Review

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Research on precision treatment of pancreatic cancer targeted by antibody-drug conjugates

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SUMMARY: Pancreatic cancer, and especially pancreatic ductal adenocarcinoma (PDAC), is extremely difficult to treat due to early asymptomatic stage, molecular heterogeneity, and resistance to conventional treatments, with a 5-year survival rate of less than 10%. Antibody-drug conjugates (ADCs), as an emerging precision therapy, show the potential to treat PDAC through the synergy of antibody targeting and cytotoxic drugs. Multiple targets (such as uPAR, Mesothelin, CLDN18.2, and TROP2) are highly expressed in PDAC, which has become the key direction of ADC development. However, the matrix barrier restricts drug delivery, heterogeneous expression leads to efficacy differentiation, and drug resistance mechanisms further limit the role of ADCs. To overcome these challenges, researchers are exploring high-stability single domain antibodies, more potent payloads and linkers, bystander effect mechanisms, and combined treatment strategies with immune, autophagy, DNA damage repair, and other pathways. Bispecific ADC, conditionally activated ADC, and penetration enhancement design have also been used to improve efficacy. On the whole, ADCs offer hope for the treatment of PDAC. Future research and development should focus on improving delivery efficiency, alleviating drug resistance, and individualized design.

Keywords: antibody-drug conjugates, pancreatic cancer, precision treatment

1. Introduction

1.1. Current status of and challenges in the treatment of pancreatic cancer

Pancreatic cancer is one of the most lethal malignancies worldwide. It is a heterogeneous disease consisting of multiple subtypes, the most common of which is pancreatic ductal adenocarcinoma (PDAC), which accounts for nearly 90% of all cases. Other types include pancreatic neuroendocrine tumors and intraductal papillary mucinous tumors (*1*). PDAC, the focus of this review, is notorious for its asymptomatic early stages, complex molecular profiles, and resistance to conventional therapies. Over the past few decades, significant advances in molecular biology and imaging technology have greatly enhanced the understanding of PDAC, revealing the complex interactions between genetic predisposition and external environmental risk factors in particular (*2*). Nevertheless, PDAC remains the leading cause of cancer-related death, with a 5-year survival rate of approximately 10%, highlighting the need for more effective treatments (*3*). Recent studies have increasingly focused on elucidating the complex mechanisms behind pancreatic tumorigenesis, which involve key gene variations (such as KRAS, TP53, SMAD4, and CDKN2A gene mutations), the dynamic role of the tumor microenvironment, and the strategies adopted by tumors to evade immune surveillance (*4-8*). At the clinical level, the advent of new therapeutic modalities, including targeted therapy and immunotherapy, has shown their potential. However, there are still major challenges. An example is chemotherapy resistance: the median progression-free survival (PFS) for the FOLFIRINOX/mFOLFIRINOX regimen is only 6.4 months (PRODIGE-24 trial) (*9*). Moreover, immunotherapy is ineffective: the objective response rate (ORR) to a programmed death receptor 1 inhibitor single agent is less than 3% (KEYNOT-158 subgroup analysis) (*10*). Furthermore, the tumor matrix is a barrier: a dense fibrous matrix accounts for more than 70% of the tumor volume, hindering drug

penetration (*7*).

Despite these advances, PDAC treatment remains severely hampered by its inherent complexities, and especially the difficulty of effectively targeting both the tumor and its microenvironment, underscoring the urgent need for novel therapeutic strategies.

1.2. Mechanism of action and advantages of ADC drugs

ADCs represent an innovative class of targeted cancer therapy that chemically links monoclonal antibodies (mAbs) to potent small-molecule cytotoxic payloads *via* a specialized linker. ADCs are designed to precisely deliver cytotoxic agents to malignant cells while sparing healthy tissues. This strategy ingeniously combines the cytotoxic potency of chemotherapeutic drugs with the specificity of mAbs, thereby improving targeting accuracy, minimizing damage to normal tissues, reducing systemic toxicity, and enhancing therapeutic efficacy (*11*). The core structure of an ADC consists of three components: the cytotoxic payload, the linker, and the mAb (Figure 1). The stability and efficacy of these components collectively determine the specificity of each ADC drug (*12*).

Compared to standard chemotherapy or immune checkpoint inhibitors, ADCs exhibit superior targeting precision and enhanced cytotoxicity against tumors that clearly express specific surface antigens. However, their efficacy might be suboptimal in poorly vascularized tumors or those with low antigen density (*12*). The mechanism of action of ADCs initiates when the mAb component specifically recognizes and binds to the target antigen on the surface of cancer cells. Subsequently, through internalization, the ADC is taken up into the cancer cell. Following internalization, lysosomal proteases cleave cleavable linkers to release the payload; if the linker is non-cleavable, the entire ADC molecule is degraded to release the payload (*13*). The released cytotoxic agents then kill the targeted cancer cells by inhibiting critical cellular functions such as microtubule assembly and DNA replication.

Notably, the bystander effect can significantly influence treatment outcomes under certain circumstances (*14*). When the released payload is membrane-permeable, it can diffuse into neighboring cells – even those that do not express the target antigen (*14*). This phenomenon is particularly crucial in tumors exhibiting heterogeneous antigen expression, where complete eradication solely through direct targeting is challenging. However, the bystander effect is a double-edged sword: the ability of cytotoxic payloads to diffuse into the tumor microenvironment can also cause various complications affecting the safety and efficacy of ADC therapy (*15*). Therefore, the magnitude of this effect largely depends on parameters such as payload properties, linker stability, and tumor architecture (*15*).

