[81] PDCs are composed of three components: a targeting peptide, a linker, and a cytotoxic payload. Compared with ADCs, they offer advantages such as a smaller molecular size, enhanced tissue penetration, lower immunogenicity, and greater feasibility for industrial synthesis and structural modification.[82,83] Currently, pharmaceutical research institutions worldwide are actively advancing the development of PDCs for targeted therapeutic applications in oncology and inflammatory diseases.

PDCs for PC Therapy

Daunorubicin is an antitumour antibiotic; however, its clinical utility is limited by its severe cardiotoxicity.[84] To mitigate this cardiotoxicity while enhancing its targeting specificity for PC, researchers designed a peptide–drug conjugate utilizing a targeting peptide (GSSEQLYL) identified via phage display and employing daunorubicin as the cytotoxic payload. Through amino acid substitutions,[85] the targeting peptide was optimized to achieve maximal conjugate activity. Subsequent in vitro cellular experiments demonstrated that the optimized conjugate efficiently targeted PC cells (PANC-1) and exerted antitumour effects through a dual mechanism involving the induction of cellular senescence culminating in apoptosis while significantly attenuating daunorubicin-induced cardiotoxicity; thus, the therapeutic potential of the optimized conjugate was promising.[86] The innovation of this study lies in the successful optimization of the targeting peptide via Ala scanning and unnatural amino acid substitution to increase its activity. However, a limitation is that the

validation was confined to in vitro cellular experiments without subsequent in vivo animal studies; moreover, a comprehensive assessment of targeting specificity and pharmacokinetic profiling is lacking.

PDCs for CP Therapy

M2 macrophages play a pivotal role in fibrosis during the advanced stages of CP.[87] Tasquinimod (Tasq), an S100A9 inhibitor, has been shown to reduce M2 macrophage infiltration; however, its clinical utility is limited by adverse effects such as nephrotoxicity.[88–90] To address this challenge, researchers developed a PDC targeting M2 macrophages, termed M2pep-Tasq, with the objective of achieving precise delivery of Tasq to M2 macrophages, thereby enhancing therapeutic efficacy while mitigating toxicity. The PDC was initially synthesized through molecular docking and chemical conjugation strategies, and its binding affinity was subsequently validated using surface plasmon resonance (SPR). Further in vitro and in vivo investigations confirmed that compared with free Tasq, M2pep-Tasq preferentially accumulated in pancreatic tissue, effectively alleviating pancreatic injury, fibrosis, and inflammation and reducing renal damage. Mechanistically, RNA sequencing analysis revealed that M2pep-Tasq exerts its effects by activating the PPARα signalling pathway, thereby suppressing NF-κB and AP-1 signalling and ultimately inhibiting M2 polarization.[91]

The key innovation of this study lies in the successful construction of M2pep-Tasq, a peptide-drug conjugate specifically targeting M2 macrophages, which enables the targeted delivery of Tasq to these cells, resulting in enhanced efficacy and reduced toxicity. This approach offers a novel strategy for targeted therapy in CP. However, a notable limitation is that the M2-targeting peptide was selected based on murine studies and its specificity and binding affinity for human M2.

PDCs for AP Therapy

Given that the S100A9 inhibitor Tasq, which is effective at treating AP,[92] is associated with nephrotoxicity, researchers have developed a PDC targeting M1 macrophages, designated M1pep-Tasq. This innovation aims to achieve precise targeting of proinflammatory M1 macrophages. The research team first employed phage display technology to screen for a peptide (M1pep) that specifically binds to M1 macrophages. This peptide was subsequently conjugated with Tasq to synthesize M1pep-Tasq. The targeting efficiency, pharmacodynamics, and toxicity of M1pep-Tasq were then validated through a series of in vitro and in vivo experiments. The results demonstrated that M1pep-Tasq more effectively ameliorated pancreatic injury, reduced serum amylase and lipase levels, and inhibited M1 macrophage polarization. Finally, through RNA-seq analysis, the team confirmed that M1pep-Tasq exerts its anti-inflammatory effects by specifically inhibiting the S100A9–TLR4–MAPK signalling pathway, thereby suppressing macrophage M1 polarization.[93]

The principal innovation of this study lies in the successful construction of M1pep-Tasq, a peptide–drug conjugate that specifically targets M1 macrophages. This approach enables the targeted delivery of Tasq to M1 macrophages, achieving the dual goals of "enhanced therapeutic efficacy, reduced toxicity" and "drug repurposing", thereby offering a novel strategy for targeted AP therapy. However, a limitation of this study is the lack of identification and characterization of the specific receptor for the M1-targeting peptide. Furthermore, although a mechanistic investigation confirmed the involvement of the S100A9-TLR4-MAPK pathway, a more comprehensive exploration of its mechanism of action is warranted in future studies.

