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Innovative Approaches in the Treatment of Pancreatic Cancer: The Role of CAR T-Cell Therapy

Jakub Paweł Kuźniar, Emilia Gabriela Chrzanowska, Julia Szlążek, Adam Jan Ząbek, Michalina Zagalska, Marta Turek, Tomasz Tamborski, Adam Grzebinoga, Barbara Roguska, Anna Katarzyna Kuźniar

Jakub Paweł Kuźniar
The Provincial Hospital in Bielsko-Biała, 101 Armii Krajowej Ave., 43-316 Bielsko Biała
Email: kuba.kuzniar@gmail.com
ORCID: 0009-0002-6716-7502

Emilia Gabriela Chrzanowska
Medical University of Silesia, 18 Medyków Street, 40-752 Katowice
Email: chrzanowska.e@gmail.com
ORCID: 0009-0001-6228-1878

Julia Szlążek
Medical University of Silesia, 18 Medyków Street, 40-752 Katowice
Email: juliaszlazek@gmail.com
ORCID: 0009-0007-6977-8856

Adam Jan Ząbek
Katowice Oncology Center, 26 Raciborska Street, 40-074 Katowice
Email: adamzabek@vp.pl
ORCID: 0009-0003-6799-1814

Michalina Zagalska
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, 20-24 Francuska Street, 40-027 Katowice
Email: michalina.zagalska24@gmail.com
ORCID: 0009-0002-7312-0065

Marta Turek
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, 20-24 Francuska Street, 40-027 Katowice
Email: martaturek74@gmail.com
ORCID: 0009-0005-7713-6875

Tomasz Tamborski
County Hospital in Zawiercie, 14 Miodowa Street, 42-400 Zawiercie
Email: tomasztam97@gmail.com
ORCID: 0009-0003-6275-1010

Adam Grzebinoga
University Clinical Center of Prof. K. Gibiński of the Silesian Medical University in Katowice, 14 Medyków Street, 40-752 Katowice
Email: adam.grzebinoga99@wp.pl
ORCID: 0009-0001-5983-7564

Barbara Roguska
Medical University of Silesia, 18 Medyków Street, 40-752 Katowice
Email: b.m.c.roguska@gmail.com
ORCID: 0009-0006-6905-7517

Anna Katarzyna Kuźniar
Wroclaw Medical Uniwersity, 1 Ludwika Pasteura Street, 50-367 Wrocław
E-mail: kuzniar.ania2gmail.com
ORCID: 0009-0005-9082-9182

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal gastrointestinal cancers, marked by late diagnosis, rapid progression, and resistance to treatment, resulting in a five-year survival rate below 10%. Chimeric antigen receptor T-cell (CAR T-cell) therapy has shown success in hematologic malignancies, sparking interest in its potential for solid tumors like PDAC. This paper reviews current knowledge on CAR T-cell therapy in PDAC, focusing on challenges, future prospects, and available studies.

Methodology

This literature review is based on a search of PubMed and Google Scholar for publications from the last 10 years. Fifty sources, including original studies, reviews, and clinical reports, were analyzed with focus on mechanisms of action, preclinical/clinical outcomes, safety, and toxicity.

Results

Studies show that CAR T-cell therapy can stabilize PDAC and even induce remission when targeting tumor-specific antigens. However, major obstacles remain: poor tumor penetration, toxicity (e.g., cytokine release syndrome), and "on-target, off-tumor" effects. Clinical trials report modest CAR T-cell expansion and persistence, suggesting the need for improved design and strategies.

Conclusions

While CAR T-cell therapy for PDAC is promising, its effectiveness is hindered by the tumor microenvironment and side effects. Future directions include better antigen targeting,

modified CAR constructs, combination therapies, and personalized or allogeneic CAR T-cell approaches to enhance outcomes in this difficult-to-treat cancer.

Keywords: *pancreatic cancer, PDAC, CAR T-cell, immunotherapy, mesothelin, CEA, CLDN18.2, PSCA, HER2, CD133, tumor microenvironment*

1. Introduction to Pancreatic Cancer

Pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC), is a serious malignancy characterized by complex pathogenesis and generally poor prognosis [1,4]. The incidence of pancreatic cancer is increasing worldwide [1]. Its often asymptomatic course and diagnostic difficulties contribute to low survival rates [4]. The primary treatment method for resectable tumors is surgery followed by adjuvant chemotherapy, while chemotherapy remains the mainstay for unresectable and metastatic cases [4].
The risk of developing the disease increases with age [5]. The most significant risk factors include smoking, overweight and obesity, long-term alcohol abuse, and a history of chronic pancreatitis [5,7]. Diabetes, a positive family history, and genetic predispositions are also important contributors [6].

The tumor microenvironment (TME) plays a crucial role in the pathogenesis of pancreatic cancer. It forms a complex and dynamic network surrounding the cancer cells, often described as an “impenetrable web.” It consists of immune cells, cytokines, metabolites, fibroblasts, and a dense desmoplastic stroma rich in hyaluronan [3]. The TME is essential in tumor progression and treatment response, as it enables cancer cells to evade immune surveillance and suppress immune responses [2,3]. A significant component of this microenvironment is cancer-associated fibroblasts (CAFs) [2,6].

Unfortunately, the prognosis for pancreatic cancer is generally poor due to late detection, early dissemination, aggressive local tumor growth, and the limited efficacy of current therapies [3,4]. Most patients are diagnosed at an advanced stage, often with distant metastases [2]. Despite advancements in research, pancreatic cancer remains one of the most

difficult cancers to treat [1]. The five-year survival rate for sporadic pancreatic cancer does not exceed 10% [4].

2. Traditional Treatment Methods and Their Limitations

Traditional treatment methods for pancreatic cancer mainly include surgery, chemotherapy, and radiotherapy [8].

