

# ADVANCES IN VACCINE-BASED APPROACHES FOR PANCREATIC CANCER IMMUNOTHERAPY

## Abstract

This chapter delves into the cutting-edge realm of immunotherapy for pancreatic cancer through the lens of vaccine-based treatments. Pancreatic cancer stands as a formidable global health challenge, with its impact underscoring the need for innovative therapeutic strategies. The chapter's introduction elucidates the gravity of pancreatic cancer's impact and establishes the rationale for exploring vaccines as potential treatments. By exploring the dynamic landscape of immunotherapy, the subsequent section explicates its significance in cancer treatment, paving the way for an in-depth exploration of various cancer vaccine types and their mechanisms of action, along with a balanced assessment of their inherent advantages and limitations. Spotlighting tumor-specific antigens, a critical focus lies on their identification, characterization, and the role they play in driving vaccine development for pancreatic cancer. The chapter rigorously examines diverse approaches to vaccine development, with each section offering nuanced insights. Peptide-based, whole-cell, dendritic cell, and viral vector-based vaccines are meticulously evaluated, considering epitope selection, adjuvant utilization, safety parameters, and clinical outcomes. As science advances, combination therapies and adjuvant incorporation emerge as crucial avenues for enhancing vaccine efficacy. Challenges inherent in vaccine development are confronted, including the complex interplay between the tumor microenvironment and immune suppression. Strategies to fortify vaccine effectiveness and the potential of emerging technologies to reshape the field are discussed, revealing promising avenues for future exploration. Ethical considerations

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and patient perspectives are given their due attention, acknowledging the moral dimensions of research and the patient's role in shaping therapeutic landscapes. The chapter concludes by synthesizing its insights, advocating for the potential of vaccines to reshape pancreatic cancer treatment paradigms. The clarion call for sustained research and clinical trials resounds, underscoring the urgency of collaborative efforts to propel vaccine-based pancreatic cancer immunotherapy towards unprecedented horizons of success.

## I. INTRODUCTION

- 1. Overview of Pancreatic Cancer and Its Impact on Global Health:** Pancreatic cancer is a deadly illness, with fatality roughly paralleling incidence (1). Pancreatic cancer is expected to become a serious public health burden in the near future, with an estimated global incidence of 18.6 cases per 100,000 people in 2050 and an average yearly rise of 1.1% (1).

Clinically, pancreatic cancer is the broad expression used to describe a cancerous growth that develops in the glandular structures of the pancreatic ductal cells. Specifically, it is known as adenocarcinoma (2), with pancreatic ductal adenocarcinoma (PDAC) being the most common type, making up for over 90% of all pancreatic cancer cases (3). At the time of diagnosis, pancreatic cancer is often in an advanced stage and has spread to other areas of the body. Thus, newer strategies and interventions for the early detection and cure of pancreatic cancer are continually under research.

- 2. Rationale for Exploring Vaccines as a Potential Treatment for Pancreatic Cancer:** Developing a successful therapeutic approach is crucial to effectively treating metastatic pancreatic cancer and improving patient outcomes. Recent studies have focused on tumor-targeted vaccinations, which offer promising potential for enhancing pancreatic cancer treatment. These vaccines work by bolstering the immune system's ability to eliminate cancer cells entirely and preventing the evasion of cancer cells from immune surveillance. Nevertheless, to activate T cells and trigger a robust immune response, a combination of immune checkpoint inhibitors and positive costimulatory molecules is essential. This synergistic approach holds significant promise in the fight against pancreatic cancer(4).
- 3. Purpose of the Chapter:** This chapter focuses on exploring potential tumor-targeted vaccines designed to target pancreatic cancer specifically. It delves into the suitable combinations of vaccine therapy and assesses the inherent advantages and challenges associated with the current treatment approaches for pancreatic cancer.

## II. IMMUNOTHERAPY AND CANCER VACCINES

- 1. An Explanation of Immunotherapy and its Role in Cancer Treatment:** Immunotherapy encompasses diverse strategies that involve the utilization of a range of substances, including drugs (such as immunosuppressants), biological agents (like cytokines, monoclonal antibodies, and antisera), essential nutrients (e.g., zinc, vitamin C, and vitamin B6), transplantation methodologies (such as bone marrow transplantation), and vaccinations (both preventive and therapeutic vaccines) to exert varying influences on immune responses. The overarching objective of immunotherapy is to modify immune function, whether by augmentation or suppression, with the intention of addressing diseases underpinned by an immune component. Such ailments encompass cancer, inflammatory conditions, infections, hypersensitivity reactions, autoimmune disorders, organ and tissue transplants, and other medical scenarios. The ultimate aim of immunotherapy is to extend and enhance the quality of life for patients grappling with these diverse health conditions (5).

Across time, numerous immunotherapeutic modalities have been devised to bolster the innate anti-cancer capabilities of the body. Among these methods are immunostimulatory cytokines, oncolytic viruses, adoptive cell transfer, and tumor-targeting (bi-specific) antibodies. These distinctive approaches function by amplifying the immune system's capacity to detect and combat cancer cells, thus fostering more potent anti-cancer responses (6). Among these, monoclonal antibodies (mAbs), also recognized as immune checkpoint inhibitors (ICI), have emerged as the most prevalent choices in contemporary clinical practice. They have earned multiple approvals from the US FDA for diverse solid tumors. Operating by modulating the patient's immune system's reactions, ICI, especially in gastrointestinal (GI) cancers, has yielded survival advantages in upper GI tumors, biliary tract tumors, and hepatocellular carcinoma (7,8). Additionally, immunotherapy proves beneficial for individuals with colorectal cancer characterized by MSI-H or dMMR tumors (9).

