Neoantigen Vaccine for Pancreatic Cancer: Current Limitations and Targeted Strategies for Enhancing Immune Response

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Abstract. Pancreatic cancer is a form of cancer regarded as the most fatal malignant tumor, facing challenges due to its strong invasiveness and limited response to traditional treatment methods. A neoantigen vaccine is a newly developed treatment method that stimulates cytotoxic T-cell response by inducing tumor-specific antigens. Although neoantigen vaccine theoretically possesses advantages of strong individualization and high immunogenicity, their therapeutic effect is limited in pancreatic cancer caused by mechanisms in the tumor microenvironment, physical barriers, immunosuppressive cells, and immune checkpoints, insufficient quantity, and function of APCs, leading to poor antigen presentation. A delivery strategy targeting Mesothelin is believed to enhance antigen presentation and break through immune tolerance due to its characteristic high expression in pancreatic cancer cells. According to the latest clinical trials, only half of the patients showed a T-cell response, suggesting the TME barrier has to be conquered. Based on this result, the delivery system targeting the highly expressed tumor marker Mesothelin significantly enhanced antigen uptake and $CD8^+$ T-cell infiltration in the mouse model. This essay focuses on the clinical application limitations and optimization strategies of neoantigen vaccine treatment for pancreatic cancer.

Keywords: Neoantigen Vaccine; Cancer Vaccine; Immune Response; Pancreatic Cancer.

1. Introduction

Pancreatic cancer is one of the deadliest forms of cancer in the entire globe. In 2020, newly diagnosed cases reached 495,000, along with 466,000 deaths. 91% is the latest diagnosed/death rate of pancreatic cancer in 2022 (WHO, 2025). Between 1992 and 2022, the percentage of new cases found among death numbers remained approximately 85-90% (NCI, 2018). Current mainstream treatment methods for pancreatic cancer include surgery, chemotherapy, and radionuclide therapy. The 5-year survival rate of pancreatic cancer patients was below 10% before 2012, regardless of the treatment received and the stage diagnosed. The number increased slightly above 10% after 2012, though still low compared with other forms of cancer, for example, leukemia. Pancreatic cancer is hard to cure mainly because of its difficulty in diagnosis, as its early symptoms are concealed, and most patients are diagnosed at an advanced stage, when cancer cells have already spread widely. Meanwhile, pancreatic cancer is not sensitive to radiotherapy and chemotherapy, and a lack of effective targeted therapeutic drugs makes pancreatic cancer deadly (NCI, 2022).

Against the backdrop of the limited efficacy of conventional cancer treatments and the extremely low response rate of immune checkpoint inhibitors (ICIs) in pancreatic cancer, various immunotherapy approaches have gradually emerged as new strategies to tackle pancreatic cancer. Among them, personalized neoantigen vaccines have attracted considerable attention in recent years (Rojas et al., 2023). Neoantigens, defined as non-autologous proteins with individual specificity generated by non-synonymous mutations in the tumor cell genome, have been recognized as ideal targets for cancer immunotherapy due to their strong immunogenicity and lack of expression in normal tissues. Different from the traditional tumor-associated antigens (TAAs), neoantigens possess stronger immunogenicity and higher affinity toward major histocompatibility complex (MHC) molecules and are not affected by central immunological tolerance. The unique characteristics of high individual specificity and immunogenicity position neoantigen vaccines as an ideal strategy to

overcome the limitations of the immunosuppressive microenvironment in pancreatic cancer (Peng et al., 2019).

2. Neoantigen Vaccine Action

2.1 Mechanism

Neoantigen refers to a specific protein fragment produced by a tumor cell due to mutations, which is recognized by the immune system as a non-self-antigen, triggering an immune response. A neoantigen vaccine aims to target these mutated antigens on the cell surface to activate the patient's T-cell immune response to attack the tumor cells (Rojas et al., 2023).

To produce a neoantigen vaccine, several steps have to be processed. To begin with, neoantigen has to be screened by tumor sequencing to perform whole exome or RNA sequencing on the patient's tumor tissue to identify particular mutations such as single-nucleotide variations, insertions, or deletions. Besides, prediction is also required. Through algorithms such as MHC binding prediction tools, select mutant peptide segments that may bind to the patient's HLA molecules (MHC-I/II classes) and give priority to candidate neoantigens with strong immunogenicity (Rojas et al., 2023).