2.1 Surgery

Surgery, particularly pancreatoduodenectomy (Whipple procedure), distal or total pancreatectomy, is a potentially curative option, but only for a limited number of patients with resectable tumors [9]. Achieving an R0 resection (microscopically negative surgical margins) is crucial, as it is associated with significantly better survival outcomes compared to R1 resections (microscopically positive margins) [9]. However, even after R0 surgery, the risk of disease recurrence remains high [10]. Moreover, these surgical procedures carry a significant risk of complications [10].

2.2 Chemotherapy

Chemotherapy is used in various stages of the disease. In unresectable and metastatic pancreatic cancer, it serves a palliative role aimed at improving survival and quality of life, but it does not result in a cure [10]. Regimens such as FOLFIRINOX and gemcitabine with nab-paclitaxel have shown improvement in median overall survival compared to gemcitabine monotherapy [8,9,10]. In the context of adjuvant (postoperative) and neoadjuvant (preoperative) treatment, chemotherapy aims to eliminate micrometastases and improve R0 resection rates, though its definitive efficacy is still under investigation [9,10]. Studies often demonstrate limited or inconclusive survival benefits, and chemotherapy regimens can be highly toxic [9,10].

2.3 Radiotherapy

Radiotherapy, like chemotherapy, plays a role in the treatment of pancreatic cancer, particularly in locally advanced disease [8]. However, the evidence supporting its effectiveness—especially in the adjuvant setting—is inconsistent [10]. Many studies have not

shown significant survival benefits, and in some cases, radiotherapy may even be harmful [6,10]. Neoadjuvant chemoradiotherapy shows some promising results in improving R0 resection rates and survival in borderline resectable tumors, but it still requires further investigation in phase III trials [9,10].

As evident, traditional treatment methods for pancreatic cancer have limited effectiveness due to the advanced stage at diagnosis in most patients [9], the high risk of recurrence after surgery [9,10], significant chemotherapy toxicity, and the inconclusive benefits of radiotherapy [10]. This highlights the need for the development of new, more effective therapies [8,10].

3. What is CAR T-Cell Therapy?

CAR T-cell therapy is an advanced form of immunotherapy in which a patient's T lymphocytes are genetically modified to combat cancer cells [11,12].
This process involves collecting T cells from the patient and introducing, in the laboratory, a gene encoding a chimeric antigen receptor (CAR) [12]. The CAR enables the modified T cells to recognize cancer cells, become activated, and release cytotoxic substances, ultimately leading to the destruction of these cells [12].
A CAR is an artificially engineered protein composed of an extracellular domain that recognizes a specific antigen on cancer cells, a transmembrane domain, and an intracellular signaling domain [11]. After the modified T cells are infused back into the patient, the CAR binds to the antigen on cancer cells, activating the T cell to destroy them [11].
CAR T-cell therapy has been extensively studied and applied, particularly in hematologic malignancies such as acute myeloid leukemia (AML), where various target antigens like CD33 and CD123 are being explored [13]. In solid tumors, CAR T-cell therapy is under investigation and in limited use, though its application is more complex and generally in earlier stages of development compared to blood cancers [14].
Despite promising results, CAR T-cell therapy faces several challenges, including difficulties in T-cell penetration into the tumor mass due to physical barriers and the immunosuppressive tumor microenvironment, antigen heterogeneity in solid tumors (not all tumor cells may express the target antigen), and "on-target, off-tumor" toxicity (when CAR T cells attack healthy tissues that also express the target antigen at lower levels) [11,17].

Additionally, observed toxicities include cytokine release syndrome and neurotoxicity, along with the possibility of tumor escape through loss of the target antigen [12,14,15,16].

4. Challenges of CAR T-Cell Therapy in the Treatment of Pancreatic Cancer

4.1 Tumor Microenvironment (TME)

The complex tumor microenvironment (TME) of pancreatic cancer presents unique barriers that hinder the efficacy of CAR T-cell therapy [19,20,23].

- Desmoplasia and stromal barrier

The abundant tumor stroma—composed of extracellular matrix components and cancer-associated fibroblasts (CAFs)—creates a physical barrier that limits the infiltration of CAR T cells [18–24].

- Heterogeneous antigen expression

The non-uniform expression of target antigens on pancreatic cancer cells may reduce the effectiveness of CAR T-cell therapy [18,20,23].

- Immunosuppression within the TME

The TME of pancreatic cancer contains immunosuppressive cells (e.g., T regulatory cells [Tregs], myeloid-derived suppressor cells [MDSCs], tumor-associated macrophages [TAMs]), immunosuppressive cytokines (e.g., IL-6, TGF-β), and immune checkpoint molecules that inhibit CAR T-cell responses [18–24].

- Inefficient trafficking and infiltration of T cells into the tumor

CAR T cells may have difficulty reaching and infiltrating the tumor site due to physical and biochemical barriers [18,19,24].

4.2 Toxicity

Toxicities associated with CAR T-cell therapy have been observed in pancreatic cancer, similar to those reported in other cancers [20]. These include cytokine release syndrome (CRS) and neurotoxicity, which require careful monitoring and management.

4.3 “On-Target, Off-Tumor” Effects

Recognition of target antigens that are also present on healthy tissues may lead to unintended toxicity and damage to non-cancerous cells [23,24].

5. Target Antigens for CAR T-Cell Therapy in Pancreatic Cancer

5.1 Mesothelin (MSLN)

Mesothelin is the most extensively studied target for CAR T-cell therapy in pancreatic cancer [24].

It is a cell surface protein that, under normal physiological conditions, is expressed at low levels in mesothelial cells lining body cavities such as the peritoneum, pleura, and pericardium [29,32]. It is also minimally expressed on epithelial cells of the trachea, ovaries, rete testis, tonsils, and fallopian tubes [29].

However, mesothelin is overexpressed in various solid tumors, including pancreatic cancer, and its overexpression often correlates with poor prognosis [29,32].