2. **Types of Cancer Vaccines:** Cancer vaccines can be broadly characterized as preventive and therapeutic vaccines. Preventive vaccines include those for the human papilloma virus and hepatitis B. On the contrary, therapeutic vaccines are used for immunotherapy in cancers such as pancreatic cancer.

Various types of pancreatic cancer vaccines will be outlined in this chapter, including peptide-based vaccines, whole-cell vaccines, dendritic-cell vaccines, viral-cell vector based vaccines, and the most recently discussed mRNA based vaccines.

3. **Mechanism of Action of Cancer Vaccines:** In recent years, the primary focus of tumor vaccines has shifted to cancer vaccines that target neoantigens. Neoantigen vaccine clinical trials have recently produced encouraging results with increased patient survival (10). T cell infiltration and selective tumor cell death were demonstrated by a melanoma vaccine using mRNA neoantigens (11). This resulted in a significant decrease in metastatic events and progression-free course (11). Although neoantigen-based personalized cancer vaccines appear promising, many predicted neoantigens only produce modest anti-tumor responses (12). Additionally, variations in tumor types and people make it difficult to use cancer vaccines that target mutated neoantigens widely. As a result, finding high-quality neoantigens is essential for the creation of successful neoantigen vaccines.

### III. TUMOR-SPECIFIC ANTIGENS IN PANCREATIC CANCER

1. **Identification and Characterization of Tumor-Specific Antigens:** According to a study by Huang et al. (13), six tumor antigens—ADAM9, EFNB2, MET, TMOD3, TPX2, and WNT7A—were found to be overexpressed and mutated in pancreatic adenocarcinoma (PAAD), and these antigens were linked to a poor prognosis and the infiltration of antigen-presenting cells. In addition, nine immune gene modules of PAAD and five immune subtypes (IS1–IS5) were found. The various immune subtypes displayed unique molecular, cellular, and clinical traits. Compared to the other subtypes, IS1 and IS2 showed immune-activated phenotypes and had higher survival rates. The tumor mutation burden was higher and immunologically colder in IS4 and IS5 tumors. There were also differences in the expression of immune checkpoints, CA125, and CA199

among the five immune subtypes, as well as immunogenic cell death modulators. The immune landscape of PAAD also revealed significant patient-to-patient heterogeneity.

- 2. Key Antigens Associated with Pancreatic Cancer:** An overview of candidate pancreatic cancer-associated antigens for immune targeting is elaborated below in **Table 1**.

**Table 1: An overview of candidate pancreatic cancer-associated antigens for immune targeting**

**Source** (14)Dodson LF, Hawkins WG, Goedegebuure P. Potential targets for pancreatic cancer immunotherapeutics. *Immunotherapy*. 2011 Apr;3(4):517–37.

Antigen	Location	Expression in tumor	Prevalence (%)	Description
CEA	Cell surface (GPI-linked)	Overexpressed	30-100	Glycoprotein, normally expressed only in oncofetal tissues. Functions as a cell-adhesion molecule. The first tumor antigen to be described
Her2-neu	Transmembrane	Overexpressed	>50	A receptor tyrosine kinase, member of the EGF-receptor family, involved in cell growth and differentiation
K-Ras	Intracellular	Mutated self	90	Mutated form of ras, a GTPase important for cell proliferation, differentiation and survival
Mesothelin	Cell surface (GPI-linked)	Overexpressed	~100	A GPI-linked glycoprotein normally expressed on the surface of mesothelial cells lining the pleura, peritoneum and pericardium at low levels. Binding partner of CA125/MUC16
MUC-1	Transmembrane	Overexpressed, hypoglycosylation	90	Type 1 transmembrane glycoprotein, expressed on apical surface of ductal and glandular epithelial cells at low levels. Extracellular domain has a polypeptide core with multiple tandem

				repeats of 20 amino acids
p53	Intracellular	Mutated self	50-70	Tumor suppressor that regulates cell cycle. Normally inhibits survivin at the transcription level and can initiate apoptosis if DNA damage is unreparable
Survivin	Intracellular	Overexpressed	80	Member of the IAP family. Inhibits caspase activation; is found in most human tumors and fetal tissue, but is completely absent in terminally differentiated cells
Telomerase	Intracellular	Overexpressed	95	Ribonucleoprotein that is responsible for the RNA-dependent synthesis of telomeric DNA. TERT is its catalytic subunit
VEGFR2	Transmembrane	Overexpressed	64	A tyrosine kinase and member of platelet-derived growth factor family. Receptor for VEGF with functions in blood vessel development

**3. The Importance of Antigen Selection for Vaccine Development:** Antigen choice plays a pivotal role in the formulation of cancer vaccines. The effectiveness of these vaccines hinges on the identification of tumor antigens that T cells can detect(15). The optimal candidate for a cancer vaccine antigen should possess strong immunogenic characteristics, be present exclusively in cancer cells (while absent in normal cells), and be vital for the sustenance of cancer cell survival(15). Tumor antigens can be divided into tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs).