Designing a vaccine is the step following neoantigen screening. The vaccine form has to be decided at first, for example, using synthetic peptide segments, mRNA, or DNA vectors to encode new antigens. Besides, adjuvants and delivery systems are also factors that need to be considered while designing a vaccine; they are often combined with adjuvants such as TLR agonists or nanoparticles to enhance immunogenicity and promote antigen presentation (Rojas et al., 2023).

The next step is to ensure immune activation of the vaccine. Antigen presentation should be considered if the neoantigens in the vaccine are taken up by dendritic cells (DCs) and presented to $CD8^+$/$CD4^+$ T cells. As well as T cell expansion, activated T cells clone and proliferate, forming specific cytotoxic T cells (CTLs) or helper T cells (Th). To make sure the vaccine works, designers have to verify if effector T cells migrate to the tumor site and directly kill tumor cells by recognizing the MHC-neoantigen complex on the surface of tumor cells (Rojas et al., 2023).

2.2 Vaccine Response and Clinical Outcome

Phase 1 clinical trial of Atezolizumab in treating PADC was conducted by providing Atezolizumab for anti-PD-L1 immunity therapy, followed by mRNA neoantigen vaccine autogene cevumeran, and lastly with chemotherapy using mFOLFIRINOX (it contains folinic acid, fluorouracil, irinotecan, and oxaliplatin). Patients must undergo this therapy for 4 periods.

Half (50%) of the patients involved in this trial were detected with a high-intensity neoantigen-specific T-cell response, particularly $CD4^+$ and $CD8^+$ (Figure 1B). Half of these patients with highly presented T cells had T cells targeting multiple vaccine neoantigens, referring to more than one target spot. The amplification of T-cells in this experiment shows that they expanded by the vaccine, accounting for 10% of the peripheral blood T cells and re-expanded after the vaccine booster (Figure 1D). These T-cells are multipotent effector $CD8^+$ T-cells and can survive for a long time. Immune memory of vaccination was shown by some patients having persistence of long-term memory T cells for more than 18 months (Figure 1C) (Rojas et al., 2023).

T-cell responders had a median recurrence-free survival (RFS) not reached, which means the majority did not relapse. In comparison, T-cell non-responders showed a median RFS of 13.4 months. The two groups showed a large difference in RFS value (Figure 1E); this result is not affected by the patients' basic immune status, as verified by the immune response to the SARS-CoV-2 mRNA vaccine. In terms of vaccine safety, the experimental results show that the vaccine is well tolerated: no dose-limiting toxicity (DLT) or serious vaccine-related adverse events were reported. The main adverse reactions were grade 1-2, including injection site reaction (58%), fatigue (33%), and low fever (25%). No dose-limiting toxicity (DLT) or vaccine-related serious adverse events (SAEs) were detected (Rojas et al., 2023).