Its biological function in normal tissues appears to be non-essential, as mesothelin knockout mice develop and reproduce normally [29]. In cancer cells, aberrant mesothelin expression plays an active role in malignant transformation and tumor aggressiveness, promoting cancer cell proliferation, local invasion, metastasis, and resistance to apoptosis induced by cytotoxic agents [29].

Due to its high expression in a wide range of solid tumors and limited expression in normal tissues, mesothelin has become an attractive target for cancer immunotherapy, including CAR T-cell therapy [29].

5.2 Carcinoembryonic Antigen (CEA)

CEA is a cell surface glycoprotein that is overexpressed in many cancers, including pancreatic cancer [31]. High CEA expression is associated with poor prognosis [23,24,25]. Its

expression is significantly elevated in various gastrointestinal tumors [35], including approximately 75% of pancreatic cancer cases [31]. CEA can also be measured as a tumor marker in the blood [35].

Preclinical studies in mouse models of pancreatic cancer have demonstrated that CEA-targeted CAR T cells can effectively eliminate orthotopic tumors without inducing autoimmune colitis in mice [28,29,32,35]. One study showed long-term tumor eradication in 67% of mice [28,32,34,35]. A meta-analysis of preclinical studies revealed that CEA-targeted CAR T cells demonstrated significantly increased cytotoxic activity [34].

5.3 Claudin 18.2 (CLDN18.2)

Claudin 18.2 is an isoform of claudin 18, a member of the tight junction protein family [28]. In healthy tissues, CLDN18.2 expression is restricted to differentiated epithelial cells of the gastric mucosa [25,33]. During tumorigenesis in pancreatic (PDAC), gastric, and gastroesophageal junction cancers, loss of cell polarity exposes the Claudin 18.2 epitopes. As a result, CLDN18.2 is strongly expressed in these cancers and in distant metastases [28,33]. CLDN18.2 is positive in over 50% of pancreatic cancer cases, with the majority showing high expression levels [33]. Due to its restricted expression in normal tissues and high expression in pancreatic cancer, CLDN18.2 is considered an ideal target for CAR T-cell therapy in advanced or metastatic PDAC [28,33,35].

5.4 Prostate Stem Cell Antigen (PSCA)

PSCA is a glycoprotein anchored to the cell membrane via a glycosylphosphatidylinositol (GPI) linkage [22]. Its exact function is largely unknown, though it is believed to be involved in intracellular signal transduction [22]. In normal tissues, PSCA is found at low levels in epithelial cells of various organs [22].

PSCA is abnormally overexpressed in several cancers, including nearly 60% of primary pancreatic ductal adenocarcinomas (PDAC), while it is not detected in normal pancreatic ducts [22]. This makes PSCA a specific biomarker for PDAC patients and a promising target

for CAR T-cell therapy [22]. A significant advantage of targeting PSCA is its elevated expression already in the early stages of pancreatic tumorigenesis, including in preinvasive intraductal lesions [22].

5.5 HER2

HER2, also known as human epidermal growth factor receptor 2 (or ERBB2), is a transmembrane glycoprotein with tyrosine kinase activity, belonging to the EGFR receptor family [18].

Under physiological conditions, HER2 plays a key role in the regulation of proliferation and differentiation of epithelial, mesenchymal, and neural cells [18]. However, HER2 is overexpressed in various cancers, including breast, gastric, and lung cancers, and—as recent studies suggest—in pancreatic cancer [32,35]. It is estimated that HER2 is overexpressed in 20% to 60% of pancreatic cancer cases [18,32,35]. In tumor cells, HER2 overexpression contributes to increased proliferation, invasion, and metastasis [35]. Therefore, HER2 is an important biomarker and therapeutic target in several cancers, particularly breast cancer [32,35]. In the context of CAR T-cell therapy, HER2 is being considered as a potential target antigen for pancreatic cancer treatment [28,32].

5.6 CD133

CD133 is a transmembrane glycoprotein expressed on hematopoietic stem cells in healthy tissues [32].

It has been shown to be highly expressed on pancreatic cancer stem cells in 60–80% of PDAC cases, as well as in other cancers such as hepatocellular and gastric carcinomas [18]. Cancer stem cells are believed to play a key role in the development and progression of pancreatic cancer, including the formation of early metastases [22].

5.7 Mucin 1 (MUC1)

Mucin 1 (MUC1) is a transmembrane glycoprotein normally located on the apical surface of epithelial cells [30]. Under physiological conditions, MUC1 plays an important role in cell signaling, adhesion, and differentiation [25].

In cancer cells, including those of breast, colon, and pancreatic adenocarcinomas, MUC1 is abnormally glycosylated and overexpressed [21,22,25]. It has been recognized as the second most promising cancer target antigen by the National Cancer Institute [30].

In pancreatic cancer, the tumor-associated form of MUC1 (tMUC1) is overexpressed in more than 80% of PDAC cases [30].

Other antigens under investigation include: CD70 [22,23], Fibroblast Activation Protein (FAP) [22,23,24], ROBO1 [18], EPH receptor A2 (EphA2) [25], Trophoblast cell-surface antigen 2 (Trop-2) [20,26], and EpCAM [22,23].

5. Review of Current Clinical Trials

6.1 Mesothelin as a Target Antigen

A phase I trial (NCT01897415) evaluated the safety and efficacy of intravenous infusions of CARTmeso cells in six patients with chemotherapy-resistant metastatic pancreatic cancer [27,28]. No cytokine release syndrome (CRS), neurological symptoms, or dose-limiting toxicities were observed [27,28]. Two patients achieved disease stabilization, with progression-free survival of 3.8 and 5.4 months, respectively [20,22,27]. One patient with mesothelin expression on biopsy showed a 69.2% reduction in metabolically active tumor volume, including complete disappearance of FDG uptake in liver lesions [18]. CAR expression was transient [27]. The results suggest potential antitumor activity of mRNA CARTmeso cells [27].