- Tumor-associated antigens (TAAs): These are alternatively recognized as tumor-associated antigens. Despite extensive focus on TAAs over the years, endeavors to develop cancer vaccines rooted in TAAs have yielded only moderate achievements(16). Furthermore, the presence of TAAs in healthy tissues escalates the potential risk of autoimmune toxicity triggered by the vaccine.
- Tumor-specific antigens (TSAs): This cluster of proteins exclusively resides within tumor cells. TSAs, or tumor-specific antigens, share a synonymous identity with

neoantigens. Neoantigens are proteins that originate in a personalized manner due to mutations in tumor cells, distinct from the person's autogenous proteins(17). Neoantigens are exclusively presented by tumor cells, facilitating a targeted T-cell reaction against the tumor with limited potential for unintended effects. These neoantigens exhibit heightened immunogenicity and a stronger binding affinity to the major histocompatibility complex (MHC) compared to TAAs.

The following characteristics ought to be connected to high-quality neoantigens: They must first exhibit a strong affinity for the human leukocyte antigen (HLA), be significantly heterologous from the wild type, be expressed by the majority of tumor cells, and be the result of mutations that have an impact on survival. These characteristics of the neoantigens could trigger a potent immune response and stop the emergence of tumor-immune escape (18).

#### **IV. APPROACHES TO VACCINE DEVELOPMENT FOR PANCREATIC CANCER**

##### **Peptide-Based Vaccines**

##### **1. Epitope Selection and Synthesis:** Epitope selection involves:

- Identifying specific antigens from pancreatic cancer cells, often mutated or overexpressed proteins,
- Predicting potential epitopes using bioinformatics tools and databases based on antigen sequences and their presentation by MHC molecules
- Ensuring strong binding affinity between predicted epitopes and MHC molecules for effective immune response.
- Considering epitope conservation for broader patient coverage or multiple epitopes for variability
- Assessing immunogenicity with computational tools or experimental studies to trigger a robust immune response.
- Checking for cross-reactivity or autoimmunity risks to avoid harmful effects on healthy tissues.
- Validating potential epitopes through in vitro and animal studies before human clinical trials.
- Designing the peptide vaccine formulation with chosen epitopes to enhance immune response and efficacy(19,20).

##### **2. Adjuvant Selection for Enhancing Immune Response:** A multitude of cancer vaccines exhibit limited clinical efficacy and suboptimal immunogenicity. To enhance their performance, adjuvants are commonly introduced into their compositions. These adjuvants serve to stimulate cytokine generation, enhance antigen durability in the bloodstream, strengthen the interaction between the antigen and antigen-presenting cells (APCs), and elicit more vigorous immune reactions. These combined effects culminate in the activation of immune cells with anti-cancer properties(21). Adjuvants can be broadly characterized into two categories:

- Depot adjuvants: These agents extend the availability of antigens over time (e.g., substances like aluminum hydroxide, emulsions, and liposomes). These additives

improve the transportation of tumor-associated antigens (TAAs) to antigen-presenting cells (APCs). A case in point is Montanide-based adjuvants, characterized as 'water-in-oil emulsions containing a mineral or a metabolizable oil along with a surfactant from the mannidemonooleate family' (22). One instance is Montanide ISA 51 VG, which is currently under examination across multiple clinical trials to amplify the immune efficacy of peptide-based cancer vaccines (23).

- Immunostimulatory adjuvants: Instances of immunostimulatory adjuvants encompass Toll-like receptor (TLR) agonists, saponins, stimulators of interferon genes (STINGs), and cytokines. These agents serve as activators of both innate and adaptive immune reactions. An illustrative example is the cytokine GM-CSF, extensively investigated and frequently employed as an immunostimulatory adjuvant in various cancer vaccines, including Provenge and GVAX(24).

- 3. Clinical Trials and Outcomes of Peptide-Based Vaccines:** In individuals diagnosed with pancreatic cancer, a range of peptide-based vaccines have demonstrated successful outcomes in provoking responses targeted at specific antigens. For instance, among patients with surgically removed or locally advanced pancreatic cancer, immunization with a 100-amino acid segment of the extracellular tandem repeat of MUC-1 led to the activation of MUC-1-specific T-cell reactions. Remarkably, two out of the 15 patients remained alive after 61 months(25). Furthermore, a distinct Phase I clinical trial involving patients with incurable pancreatic or biliary cancer revealed the generation of circulating anti-MUC-1 antibodies through the use of the same 100-amino acid peptide vaccine. However, no observable enhancement in survival rates was identified in this trial (25)

Individuals diagnosed with advanced pancreatic cancer have been administered gemcitabine alongside the VEGF receptor (VEGFR)2-169 peptide epitope vaccine in analogous investigations. Among the recipients of this vaccine, a notable 83% demonstrated antigen-specific delayed-type hypersensitivity (DTH) responses, and 61% exhibited VEGFR2-specific CD8+ cells. The median overall survival duration reached 8.7 months. Concurrently, an ongoing randomized, multicenter Phase II/III trial is assessing the effectiveness of the VEGFR2-169 peptide vaccine in combination with gemcitabine among patients with unresectable advanced or recurring pancreatic cancer (14).

