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Independent Research

8 August 2026

CAR-T Cell Therapy for Pancreatic Cancer: Current Evidence, Biological Barriers, and Future Directions

Introduction

Pancreatic cancer is disproportionately lethal relative to how often it occurs. Pancreatic cancer accounts for only a small share of new cancer diagnoses in the United States each year, yet it ranks among the leading causes of cancer death, trailing only lung and colorectal cancer. The five-year relative survival rate for all stages combined remains low, and outcomes are strongly dependent on stage at diagnosis: patients whose disease is still localized to the pancreas have a meaningfully better five-year survival rate than those whose cancer is diagnosed after it has spread to distant organs. Because early symptoms are vague or absent, the majority of cases are found only after the disease has spread regionally or distantly, which is the central reason survival statistics for this cancer have remained difficult to improve (National Cancer Institute, “Cancer Stat Facts”).

Pancreatic cancer is also a disease of older age, with a median age at diagnosis in the early seventies, and incidence has been rising gradually for several decades even as death rates from many other cancers have declined (National Cancer Institute, “Cancer Stat Facts”). This combination of late detection, aggressive biology, and resistance to conventional chemotherapy and radiation has motivated researchers to explore immunotherapy, and in particular chimeric antigen receptor (CAR) T-cell therapy, as a new avenue of treatment. This paper first establishes why pancreatic cancer is such a difficult clinical problem, then explains how CAR-T therapy

works and why it is being pursued for this disease, examines the specific biological obstacles that have limited its success, reviews the antigen targets and trial evidence assembled so far, and considers where the field is heading alongside the practical barriers of cost and access that accompany the science.

Background: The Biology of Pancreatic Cancer

The pancreas performs two distinct functions: an exocrine function, producing digestive enzymes released into the small intestine, and an endocrine function, producing hormones such as insulin. More than 90% of pancreatic cancers arise from the exocrine compartment, and the overwhelming majority of these are pancreatic ductal adenocarcinoma (PDAC), a cancer of the cells lining the pancreatic ducts. A much smaller number of cases are pancreatic neuroendocrine tumors, which arise from hormone-producing cells, tend to grow more slowly, and generally carry a better prognosis than PDAC. Because PDAC represents the large majority of cases and drives most of the disease's mortality, it is the focus of nearly all CAR-T research discussed in this paper (American Cancer Society).

PDAC is characterized by a small number of recurrently mutated driver genes. Mutations in the KRAS oncogene are present in roughly 90% of PDAC tumors and are considered the primary initiating event in most cases, followed by inactivating mutations in tumor-suppressor genes such as TP53, CDKN2A, and SMAD4 as the disease progresses. This genetic profile helps explain why PDAC is so resistant to many targeted therapies that work well in other cancers, which is part of why researchers have turned to immunotherapy approaches like CAR-T that target proteins on the cell surface rather than trying to correct the internal mutations driving the cancer (El Bejjani et al.).

Established risk factors for PDAC include cigarette smoking, chronic pancreatitis, long-standing type 2 diabetes, obesity, and a family history of pancreatic cancer, including inherited mutations such as BRCA1, BRCA2, and PALB2 (American Cancer Society). Even accounting for these known factors, a substantial share of the recent rise in incidence, particularly among younger adults and specific demographic groups, is not fully explained, which is why population surveillance remains an important tool for identifying emerging patterns that point researchers toward new hypotheses.

Epidemiology: National Cancer Institute Public Data

The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program is the primary source of population-based cancer statistics in the United States and publishes its data without a paywall or login requirement through SEER*Explorer, an interactive statistics browser, and the SEER Cancer Stat Facts pages, which summarize incidence, mortality, stage distribution, and survival for individual cancer sites.

Table 1. Summary of national pancreatic cancer statistics from NCI SEER public data (National Cancer Institute, “Cancer Stat Facts”).