Selecting appropriate surface target proteins is paramount for ADC safety and efficacy. An ideal target antigen should possess the following characteristics: *i*) Expression is exclusive or predominant in tumor cells, with minimal to no expression in normal tissues; *ii*) It should be non-secreted, because a circulating antigen can cause off-target binding of ADC outside the tumor site, reducing tumor targeting and causing safety concerns; *iii*) It should efficiently internalize upon binding to its corresponding antibody, enabling the ADC-antigen complex to enter the cell and release the cytotoxic payload (*16,17*).

In summary, ADCs function by binding target antigens, undergoing internalization, releasing cytotoxic payloads, and killing cancer cells. While the bystander effect can overcome antigen heterogeneity, it also

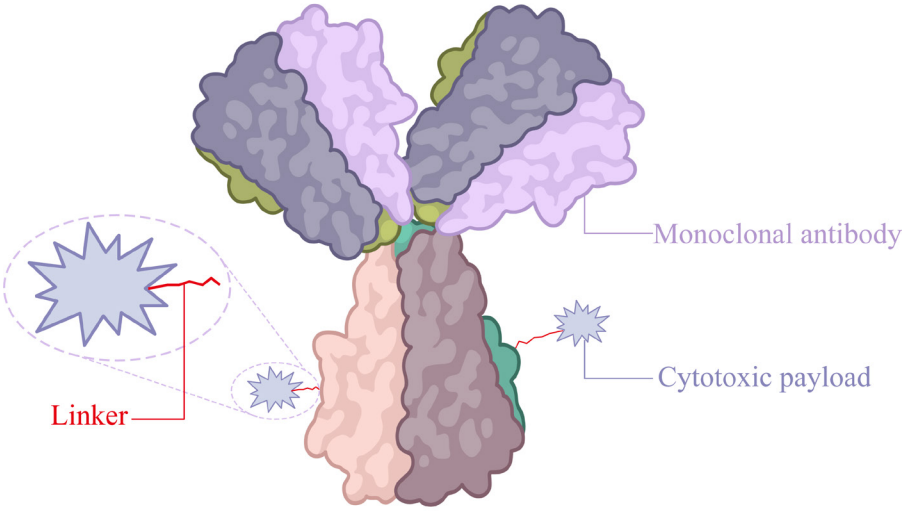

Figure 1. Schematic diagram of antibody drug conjugates. The core structure of an ADC consists of three components: the cytotoxic payload, the linker, and the monoclonal antibody.

introduces potential risks. Optimizing the three core ADC components - the antibody, linker, and cytotoxic payload - remains key to enhancing their safety profile and therapeutic efficacy (*18*). The purpose of this review is to comprehensively summarize the current status of and challenges with the treatment of PDAC and the progress of research on ADC drugs in PDAC. Finally, this review summarizes the challenges faced by ADC treatment for PDAC, it proposes strategies to overcome these challenges, and it suggests directions for future research in this area.

2. Progress of research on ADC targets in PDAC

In PDAC, several targets are under active investigation for ADC development. Urokinase plasminogen activator receptor (uPAR) is overexpressed in approximately 80% of PDAC and is abundantly present in both tumor and stromal cells, enabling dual tumor-stroma cytotoxicity in desmoplastic tumors. Mesothelin, expressed in about 50% of PDAC, shows limited physiological function in normal tissues; while clinical antibody therapies have yielded modest benefits, next-generation ADCs may exhibit enhanced efficacy by inducing pyroptosis and stimulating antitumor immunity. Claudin-18 isoform 2 (CLDN18.2) is highly expressed in roughly 40% of PDAC, and early trials of ADCs and bispecific antibodies have resulted in encouraging response and disease control rate (DCR) (Table 1).

2.1. uPAR

The uPAR is highly expressed in 80% of PDAC, promoting its invasion and metastasis. A point worth noting is that PDAC exhibits the highest levels of uPAR mRNA among all other tumor types and displays significant differences in expression compared to the normal pancreas and chronic pancreatitis (*19-21*). uPAR is also widely present in various non-cancer cells in activated tumor-associated stroma, including cancer-associated fibroblasts, macrophages, neutrophils, and endothelial cells (*19*). The simultaneous expression of tumors and stroma may provide better therapeutic gains in PDAC and stromal-rich tumors by promoting targeted and orthogonal anti-tumor activity (*22*). The difficulty in research on ADC drugs in PDAC lies in its fibrogenic tumor matrix microenvironment. The dense extracellular matrix forms a physical barrier that blocks the penetration of chemotherapy drugs, which is also a key reason for its poor response to different types of chemotherapy (*10*). Therefore, by taking advantage of the extensive expression of uPAR in both tumor cells and the surrounding stroma of dense tumors, a site-specific ADC can be developed using the high-affinity, cross-species reactive, and efficiently internalizing anti-uPAR mAb FL1 (*23*), conjugated with the potent anthracycline derivative PNU-158692.