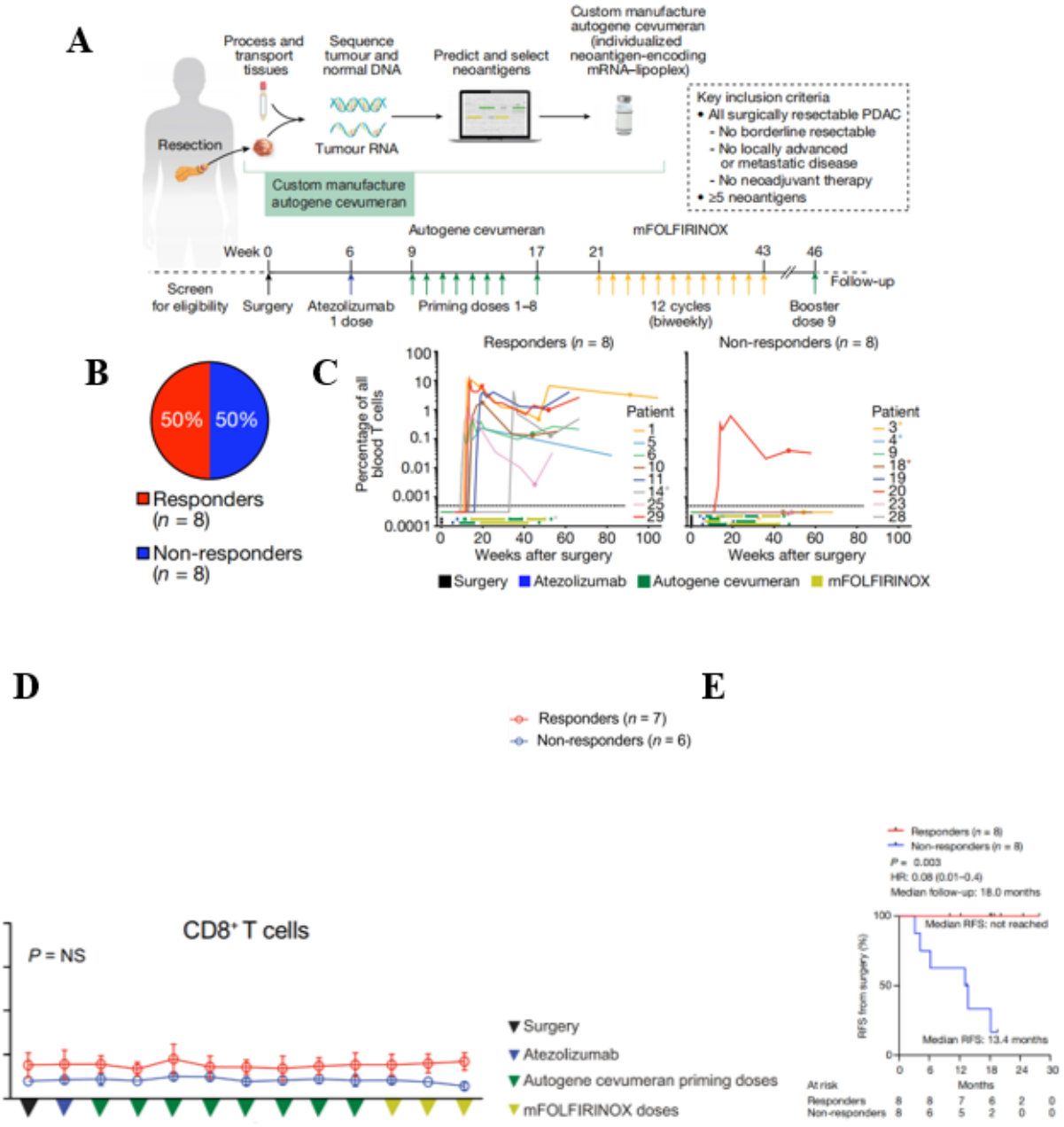

Figure 1. Clinical outcome data. A) Trial design. **B)** Proportion of vaccine responders and non-responders. **C)** Vaccine-expanded clones identified by CloneTrack: longitudinal aggregate percentage; inverted triangles indicate collection times for single-cell sequencing and circles indicate vaccine booster. **D)** $CD8^+$ T cells in the peripheral blood of autogene cevumeran responders and non-responders during vaccination. Analyses in $n = 13$ patients with identical study-specified treatment schedules and thus eligible for direct comparison. Circle = mean, error bars = standard error of the mean; n = individual patients. P values by the two-tailed Mann-Whitney test. **E)** OS and RFS in $n = 19$ patients in the safety-evaluable cohort. **b**, RFS from surgery and from landmark time (date of the last vaccine priming dose) stratified by vaccine response in patients in the biomarker-evaluable cohort. n indicates individual patients. HR indicates hazard ratio with 95% CI. P values calculated using a two-tailed log-rank test. (Rojas et al., 2023).