Another phase I study (NCT02159716) assessed the safety and feasibility of second-generation lentivirus-transduced CAR T cells targeting mesothelin in solid tumors [28]. Five of the 15 patients enrolled had pancreatic cancer [28]. Patients received a single intravenous infusion of anti-MSLN CAR T cells ($1–3 \times 10^7$ or $1–3 \times 10^8$ cells/m^2), with or without lymphodepleting cyclophosphamide [28]. No significant antitumor activity was observed; the best response was disease stabilization [28]. CAR T cells showed moderate expansion and poor persistence [28]. A phase I trial (NCT01355965) also investigated mesothelin-targeted mRNA CAR T-cell therapy in pancreatic cancer [29,39]. This study demonstrated that the therapy was safe and feasible in patients with advanced solid tumors, including one patient with metastatic pancreatic cancer who derived clinical benefit [29,30]. The therapy was well tolerated with no significant "on-target, off-tumor" toxicity (e.g., pleuritis, pericarditis, peritonitis) or severe CRS [18,29].

Additional trials targeting mesothelin include NCT03054298, NCT03323944, NCT02706782, NCT02959151, NCT02580747, NCT03182803, NCT03638193, and NCT03747965 [18,31].

6.2 CEA as a Target

The clinical trial NCT01212887, evaluating CEA-targeted CAR T cells in various advanced cancers, including pancreatic cancer, was terminated due to respiratory toxicity and lack of sustained therapeutic response [22,46]. The likely cause of toxicity was CEA expression on lung epithelium, which was exacerbated by preconditioning [22]. Similar issues were reported in another trial using CEA-targeted TCR-T cells in metastatic colorectal cancer [22]. Despite these challenges, clinical trials continue to evaluate the safety and efficacy of CEA-targeted CAR T cells in CEA-positive cancers, including pancreatic and gastrointestinal tumors [25]. In trial NCT02850536, CAR T therapy was shown to be safe. One pancreatic cancer patient with liver metastases achieved a complete metabolic response lasting 13 months [49]. Trial NCT02349724 evaluated the safety and efficacy of CEA-targeted CAR T therapy in patients with metastatic CEA-positive colorectal cancer. Among 10 patients, 7 with progressive disease achieved disease stabilization. Two maintained stable disease for over 30 weeks, and two showed tumor reduction on PET/CT and MRI scans [36]. Other ongoing studies include NCT05538195.

6.3 Claudin 18.2 (CLDN18.2) as a Target

An open-label, single-arm phase Ib trial (NCT04404595) studied autologous CAR T cells (CT041) in patients with CLDN18.2-positive advanced gastric or pancreatic adenocarcinoma. Eleven patients were enrolled (5 with gastric and 6 with pancreatic cancer). No dose-limiting toxicities, treatment-related deaths, severe CRS, ICANS, or gastrointestinal toxicities were observed. Of the first five pancreatic cancer patients assessed, two had stable disease with tumor shrinkage, and three experienced disease progression after initial biochemical response [43].

Trial NCT03159819 evaluated CAR-CLD18 T therapy in advanced gastric and pancreatic adenocarcinomas [18]. Treatment was well tolerated, with all CRS cases being grade 1 or 2. Among 11 evaluable patients, 1 achieved complete response (gastric cancer), 3 partial responses (2 gastric, 1 pancreatic), 5 stable disease, and 2 disease progression. The overall response rate was 33.3%, and the median progression-free survival was 130 days [50]. In phase I trial NCT03874897, CT041 CAR T therapy was tested in CLDN18.2-positive tumors, including five pancreatic cancer patients: one achieved partial response, three had stable disease, and one showed no response. Adverse events included grade ≥3 hematologic toxicity and grade 1–2 CRS. No deaths, neurotoxicity, or dose-limiting toxicities were reported [20,47].

A case report described complete remission in a 72-year-old man with advanced pancreatic cancer treated with Claudin 18.2-targeted CAR T cells after multiple prior treatments. He experienced grade 2 CRS and gastric mucosal injury, both managed successfully. Complete response was achieved one month post-treatment and lasted 8 months. Recurrence occurred with loss of Claudin 18.2 expression, but the prolonged remission highlights the potential efficacy of this therapy [33].

6.4 PSCA (Prostate Stem Cell Antigen)

Preclinical studies using first-generation PSCA-targeted CAR T cells demonstrated specific cytotoxicity against PSCA-positive pancreatic cancer cells in vitro, without harming PSCA-negative cells [22,28]. Subsequent studies comparing CAR designs showed strong antitumor activity in mouse models of human pancreatic cancer. Although third-generation CARs (CD28 and CD137 domains) offered better in vivo persistence, second-generation CARs without CD137 had stronger antitumor effects, eradicating tumors in 40% of mice [22].

However, the clinical trial NCT02744287, evaluating BPX-601 CAR T cells targeting PSCA in metastatic pancreatic and castration-resistant prostate cancer, was terminated due to severe adverse events, including two patient deaths [48].

6.5 HER2 as a Target

Phase I trial NCT01935843 assessed the safety, feasibility, and activity of HER2-targeted CAR T cells in 11 patients with advanced biliary and pancreatic cancers [18,20,22,28]. The therapy was well tolerated. Among the two pancreatic cancer patients, both achieved disease stabilization [28,42].

A separate trial (NCT04660929) evaluated HER2-targeted CAR macrophages, demonstrating safety and potential therapeutic benefit in HER2-positive cancers [44].

6.6 CD133 as a Target

Phase I trial NCT02541370 evaluated CD133-targeted CAR T cells in patients with various metastatic cancers, including 7 with pancreatic cancer [28,31,32,45]. Two patients showed significant tumor reduction, three had stable disease, and two showed no response [32,45].

Adverse events included grade 2–3 leukopenia, thrombocytopenia, anemia, anorexia, nausea, and mucosal hyperemia. One patient experienced grade 4 leukopenia [18].