Table 1. Comparison of main targets in PDAC ADC development

Target	Expression rate	Clinical trial phase	Representative drug	Preliminary efficacy data	Main advantages	Main limitations
uPAR	High expression in PDAC	Preclinical/Early Phase	Example: ABT-414	No publicly available clinical efficacy data	Highly specific targeting of tumor cells, potential for low toxicity	High expression heterogeneity, potentially leading to unstable efficacy; lack of extensive clinical validation data
Mesothelin	Moderate to high expression	Phase I/II	Example: Anetumab ravtansine	No publicly available clinical efficacy data	Expressed in various solid tumors, potentially applicable to multiple cancer types; some efficacy in other cancer types	Expression in normal tissues may cause off-target toxicity; expression and efficacy in PDAC still need further validation
CLDN18.2	High expression in PDAC	Phase I/II	Example: IBI343	ORR: 23.3%, DCR: 81.4%, PFS: 5.3 months	High expression in PDAC, likely applicable to most patients; some efficacy in other cancer types	Expression in normal gastric mucosa may cause off-target toxicity; expression and efficacy in PDAC still need further validation

2.2. Mesothelin

Mesothelin is positive in 50% of PDAC, and its high expression is mainly confined to pericardium, pleura, peritoneum, and vaginal membrane. Mesothelin does not seem to have significant biological functions in normal adult tissues. Mesothelin is highly expressed in mesothelioma, serous ovarian cancer, PDAC, and some gastric cancer and lung adenocarcinoma, and it is involved in tumor proliferation, metastasis, resistance to chemotherapy or radiotherapy, and immune escape (*24*). So far, antibodies, ADCs, and bispecific antibodies with immune checkpoints have been studied in malignant tumors expressing mesothelin. In clinical studies targeting antibodies against mesothelin, the therapeutic benefits are relatively small. The use of novel mesothelin targeted delivery, ADCs, and more effective payloads in immune checkpoint inhibitors could improve therapeutic efficacy (*25,26*). An anti-mesothelin targeted ADC induced pyroptosis and stimulated anti-tumor immune response in a mouse cancer model. Microtubule lytic enzymes and ADCs containing microtubule lytic enzymes can induce pyroptosis, which is crucial for anti-tumor immune and therapeutic responses due to thermogenic cell death (*27*). Anetumab ravtansine is an ADC of the anti-mesothelin antibody linked to the maytansinoid N2′-deacetyl-N2′-(3-mercapto-1-oxopropyl)-maytansine, and it has been studied in 45 patients across 10 dose escalation cohorts. The most common drug-related adverse events include fatigue, nausea, diarrhea, anorexia, vomiting, peripheral sensory neuropathy, and keratitis/corneal disease. There were no drug-related deaths. The pharmacokinetics of anetumab ravtansine are directly proportional to its dosage; its average half-life is 5.5 days. Among 148 cases of mesothelioma, ovarian cancer, PDAC, non-small cell lung cancer and breast cancer, complete remission occurred in 1 case, partial remission occurred in 11, and stable disease occurred in 66 cases. Anetumab ravtansine has shown controllable safety and favorable pharmacokinetic characteristics in patients with mesothelin-expressing solid tumors who have undergone severe pretreatment, and it has demonstrated encouraging preliminary anti-tumor activity (*28*).

2.3. CLDN18.2

CLDN18.2, a tight junction protein selectively expressed in cancer cells with lower levels in normal tissues, is an attractive target for therapy (*29*). It is highly expressed in 40% of PDAC cases and is associated with cancer progression, metastasis, and prognosis, making it a potential therapeutic target (*30,31*). mAbs, bispecific antibodies, and ADCs have shown promise in improving clinical outcomes. Early clinical trials have confirmed its strong anti-tumor activity, and especially when combined with chemotherapy and immunotherapy (*31,32*).

CMG901 is a novel ADC that links humanized anti-CLDN18.2 antibodies to the microtubule disruptor monomethyl auristatin (MMA) E (*33,34*). Additionally, several early-phase trials presented at American Society of Clinical Oncology 2024 explored other CLDN18.2-targeting strategies, including ADCs like LM-302 and IBI343, bispecific anti-CLDN18.2/CD3 antibodies (IBI389), and chimeric antigen receptor (CAR) T-cell therapy (CT041) for CLDN18.2-positive refractory advanced solid tumors (*35*). In patients treated with IBI343, 80% experienced treatment-related adverse events (TRAEs), with 25.7% experiencing grade ≥ 3 TRAEs. Common adverse events included anemia (42.9%), nausea (25.7%), and vomiting (25.7%). As of January 15, 2024, 25 of 89 evaluable patients showed partial response, resulting in an ORR of 28% and DCR of 80%. In the 6-mg/kg group with ≥ 60% CLDN18.2 expression, the ORR was 38.5% and DCR 84.6%, with a 40% ORR in PDAC patients (*36*). In a study of IBI389 involving 64 patients with CLDN18.2-positive PDAC (84.4% of whom were stage IV), TRAEs occurred in 96.9% of patients, with 54.7% experiencing grade ≥ 3 events. Common grade ≥ 3 TRAEs included elevated gamma-glutamyl transferase (20.3%) and a decreased lymphocyte count (9.4%). Cytokine release syndrome occurred in 51.6% of patients, though no grade ≥ 3 cytokine release syndrome was observed. As of January 31, 2024, among 23 evaluable patients, 7 had partial response and 9 had stable disease, with an ORR of 30.4% and DCR of 69.6% (*37*). These innovative approaches could extend CLDN18.2-targeted therapy to more tumor types, benefiting those with lower CLDN18.2 expression.