This trial still has several limitations; the first is the small sample size due to only 12 patients being evaluated, and larger-scale validation is required. More than that, combination therapy interference means it is difficult to distinguish the effect of the vaccine alone (chemotherapy and PD-L1 inhibitors may synergistically enhance the effect). Immunosuppressive pancreatic cancer is also an issue, as

some patients still show no response, suggesting the need for combined therapy targeting the microenvironment, including CD40 agonists (Rojas et al., 2023; Program Guide – ASCO Meeting Program Guide, 2025; Memorial Sloan Kettering Cancer Center & Genentech, Inc., 2023).

Current developments of neoantigen vaccines show several advantages, including being highly personalized, targeting patient-specific mutations to reduce the risk of off-target, reducing the risk of targeting other surrounding target spots, accelerating mutation, and hence the development of the tumor. The vaccine also provides immune memory, which may induce long-term anti-tumor immune memory and prevent recurrence.

3. Mesothelin Targeted Delivery Strategy

3.1 Biological Characteristics of Mesothelin

Due to numerous challenges in pancreatic cancer treatment, enhancing the infiltration and function of tumor-specific T cells is considered a critical focus for boosting the success of neoantigen vaccines. In recent years, Mesothelin (MSLN), a 40-kDa glycosylphosphatidylinositol (GPI)-anchored protein, has gained attention because of its distinctive expression profile. This protein is highly expressed in many solid tumors, including pancreatic cancer, while remaining at low expression levels in normal tissues such as the pleura, peritoneum, and pericardium. This contrasting expression pattern makes Mesothelin an attractive target for tumor-specific delivery strategies, enabling the selective targeting of malignant cells while preserving healthy tissues. Additionally, the localization of Mesothelin on the surface of tumor cells promotes the effective binding of therapeutic ligands, hence enhancing the success of targeted delivery and reducing the risk of affecting healthy tissues.

3.2 Response in Mouse Model

In recent years, optimizing antigen delivery to break through the immunosuppressive microenvironment in pancreatic ductal adenocarcinoma (PDAC) has become a key direction for augmenting the effectiveness of immunotherapy. Against this backdrop, Zhixiong Cai et al developed a nanoparticle delivery system targeting Mesothelin, aiming to raise the uptake efficiency of tumor-specific antigens by antigen-presenting cells (APCs), thereby activating the T-cell-mediated anti-tumor immune responses (Cai et al., 2025).

Regarding the delivery system, the Mesothelin-targeted delivery system achieves tumor-specific accumulation through the selective recognition of Mesothelin. When administered systemically, the delivery system binds to tumor cells with high levels of Mesothelin expression, thereby promoting the localized release of neoantigen payloads in proximity to antigen-presenting cells (APCs), particularly dendritic cells (DCs). This targeted accumulation enhances the efficiency of antigen uptake and processing by DCs, which leads to cross-presentation of neoantigens via MHC class I molecules (Cai et al., 2025).

In this case, the enhanced antigen presentation promotes the activation and tumor infiltration of cytotoxic T lymphocytes (CTLs), performing its characteristic of greater $CD8^+$ T cell infiltration and the increased expression levels of effector molecules such as IFN-γ and Granzyme B. By taking advantage of the specific expression pattern of Mesothelin in the tumor region, the strategy not only improves the accuracy of antigen delivery, but also strengthens the intensity of the tumor-specific immune responses while minimizing off-target effects (Cai et al., 2025)

To prove the role of Mesothelin (MSLN) targeting strategy in enhancing efficacy of personalized neoantigen vaccines, the research team conducted a systematic experiment in an orthotopic pancreatic cancer mouse model. The results indicated that both the αMSLN antibody and the neoantigen vaccine (PanNV) could inhibit tumor growth to a certain extent independently. Yet, the combination therapy exhibited the most significant tumor suppression. By day 28, the combined treatment group displayed a significant regression in tumor burden, with some mice reaching Partial Response (PR) ($p = 0.0255$), which was significantly different from the other three groups (PBS, αMSLN, PanNV) ($p < 0.0001$) (Figure 2A) (Cai et al., 2025)