Peptide Vaccine Combined with Chemotherapy

There is a lack of effective therapeutic options for advanced PC. Human Telomerase Reverse Transcriptase (hTERT) is overexpressed in 85–90% of patients with PC,[94] making it an ideal vaccine target. Based on this rationale, researchers hypothesized that the telomerase peptide vaccine GV1001, administered in combination with gemcitabine chemotherapy[95] and a GM-CSF adjuvant, could potentiate antitumour immune responses. Through both in vivo and in vitro experiments, the safety profile of GV1001 combined with gemcitabine was evaluated, along with the effects of different administration schedules on immunogenicity, and the correlations between immune responses and clinical outcomes were analysed. The results demonstrated that GV1001 combined with gemcitabine was safe and feasible, with

manageable adverse effects. Concurrent chemotherapy induced increased rates of immune response and significantly reduced regulatory Treg frequencies.[96]

The innovation of this research lies in that it represents the first comparative investigation of the immunological effects of concurrent versus sequential GV1001 administration with chemotherapy, complemented by multidimensional immune monitoring integrating DTH (delayed-type hypersensitivity), proliferation assays, ELISPOT, and cytokine profiling.[97] These findings provide direction for advanced PC treatment, suggesting that future research should focus on early-stage patients and combination strategies with immune checkpoint blockade.

Peptide Receptor Radionuclide Therapy

In recent years, the incidence of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) has been increasing annually.[98] In response, researchers have developed peptide receptor radionuclide therapy (PRRT),[99–101] which comprises three main components: a DOTA, the chelating agent DOTA, and the radioisotope ^{177}Lu. By targeting tumour cells expressing somatostatin receptors, this therapeutic modality achieves the internalization and subsequent release of β-radiation, inducing tumour cell death and achieving therapeutic efficacy. This therapy, which has received FDA approval, has advanced to Phase III clinical trials.

NETTER-2 represents the first phase III randomized trial specifically designed for newly diagnosed advanced G2–G3 well-differentiated GEP-NETs, which compared the efficacy and safety of first-line ^{177}Lu-Dotatate combined with octreotide versus high-dose octreotide monotherapy. In total, 226 patients were included in this study, and the results revealed significantly longer median progression-free survival (PFS) in the ^{177}Lu-Dotatate group (22.8 months) than in the control group (8.5 months), along with substantially improved response rates and a manageable safety profile. This research addresses a critical gap in clinical studies of higher-grade GEP-NETs and further supports the use of ^{177}Lu-Dotatate as an effective therapeutic option for patients with GEP-NETs.[102–104]

Clinical Translation of Peptide Drugs for Pancreatic Diseases

Based on this systematic review of the applications of peptide drugs in the diagnosis and treatment of pancreatic diseases, these therapeutic agents offer distinct advantages owing to their high target selectivity, favourable biosafety profile, and modifiability of sequence and structure for both diagnostic and therapeutic purposes. Consequently, numerous pharmaceutical companies and research institutions have substantially increased their investments in peptide drug development. Currently, peptide drug research is predominantly focused on two major areas—PC and DM—aiming to overcome the limitations of existing therapeutic modalities. This substantial increase in research and development efforts has already yielded a series of clinical translation outcomes; in recent years, multiple peptide drugs targeting pancreatic diseases have successively entered various phases of clinical trials. To better illustrate the research progress in this field, Table 1 below

Table 1 Summary of Peptide-Based Drugs for Pancreatic Diseases That Have Entered Clinical Trials in Recent Years

Generic Name	Target	Indications	Status	Source
^{177}Lu-Dotatate	SSTR2	GEP-NETs	Apply for listing	[102,105,106]
Semaglutide	GLP1R INSR	T2D	Phase III	[107,108]
Tedopi	Not applicable	PDAC	Phase II	[109]
DiaPep277	TLR2	T1D	Phase III	[110]
Ecnoglutide	GLP1R	T2D	Phase III	[111,112]
Mazdutide	GLP1R GCGR	T2D	Going public	[113–115]
rExenatide-4	GLP1R	T2D	Phase III	[116]
Albenatide	GLP1R	T2D	Apply for listing	[117]
Efsubaglutide Alfa	GLP1R	T2D	Approval for listing	[118–120]
Visepegenatide	GLP1R	T2D	Approval for listing	[13,121]

summarizes representative peptide drugs related to pancreatic diseases that have entered clinical trials in recent years, aiming to provide references and insights for future research and development.