6.7 EGFR (Epidermal Growth Factor Receptor)

Phase I trial NCT01869166 involved 16 patients with metastatic pancreatic cancer with EGFR expression >50% [41]. Patients received up to three CAR T-cell infusions after conditioning chemotherapy [28]. CAR T-cell expansion was adequate, but persistence was limited [28]. Grade ≥3 adverse events included fever/fatigue, nausea/vomiting, mucocutaneous toxicity, pleural effusion, and interstitial lung infiltrates, all reversible. No study-related deaths occurred [41]. Of 14 evaluable patients, 4 had partial responses lasting 2–4 months, and 8 achieved disease stabilization for 2–4 months. Median progression-free survival was 3 months, and median overall survival was 4.9 months [18,20,28,41]. Ongoing trials are also exploring EGFR-CAR T-cell therapy in solid tumors, including: - NCT03618381: Phase I, open-label, non-randomized study in children and young adults with advanced solid tumors (esophageal, gastric) [25] - NCT03182816: Phase I/II trial of EGFR-CAR T cells co-expressing anti-CTLA-4 and anti-PD-1 antibodies in EGFR-positive solid tumors [18]

6. Future Perspectives

Future directions and perspectives in the development of CAR T-cell therapy include numerous promising areas of research and innovation aimed at increasing the efficacy and safety of this treatment, particularly for hard-to-treat solid tumors. Key areas of advancement include:

7.1 Discovery and Validation of New, More Specific Target Antigens

Intensive research into neoantigens—unique to an individual patient's cancer cells—holds promise for higher specificity and reduced risk of toxicity [24]. Scientists are seeking novel surface antigens that are strongly and specifically overexpressed in pancreatic cancer cells, with minimal expression in healthy tissues. Potential targets include CLDN18.2,

GPC3, tMUC1, ROBO1, among others [18,28].
The development of dual-targeting CARs, designed to recognize two different antigens on cancer cells, may improve specificity and reduce the risk of off-target toxicity and tumor escape due to antigen loss [28,29,34].
Another approach involves targeting the tumor microenvironment (TME), for example, fibroblast activation protein (FAP) on cancer-associated fibroblasts, to indirectly attack the tumor [22,23,24].

7.2 Overcoming the Immunosuppressive Tumor Microenvironment (TME)
Overcoming TME barriers involves several key strategies. One is designing CAR T cells capable of modulating the TME, such as by expressing enzymes that degrade the tumor stroma (e.g., heparanase), facilitating T-cell infiltration [19].
Another strategy includes combining CAR T therapy with treatments that neutralize the immunosuppressive components of the TME, such as immune checkpoint inhibitors, agents reducing Tregs, TAMs, and MDSCs, or even engineering CAR T cells to directly target antigens expressed on these suppressive immune cells [20].
Genetic engineering of CAR T cells may also involve expression of chemokine receptors to improve tumor homing, or cytokine receptors that counteract inhibitory signals within the TME [29,38].

7.3 Optimization of CAR Receptor Design – Improving Specificity and Safety
Further development includes fourth- and fifth-generation CARs with additional co-stimulatory and signaling domains and the ability to secrete therapeutic molecules [18]. Gated CARs (“AND-gate” and “NOT-gate” systems) require the recognition of multiple antigens or the absence of antigens on healthy tissues to activate cytotoxic functions, enhancing safety [32].

Switchable CARs allow for exogenous control of CAR T-cell activity, enabling on/off switching and even retargeting to different antigens [29,32].
Suicide genes, such as HSV-tk, iCasp9, or truncated EGFR (EGFRΔ), can be introduced to allow pharmacologic elimination of CAR T cells in case of severe adverse events [29,32,35].

7.4 Combination Therapies

Combining CAR T therapy with other modalities—such as chemotherapy, radiotherapy, targeted therapies, oncolytic viruses (OVs), cancer vaccines, and other immunotherapies—aims to enhance antitumor responses [18,28,31]. Oncolytic adenoviruses armed with cytokines (e.g., TNF-α and IL-2) combined with mesothelin-targeted CAR T cells have shown promising preclinical results [37].

7.5 Development of Allogeneic ("Off-the-Shelf") CAR T Cells

Developing universal, ready-to-use CAR T cells derived from healthy donors could reduce costs and treatment delays [28,32]. The main challenge is minimizing the risk of graft-versus-host disease (GvHD) and transplant rejection [26,28,32].

7.6 Use of Alternative Immune Cells

CAR natural killer (NK) cells represent a promising alternative to allogeneic T cells due to their innate tumor-killing abilities without prior sensitization and a lower risk of GvHD [18,28,31].

7.7 Personalization of Therapy

Personalization involves tailoring target antigens, CAR constructs, and treatment strategies to individual patient and tumor characteristics, including genetic and immunologic profiles [24]. Patient-specific preclinical models, such as organoids, could be used to predict treatment response and optimize therapeutic strategies [18].

The future of CAR T-cell therapy in oncology—including pancreatic cancer—appears promising. It will likely rely on a multi-faceted and personalized approach, combining advanced CAR T-cell engineering with therapies that modulate the TME, precision delivery strategies, and sophisticated preclinical models to optimize treatment and predict individual

responses [38]. Further research into innovative strategies has the potential to significantly improve treatment outcomes and the quality of life for patients [23,24].

Conclusions

Pancreatic cancer is associated with high mortality, primarily due to late diagnosis and the limited efficacy of standard treatment modalities, creating an urgent need for the development of novel therapeutic strategies. One promising approach is the use of genetically modified T lymphocytes (CAR T-cell therapy), which has already demonstrated antitumor potential in early-stage studies—even against difficult-to-treat solid tumors.
However, the effectiveness of CAR T-cell therapy in pancreatic cancer is significantly hindered by the tumor's complex and immunosuppressive microenvironment. The presence of a dense desmoplastic stroma, fibroblasts, and numerous immunosuppressive factors limits both infiltration and activity of therapeutic cells. Additionally, the risk of treatment-related toxicities, including the "on-target, off-tumor" phenomenon, remains a major challenge, highlighting the need for further research into optimizing CAR receptor designs and strategies for controlling T-cell activity.