Further immunological analysis discovered that in the combined treatment group, the infiltration of $CD8^+$ T cells in tumor tissues had a significant increase ($p < 0.001$), with the proportion of neoantigen-specific T cells (Slc16a13-specific $CD8^+$ T cells) reaching a peak ($p < 0.0001$) (Figure 2B). Besides, the proportion of $CD69^+$ $CD8^+$ T cells - a type of activated tissue-resident T cells - was markedly elevated in the group ($p = 0.0037$) (Figure 2C), and is considered to be vaccine-induced tumor-specific T cells (Cai et al., 2025)

Tumor cytotoxicity assays confirmed the enhancement of the combined treatment group on T cell effector function. The tumor-killing efficiency of $CD69^+$ $CD8^+$ T cells isolated from the combined treatment group against tumor cells was 8 times that of the PBS group and 2 times that of the PanNV monotherapy group ($p < 0.0001$) (Figure 2D). Moreover, the proportion of mature dendritic cells ($CD80^+$ $CD86^+$) in the lymph nodes and effector memory $CD8^+$ T cells ($CD44^+$ $CD62L^-$) in the spleen also underwent a significant increase in the combined treatment group ($p = 0.0001$ and $p = 0.0318$, respectively) (Figure 2E, F) (Cai et al., 2025).

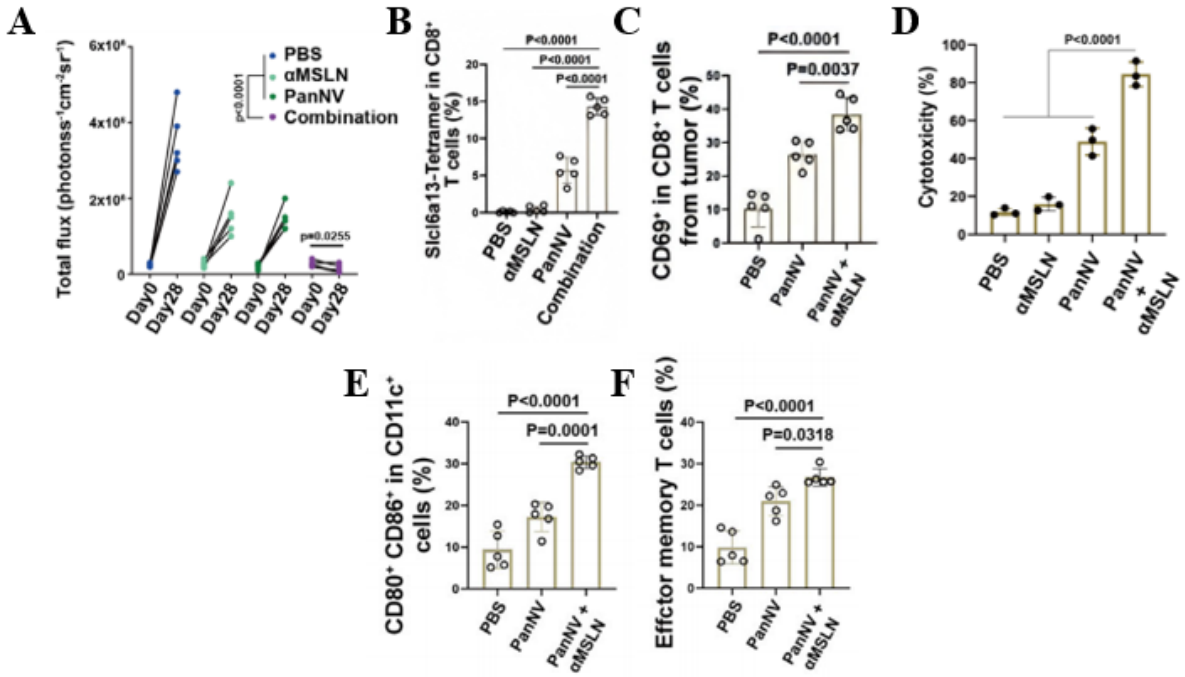

Figure 2. The antitumor effects of the combined treatment of PanNV plus αMSLN in orthotopic pancreatic cancer. A) Statistical analysis of PBS, αMSLN, PanNV, and αMSLN plus PanNV (Combination) treated mice. **B)** in tumor tissues by flow cytometry (n = 3; one-way ANOVA). **C)** The percentage of CD8+CD69+ T cells detected in tumor tissue by flow cytometry (n = 5; one-way ANOVA). **D)** In vitro cytotoxicity analysis induced by $CD8^+$ $CD69^+$ T cells against Panc02 cells determined by LDH assay (n=3). **E)** The percentage of matured DCs with CD80 and CD86 co-expression in the lymph nodes detected by flow cytometry (n = 5; one-way ANOVA). **F)** The percentage of effector memory T cells in splenic CD8+ T cells detected by flow cytometry (n = 5; one-way ANOVA) (Cai et al., 2025).