Peptide Vaccines and Immunotherapy

ELI-002 is a lymph-node-targeted amphiphile mKRAS peptide vaccine and represents the most advanced clinical translation in the field of pancreatic cancer peptide vaccines. AMPLIFY-201 (NCT04853017) was a Phase I clinical trial that enrolled 25 patients with minimal residual disease after locoregional treatment, including 20 with pancreatic cancer and 5 with colorectal cancer The vaccine utilizes amphiphile-modified G12D and G12R mutant KRAS peptides in combination with a CpG oligonucleotide adjuvant (Amph-CpG-7909) to enhance lymph node delivery and immune response.[122]

Key Efficacy Data

Direct ex vivo assays demonstrated that 21 of 25 patients (84%) developed mKRAS-specific T cell responses, with 59% exhibiting both $CD4^+$ and $CD8^+$ T cell responses; a response in tumor biomarkers (ctDNA and/or serum tumor antigens) was observed in 84% (21/25) of patients, among whom 6 (24%) achieved complete biomarker clearance; median relapse-free survival (mRFS) reached 16.33 months. Importantly, T cell response magnitude correlated significantly with clinical benefit: patients with T cell responses above the median fold increase over baseline (12.75-fold) had a median tumor biomarker reduction of-76.0% versus-10.2% in those below this threshold ($P<0.0014$); mRFS was not reached in the above-median group, whereas it was only 4.01 months in the below-median group (HR=0.14, P=0.0167). No dose-limiting toxicities were observed, and the recommended Phase II dose was established at 10.0 mg of Amph-CpG-7909.[122]

Limitations

The study employed a single-arm, open-label design with a limited sample size; enrollment criteria requiring MRD positivity may have selected a subgroup with a relatively poor prognosis, potentially introducing selection bias.

Targeted Cyclic Peptide Drugs

Certepetide (formerly LSTA1/CEND-1) is a novel iRGD cyclic peptide that enhances the penetration of co-administered chemotherapeutic agents into tumor parenchyma and stroma by binding to neuropilin-1 receptors on tumor vascular endothelial cells and tumor cells. The ASCEND phase II trial (NCT05042128) was a randomized, double-blind, placebo-controlled phase II clinical trial that enrolled 95 patients with untreated metastatic PDAC, randomized 2:1 to receive gemcitabine plus nab-paclitaxel (GEM/NAB-PAC) plus certepetide (3.2 mg/kg) or placebo.[123]

Key Efficacy Data

The primary endpoint of 6-month PFS rate was 49.0% (95% CI: 36.4%, 60.5%) in the certepetide group and 40.8% (95% CI: 22.6%, 58.3%) in the placebo group, which did not achieve the pre-specified target improvement (from 47% to 63%); the median PFS was 5.5 months in both groups. However, clinically meaningful signals were observed in secondary endpoints: median OS was prolonged from 9.72 months to 12.42 months; the objective tumor response rate (OTRR) improved from 26.9% to 38.3%; and notably, 4 complete responses (CRs) were observed in the certepetide group versus 0 in the placebo group. In the ECOG 0 subgroup, the 6-month PFS rate difference was more pronounced—68.1% versus 36.4%—suggesting that patients with good performance status may derive greater benefit. Regarding safety, grade ≥3 toxicities were similar between the two groups (16% in the certepetide group vs. 15% in the placebo group).[124]

Limitations

The ASCEND trial employed a non-comparative randomized phase II design, and the primary endpoint did not reach statistical significance; the improvements in OS and OTRR represent exploratory signals. The ongoing ASCEND Cohort B, which is evaluating the addition of a second dose of certepetide, will provide further data for validation.