2.4. Other targets

In addition to the aforementioned studies, ADC development for multiple targets such as TROP2, HER2, B7-H3, and EGFR in PDAC has also been studied, as shown in Table 2, and each target has different expression rates, clinical stages, and treatment challenges.

In addition to the well-studied targets, recent research has identified several other promising molecules for PDAC ADC therapy. One such example is ozuriftamab vedotin (BA3021), a novel conditionally active biologic ADC directed against receptor tyrosine kinase-like orphan receptor 2 (ROR2). Importantly, this agent is designed to selectively bind ROR2 only under the acidic conditions of the tumor microenvironment, thereby improving tumor specificity and minimizing off-target toxicity. Preclinical studies demonstrated that this conditionally active construct is both effective and well tolerated, suggesting that ROR2-targeted ADCs may offer a viable treatment strategy for patients with ROR2-expressing tumors (*52*).

Another potential target is transforming growth factor alpha (TGF-α), which is markedly overexpressed in pancreatic adenocarcinoma relative to normal pancreatic tissues. When mAbs against TGF-α are conjugated to

Table 2. Pancreatic cancer-associated targets in ADC development

Target	Expression rate	Furthest clinical trial stage	Representative drugs	Present situation
TROP2	50–70%	Phase II/ III	Sacituzumab govitecan	● Bone marrow toxicity (≥ grade 3 neutropenia 35%) (*38-40*) ● The cytoprotective role of autophagy in the combination of TROP2-targeted antibody-driven drugs in the treatment of PDAC provides a new perspective for exploration of the mechanism of and formulation of a treatment strategy for PDAC (*41*). The Phase III ASCENT clinical study showed that the total survival time of triple negative breast cancer was nearly doubled. The median OS was 11.8 months (sacituzumab govitecan group) *vs.* 6.9 months (monotherapy group) (*42*). ● HuNb (TROP2-HSA) - MMAE (characterized by the use of nanobodies to counteract TROP2 and human serum albumin (HSA)) has good affinity, internalization efficiency, and anti-tumor activity (*43*).
HER2	5–10%	Phase III	Trastuzumab deruxtecan (T-DXd)	● Trastuzumab deruxtecan (T-DXd) is an antibody drug conjugate targeting human epidermal growth factor receptor 2 (HER2) (*44-47*) ● Among 267 patients receiving T-DXd treatment, the ORR was 37.1% (n=99; [95% CI, 31.3 to 43.2]), with responses observed in all cohorts. The median DOR was 11.3 months (95% CI, 9.6-17.8), the median PFS was 6.9 months (95% CI, 5.6-8.0), and the median OS was 13.4 months (95% CI, 11.9-15.5). In patients with HER2 IHC 3+expression in the central nervous system (n=75), the ORR was 61.3% (95% CI, 49.4 to 72.4), the median DOR was 22.1 months (95% CI, not reaching 9.6), the median PFS was 11.9 months (95% CI, 8.2 to 13.0), and the median OS was 21.1 months (95% CI, 15.3 to 29.6). ≥ grade 3 drug-related adverse events were observed in 40.8% of patients; 10.5% of patients experienced drug-related interstitial lung disease (ILD), with three deaths (*48*).
B7-H3	50–60%	Phase I	Vobramitamab Duocarmazine	● Immune checkpoint functions are complex, and multiple drug developments have failed (*49,50*)
EGFR	70–90%	Development terminated	Depatuxizumab mafodotin	● Overexpression of EGFR is a potential mechanism of resistance to T-DXd, which can be overcome through combination therapy strategies targeting EGFR (*45,51*)

cytotoxic payloads such as MMAF, the resulting ADCs exhibit significant anti-proliferative effects, effectively reducing the viability of TGF-α-expressing PDAC cells. These findings highlight TGF-α as a promising candidate for further preclinical exploration and clinical development in ADC therapy (*53*).

HER3 has also emerged as an attractive target. In December 2024, the U.S. Food and Drug Administration granted accelerated approval for the bispecific antibody zenocutuzumab, which simultaneously targets HER3 and HER2, for the treatment of non-small cell lung cancer and PDAC harboring NRG1 fusions. NRG1 encodes neuregulin-1, a high-affinity ligand of HER3 that drives oncogenic signaling. Parallel to this, AMT-562, a next-generation HER3-targeted ADC, is being investigated for its potential to expand therapeutic options across HER3-expressing tumors (*54,55*).

Nectin-4 is another target of increasing interest. A Nectin-4-directed ADC, Nectin-4-MMAE, was shown to induce apoptosis and cell death in Nectin-4-positive PDAC cell lines (BxPC-3 and YAPC). Mechanistic studies further revealed that Nectin-4-MMAE inactivates the AKT/mTOR pathway, thereby inducing autophagy. In xenograft models, Nectin-4-MMAE alone displayed potent anti-tumor activity, and its efficacy was enhanced when combined with autophagy inhibitors, leading to greater tumor regression than either agent alone. These results suggest that both monotherapy and combination approaches targeting Nectin-4 could provide promising therapeutic avenues in PDAC (*56,57*). Moreover, clinical data from the Phase I EV-101 trial of enfortumab vedotin, an FDA-approved Nectin-4-targeted ADC, showed an ORR of 43%, with a median overall survival (OS) of 12.3 months and a one-year OS rate of 51.8% (*58*).

Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) represent another important family of targets. CEACAM5, a glycosylated surface protein rarely expressed in normal adult tissues but frequently overexpressed in multiple cancers, has been implicated in tumor progression and metastasis. A novel human single-domain ADC targeting CEACAM5 demonstrated potent anti-tumor activity in both *in vitro* and *in vivo* models (*59*). While CAR-T therapies against CEACAM5 remain in the preclinical stage, they may offer an alternative or complementary strategy for patients resistant to ADCs (*60*). Similarly, CEACAM6 has been investigated as a potential target, with strategies such as delivering BET protein degraders *via* CEACAM6-targeted ADCs showing promise preclinically (*61,62*). Dual-targeting approaches have also been developed: CT109-SN-38, an ADC with specificity for both CEACAM5 and CEACAM6, has shown efficacy in selectively killing PDAC cells (*31,63*). More recently, EBC-129, an ADC designed to selectively bind tumor-specific N-glycosylation epitopes on CEACAM5/6, demonstrated encouraging preliminary results in a Phase I expansion cohort of PDAC. At doses

of 1.8 mg/kg and 2.2 mg/kg, the ORR was 25% and 20%, respectively, while the DCR reached 87.5% and 63.6%. The median PFS was 19 and 12 weeks, respectively, and notably, 82% of patients exhibited antigen expression levels considered suitable for EBC-129 therapy (*64*).

In addition, several other tumor-associated antigens have been investigated as potential ADC targets. hSD5-vedotin, an auristatin-based ADC directed against EphA2, exploits the tumor-specific expression of EphA2 in PDAC cells to drive endocytosis, release its MMAE payload, and exhibit potent anti-tumor action even at low antibody concentrations (*65*). SGN-B6A, another vedotin-based ADC, targets integrin β6 and has shown promise in preclinical PDAC studies (*66*). Oba01 has been developed to target death receptor 5, providing a novel biological rationale for future clinical evaluation in PDAC (*67*). SGN-CD228A is an investigational vedotin ADC directed at melanotransferrin (CD228/MELTF/p97), a glycoprotein associated with tumor progression (*68*).

Other notable targets include MUC1, intercellular adhesion molecule-1 (ICAM1), and related surface proteins. HzMUC1-ADC represents a new approach to exploit the overexpression of MUC1 in pancreatic and other solid tumors (*69*). ICAM1 is differentially upregulated on PDAC cells but minimally expressed in normal tissues, enabling selective tumor recognition. ICAM1-targeted ADCs, developed with optimized linkers and cytotoxic payloads, have shown potent anti-tumor activity, and their efficacy can be further evaluated using molecular imaging techniques such as magnetic resonance imaging-based non-invasive monitoring of therapeutic response (*70,71*).

In addition to established targets, several novel candidates are under active investigation for ADC development. Plectin, also referred to as cell surface reticulin when localized on the plasma membrane of malignant cells, is highly expressed and readily accessible, making it an attractive molecular target for ADC-based strategies (*2*). Another promising molecule is prostate stem cell antigen (PSCA), which is consistently expressed across all stages of prostate cancer, including advanced androgen-independent disease and bone metastases. Preclinical studies have shown that the ADC F12-MMAE, consisting of the anti-mitotic agent MMAE conjugated to IgG1 F12, exhibits dose-dependent efficacy and specificity in a PSCA-positive PC-3 xenograft model in NOD/SCID gamma mice. Beyond prostate cancer, PSCA has also been proposed as a valuable diagnostic and therapeutic marker in PDAC (*72*).

Fibroblast activation protein, a membrane-associated protein, is another noteworthy target. Its multifaceted interactions with both tumor cells and the surrounding tumor microenvironment highlight its potential relevance in both diagnostic applications and therapeutic intervention (*73*). Likewise, glypican family member phosphatidylinositol proteoglycan-1 has been identified as a potential target that could facilitate the design of innovative therapeutic strategies for PDAC (*74*).

While these findings expand the pool of potential targets and highlight novel avenues for ADC-based therapy, their successful translation into clinical practice remains uncertain.

3. Challenges in ADC development for PDAC

The development of ADCs for PDAC faces several significant barriers, limiting their clinical success. A major challenge is the lack of high-density tumor-specific antigens, as PDAC exhibits low expression of highly specific antigens that are essential for effective targeting by ADCs. Additionally, stromal barriers surrounding PDAC tumors impede the penetration of ADCs into the tumor cells, reducing therapeutic efficacy. Antigen heterogeneity within the tumor further complicates treatment, as varying levels of antigen expression, coupled with resistance mechanisms such as drug efflux and target loss, contribute to suboptimal therapeutic outcomes. Moreover, ADCs often induce dose-limiting toxicities, such as myelosuppression and corneal toxicity, particularly in PDAC patients, which severely impact the therapeutic index. Finally, despite promising preclinical data, low clinical translation rates pose a critical issue, with many ADCs failing to progress beyond Phase I trials due to limited efficacy or unexpected safety concerns. These factors collectively underscore the complex challenges in advancing ADCs for PDAC treatment, necessitating further research and innovation to overcome these obstacles (Figure 2).