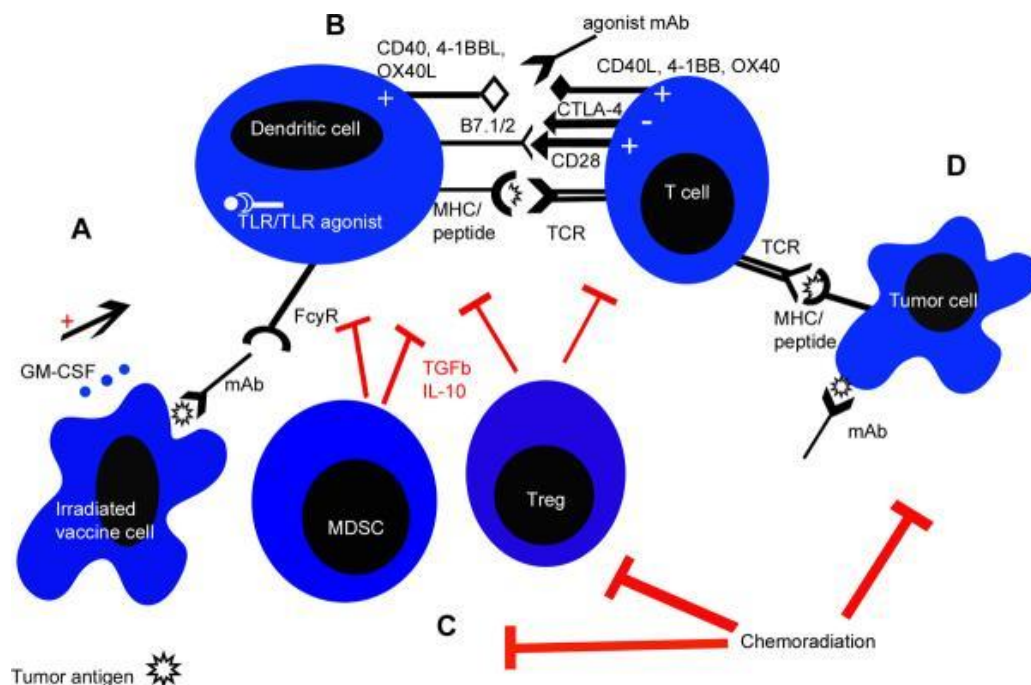
The investigations involving K-Ras-targeted peptide vaccines have yielded particularly intriguing outcomes. In a pilot vaccine study, individuals with pancreatic and colorectal conditions underwent personalized K-Ras peptide vaccinations. K-Ras engendered a disease-specific immune reaction in three of the five pancreatic cancer patients. Strikingly, the two non-responsive pancreatic cancer patients witnessed disease progression, while the responsive ones exhibited no signs of illness. Patients with pancreatic cancer experienced a mean disease-free survival of 35.2+ months and a mean overall survival of 44.4+ months. In a more extended study, patients were tracked for up to a decade post-pancreatic adenocarcinoma surgery, during which they received simultaneous GM-CSF and K-Ras peptide vaccinations (26). Interestingly, a substantial 20% of vaccine-receiving patients were still alive at the end of this period. Immunological assessments revealed that 75% of these survivors sustained an active memory T-cell



response. These outcomes present highly encouraging results in the context of peptide vaccines.

## Whole-cell vaccines

**1. Types of Whole-Cell Vaccines:** A form of immunotherapy currently under investigation and clinical evaluation centers around modified whole-cell cancer vaccines. These comprehensive tumor cell formulations offer the benefit of encompassing all conceivable tumor antigens, thereby obviating the necessity to pinpoint the optimal antigen for targeting within a specific cancer variety. This stands in contrast to the utilization of a singular protein or peptide tumor antigen for vaccination purposes. (**Figure 1**) (27). Furthermore, by concurrently addressing numerous tumor antigens and fostering immune reactions against this array, potential issues stemming from tumor antigen loss can be circumvented (27).



**Figure 1:** Interactions of the immune system with a whole-cell vaccine approach (GM-CSF-secreting tumor cell vaccine as one example) and other immune modulating therapies for the treatment of cancer

[Source (27):Keenan BP, Jaffee EM. Whole Cell Vaccines — Past Progress and Future Strategies. *SeminOncol.* 2012 Jun;39(3):276.]

- GM-CSF is released by irradiated vaccine cells, attracting dendritic cells (DCs) to the antigen site. DCs take up and present the antigen. Monoclonal antibodies (mAbs) binding tumor antigens on vaccine cell surfaces via Fc receptors or modified vaccine cells secreting other cytokines stimulate DCs. Toll-like receptor (TLR) agonists and immunomodulatory agents like paclitaxel stimulate DCs through TLRs, enhancing antigen presentation and cytokine production.