Peptide Drugs in DM

Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist and represents the most mature example of clinical translation among incretin-based peptide drugs. Its subcutaneous and oral formulations have successively received approval for multiple indications, including T2D, weight management, and cardiovascular risk reduction, and it has become the first oral GLP-1 receptor agonist globally.[125]

Key Efficacy Data

Multiple large-scale phase III trials have confirmed the multidimensional clinical benefits of semaglutide. The SOUL trial, which enrolled 9650 participants with T2D and atherosclerotic cardiovascular disease and/or chronic kidney disease, demonstrated that oral semaglutide reduced the risk of major adverse cardiovascular events (MACE) by 14% over a mean follow-up of 47.5 months (HR 0.86, 95% CI: 0.77–0.96); notably, this benefit persisted regardless of concomitant SGLT2 inhibitor therapy. The FLOW trial was the first dedicated kidney outcomes trial in the GLP-1 receptor agonist class, enrolling 3,533 patients with T2D and chronic kidney disease; it demonstrated that once-weekly subcutaneous semaglutide reduced the risk of the primary kidney composite endpoint by 24% compared with placebo, while simultaneously reducing all-cause mortality by 20% over a median follow-up of 3.4 years. The STRIDE trial enrolled 792 patients with T2D and symptomatic peripheral artery disease and showed that semaglutide significantly improved maximal walking distance by 13% compared with placebo at 52 weeks (ETR 1.13, 95% CI: 1.06–1.21, P = 0.0004), with the benefit being independent of baseline BMI or HbA1c levels. In the context of combination therapy, the phase III REDEFINE 2 trial demonstrated that the fixed-dose combination of CagriSema (cagrilintide/semaglutide) achieved a 15.7% body weight reduction at 68 weeks (vs. 3.1% with placebo) in patients with T2D and overweight/obesity, with 89.7% of patients achieving ≥5% weight loss.[126,127]

Limitations

Several challenges remain in the clinical application of semaglutide. Gastrointestinal adverse events are the primary cause of treatment discontinuation—a recent prospective observational study demonstrated that 43% of T2D patients experienced gastrointestinal symptoms, with an overall discontinuation rate of 9%, 6 percentage points of which were attributable to gastrointestinal intolerance.[107] The oral formulation has a bioavailability of only approximately 0.8% and requires strict fasting administration with a minimum 30-minute post-dose wait before eating or taking other medications. During weight loss mediated by semaglutide, the loss of lean body mass may account for 15–40% of total weight loss; consequently, the risk of sarcopenia and frailty in elderly patients with T2D warrants particular attention; a 24-month retrospective cohort study demonstrated that semaglutide treatment significantly reduced muscle mass and was associated with functional decline in older adults with T2D, especially at higher doses. The risks of cholelithiasis and acute pancreatitis during long-term GLP-1 receptor agonist use require ongoing monitoring. Furthermore, long-term safety evidence in patients with severe renal impairment remains insufficient, and implementing individualized dosing in special populations continues to be a critical focus in current clinical practice.

Discussion

Specific Design Strategies to Overcome Enzymatic Degradation

The unique microenvironment of pancreatic diseases, particularly pancreatic cancer and pancreatitis, is abundant in diverse proteolytic enzymes, posing a significant barrier to the clinical translation of peptide drugs. To overcome this challenge, researchers have developed two complementary design strategies: chemical modification at the molecular level and nano-encapsulation at the delivery system level.

At the chemical modification level, D-amino acid substitution is a well-established and highly effective strategy for conferring resistance to proteolysis. Since natural proteases almost exclusively recognize peptide bonds composed of L-amino acids, substituting key cleavage sites within the peptide sequence with D-amino acids can significantly enhance proteolytic resistance. Furthermore, strategies including N-terminal acetylation, C-terminal amidation, cyclization (such as the cyclic iRGD structure of Certepetide), and the incorporation of β-amino acids or peptoid backbones can shield susceptible cleavage sites of exopeptidases and endopeptidases differentially.[128,129]

At the delivery system level, nano-encapsulation provides a physical protective barrier. The PLGA-PEG nanocarriers previously described for diagnostic purposes represent a typical example: the hydrophobic PLGA core enables efficient encapsulation of hydrophobic therapeutic peptides, while the PEG hydrophilic shell confers "stealth" properties, reducing opsonin adsorption and clearance by the reticuloendothelial system. These same carriers can also serve as protective delivery systems for therapeutic peptides—in animal models of pancreatic cancer, PLGA-PEG-encapsulated pro-apoptotic peptides are not only shielded from degradation by circulating proteases but also passively accumulate at tumor sites via the enhanced permeability and retention effect, significantly improving bioavailability and reducing systemic toxicity.[130]