Measure	Value
Share of all new U.S. cancer cases	~3.3%
Rank among causes of U.S. cancer death	3rd (behind lung and colorectal cancer)
Age-adjusted incidence rate	~13.8 per 100,000 people per year
Age-adjusted death rate	~11.3 per 100,000 people per year
Overall 5-year relative survival	~13%
5-year survival – localized stage	~44%
5-year survival – regional stage	~17%
5-year survival – distant stage	~3%
Median age at diagnosis	71 years

These figures illustrate why stage at diagnosis is treated as the single most important prognostic factor in PDAC, and why researchers are motivated to find treatments, including cellular immunotherapies, that can work even after the disease has spread beyond the pancreas, since only a small minority of patients are diagnosed while the tumor is still localized.

Population studies also show that pancreatic cancer does not affect every demographic group equally. Age-adjusted incidence is consistently higher in men than women, roughly 14.8 per 100,000 in men versus 11.6 per 100,000 in women, and Black patients have the highest incidence rate of any racial group studied, approximately 15.4 per 100,000, compared to roughly 13.2 per 100,000 for non-Hispanic White patients and 11.6 per 100,000 for Hispanic patients. Incidence rises steeply with age across every group. A separate analysis found that incidence is rising fastest in younger women under 55, with the steepest increases in young Hispanic and Black women, a pattern that is not fully explained by known risk factors such as smoking, obesity, and diabetes and remains an active area of epidemiological research (Samaan et al.).

Long-run SEER data show that incidence trends have not moved in a single direction over time: rates among white men declined from the mid-1970s through the mid-1990s before rising again, while rates among Black men and women have remained comparatively stable but consistently higher than other groups throughout the observation period. More recent analyses found that incidence continued to climb across nearly all racial and ethnic groups between 2000 and 2017, with the steepest annual percentage increases seen in American Indian/Alaska Native and Hispanic patients (National Cancer Institute, “SEER*Explorer”).

CAR-T Cell Therapy: Mechanism and Evolution

CAR-T therapy is a form of adoptive cell therapy in which a patient's own T cells are collected via a blood-filtering process called leukapheresis, genetically engineered to express a

synthetic chimeric antigen receptor on their surface, expanded in the laboratory to large numbers, and then infused back into the patient, typically after a short course of lymphodepleting chemotherapy that makes room for the new cells to expand in the body. The chimeric receptor allows the T cell to recognize a specific protein, or antigen, on the surface of cancer cells independent of the major histocompatibility complex, which is the mechanism T cells normally rely on and which cancer cells frequently learn to evade. Once a CAR-T cell binds its target antigen, it activates and can kill the cancer cell directly (El Bejjani et al.).

Table 2. Evolution of chimeric antigen receptor design (El Bejjani et al.).

Generation	Design and purpose
First	Antigen-binding domain fused directly to a CD3-zeta signaling chain only; produced weak T-cell activation and poor persistence in early trials.
Second	Adds one co-stimulatory domain (commonly CD28 or 4-1BB) alongside CD3-zeta; the basis of nearly all currently investigational CAR-T products discussed in this paper.
Third	Combines two co-stimulatory domains for stronger activation; used less often clinically due to a narrower safety margin.
Fourth ('armored'/TRUCK)	Adds engineered secretion of cytokines or other payloads directly at the tumor site to counteract the immunosuppressive microenvironment; an active area of PDAC-specific research.

Most CAR-T products in clinical use today, and nearly all of the pancreatic-cancer trials discussed later in this paper, are second-generation designs. Fourth-generation, or “armored,” CAR-T cells are of particular interest for PDAC specifically because the tumor microenvironment poses such a strong barrier to T-cell function, and engineering the T cell to fight that environment directly is one of the more active areas of current research.

Producing a patient-specific CAR-T product is logistically demanding. After leukapheresis, cells are shipped to a manufacturing facility, genetically modified, expanded, tested for quality and safety, and shipped back to the treating hospital for infusion. Published estimates for currently used CAR-T products put the median time from leukapheresis to product

delivery at roughly two to eight weeks, and manufacturing failures or delays can mean a patient's disease progresses before the product is ready. This timeline is a meaningful practical constraint for PDAC, a cancer that can progress quickly (“High Cost of Chimeric Antigen Receptor T-Cells”).