- DCs present tumor antigen from vaccinating cells to CD4<sup>+</sup> and CD8<sup>+</sup> T cells as peptide/MHC complexes. T cells bind these with their T cell receptor (TCR). Activated DCs or agonist antibodies to co-stimulatory receptors like anti-CD40, anti-4-1BB, and anti-OX40 provide additional signals for T cell stimulation. Blocking antibodies to immune checkpoint molecules like CTLA-4 and PD-1 enhances the activation and proliferation of tumor antigen-specific T cells.
  - Inhibitory cytokines like TGF- $\beta$  and IL-10 from suppressive immune cell populations such as MDSCs and Tregs suppress APCs and T cells. Immunomodulatory doses of chemotherapy (e.g., cyclophosphamide, gemcitabine) and radiation inhibit these populations.
  - Effector CD8<sup>+</sup> T cells expressing TCR recognize tumor antigens presented by MHC on tumor cells, leading to tumor cell killing. Efficiently activated CD8<sup>+</sup> T cells can synergize with traditional treatments (chemotherapy, radiation, and mAbs) for tumor inhibition or elimination.
- 2. Tumor Cell Modification and Preparation:** To augment the immune response triggered by injected radioactive tumor cells, genetic modifications have been applied to whole-cell vaccines, introducing cytokines, chemokines, or co-stimulatory molecules (28). The practical application of this technique involves ex-vivo gene transfer of GM-CSF, tumor removal, cultivation of cancer cells, and patient inoculation with genetically engineered, lethally irradiated self-originating cancer cells (28). Numerous phase I and II investigations have demonstrated the safety of this approach across various cancer types. Traditionally, vaccine-induced immune reactions have been evaluated by gauging delayed-type hypersensitivity responses (DTH) to autologous tumor cells. Although tumor cells alone do not incite a DTH, instances of DTH reactions have been observed to align with improved survival rates among patients administered genetically modified vaccine cells.
- 3. Clinical Trials and Outcomes of Whole-Cell Vaccines :** Currently, a multitude of active and concluded clinical trials are meticulously investigating whole-cell vaccines within the realm of pancreatic cancer patients. The most extensively scrutinized cell line is GVAX, which is composed of two distinct human allogeneic pancreatic tumor cell lines. Preliminary clinical trials have unveiled enhanced clinical outcomes and heightened disease-free survival rates associated with GVAX, either as a standalone intervention or when used in conjunction with other chemotherapeutic protocols (24).

Another whole-cell vaccine appraised for its potential in pancreatic cancer is Algenpantucel-L from NewLink Genetics Corporation. This vaccine is constituted by two irradiated human pancreatic ductal adenocarcinoma cell lines (HAPa-1 and HAPa-2), genetically engineered to express the murine enzyme (1,3)-galactosyltransferase (29). Originating from preclinical murine models, Algenpantucel-L elicits an immune reaction by initiating hyperacute rejection and phagocytosis of the Gal epitopes present on the vaccine tumor cells. This initial response then prompts the patient's immune effector cells to acclimate in recognizing other tumor-associated antigens (TAAs) presented by the vaccinated cells (30). Regrettably, a phase 3 Impress clinical trial yielded no supplementary advantage, showcasing no enhancement in overall survival for individuals with surgically resected pancreatic cancer who were treated with Algenpantucel-L.

Subsequent trials have been halted due to the lack of efficacy exhibited by this therapeutic vaccine (31).

## Dendritic Cell Vaccines

- 1. The Utility of Dendritic Cells (DC) in an Immune Response:** Dendritic cells are found mainly in tissue and serve as sentinels before coming into contact with antigens (Ag) (32). As a result of DC's unique properties, Ag is efficiently taken up, internalized, and converted into peptides, which are subsequently displayed to MHC class I and II molecules (32). Toll cell receptors (TCR) of CD8+ and CD4+ T cells can subsequently recognize these complexes, after which DCs go to lymphoid organs like lymph nodes and spleen, where they come into contact with and stimulate antigen-specific T cells using the TCR (signal 1)(32). Via signal 2 including the B7 family of molecules, DC also transmits costimulatory signals to T cells, causing their growth and clonal selection (32). Because DCs have a variety of receptors for recognizing injured, apoptotic, and necrotic cells, apart from viral and microbial pathogens, environmental stimuli can also stimulate DC maturation.
- 2. Isolation and Activation of Dendritic Cells for Vaccine Production:** Two techniques have been used to employ dendritic cells to control the immune system, particularly with regards to cancer treatment: (i) isolating dendritic cells *ex vivo*, introducing them to antigens and activating them with cytokine cocktails, and then injecting them back, commonly through intradermal or subcutaneous injections; and (ii) directly delivering antigens to dendritic cells *in vivo* (33,34). Culturing *ex vivo* differentiated DCs from leukapheresis-isolated CD14+ monocytes with the integration of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4) is the most prevalent strategy utilized in registered clinical trials utilizing DC vaccines(35).
- 3. Clinical Trials and Outcomes of Dendritic Cell Vaccines:** An FDA-approved whole-cell DC vaccine is Sipuleucel-T, which is made up of isolated peripheral blood mononuclear cells grown with a prostatic acid phosphatase fusion protein or GM-CSF(34). It showed a 4.1-month increase in overall survival of patients with metastatic prostate cancer, with no associated delay in disease progression (34).

In a study conducted by Carreno BM et al, for patients with metastatic melanoma, a dendritic cell vaccine increased naturally existing neoantigen-specific immunity and identified initially undetected HLA class I-restricted neoantigens(36).