Advantages and Limitations of Peptide Drugs Relative to Small Molecules and Monoclonal Antibodies

To more clearly delineate the role of peptide drugs in the treatment of pancreatic diseases, Table 2 systematically compares the key characteristics of peptide drugs with those of small-molecule drugs and mAbs. Compared with small-molecule drugs, peptides possess significantly higher target specificity;[131,132] small molecules often cause dose-limiting toxicity due to off-target effects, whereas peptides, due to their larger interaction interface, can precisely recognize specific protein-protein interaction interfaces or conformational epitopes. For example, Certepetide selectively binds to neuropilin-1, and integrin αvβ6-targeting peptides only recognize tumor cells overexpressing αvβ6, thereby dramatically reducing systemic adverse reactions. Compared with mAbs, peptides (typically 1–10kDa) are two orders of magnitude smaller in molecular weight. This size difference confers superior tumor tissue penetration capacity and homogeneous distribution characteristics, along with substantially lower manufacturing costs and, due to the lack of an Fc fragment, theoretically lower immunogenicity with a reduced propensity to trigger complement activation or antibody-dependent enhancement.[133–135]

However, peptide drugs also face two inherent limitations. First, their oral bioavailability is extremely low, resulting from the combined effects of the gastrointestinal enzymatic barrier and poor permeability across the intestinal epithelium, which currently necessitates that virtually all peptide drugs in the pancreatic disease field be administered via subcutaneous injection or intravenous infusion.[141,142] Second, their in vivo half-life is short—native peptides can be cleared within minutes through the action of plasma proteases and glomerular filtration.[140] Notably, these limitations are being progressively overcome through multiple strategies: chemical modifications can extend the half-life to several days or even a week; the absorption enhancer SNAC has made oral semaglutide a reality; and nanocarrier encapsulation addresses both the needs for oral delivery and prolonged circulation. Consequently, the unique balance that peptide drugs achieve between "high specificity" and "favorable safety" makes them an ideal intermediate modality between small molecules and mAbs, progressively expanding their clinical applicability in pancreatic diseases.

Table 2 Summarizes the Differences Between Peptide Drugs, Small Molecule Drugs, and Monoclonal Antibodies Across Multiple Dimensions, Including Targeting, Specificity, and Toxicity

Dimension	Peptide Drugs	Small Molecule Drugs	Monoclonal Antibodies
Cost	Low	Low	High
Specificity	High[21,136]	Low[136,137]	Extremely High[131,138]
Targeting Scope	Broad and Unique[131,132]	Restricted[137,138]	Predominantly Extracellular[131,138]
Systemic Toxicity	Low[133,139]	Variable[137,139]	Predominantly on-target toxicity[131,138]
Immunogenicity	Low[133,134]	Low[137]	High[131,134]
Tissue Penetration	Strong[135]	Excellent[137,138]	Poor[132,138]
Half-Life	Ultrashort[140]	Variable[137]	Extremely Long[131,138]
Oral Bioavailability	Extremely Low[141,142]	High[137,138]	Negligible[131,138]

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Comparative Analysis of Peptide-Based Strategies

The peptide-based strategies applied to pancreatic diseases primarily include peptide probes, PDCs, peptide vaccines, and PRRT, which differ markedly in mechanism of action, stage of clinical translation, and inherent limitations, warranting a systematic comparison.

Peptide probes offer the advantage of excellent signal-to-noise ratios conferred by high specificity, enabling non-invasive visualization of pancreatic cancer and its metastases at the molecular level and providing critical information for early diagnosis and surgical planning. However, peptide probes are limited by poor in vivo stability; certain linear peptides are rapidly degraded in the circulation, resulting in suboptimal tumor uptake. Peptide-drug conjugates embody the principle of "precision delivery" by covalently linking a cytotoxic payload to a targeting peptide—for instance, PDCs guided by macrophage-targeting peptides can facilitate drug accumulation at the lesion site. Their limitations, however, include potential instability of the linker in circulation, the heterogeneous intratumoral release of the payload, and potential off-target toxicity, which becomes more pronounced when the target is also expressed constitutively in normal organs. Peptide vaccines have the core advantage of eliciting durable antigen-specific T cell immune responses, which may even lead to complete biomarker clearance and long-term relapse-free survival. Nevertheless, their limitations are equally evident: immune response rates are highly heterogeneous across patients, restricting the eligible population, and monotherapy demonstrates limited efficacy in patients with advanced, high-burden disease. PRRT, represented by ^{177}Lu-DOTATATE, is currently the only peptide-based therapeutic modality approved for pancreatic neuroendocrine tumors. Its primary advantage is the precise delivery of radiotoxicity to somatostatin receptor-positive tumor cells; this approach is supported by robust phase III evidence demonstrating high objective response and disease control rates. Its limitations include long-term toxicities such as nephrotoxicity and myelosuppression, ineffectiveness against lesions with low or absent SSTR expression, and limited accessibility due to the requirement for nuclear medicine infrastructure.