Barriers to CAR-T Efficacy in Pancreatic Cancer

CAR-T therapy has produced durable remissions in certain B-cell leukemias and lymphomas, but solid tumors such as PDAC have proven far more resistant, for several distinct and compounding biological reasons.

PDAC tumors are surrounded by an unusually dense layer of connective tissue and non-cancerous cells, often called the desmoplastic stroma, which in some tumors can make up the majority of the total tumor mass. This barrier can physically block CAR-T cells from reaching tumor cells and is a defining structural feature that distinguishes PDAC from the blood cancers where CAR-T has succeeded (El Bejjani et al.).

Beyond the physical stroma, PDAC tumors actively recruit and sustain an immune environment that suppresses T-cell activity. Regulatory T cells and myeloid-derived suppressor cells accumulate within the tumor and release signals that dampen the activity of infiltrating immune cells, while poor blood supply within the tumor creates areas of low oxygen that further impair T-cell metabolism and function. Together, these features mean that even CAR-T cells that reach the tumor often encounter conditions that push them toward a non-functional, or “exhausted,” state rather than sustained anti-tumor activity (“CAR-T Cell Therapy for Pancreatic Cancer”).

Unlike the B-cell malignancies where CAR-T therapy has succeeded, PDAC tumors do not express one single antigen uniformly across all cancer cells, and many of the antigens under

investigation are also present, at lower levels, on healthy tissue. This raises the risk that CAR-T cells could attack normal organs, a problem researchers call on-target, off-tumor toxicity, which limits how aggressively these therapies can currently be dosed (El Bejjani et al.).

Even when CAR-T cells are successfully infused, three separate steps must each succeed for treatment to work: the cells must traffic to the tumor site, infiltrate through the stroma, and then persist and remain functionally active over time rather than becoming exhausted. Early-phase PDAC trials have repeatedly identified weak persistence as a limiting factor and one of the main reasons responses have so far been partial or short-lived rather than durable (“CAR-T Cell Therapy for Pancreatic Cancer”).

Antigen Targets Under Investigation

Because PDAC lacks a single ideal target, researchers have tested CAR-T constructs against several different surface proteins that are more common on pancreatic tumor cells than on healthy tissue.

Mesothelin is a cell-surface glycoprotein expressed on normal mesothelial cells lining the pleura, peritoneum, and pericardium, but it is overexpressed in an estimated 80% of PDAC tumors while remaining largely absent from other normal tissue. A related engineered T-cell approach, a mesothelin-targeting T-cell receptor fusion construct called gavocabtagene autoleucel, reported in a phase 1/2 trial of 32 patients with mesothelin-expressing solid tumors an overall response rate of 20%, a disease control rate of 77%, and a six-month overall survival rate of 70%; grade 3-or-higher cytokine release syndrome occurred in 25% of all patients (Adusumilli et al.).

Carcinoembryonic antigen, or CEA, is elevated in an estimated 30-60% of PDAC cases and has been used both as a diagnostic blood marker and as a CAR-T target. Because CEA is

also present at low levels on healthy gastrointestinal epithelium, one trial delivered anti-CEA CAR-T cells regionally, directly into the hepatic artery, rather than intravenously, specifically to concentrate the dose in liver metastases while limiting systemic exposure; six of eight enrolled patients completed the protocol (Katz et al., “Phase I”). A follow-on trial added pressure-enabled drug delivery technology, reported to improve CAR-T delivery to liver metastases roughly 5.2-fold compared to standard infusion (Katz et al., “HITM-SURE”).

Claudin 18.2 is a tight-junction protein whose expression is largely restricted to the stomach lining in healthy tissue but is also found in pancreatic and other gastrointestinal cancers. In a phase 1 trial of the Claudin18.2-targeted CAR-T product CT041 in 37 patients with previously treated Claudin18.2-positive digestive system cancers, the overall response rate was 48.6% and the disease control rate was 73.0%; cytokine release syndrome occurred in 94.6% of patients but was grade 1 or 2 in nearly all cases, with no grade 3-or-higher cytokine release syndrome, neurotoxicity, or treatment-related deaths reported. These results led to a Phase 3 randomized trial, making Claudin18.2 one of the leading candidates to become the first CAR-T therapy specifically approved for a gastrointestinal solid tumor (Qi et al.).