Although clinical trials have shown some promising outcomes, additional studies are necessary to identify the most appropriate target antigens and to develop CAR T-cell constructs with improved specificity and safety. Looking ahead, the advancement of genetic engineering technologies, along with a deeper understanding of tumor-host interactions, opens new therapeutic possibilities.

The implementation of combination strategies—such as dual-targeting systems, switchable CARs, and the use of allogeneic CAR T cells—may overcome barriers imposed by the tumor microenvironment and enable treatment personalization based on individual genetic and immunologic profiles.

In conclusion, despite the limitations of conventional therapies, CAR T-cell therapy represents an innovative and promising strategy which, after overcoming current challenges, has the potential to significantly improve treatment outcomes in pancreatic cancer.

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Author's contribution

All authors contributed to the article.

Project administration: Kuźniar J

Conceptualization: Kuźniar J

Methodology: Chrzanowska E, Ząbek A

Software: Roguska B, Tamborski T

Formal analysis: Szlążek J, Turek M

Investigation: Tamborski T, Szlążek J

Resources: Grzebinoga A, Ząbek A

Data curation: Grzebinoga A, Zagalska M

Writing - rough preparation: Chrzanowska E, Roguska B

Writing - review and editing: Kuźniar A, Turek M

Visualization: Kuźniar A, Zagalska M

Supervision: Kuźniar J, Chrzanowska E

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References:

1. Torphy RJ, Fujiwara Y, Schulick RD. Pancreatic cancer treatment: better, but a long way to go. *Surg Today*. 2020;50(10):1117–1125. doi:10.1007/s00595-020-02028-0. PMID: 32474642; PMCID: PMC7837389.

2. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. JAMA. 2021 Sep 7;326(9):851-862. doi: 10.1001/jama.2021.13027. PMID: 34547082; PMCID: PMC9363152.

3. Jiang S, Fagman JB, Ma Y, Liu J, Vihav C, Engstrom C, Liu B, Chen C. A comprehensive review of pancreatic cancer and its therapeutic challenges. *Aging (Albany NY).* 2022 Sep 28;14(18):7635–7649. doi:10.18632/aging.204310. PMID: 36173644; PMCID: PMC9550249.

4. Domagała-Haduch M, Gorzelak-Magiera A, Michalecki Ł, Gisterek-Grocholska I. Radiochemotherapy in Pancreatic Cancer. *Curr Oncol*. 2024;31(6):3291–3300. doi:10.3390/curroncol31060250. PMID: 38920733; PMCID: PMC11202861.

5. Goral V. Pancreatic Cancer: Pathogenesis and Diagnosis. *Asian Pac J Cancer Prev*. 2015;16(14):5619–24. doi:10.7314/apjcp.2015.16.14.5619. PMID: 26320426.

6. Wood LD, Canto MI, Jaffee EM, Simeone DM. Pancreatic cancer: pathogenesis, screening, diagnosis, and treatment. *Gastroenterology*. 2022 Aug;163(2):386-402.e1. doi: 10.1053/j.gastro.2022.03.056. PMID: 35398344; PMCID: PMC9245559.

7. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev Gastroenterol Hepatol*. 2021;18(7):493–502. doi:10.1038/s41575-021-00457-x. PMID: 34002083; PMCID: PMC9265847. PubMed

8. Zhao ZY, Liu W. Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment. *Technol Cancer Res Treat*. 2020 Jan-Dec;19:1533033820962117. doi:10.1177/1533033820962117. PMID: 33357065. PMCID: PMC7768873.

9. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J*

Gastroenterol. 2018 Nov 21;24(43):4846–61. doi:10.3748/wjg.v24.i43.4846. PMID: 30487695. PMCID: PMC6247289.

10. Kolbeinsson HM, Chandana S, Wright GP, Chung M. Pancreatic Cancer: A Review of Current Treatment and Novel Therapies. *J Invest Surg*. 2023;36(1):2129884. doi:10.1080/08941939.2022.2129884. PMID: 36191926.

11. Zhang Q, Ping J, Huang Z, Zhang X, Zhou J, Wang G, et al. CAR-T Cell Therapy in Cancer: Tribulations and Road Ahead. *J Immunol Res*. 2020 Jan 17;2020:1924379. doi:10.1155/2020/1924379. PMID: 32411789; PMCID: PMC7219183.

12. Benmebarek MR, Karches CH, Cadilha BL, Lesch S, Endres S, Kobold S. Killing Mechanisms of Chimeric Antigen Receptor (CAR) T Cells. *Int J Mol Sci*. 2019 Mar 14;20(6):1283. doi:10.3390/ijms20061283. PMID: 30875739; PMCID: PMC6471606.

13. Almotiri A. CAR T-cell therapy in acute myeloid leukemia. *Saudi Med J*. 2024 Oct;45(10):1007–1019. doi:10.15537/smj.2024.45.10.20240330. PMID: 39379118; PMCID: PMC11463564.

14. Wagner J, Wickman E, DeRenzo C, Gottschalk S. CAR T Cell Therapy for Solid Tumors: Bright Future or Dark Reality? *Mol Ther*. 2020 Nov 4;28(11):2320–39. doi:10.1016/j.ymthe.2020.09.015. PMID: 32979309; PMCID: PMC7608013.

15. Fischer JW, Bhattarai N. CAR-T Cell Therapy: Mechanism, Management, and Mitigation of Inflammatory Toxicities. *Front Immunol*. 2021 Jun 18;12:693016. doi:10.3389/fimmu.2021.693016. PMID: 34220853; PMCID: PMC8250150.

16. Sun D, Shi X, Li S, Wang X, Yang X, Wan M. CAR-T cell therapy: A breakthrough in traditional cancer treatment strategies (Review). *Mol Med Rep.* 2024 Mar;29(3):47. doi:10.3892/mmr.2024.13171. PMID: 38275119; PMCID: PMC10835665.

17. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J*. 2021 Apr 6;11(4):69. doi:10.1038/s41408-021-00459-7. PMID: 33824268; PMCID: PMC8024391.

18. Yeo D, Giardina C, Saxena P, Rasko JEJ. The next wave of cellular immunotherapies in pancreatic cancer. *Mol Ther Oncolytics*. 2022 Feb 1;24:561–76. doi:10.1016/j.omto.2022.01.010. PMID: 35229033; PMCID: PMC8866953.

19. Henze J, Tacke F, Hardt O, Alves F, Al Rawashdeh W. Enhancing the Efficacy of CAR T Cells in the Tumor Microenvironment of Pancreatic Cancer. *Cancers (Basel)*. 2020 May 28;12(6):1389. doi:10.3390/cancers12061389. PMID: 32481570; PMCID: PMC7352751.

20. Czaplicka A, Lachota M, Pączek L, Zagożdżon R, Kaleta B. Chimeric Antigen Receptor T Cell Therapy for Pancreatic Cancer: A Review of Current Evidence. *Cells*. 2024 Jan 4;13(1):101. doi:10.3390/cells13010101. PMID: 38201305; PMCID: PMC12601305.

21. DeSelm CJ, Tano ZE, Varghese AM, Adusumilli PS. CAR T-cell therapy for pancreatic cancer. *J Surg Oncol*. 2017 Jul;116(1):63–74. doi:10.1002/jso.24627. PMID: 28346697; PMCID: PMC5491361.

22. Ali AI, Oliver AJ, Samiei T, Chan JD, Kershaw MH, Slaney CY. Genetic Redirection of T Cells for the Treatment of Pancreatic Cancer. *Front Oncol*. 2019 Feb 12;9:56. doi:10.3389/fonc.2019.00056. PMID: 30809507; PMCID: PMC6379296.

23. Akce M, Zaidi MY, Waller EK, El-Rayes BF, Lesinski GB. The Potential of CAR T Cell Therapy in Pancreatic Cancer. *Front Immunol.* 2018 Sep 25;9:2166. doi:10.3389/fimmu.2018.02166. PMID: 30319627; PMCID: PMC6167429.

24. Li T, Li H, Li S, Xu S, Zhang W, Gao H, Xu H, Wu C, Wang W, Yu X, Liu L. Research progress and design optimization of CAR-T therapy for pancreatic ductal adenocarcinoma. *Cancer Med*. 2019 Sep;8(11):5223–31. doi:10.1002/cam4.2430. PMID: 31339230; PMCID: PMC6714042.

25. Li W, Huang Y, Zhou X, Cheng B, Wang H, Wang Y. CAR-T therapy for gastrointestinal cancers: current status, challenges, and future directions. *Braz J Med Biol Res*. 2024 Oct 14;57:e13640. doi:10.1590/1414-431X2024e13640. PMID: 39417449; PMCID: PMC11484376.

26. Feng Q, Sun B, Xue T, Li R, Lin C, Gao Y, Sun L, Zhuo Y, Wang D. Advances in CAR T-cell therapy in bile duct, pancreatic, and gastric cancers. *Front Immunol*. 2022 Oct 6;13:1025608. doi:10.3389/fimmu.2022.1025608. PMID: 36341440; PMCID: PMC9628995.

27. Beatty GL, O'Hara MH, Lacey SF, Torigian DA, Nazimuddin F, Chen F, et al. Activity of mesothelin-specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase 1 trial. *Gastroenterology.* 2018 Jul;155(1):29–32. doi:10.1053/j.gastro.2018.03.029. PMID: 29567081; PMCID: PMC6035088.

28. Drougkas K, Karampinos K, Karavolias I, Gomatou G, Koumprentziotis IA, Ploumaki I, Triantafyllou E, Kotteas E. CAR-T Cell Therapy in Pancreatic and Biliary Tract Cancers: An Updated Review of Clinical Trials. *J Gastrointest Cancer*. 2024;55(3):990–1003. doi:10.1007/s12029-024-01054-2

29. Morello A, Sadelain M, Adusumilli PS. Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors. *Cancer Discov*. 2016 Feb;6(2):133–46. doi:10.1158/2159-8290.CD-15-0583. PMID: 26503962; PMCID: PMC4744937.

30. Yazdanifar M, Zhou R, Grover P, Williams C, Jensen R, Kolhe R, Copik A, Shanker A. Overcoming Immunological Resistance Enhances the Efficacy of a Novel Anti-tMUC1-CAR T Cell Treatment against Pancreatic Ductal Adenocarcinoma. *Cells*. 2019 Sep 5;8(9):1070. doi:10.3390/cells8091070

31. Varghese AM. Chimeric antigen receptor (CAR) T and other T cell strategies for pancreas adenocarcinoma. Chin Clin Oncol. 2017 Dec;6(6):66. doi: 10.21037/cco.2017.09.04.

32. Cutmore LC, Brown NF, Raj D, Chauduri S, Wang P, Maher J, Wang Y, Lemoine NR, Marshall JF. Pancreatic Cancer UK Grand Challenge: Developments and challenges for effective CAR T cell therapy for pancreatic ductal adenocarcinoma. *Pancreatology.* 2020 Apr;20(3):394-408. doi: 10.1016/j.pan.2020.02.006. PMID: 32173257; PMCID: PMC7314409.

33. Zhong G, Zhang X, Guo Z, Gao Y, Zhao B, Liu X, Chen L, Qiao J, Yu C, Wang L, Li Y, Yu L. Complete remission of advanced pancreatic cancer induced by claudin18.2-targeted CAR-T cell therapy: a case report. *Front Immunol*. 2024;15:1325860. doi:10.3389/fimmu.2024.1325860.