4. Promoting the multi-dimensional progress of ADC therapy for PDAC

One of the main scientific challenges facing the development of PDAC ADC is the extremely low drug delivery efficiency. Pancreatic cancer has a highly fibrotic tumor matrix, which constitutes a dense physical barrier, that greatly hampers drug penetration and severely limits the therapeutic effect of a drug. To address this issue, researchers have developed human universal domain antibodies (UdAb) with smaller structures and higher stability. The n501 UdAb targeting carcinoembryonic antigen 5T4 exhibits extremely high stability, and its conjugate n501-SN38 demonstrates the ability to penetrate deeper tumor tissue, a higher rate of tumor uptake, and a faster rate of tumor accumulation in a mouse model, thereby displaying significantly enhanced anti-tumor action. This result shows that an ADC based on UdAb has good therapeutic prospects and is especially suitable for tumor types with significant tissue barriers such as solid tumors (*75*).

That said, the design strategy of bispecific ADCs also offers new ideas for improving targeting accuracy and efficacy. For example, BL-B01D1 is an EGFR-HER3

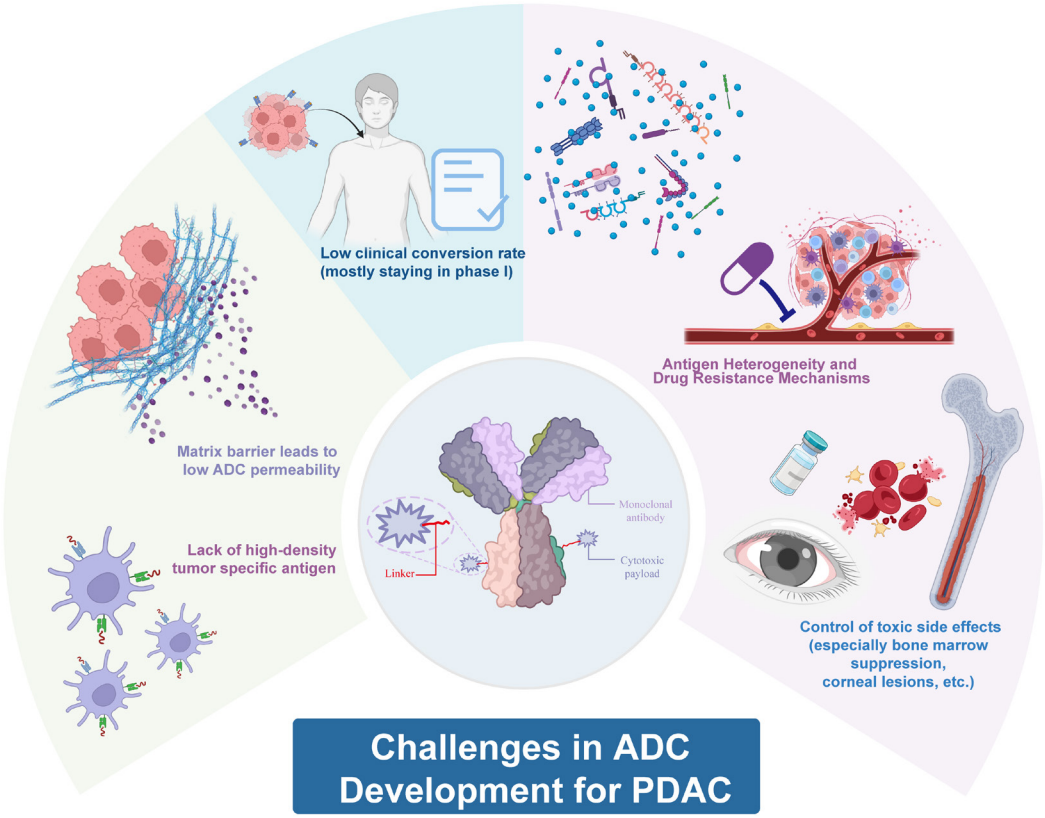

Figure 2. Challenges in developing ADCs for PDAC. Key barriers include the low expression of tumor-specific antigens, stromal barriers limiting ADC penetration, antigen heterogeneity, resistance mechanisms such as drug efflux and target loss, and dose-limiting toxicities like myelosuppression and corneal toxicity. Despite promising preclinical data, low clinical translation rates hinder progress beyond Phase I trials. These challenges highlight the need for continued research and innovation in ADC development for PDAC.

bispecific ADC developed specifically for patients with locally advanced or metastatic solid tumors, and it has shown excellent targeting efficiency and toxicity control in clinical studies (*76*) as well as being a dual-targeted ADC that can simultaneously counteract mesenchymal epithelial transition (MET) and origin receptor (RON) for the treatment of cancers with high phenotypic heterogeneity. A dual-targeted approach in the form of an ADC is highly effective and has long-lasting therapeutic effects on tumors exhibiting MET/RON heterogeneous phenotypes, indicating that ADCs dually targeting MET and RON can serve as a new strategy for treating tumors with expression phenotype heterogeneity (*77*). The bispecific antibody IMV-M is designed to selectively bind to and aggregate death receptor 5 by a novel mechanism of aggregating multiple IMV-M molecules onto a single MUC16 molecule and binding to the tumor antigen MUC16. MUC16 is overexpressed in most subtypes of ovarian cancer, PDAC, and lung cancer and is minimally expressed in normal tissues, indicating that this bispecific antibody has wide applicability (*78*). With advances in modern biotechnology, new carefully designed antibodies have ultimately paved the way for the successful clinical treatment of various cancers, which includes precise tumor immunotherapy (*79*).