Human epidermal growth factor receptor 2 (HER2) is overexpressed in a subset of PDAC tumors and is also being tested in other solid-tumor CAR-T programs, though PDAC-specific trial data remain limited. Cell-surface GRP78 is a newer, still-preclinical target: in laboratory studies, GRP78-directed CAR-T cells killed several human pancreatic cancer cell lines and shrank tumors in mouse models, and the effect was enhanced when combined with the chemotherapy drug gemcitabine (Yuan et al.).

Several research groups are also testing dual-targeting or combination CAR-T designs, engineering T cells to recognize two antigens at once or pairing CAR-T infusion with

chemotherapy or checkpoint inhibitors, as a way to reduce the chance that antigen-negative tumor cells escape treatment (“CAR-T Cell Therapy for Pancreatic Cancer”).

Clinical Trial Landscape

Public, U.S. government-run registries make it possible to track the current landscape of CAR-T trials in pancreatic cancer without any subscription or account. ClinicalTrials.gov, maintained by the National Library of Medicine, is the standard reference for this: trials are indexed by an identifier, condition, intervention, phase, and recruitment status (National Library of Medicine). The table below summarizes the trials discussed above as a representative, not exhaustive, snapshot of the field.

Table 3. Representative CAR-T clinical trials relevant to pancreatic cancer (National Library of Medicine).

NCT ID	Target	Phase	Key reported result
NCT03907852	Mesothelin	1/2	ORR 20%, DCR 77%, 6-mo OS 70% in 30 evaluable patients (mixed solid tumors)
NCT06054308	Mesothelin	Feasibility	Neoadjuvant CAR-T in resectable PDAC; results pending
NCT02416466	CEA	1b	Hepatic artery infusion + radioembolization; 6/8 patients completed protocol
NCT02850536	CEA	1b	Pressure-enabled hepatic artery delivery; ~5.2x improvement reported
NCT03874897	Claudin18.2	1	ORR 48.6%, DCR 73.0% in 37 patients; no grade ≥ 3 CRS/neurotoxicity
NCT07103668	Claudin18.2	3	Randomized confirmatory trial; recruiting/ongoing

Most PDAC-directed CAR-T trials remain early-phase, reflecting how early this field still is compared to CAR-T therapy for blood cancers. Reported outcomes generally show a manageable safety profile, but efficacy remains limited outside of the Claudin18.2 program.

Because trial status changes frequently, this table should be treated as a snapshot rather than a complete listing.

Emerging Strategies and Future Directions

Researchers are engineering CAR-T cells to secrete cytokines such as interleukin-12 or interleukin-18 directly within the tumor, to express dominant-negative receptors that block inhibitory signals like PD-1, or to include synthetic “switches” that let physicians control CAR-T activity if toxicity develops. Each of these modifications targets one of the specific barriers described above (“CAR-T Cell Therapy for Pancreatic Cancer”).

Because no single antigen is expressed uniformly across PDAC tumors, dual-antigen and combination strategies are an active focus of current research, including CAR-T cells engineered to require two antigens simultaneously or to recognize either of two antigens. Combining CAR-T with chemotherapy, radiation, or checkpoint inhibitors is also being explored as a way to condition the tumor microenvironment before or alongside T-cell infusion (El Bejjani et al.).

Decentralized and point-of-care manufacturing platforms are being developed to shorten the leukapheresis-to-infusion timeline and to reduce production costs, addressing one of the practical barriers discussed in the next section (Palani et al.).