AI-Driven Artificial Intelligence and Drug Design

In recent years, computational tools and AI methods have demonstrated immense potential in accelerating peptide drug development, significantly impacting the design and optimization of PDCs and targeting peptides.

Regarding molecular docking and rational design, we previously detailed how these techniques simulate interactions between the M2pep peptide (which targets M2-type tumor-associated macrophages) and its specific target. By analyzing conformational complementarity, hydrogen bond networks, and hydrophobic contacts of the binding pocket at the atomic level, researchers can guide the rational design of M2pep-Tasq conjugates, optimizing binding orientation and affinity prior to synthesis and thus significantly reducing the time and cost required for traditional trial-and-error approaches.

More cutting-edge trends lie in de novo peptide design algorithms and AI-driven affinity maturation technologies. Leveraging deep generative models and protein language models, researchers are now able to generate entirely novel peptide sequences de novo with predetermined structural features and physicochemical properties, while accomplishing multi-objective optimization in virtual space using reinforcement learning. For example, frameworks such as HELM-GPT and Peptide-GPT have preliminarily validated the feasibility of using generative pre-trained Transformer models for the de novo design of macrocyclic peptides or the generation of functional peptides.[80] These computational and AI methods are markedly improving the efficiency and precision of discovery and optimization of high-affinity targeting peptides for PDCs, holding the promise of shortening the development cycle of peptide drugs for pancreatic diseases from years to months.

Bridging the Gap Between Preclinical Research and Clinical Translation

Despite the remarkable efficacy demonstrated by peptide drugs in preclinical models of pancreatic diseases—ranging from targeted cytotoxicity and immune activation to high-contrast imaging—a substantial gap remains between experimental validation and successful clinical application. This gap largely stems from the inability of animal models to fully recapitulate the complex microenvironment of human pancreatic tumors, inadequate clinical validation of biomarkers, and the limited efficacy of monotherapies in a highly heterogeneous disease.[143] By systematically synthesizing the

available evidence, this review identifies several specific, translatable elements, aiming to provide concrete pathways toward narrowing this divide.

First, regarding clinically actionable biomarkers, liquid biopsies based on peptide nucleic acids and protease activity assays using peptide substrates have demonstrated diagnostic performance superior to that of the conventional tumor marker CA19-9. Concurrently, by profiling total protease cleavage patterns in plasma, a fluorescence resonance energy transfer peptide substrate array distinguished pancreatic cancer from benign pancreatic diseases, achieving an area under the curve (AUC) of 0.8 in a small validation cohort. Owing to their low cost, ease of use, and compatibility with existing clinical laboratory workflows, these peptide-based diagnostic strategies provide a direct foundation for developing tools for early screening and recurrence monitoring of pancreatic cancer. Second, combination therapeutic strategies represent another key translatable element for bridging the gap between inadequate monotherapy efficacy and unmet clinical needs. The tumor-penetrating peptide Certepetide, combined with gemcitabine/nab-paclitaxel, demonstrated prolonged overall survival and signals of complete response in the phase II ASCEND trial, confirming the clinical feasibility of enhancing chemotherapeutic efficacy through peptide-mediated modulation of the tumor stroma. For pancreatic neuroendocrine tumors, retrospective data suggest that PRRT combined with chemotherapy (eg., capecitabine) can further prolong progression-free survival, and prospective trials of such combined regimens are being planned. These combination strategies target the drug delivery barriers, immunosuppression, and resistance mechanisms characteristic of pancreatic diseases, and thus represent core directions for narrowing the gap between preclinical and clinical application. Moving forward, prospective clinical trials conducted under the premise of biomarker-driven patient stratification will be essential to systematically validate the benefits of these combination approaches and ultimately achieve translational implementation.