For pancreatic cancer, Mulé JJ combined gene therapy and immunotherapy (37). To present antigens from dying tumor cells, he used DCs which were injected intratumorally and to induce tumor apoptosis or necrosis, he injected locally a tumor necrosis factor-alpha gene vector(37).

## Viral vector-based vaccines

- 1. Use of Viral Vectors for Antigen Delivery:** T cells that are specific to an antigen circulate freely and assemble only at the locations where the antigen is expressed(38). Retroviral particles adhere to the surface of T cells nonspecifically, or "hitchhike," which

improves the targeting and lifespan of systemically injected viral vectors(38). When adoptive T-cell transfer was ineffective alone, Herpes Simplex Virus thymidine kinase (HSVtk) or interleukin 12 loaded antigen-specific T cells were adopted and used to treat metastatic illness (38).

- 2. Safety and Efficacy Considerations:** Some of the dangers include alterations in the host genome; HSV is more worrisome since it duplicates in the host cell nucleus and has the potential to integrate into the host genome (41). The Vaccinia virus lacks the ability to promote disease in healthy humans, but given that 50% of the viral genes have unidentified activities, this virus is unpredictable (39).

The rampancy of anti-adenovirus (Ad) immunity and a new finding in an Ad-based vaccine for HIV study showing escalated HIV-1 uptake when circulating anti-Ad5 neutralizing antibodies were present, pose significant obstacles to the use of Ad vectors(40).

Billions of people have now received adenoviral vector vaccines throughout the world. Thrombosis with thrombocytopenia syndrome (TTS), a relatively rare clotting disorder, has been linked to two vaccines(41).

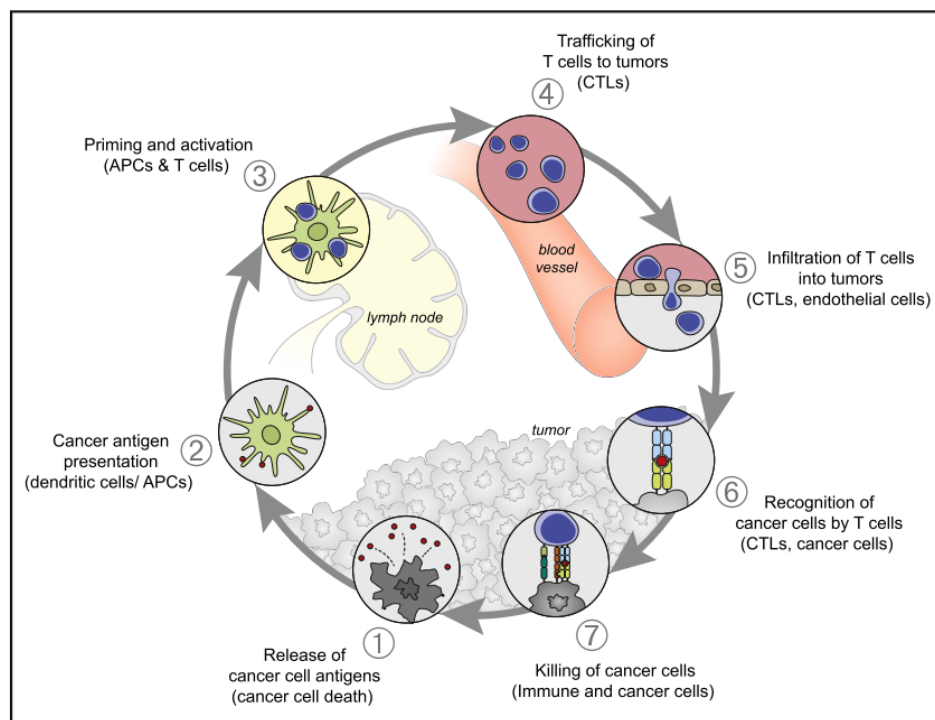
- 3. Clinical Trials and Outcomes of Viral Vector-Based Vaccines:** In 1999, Mastrangelo et al. showed that for patients with melanoma, a GM-CSF recombinant vaccinia virus can be safely administered in progressive doses in order to induce tumor regression (42). Pollard AJ et al. were the first to conduct a phase 2 study to assess the effectiveness of the heterologous Ebola vaccine. The authors demonstrated that because antibody responses were stronger in 28-day and 56-day dosage intervals than in 21-day dosing intervals, and both cellular and humoral responses sustained in 98-100% of individuals after 1 year, a heterologous prime-boost regimen was found to be more immunogenic than a single dose (43).

### Messenger RNA (mRNA) vaccines

- 1. How do mRNA Vaccines Work?:** The ability to steer the immune system to neoantigens or particular tumor associated antigens (TAAs) is the basic idea of mRNA cancer vaccines (44). TAAs are highly expressed in cancer cells, whereas neoantigens are brand-new proteins created as a result of cancer cell mutations (44). The vaccines seek to trigger an immune response that selectively eliminates cancer cells while sparing healthy cells by employing mRNA to encode these particular antigens (44).
- 2. Clinical Trials and Outcomes of mRNA Vaccines:** In a phase 1 clinical trial conducted in 2023, the research team gave 16 PDAC patients who had undergone surgical resection a customised mRNA vaccine called autogenecevumiran that expressed up to 20 neoantigens and was administered using LNPs intravenously (44,45). This was done in conjunction with chemotherapy and immune checkpoint therapy (44,45). In 50% of the patients, a significant T cell response was seen, and no patients showed recurrence at 18 months follow-up, showing the potential for this customised mRNA vaccination to stimulate stronger immune responses (44,45).