3.3 Advantages

The combination of anti-Mesothelin (MSLN) antibody and personalized neoantigen vaccines has several advantages in enhancing anti-tumor immune responses. Firstly, Mesothelin antibodies can specifically target and eliminate tumor cells expressing MSLN, thereby reducing antigen-presenting cancer-associated fibroblasts (apCAFs) - cells known to inhibit T-cell infiltration and promote immune evasion. The targeted elimination of apCAFs not only alleviates physical barriers in the TME but also interrupts pathological conversion of naïve $CD4^+$ T cells into regulatory T cells (Tregs), thus offering a more favorable environment for effector immune cells to infiltrate and exert cytotoxic functions (Cai et al., 2025).

In addition, the neoantigen vaccine serves to produce tumor-specific $CD8^+$ T cells with high precision, ensuring that the immune responses they induce are against specific antigens on the tumor. The effect of combining these two strategies has been fully verified in orthotopic pancreatic cancer mouse models, with a remarkable increase in neoantigen-specific $CD8^+$ T cells' infiltration and activation, which means superior tumor regression was observed compared to monotherapies (Cai et al., 2025).

Besides, in the preclinical phase of the clinical trial, the combined treatment performed well from a safety perspective. The observation of no noticeable changes in major organs or tissue structure illustrates a promising potential for clinical translations without inducing any systemic toxicity (Cai et al., 2025).

However, the strategy still has several limitations that need to be considered. For instance, the efficacy relies on high expression of MSLN on tumor cells and stromal cells to a large extent. In this case, the therapeutic results may experience significant falls in those who express MSLN at a low level (Cai et al., 2025).

3.4 Comparative Evaluation

Neoantigen vaccines exhibit limited immunogenicity due to inefficient antigen delivery and a complicated immunosuppressive TME. Despite the fact that non-targeted neoantigen vaccines are capable of inducing tumor-specific T cell responses, their therapeutic effects are still unsatisfactory. By combining Mesothelin (MSLN)-targeted delivery with vaccine strategies, some of the current problems are expected to be solved because of improved antigen delivery and T cell infiltration. This section compares the immune responses and therapeutic outcomes between MSLN-targeted and non-targeted vaccine strategies (Cai et al., 2025).

Compared with conventional non-targeted neoantigen vaccines, the Mesothelin (MSLN)-targeted delivery strategy shows considerable advantages in terms of boosting antigen delivery and T cell activation. In non-targeted strategies, for instance, the lipoplex mRNA neoantigen vaccine studied by Rojas et al., only approximately 50% of patients could induce neoantigen-specific T cell responses, with the IFN-γ ELISpot reaction intensity between 100 and 2000 spots per million PBMCs. Out of 16 patients, 8 experienced their T cells expanding in clones, and some clones accounted for 10% of the total peripheral T cells. Although these results demonstrate the immunogenic potential of neoantigen vaccines, the overall therapeutic effect is still greatly constrained due to the low efficiency of antigen delivery and limited infiltration of T cells into the TME (Cai et al., 2025; Rojas et al., 2023).

In contrast, in the orthotopic pancreatic cancer mouse model, the MSLN-targeted delivery strategy markedly improved antigen delivery efficiency and promoted neoantigen-specific $CD8^+$ T cell infiltration and activation. The infiltration level of $CD8^+$ T cells in the tumor tissues of the MSLN-targeted group was much higher than that of the non-targeted vaccine group ($p < 0.001$), with a substantial increase in the proportion of $CD69^+$ $CD8^+$ activated T cells ($p = 0.0037$). The functional cytotoxicity assays further revealed that the killing efficiency of T cells in the targeted group was twice as high as that of the non-targeted group ($p < 0.0001$). Nevertheless, the MSLN-targeted strategy has resulted in apparent tumor regression in vivo, which is a phenomenon that has not been directly verified in clinical studies of non-targeted vaccines (Cai et al., 2025).