Advances in platform technology have also provided key support tools for ADC therapy. Electron microscopy can study the interactions between tumor microbiota and cancer cell migration and also assist in the development of targeted therapies such as ADCs and aptamer-drug conjugates (*80*). In addition, innovative biological delivery strategies are also being developed. For example, the system that combines genetically modified Salmonella typhimurium VNP20009 with aptamer drug conjugate utilizes the natural chemotaxis of bacteria towards the hypoxic microenvironment in tumor areas to achieve targeted drug delivery and local release of the drug. A study found that this strategy can prolong the serum stability of aptamer drug conjugate to 48 hours, significantly increase the drug concentration at the tumor site, and promote bacterial colonization, tumor cell death, and enhanced T-cell infiltration (*81*).

The introduction of synthetic lethal mechanisms also provides a new therapeutic approach for ADC therapy. By combining drugs targeting the DNA repair pathway such as ADC and ataxia telangiectasia and rad3-related kinase (ATR) inhibitors, treatment selectivity can be enhanced without increasing toxicity and adverse reactions, providing a more strategic therapeutic breakthrough for PDAC, the "silent killer" (*82*).

5. Current breakthroughs in and the future design blueprint for ADC treatment for PDAC

Due to the matrix-rich microenvironment and the lack of a high-density tumor-specific antigen in PDAC, PDAC is still a disease that is difficult to target. The next generation of ADCs needs to integrate penetration-enhancing antibodies + immune regulatory payloads + intelligent linkers. Research has found that targeting proteoglycan-1 (GPC1) on cancer associated fibroblasts using GPC1 ADCs conjugated with phosphatidylinositol GPC1 and MMAE in matrix-rich tumors such as PDAC is a useful method (*83,84*). Thus, the necessity of customized ADC design to enhance the outcomes of various types of cancer needs to be recognized (*13*). A humanized anti- tissue factor (TF) Ab (clone. 1084), coupled with MMAE or deruxtecan (DXd), showed more potent anti-tumor activity in tumors with strong and uniform TF expression, while a DXd-coupled anti-TF ADC was more effective in tumors with weak and heterogeneous TF expression. An analysis of a PDAC tissue array showed that TF expression was weak and uneven in most TF-positive specimens, which suggests that DXd's response rate to cancer might be higher than an MMAE-coupled anti-TF ADC. However, findings have indicated that optimizing the ADC payload separately in each patient can maximize the potential of ADC therapy (*85,86*). Extending the half-life of single domain ADCs through albumin binding enhances anti-tumor efficacy (*87*).

6. Strategies to overcome barriers in ADC development

6.1. Penetration enhancement

Improving the penetration of ADCs into tumors is a critical challenge. Tumors, and particularly those with dense extracellular matrices, often prevent effective drug delivery. Studies are exploring methods to enhance drug penetration, such as modifying the physical properties of ADCs or utilizing targeted agents to break down tumor barriers (*7,10*).

6.2. Novel linkers and payloads

Several studies have focused on developing more efficient payloads (*e.g.*, exatecan, MMAE, and muscarine alkaloids) and optimized linkers (*e.g.*, cleavable or stable linkers) to improve ADC internalization and cytotoxicity. For instance, a study using triptolide as a payload for PDAC employed silyl ether as a cleavable linker. This linker offers easy synthesis and controllable drug release rates by modifying the silyl ether group (*88*). Additionally, a second-generation amanitin-based ADC (ATAC) targeting TROP2, with Trodelvy's humanized RS7 antibody (hRS7), showed superior efficacy to Trodelvy in treating refractory PDAC and triple negative breast cancer, completely eradicating the tumors (*89*). Similarly, a BET protein degradation product that was delivered *via* a CEACAM6-targeted ADC demonstrated inhibition of tumor growth in PDAC models (*90*).

6.3. Bispecific and conditionally activated ADCs

To address tumor heterogeneity and improve specificity, bispecific ADCs and conditionally activated ADCs are being explored. For instance, ADCs with bystander effects can overcome antigen heterogeneity by enabling the cytotoxic payload to kill tumor cells of different phenotypes. This approach is particularly useful for tumors that exhibit diverse antigen expression profiles. By optimizing adapters and conjugation methods, a novel ADC has been developed, and it displays excellent anti-tumor efficacy and a strong bystander killing effect both *in vivo* and *in vitro* (*91*). Moreover, ADCs can be conditionally activated in the tumor microenvironment through enzymatic hydrolysis, reducing toxicity to normal tissues while enhancing tumor-specific activity.

6.4. Combination therapies

Combining ADCs with other therapeutic agents, such as immune checkpoint inhibitors, autophagy inhibitors, and ATR inhibitors, can enhance ADC efficacy by leveraging multi-target and multi-mechanism synergism. This approach is particularly beneficial in overcoming the challenges posed by the "immune desert" microenvironment of PDAC. For example, combining Nectin-4-targeted ADCs with autophagy inhibitors has demonstrated more potent anti-tumor action (*56*).

7. Conclusions and future directions

PDAC, one of the most invasive and drug-resistant solid tumors, remains a significant challenge in clinical oncology. The efficacy of traditional therapies, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, is limited in PDAC, particularly due to the complex tumor microenvironment, significant antigen heterogeneity, and the dense fibrotic matrix that severely impedes the efficient delivery of therapeutic drugs. In this context, ADCs have emerged as a promising therapeutic approach, combining the specificity of mAbs with the potent cytotoxicity of payloads, demonstrating significant progress across multiple solid tumors and showing potential in PDAC.