Pharmacokinetic Considerations and Safety Challenges in Clinical Translation

Pharmacokinetic Challenges

The first major challenge is bioavailability. The oral bioavailability of peptide drugs is notably low (typically <1–2%), primarily attributed to degradation by gastrointestinal proteases, the physical barrier posed by the intestinal epithelium, and limited transcellular transport due to their relatively high molecular weight. Consequently, the vast majority of peptide drugs for pancreatic cancer are administered via subcutaneous injection or intravenous infusion.[144] The second challenge is metabolism and clearance. Peptide drugs undergo rapid in vivo metabolism, posing a significant barrier to their clinical application. The half-life of natural peptides usually ranges from minutes to a few hours, with clearance occurring predominantly through three pathways: glomerular filtration and tubular degradation in the kidneys, proteolytic hydrolysis in plasma, and hepatic metabolism.[145] Chemical modification strategie—including N-terminal acetylation, C-terminal amidation, D-amino acid substitution, and the incorporation of non-natural amino acids—have been widely employed to extend half-life. However, these modifications may affect peptide conformation, target affinity, or immunogenicity and must be systematically evaluated in the preclinical phase.

Safety Challenges

The first safety challenge is immunogenicity, which presents a dual nature for peptide drugs. For peptide vaccines, immunogenicity is central to their therapeutic mechanism, aiming to induce a robust antitumor T-cell immune response. For other peptide therapeutics, however, unintended immunogenicity may lead to the production of anti-drug antibodies, which can in turn trigger hypersensitivity reactions or compromise therapeutic efficacy.[146] Among the peptide drugs that have entered clinical trials, the majority of adverse events are grades 1–2, manifesting primarily as injection site reactions, fatigue, and fever. The second challenge is off-target toxicity. Although the high target selectivity of peptide drugs theoretically reduces off-target effects, caution is still warranted in clinical practice. In PRRT, while radiolabeled somatostatin analogs target tumor tissue, they can also accumulate in normal organs such as the kidneys, posing a risk of nephrotoxicity.[105] The NETTER-1 trial of ^{177}Lu-DOTATATE has documented late toxicities including renal function impairment and myelosuppression during long-term follow-up.