Apart from these immunological advantages, the success of the strategy heavily depends on the expression levels of MSLN in tumor cells and stromal components, which means there will be limitations in the treatment of low-expressing MSLN or highly specific tumors. Besides, as the current evidence for the MSLN-targeted strategy mainly comes from preclinical mouse models, its therapeutic efficacy in humans still requires further clinical verification. Despite these shortcomings, the targeted delivery strategy has a mechanism-based advantage in breaking through physical and immunosuppressive barriers—a key issue that non-targeted neoantigen strategies have difficulty resolving effectively (Cai et al., 2025; Rojas et al., 2023).

4. Key Limitations

To look at the limitations of the neoantigen vaccine in pancreatic cancer, typical characteristics of pancreatic cancer should first be discussed. The stroma of PDAC (pancreatic ductal adenocarcinoma) is rich in collagen, hyaluronic acid, and fibronectin, forming a physical barrier that restricts the penetration of T cells and drugs. Current clinical trials show that although some patients do produce neoantigen-specific T-cells, the tumor infiltration is still limited, which may be related to interstitial obstruction (Rojas et al., 2023).

So why can't neoantigen vaccines be injected into pancreatic cancer? What mechanisms in the TME hinder this process? The answer is immunosuppressive cell infiltration and signaling pathways (Treg, MDSC, PD-L1). Among immunosuppressive cells, Tregs (regulatory T cells) and MDSCs (myeloid-derived suppressor cells) are enriched in PDAC, inhibiting the function of $CD8^+$T cells. PD-L1 acts as an immune checkpoint; upregulation of PD-L1 causes tumor cells and CAFs (cancer-associated fibroblasts) to highly express PD-L1, leading to T cell exhaustion. Research backs up this point as the combination of Atezolizumab (anti-PD-L1) only partially reversed the inhibition, suggesting the need for multi-target intervention (such as the combination with CD40 agonists) (Rojas et al., 2023).

Meanwhile, the quantity and function of APCs are insufficient, resulting in poor antigen presentation. The quantity and functional defects of DC resulting in the infiltration of dendritic cells (DCs) in PDAC are low, and their maturity is low (the proportion of $CD80^+$ and $CD86^+$ DCS is low), resulting in poor antigen presentation efficiency. Study proves mRNA vaccines rely on local DC uptake through intramuscular injection, but the pancreatic TME may restrict DC migration to the tumor site (Rojas et al., 2023)

5. Future Directions to Optimize Efficacy

Table 1. Future Directions to Optimize Efficacy

Obstacles	Strategies to overcome (future directions)
Low antigen delivery efficiency, difficult to break through fibrotic barrier	Targeted delivery therapy, such as MSLN-guided nanoparticles. Intelligent responsive nanoparticles, such as pH or enzyme responsive. Combined immunomodulators to enhance DC and T-cell initiation.
Immunosuppressive TME (Treg, CAFs)	Combined with MSLN-targeted antibodies to clear antigen presenting CAFs. Reshape TME with CD40 agonists or CXCR4 inhibitors to promote T cell infiltration. Combined immune checkpoint inhibitors.
Insufficient immunogenicity and complex development of neoantigen vaccines	Develop multi-epitope vaccines and incorporate shared neoantigens. Predict new antigens with high MHC binding affinity.
Large variation in patients' responses to vaccines	Stratify patients by expression level of MSLN and optimize delivery strategy of each level. Dynamic monitor the clonality and memory cell formation to adjust vaccination plan.
Small sample size of current clinical trials	Explore reasonable combination therapies. Conduct large-scale clinical trial to verify safety and efficacy.

Clinical success of neoantigen vaccines in treating pancreatic cancer is limited, as drugs are still in the process of phase three clinical trials, despite their strong theoretical potential, highlighting key challenges that must be addressed.