34. Sahlolbei M, Dehghani M, Kheiri Yeghane Azar B, Vafaei S, Roviello G, D'Angelo A, Madjd Z, Kiani J. Evaluation of targetable biomarkers for chimeric antigen receptor T-cell (CAR-T) in the treatment of pancreatic cancer: a systematic review and meta-analysis of preclinical studies. *Int Rev Immunol*. 2020;39(5):223–32. doi:10.1080/08830185.2020.1776274. PMID: 32546036.

35. Jindal V, Arora E, Masab M, Gupta S. Chimeric antigen receptor T cell therapy in pancreatic cancer: from research to practice. Med Oncol. 2018 May;35(6):84. PMID: 29728788; PMCID: PMC5937012.

36. Zhang C, Wang Z, Yang Z, Wang M, Li S, Li Y, et al. Phase I Escalating-Dose Trial of CAR-T Therapy Targeting CEA+ Metastatic Colorectal Cancers. *Mol Ther.* 2017 May;25(5):1248–1258. doi:10.1016/j.ymthe.2017.03.010. PMID: 28392141; PMCID: PMC5417843.

37. Watanabe K, Luo Y, Da T, Guedan S, Ruella M, Scholler J, Keith B, Young RM, Engels B, Sorsa S, Siurala M, Havunen R, Tähtinen S, Hemminki A, June CH. Pancreatic cancer therapy with combined mesothelin-redirected chimeric antigen receptor T cells and cytokine-armed oncolytic adenoviruses. *JCI Insight*. 2018 Apr 5;3(7):e99573. doi:10.1172/jci.insight.99573. PMID: 29669915; PMCID: PMC5928866.

38. Somala M, Sukumaran S, Bajgain P, Watanabe N, Heslop HE, Rooney CM, et al. Improving chimeric antigen receptor-modified T cell function by reversing the immunosuppressive tumor microenvironment of pancreatic cancer. *Mol Ther.* 2017 Jan 4;25(1):249-258. doi:10.1016/j.ymthe.2016.10.016. PMID: 28129119; PMCID: PMC5205691.

39. Beatty GL, Haas AR, Maus MV, Torigian DA, Soulen MC, Plesa G, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce antitumor activity in solid malignancies. Cancer Immunol Res. 2014 Feb;2(2):112–20. PMID: 24579088; PMCID: PMC3932715

40. Haas, A.R.; Tanyi, J.L.; O′Hara, M.H.; Gladney, W.L.; Lacey, S.F.; Torigian, D.A.; Soulen, M.C.; Tian, L.; McGarvey, M.; Nelson, A.M.; et al. Phase I Study of Lentiviral-Transduced Chimeric Antigen Receptor-Modified T Cells Recognizing Mesothelin in Advanced Solid Cancers. Mol. Ther. 2019, 27, 1919–1929

41. Liu, Y.; Guo, Y.; Wu, Z.; Feng, K.; Tong, C.; Wang, Y.; Dai, H.; Shi, F.; Yang, Q.; Han, W. Anti-EGFR chimeric antigen receptor modified T cells in metastatic pancreatic carcinoma: A phase I clinical trial. Cytotherapy 2020, 22, 573–580

42. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, et al. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell. 2018 Oct;9(10):838–847. PMID: 28710747; PMCID: PMC6143031.

43. Botta GP, Becerra CR, Jin Z, Kim DW, Zhao D, Lenz HJ, et al. Multicenter phase Ib trial in the U.S. of salvage CT041 CLDN18.2-specific chimeric antigen receptor T-cell therapy for

patients with advanced gastric and pancreatic adenocarcinoma. *J Clin Oncol*. 2022;40(16_suppl):2538. doi:10.1200/JCO.2022.40.16_suppl.2538

44. Reiss KA, Angelos MG, Dees EC, Yuan Y, Ueno NT, Pohlmann PR, et al. CAR-macrophage therapy for HER2-overexpressing advanced solid tumors: a phase 1 trial. *Nat Med.* 2025 Feb 7. doi:10.1038/s41591-025-03495-z. PMID: 39920391

45. Zhou J, Shen L, Huang C, Zhang W, Zhang Y, Chen H, et al. Efficacy and biomarker analysis of CD133-directed CAR T cells in advanced hepatocellular carcinoma: a single-arm, open-label, phase II trial. *Nat Cancer*. 2023;4:166–180. doi:10.1038/s41571-022-00698-9.

46. Thistlethwaite FC, Gilham DE, Guest RD, Rothwell DG, Pillai M, Burt DJ, et al. The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. *Cancer Immunol Immunother.* 2017 Nov;66(11):1425–1436. doi:10.1007/s00262-017-2034-7. PMID: 28664249; PMCID: PMC5645435.

47. Qi C, Gong J, Li J, Liu D, Qin Y, Ge S, et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. *Nat Med*. 2022;28(6):1189–98. PMID: 35534566; PMCID: PMC9155576. doi:10.1038/s41591-022-01800-8

48. Stein MN, Dumbrava EE, Teply BA, Gergis US, Gutierrez ME, Reshef R, et al. PSCA-targeted BPX-601 CAR T cells with pharmacological activation by rimiducid in metastatic pancreatic and prostate cancer: a phase 1 dose escalation trial. *Nat Commun.* 2024 Dec 30;15(1):10743. doi:10.1038/s41467-024-53220-6. PMID: 39737899; PMCID: PMC10812345.

49. Katz SC, Moody AE, Guha P, Hardaway JC, Prince E, LaPorte J, et al. HITM-SURE: Hepatic immunotherapy for metastases phase Ib anti-CEA CAR-T study utilizing pressure enabled drug delivery. *J Immunother Cancer.* 2020 Aug;8(2):e001097. doi:10.1136/jitc-2020-001097. PMID: 32843493; PMCID: PMC7445205.

50. Zhan X, Wang B, Li Z, et al. Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma. *J Clin Oncol*. 2019;37(15_suppl):2509. doi:10.1200/JCO.2019.37.15_suppl.2509.