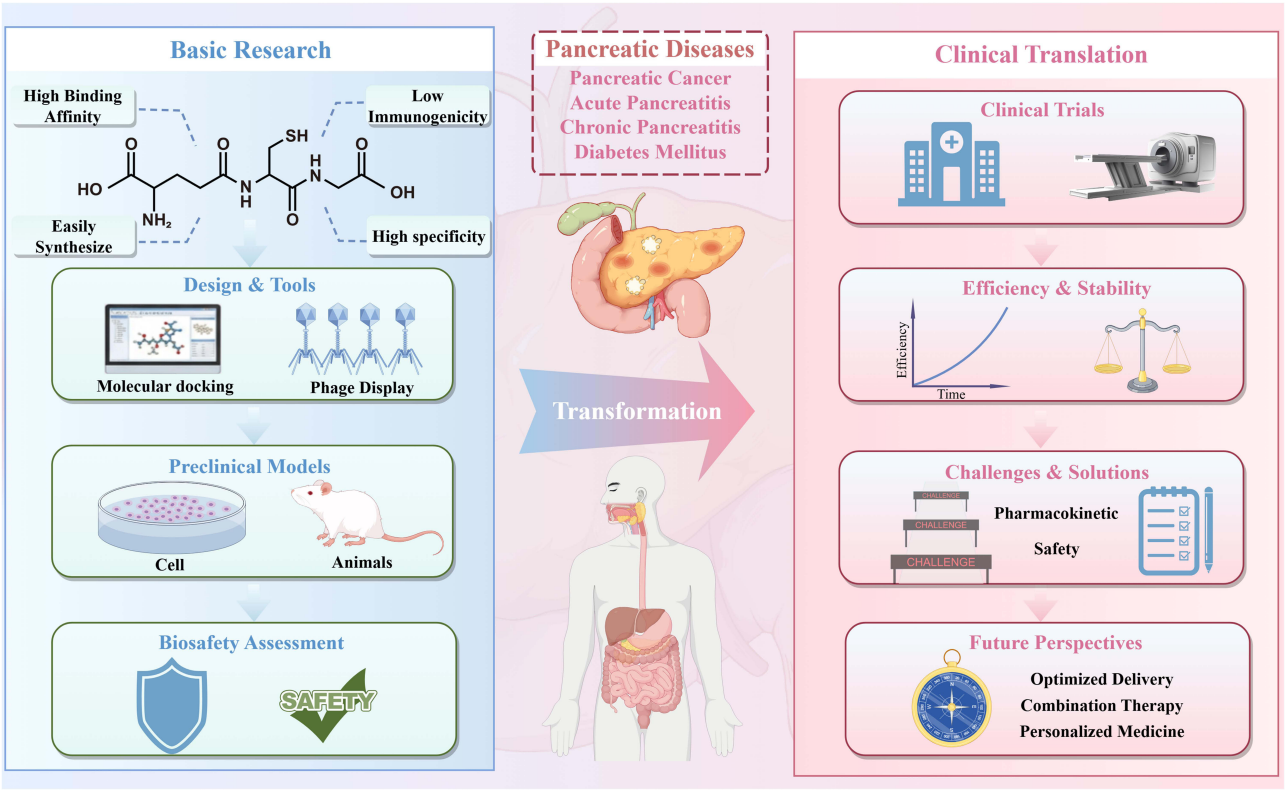

Figure 4 Applications and clinical translation of peptides in the diagnosis and treatment of pancreatic diseases. This comprehensive roadmap synthesizes the current status of peptide utilization in both the diagnosis and treatment of pancreatic ailments, bridging foundational inquiry with clinical implementation. In basic research, the schematic highlights the intrinsic advantages of peptides, essential design and screening frameworks, preclinical modeling, and biosafety evaluations. It then outlines the clinical translation phase, encompassing trial protocols, safety and efficacy assessments, prevailing obstacles, and prospective trajectories. Ultimately, this strategic overview is dedicated to surmounting the complex challenges inherent in the diagnosis and therapeutic management of pancreatic diseases.

Summary and Future Perspectives

This review evaluates the diagnostic and therapeutic utility of peptides in pancreatic disorders, emphasizing their superior binding affinity and minimal immunogenicity. Although China's healthcare trajectory increasingly aligns with "precision medicine," as illustrated by the current clinical translation landscape in Figure 4, critical research gaps must be addressed to unlock this potential. Key hurdles include peptide instability, which demands rigorous engineering; emerging drug resistance, which requires innovative countermeasures; and the lack of standardized clinical evaluation protocols, which has fragmented the evidence base and impeded widespread adoption. Future progress hinges on merging the innate advantages of natural peptides with conventional design strategies to surmount physicochemical barriers. Emerging modalities—such as AI-driven peptide design, novel peptide-based tools, therapeutic peptides, and PDCs—are poised to expand the diagnostic and therapeutic frontier. By addressing these specific vulnerabilities, peptides will transition from promising candidates to indispensable tools, driving paradigm shifts in disease management through concrete advances in diagnostics, targeted therapies, and streamlined clinical translation.

Abbreviations

PC, pancreatic cancer; AP, acute pancreatitis; CP, chronic pancreatitis; DM, diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; SPPS, solid-phase peptide synthesis; PEG, polyethylene glycol; PDCs, peptide–drug conjugates; CA19-9, carbohydrate antigen 19-9; ANXA2, annexin A2; OS, overall survival; DFS, disease-free survival; NIRF, near-infrared fluorescence; MRI, magnetic resonance imaging; MMPs, matrix metalloproteinases; PAC-MANN, protease-cleaved nanosensors; CCP, charge change protease; T2D, type 2 diabetes mellitus; hIAPP, human islet amyloid polypeptide; mAbs, monoclonal antibodies; OLISA, organelle-localized induced self-assembly; ADCs, antibody–drug conjugates; SPR, surface plasmon resonance; GEP-NETs, gastroenteropancreatic neuroendocrine tumours; PRRT, peptide receptor

radionuclide therapy; PFS, progression-free survival; mRFS, median relapse-free survival; OTRR, objective tumor response rate; CRs, complete responses; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular events; Mito-FF, mitochondria-targeting self-assembling peptide; hTERT, Human Telomerase Reverse Transcriptase; Tasq, Tasquinimod; ^{177}Lu, Lutetium-177.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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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 declare no conflict of interest. We certify that this investigation was executed in a vacuum of commercial or fiscal entanglements, ensuring no relationships exist that might be construed as a potential conflict of interest.

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