Future directions include, first, enhancing antigen delivery and uptake. Methods could be targeted nanoparticle systems, Mesothelin (MSLN)-guided delivery platforms that improve tumor-specific accumulation of neoantigens, boosting dendritic cell (DC) uptake and cross-presentation. This method could also be used to exploit other tumor-specific presentations (Cai et al., 2025). Intelligent responsive nanoparticles can be used, pH/ enzyme responsiveness: The TME of pancreatic cancer is acidic and rich in matrix metalloproteinases (MMPs), which can be designed to release antigens at the tumor site specifically. Studies show MSLN-targeted nanoparticles significantly enhance antigen delivery to DCs and increase $CD8^+$ T cell infiltration in the PDAC model ($p = 0.001$). Combination with immune modulators, referring to co-delivery of adjuvants (e.g., TLR agonists, STING activators), may further amplify DC activation and T-cell priming. Multi-target composite delivery using a dual-targeting strategy can also be considered; for instance, co-delivering neoantigens and STING agonists (such as cGAMP) can simultaneously activate innate immunity (type I IFN) and adaptive immunity.

Besides, overcoming the immunosuppressive TME is also considered an essential future direction. Dual Targeting of Stromal Barriers: Pancreatic tumors are rich in immunosuppressive cells (Tregs, CAFs) and dense stroma. Combining neoantigen vaccines with MSLN-targeted antibodies to deplete antigen-presenting CAFs (apCAFs) (Cai et al., 2025). CD40 agonists or CXCR4 inhibitors to remodel the TME and enhance T-cell infiltration. Checkpoint Inhibitor Synergy: PD-1/CTLA-4 blockade may rescue exhausted T cells, as seen in partial responders (Rojas et al., 2023).

Improving Neoantigen Selection & Design is also an objective, including multi-epitope vaccines and inclusion of shared neoantigens. Prioritizing neoantigens with high MHC-binding affinity and immunogenicity (e.g., via AI-predicted TCR recognition). Targeting recurrent mutations (e.g., KRAS G12D) could enable "off-the-shelf" vaccines for subsets of patients (Rojas et al., 2023).

Moreover, biomarker-driven personalization, MSLN expression screening has always been a pivotal study for neoantigen. Patient stratification based on MSLN levels may predict response to targeted vaccine delivery (Cai et al., 2025). Dynamic Immune Monitoring: Tracking neoantigen-specific T-cell clonality and memory formation (e.g., $CD69^+$ $CD8^+$ T cells) to refine vaccination schedules.

A clinical trial is one of the critical factors in the development of neoantigen vaccines. Earlier intervention, which is testing vaccines in resectable or minimal residual disease (MRD) settings, where the TME is less suppressive. People should also be aware of rational combination therapy as a control factor in clinical trials. Sequential or concurrent therapy with chemotherapy (e.g., mFOLFIRINOX), radiotherapy, or adoptive cell therapy (TCR-T/CAR-T), as well as an increasing amount of large-scale clinical trials and translational medical research. In the future, it is necessary to verify the efficacy and safety in a larger sample (Rojas et al., 2023).

6. Conclusion

The highly immunosuppressive TME of pancreatic cancer is still the core obstacle restricting neoantigen vaccines' clinical efficacy. The dense stromal structure not only hinders the infiltration of immune cells and effective antigen delivery but also makes it difficult for T cells to penetrate the tumor tissues. As a result, the accumulation of immunosuppressive cells such as Tregs and MDSCs, as well as the elevated expression of checkpoint molecules including PD-L1, makes it difficult for T cells to kill efficiently even though they have already been activated. A more troublesome problem is that the general limitations on APCs' quantity and function directly lead to poor vaccine-induced immune responses.

Mesothelin-targeted delivery strategies have been proposed in recent years and have shown great potential for improving antigen presentation efficiency and T cell infiltration in preclinical studies. However, problems such as high dependence on high Mesothelin expression levels in tumor tissues and the complex interference brought by immunosuppressive microenvironment highlight the necessity for multifaceted optimization. The combined application is expected to break through the immune resistance barrier and improve the therapeutic effect of pancreatic cancer.

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