## Combination Therapies and Adjuvants

- Rationale:** Tumors use a variety of ways to reduce the effectiveness of anti-tumor immunity in a process called "cancer immune-editing." As a result, the Cancer-Immunity Cycle (**Figure 2**) gets disrupted. Because of the complex immunity network, it makes sense to integrate relevant immunotherapeutic treatments to prepare and advance the Cancer-Immunity Cycle. Neoantigen vaccines, for example, can skip the first two phases and directly trigger an immune cycle. Immunological checkpoint inhibitors can aid in the overcoming of immunological suppression in phases 3 and 6(46).



**Figure 2:** The cancer immunity cycle (46): **Step 1** – Tumors release neoantigens as they die off. **Step 2** – They get caught by the antigen presenting DCs, which makes the antigens generate peptides that bind to MHCs which are then presented to T cells. **Step 3** – Effector T cells are activated to respond to tumor antigens. **Step 4** – Activated T cells migrate to the tumor location. **Step 5** – T cells infiltrate the tumor. **Step 6** – Activated T cells attach to cancer cells. **Step 7** – T cells that have been activated destroy cancer cells. To sustain the cycle and increase the anticancer response, the dying cancer cell releases more cancer-specific neoantigens (Step 1). [Source (47): Chen DS, Mellman I. *Immunity*. 2013;doi:10.1016/j.immuni.2013.07.012. ]

- Combination of Vaccines with Immune Checkpoint Inhibitors:** An appealing notion that is being investigated in several ways is establishing tumor-specific immunity using a vaccination and then boosting it with checkpoint blockage. Immune checkpoint inhibition reduces T-cell activation inhibitory signals, allowing tumor reactive T cells to evade regulatory processes and establish an efficient antitumor response (48). Some of the common methods used are CTLA-4 blockade and PD-1 blockade, trials of which have been described later.

- 3. Use of Adjuvants to Enhance Vaccine Efficacy:** Adjuvants were described by Gaston Ramon as “substances used in combination with a specific antigen that produce more immunity than the antigen alone” (49). There are two basic categories of adjuvants: (a) particulate adjuvants, which primarily serve as antigen depots or transport systems, and (b) immunostimulatory molecules, which activate innate immune receptors (49).

It has been shown in recent years that a variety of nanobiomaterials have a great deal of potential to boost the cancer vaccination cascade, enhance their anticancer efficacy, and lessen the off-target effect (50). Biomimetic nanobiomaterials-based nanovaccines, nucleic acid-based nanovaccines, and antigen peptide/adjuvant based nanovaccines are some of the several cancer nanovaccines(50).

- 4. Clinical Trials and Outcomes of Combination Therapies and Adjuvant Use:** Preconditioning the injection site of DC vaccines with a strong recall antigen (e.g., tetanus/diphtheria toxoid) significantly enhances lymph node migration and effectiveness of tumor-specific DCs, observed in a study of 12 glioblastoma patients. In a larger trial involving 39 melanoma patients, combining DC vaccines and CTLA-4 checkpoint blockade (ipilimumab), notable overall response rates were observed with 8 complete and 7 partial clinical responses, indicating a promising combination approach for further exploration (32,52). For newly diagnosed glioblastoma, a study by Liao LM et al. randomized patients (2:1) to receive temozolomide and placebo or temozolomide with an autologous tumor lysate-pulsed dendritic cell vaccine post-surgery and chemoradiotherapy. This research suggested the safety and feasibility of adding the vaccine to standard therapy, potentially extending survival(53).

Using lipid nanoparticles carrying mRNA for tumor-associated antigens gp100 and TRP2, Oberli MA et al. demonstrated tumor reduction and increased survival in B16F10 melanoma mice (54). The addition of the adjuvant lipopolysaccharide can significantly enhance the immune response(54).

In the context of pancreatic ductal adenocarcinoma (PDAC), a study assessed the combination of GV1001, a telomerase peptide vaccine, with gemcitabine. While GV1001 alone did not affect PDAC cell proliferation or apoptosis, the combined therapy demonstrated tumor size reduction, increased apoptosis, and reduced fibrosis(55).

## V. CHALLENGES AND FUTURE PERSPECTIVES

- 1. Hurdles in vaccine development for pancreatic cancer:** Despite recent evidence of vaccines causing systemic regression of big tumors and prolonging survival, small sized clinical trial, relatively small survival benefits, chance of tumor immune escape, difficulty of recognizing appropriate antigens, and resource-intensive approaches have held the field from achieving wider adoption and sparked justified uncertainty (44,56). Due to their low molecular weight, easy breakdown, exclusive peptide epitopes, and brief half-life, peptide vaccines are restricted (57).

Neoantigen expression was widely thought to trigger adaptive immunity and disease repression, which was the basis of upcoming neoantigen vaccines. But unexpectedly in PDAC, neoantigen expression leads to the fibro-inflammatory

microenvironment's worsening, which promotes metastasis, which is caused by pathogenic TH17 responses (58).