Cost, Access, and Equity Considerations

Even a scientifically successful PDAC-directed CAR-T therapy would face substantial practical barriers to reaching patients broadly. Currently approved CAR-T products for blood cancers typically carry list prices exceeding \$400,000 per patient, and real-world total costs of care, including hospitalization and management of side effects, have been reported with a median around \$600,000 and can exceed \$1 million in some cases. Roughly two-thirds of health

plans place restrictions on coverage for cellular and gene therapies (“High Cost of Chimeric Antigen Receptor T-Cells”).

These cost and access barriers are not distributed evenly. Published research has documented geographic and racial disparities in access to CAR-T clinical trials for other cancers, and smaller or rural health systems frequently lack the specialized infrastructure needed to administer CAR-T therapy, concentrating access in large academic medical centers (Alqazaqi et al.). Because pancreatic cancer incidence is already highest among Black patients, any future PDAC-directed CAR-T therapy that follows the same access patterns seen in blood-cancer CAR-T therapy risks reaching the patients who need it least evenly (“CAR T-Cell Therapy Remains Underutilized”). Efforts to address this gap include point-of-care manufacturing models; one demonstration project in India reported a total cost near \$35,000 using an automated, closed manufacturing platform, versus over \$400,000 for comparable commercial products in the United States (Palani et al.). None of these solutions is yet standard practice in the United States, which means cost and access should be treated as an open problem alongside the scientific challenges, not as a detail to be resolved automatically once the biology is solved.

Public NCI Data Resources for Further Research

All of the following resources are free, public, and designed for independent research projects like this one. SEER Cancer Stat Facts (seer.cancer.gov/statfacts) offers one-page statistical summaries per cancer type with open access and no login. SEER*Explorer (seer.cancer.gov/statistics/interactive.html) is an interactive tool for building custom incidence, mortality, and survival tables by year, age, sex, race, and stage (National Cancer Institute, “SEER*Explorer”). The Genomic Data Commons Data Portal (portal.gdc.cancer.gov) offers open-access genomic and clinical data from thousands of cancer patients, searchable by cancer

type (National Cancer Institute, “GDC Data Portal”). ClinicalTrials.gov is a registry of federally and privately funded clinical trials in the United States, including every registered CAR-T pancreatic cancer trial, searchable by condition, intervention, and status (National Library of Medicine).

Discussion

Taken together, the SEER data and the clinical trial evidence point to the same conclusion from two different directions. The epidemiological data show that pancreatic cancer's poor prognosis is driven overwhelmingly by late-stage diagnosis, which means any new therapy needs to be effective against disease that has already spread, and that the burden of this disease already falls unevenly across demographic groups before any treatment is even considered. The clinical trial data show that CAR-T therapy, despite strong biological rationale, has not yet cleared that bar for PDAC the way it has for blood cancers, largely because of the tumor microenvironment and antigen-related challenges described above. The most promising near-term direction in the literature is combination and engineering strategies, such as armored CAR-T designs, dual-antigen targeting, and CAR-T paired with chemotherapy or checkpoint inhibitors, rather than any single-antigen CAR-T product on its own. At the same time, the cost and access data suggest that scientific success alone will not guarantee that a future PDAC-directed CAR-T therapy reaches patients equitably; that will depend on parallel progress in manufacturing, reimbursement, and health-system infrastructure.

Conclusion

Pancreatic cancer's high mortality relative to its incidence is the central reason it remains a priority target for new therapies, and the demographic disparities embedded in that same data are a reminder that any future treatment's benefit will depend on how equitably it reaches

patients. CAR-T cell therapy offers a scientifically compelling approach because it can be engineered against tumor-specific antigens, but pancreatic ductal adenocarcinoma's dense stroma, immunosuppressive microenvironment, heterogeneous antigen expression, and limited T-cell persistence have so far limited its real-world effectiveness to early-phase, mostly safety-focused trials. Continued research into armored and combination CAR-T approaches, tracked through open NCI and NIH data resources, alongside parallel progress on manufacturing cost and access, will determine whether this therapy can eventually be translated from promising laboratory and early clinical results into a meaningful and equitably distributed survival benefit for pancreatic cancer patients.

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