However, the clinical use of ADCs in PDAC still faces several challenges. The first major hurdle is the accessibility and specificity of suitable targets. PDAC lacks highly dense, tumor-specific antigens, and although targets like uPAR, Mesothelin, and CLDN18.2 show promise, their significant heterogeneity leads to inconsistent ADC efficacy. Moreover, the dense tumor matrix not only restricts drug penetration but also

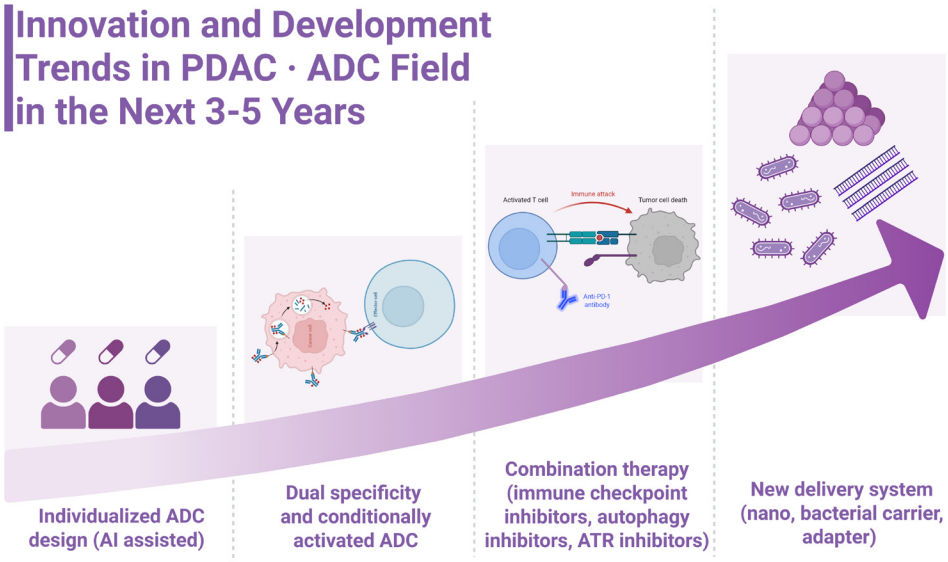

Figure 3. Innovation and development trends in the area of PDAC·ADC over the next 3-5 years. Future directions in antibody-drug conjugate development. Bispecific and conditionally activated ADCs will enhance precision targeting and release by responding to tumor-specific conditions. AI-assisted personalized ADC design, leveraging multi-omics and machine learning, will enable customized anti-cancer strategies. Combination therapies with immune checkpoint inhibitors, autophagy inhibitors, and ATR inhibitors are expected to improve efficacy and overcome drug resistance. Advanced delivery systems, such as nanoparticles, engineered bacterial carriers, and adapter platforms, will enhance tissue penetration, improve drug stability, and offer novel solutions for treating refractory solid tumors.

contributes to immune evasion and the development of drug resistance, preventing therapeutic drugs from reaching effective concentrations at the tumor site. Emerging resistance mechanisms, such as lysosomal dysfunction and exosome-mediated drug efflux, further limit ADC efficacy.

To overcome these challenges, future research must focus on optimizing ADCs at multiple levels. Over the next 3-5 years, the area of ADCs is poised for multidimensional innovation and integrated development. First, bispecific and conditionally activated ADCs will offer more precise targeting and release, recognizing two different tumor-associated antigens or responding to specific conditions in the tumor microenvironment (such as a low pH or specific enzyme activity). This approach is expected to significantly improve the therapeutic window and reduce toxicity risks. Second, artificial intelligence-assisted personalized ADC design will leverage multi-omics data and machine learning models to select the most suitable antibodies, linkers, and drug-loading regimens for individual patients, leading to a truly "customized" anti-cancer strategy. The combination therapy model is poised to significantly expand the therapeutic potential of ADCs. When paired with immune checkpoint inhibitors, autophagy inhibitors, and DNA damage repair pathway inhibitors, ADCs are expected to produce synergistic anti-tumor effects and help overcome drug resistance. These combinations may prove particularly effective in addressing the "immune desert" state often seen in PDAC, enabling more comprehensive tumor targeting and enhancing immune-mediated responses. Additionally, innovative drug delivery systems, including nanoparticles, engineered bacterial carriers, and adapter platforms, can circumvent the delivery challenges faced by traditional ADCs. These advanced delivery mechanisms will improve tissue penetration, enhance drug stability, and provide novel therapeutic avenues for treating refractory solid tumors (Figure 3).

An important point to emphasize is that ADCs are not a "universal key" but rather a "customized weapon" that requires precise tumor typing, personalized design, and dynamic monitoring during treatment. As interdisciplinary tools such as nanotechnology, artificial intelligence, and bioinformatics continue to develop, future ADCs will likely become more intelligent, accurate, and efficient. The integration of emerging delivery systems, like bacterial vectors and aptamer platforms, along with synthetic lethal strategies, holds great promise in enhancing the scope of ADC treatment for refractory solid tumors such as PDAC.

This review has sought to provide a comprehensive reference for the future development of PDAC precision therapies, highlighting the critical research directions that will guide the next phase of ADC innovation. It also calls for increased clinical-translational research to bridge the gap between preclinical advances and clinical use, ultimately driving breakthroughs in PDAC treatment. ADCs offer a glimmer of hope for PDAC patients, and through collaboration, mechanistic research, and clinical validation, they may become an effective weapon in improving survival outcomes for this challenging cancer.

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