The timing of the administration of prophylactic vaccines is crucial to their immunopreventive effectiveness, giving a required role for both established and newly developed biomarkers for screening and early diagnosis (59). One of the additional issues is the lack of availability. Outside of cutting-edge research centres, it is difficult to spread the use of some vaccines in the community because their manufacture or distribution is facility-dependent (60).

- 2. Overcoming Immune Suppression in the Tumor Microenvironment:** Recent research has shown that TLR 7/8 ligands, like R848, have an antitumor activity in pancreatic cancer by altering the immunosuppressive tumor microenvironment, which can enhance the effectiveness of tumor vaccines(61). In tumor tissue, TIM-3 antibody significantly decreased Tregs while increasing IFN- and IL-12P70 levels (57). With the use of neoantigen vaccinations, it successfully slowed the evolution of HCC in situ and encouraged CD8+ T cell infiltration (57). The route of administration had an impact on how well the vaccine responded. In comparison to intravenous and intramuscular injection, subcutaneous injection triggered neoantigen-specific T cell responses 20 and 7 times more, respectively, but intravenous mode was superior if used following checkpoint blockade (57).
- 3. Potential Strategies for Improving Vaccine Effectiveness:** Selecting the optimal injection route and depth to enhance safety and immunogenicity requires considering the vaccine's chemical and immunological attributes, which could affect local tissue impact or alter the immune process (60). Moreover, the vaccine's delivery technique can influence the response of circulating and tissue-resident memory T cells, both potentially essential for effectiveness (60).
- 4. Emerging Technologies and Advancements in Vaccine Development:** Advancements of technology in data science, genomics, and cancer immunotherapy now allow for the quick mapping of mutations in a genome, rational vaccinen target selection, and as needed manufacture of a therapy tailored to the patient's specific tumor(62). With emerging digital age breakthroughs promoting vaccine development, immunising a patient with unique tumor mutations could end up being the first real individualised cancer treatment (62).

## VI. Ethical Considerations and Patient Perspectives

- 1. Ethical Implications of Cancer Vaccine Research and Clinical Trials:** Cancer vaccine research and clinical trials involve significant ethical concerns. As scientists work to develop novel immunotherapies to battle cancer, problems about informed consent and patient autonomy emerge. In any clinical research, informed consent is essential, and cancer vaccination studies are no exception. Patients must be thoroughly informed about the risks and benefits of participating in experimental studies (63). Furthermore, it is critical to provide equal access to these trials and to avoid exploitation of disadvantaged groups (63). Another ethical quandary emerges about resource allocation, as funds and attention given to vaccine research may have an impact on other areas of cancer

prevention and treatment (63). Striking a balance between improving scientific knowledge and protecting patients' well-being is a difficult but necessary challenge.

- 2. Patient Perspectives on Vaccine-Based Cancer Treatments:** Vaccine-based cancer treatments have garnered significant attention and enthusiasm among both patients and the medical community. For patients facing the daunting challenges of cancer, these treatments offer a ray of hope and the potential for improved outcomes, but sometimes, they often have heightened expectations, as shown in a study done by Bergerot CD et al where 23% of patients with advanced GU malignancies had incorrect expectations about the potential efficacy of immunotherapy despite rigorous counseling regarding potential clinical outcomes (64).
- 3. Access and Affordability of Pancreatic Cancer Vaccines:** Pancreatic cancer has a very high mortality rate, and innovative therapies like vaccines hold promise for improved survival outcomes. However, the high costs associated with research, development, and production of these vaccines can create barriers to access for many patients (65). Individuals with an annual household income of less than \$50,000 had a 32% lower odds of participating in a cancer clinical trial than higher-income participants (65). Autogenecevumeran, the tailor made mRNA vaccine, has been estimated to be just under \$100,000.

## VII. CONCLUSION

Various types and mechanisms of pancreatic cancer vaccines were highlighted, including peptide-based vaccines, whole-cell vaccines, dendritic-cell vaccines, viral-cell vector based vaccines, and mRNA based vaccines. Through stimulating the immune system to identify and target cancer cells specifically, these vaccines offer a novel and targeted approach to treatment. While research is still ongoing and challenges remain, the advancement of personalized vaccine therapies and combination strategies provides hope for improved outcomes and increased survival rates for patients with pancreatic cancer. The potential role of vaccines in the future of pancreatic cancer treatment holds promising prospects. Cancer vaccines aim to activate the immune response against tumor cells, specifically tailored to pancreatic cancer antigens. Research in this field has led to the development of a variety of personalized vaccines, ranging from peptide-based vaccines that deliver cancer-specific antigens to boost the immune system's recognition of malignant cells, to DC vaccines, which are DCs that have been exposed to antigens *ex vivo* and have been activated with cytokine cocktails to trigger specific immune responses. Combining vaccines with immune checkpoint inhibitors, such as anti-PD-1/PD-L1 agents, is another avenue to enhance the anti-tumor response. Nonetheless, further investigation and clinical trials are essential to optimize vaccine strategies and determine their efficacy in improving pancreatic cancer outcomes. If successful, cancer vaccines could revolutionize pancreatic cancer treatment by offering a targeted, minimally invasive, and potentially curative approach.

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