



A Vaccine with Your Name on It: Personalized mRNA Targets Pancreatic Cancer Neoantigens

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Genetic vaccines have reshaped modern immunology by replacing traditional administration of weakened pathogens or purified proteins with direct delivery of genetic instructions encoding target antigens. Rather than introducing a preformed antigen, these platforms allow host cells to synthesize proteins internally, leading to endogenous antigen processing and presentation through major histocompatibility complex (MHC) pathways. Early plasmid DNA vaccination studies in the 1990s demonstrated that injected genes could induce both humoral and cellular immune responses.¹ Decades later, improvements in nucleic acid stabilization, vector engineering, and lipid nanoparticle delivery systems culminated in the clinical success of messenger RNA vaccines.^{2,3,4} These advances established genetic vaccination as flexible and rapidly adaptable therapeutic mRNA platforms, which were demonstrated during the SARS-CoV-2 pandemic.⁵⁻⁸ The implications of this approach extend beyond infectious disease. If host cells can be programmed to produce viral antigens, they may also be directed to express tumor-specific targets. This concept is especially relevant in oncology, where therapeutic vaccines targeting non-mutated self-antigens have historically shown limited efficacy due to immune tolerance and weak T cell activation.⁹ Tumors arise from somatic tissue and therefore share most of their antigenic repertoire with normal cells. Immune tolerance, tumor heterogeneity, and suppressive microenvironments have repeatedly limited attempts to generate durable anti-cancer immunity.¹⁰

The major obstacle has been target selection rather than immune stimulation itself. Cancer genomics offered a solution through the discovery of neo-antigens, mutated peptides generated by somatic DNA alteration within tumor cells. Because neoantigens arise from tumor-specific somatic mutations and are absent from normal tissues during T cell development, the immune system is not centrally tolerized to

these novel targets in the same way it is to self-antigens. As a result, neoantigens can be recognized as foreign and may serve as highly specific immune targets.^{9,12} Evidence from pancreatic cancer further supports this concept, as long-term survivors exhibit enhanced neoantigen-specific T cell responses that correlate with improved outcomes.¹¹

In their 2023 paper in *Nature*, Rojas *et al.* investigated whether a personalized mRNA neoantigen vaccine could elicit an effective immune response against tumor cells harboring pancreatic ductal adenocarcinoma (PDAC), a cancer that is typically resistant to immunotherapy and associated with poor survival.⁸ In this clinical study, tumors from patients were sequenced to identify individual mutations, results were then used to design mRNA vaccines encoding up to twenty patient-specific neoantigens. These vaccines were given along with anti-PD-L1 immunotherapy and standard chemotherapy to improve T cell activation. The results showed that 50% of patients developed neoantigen-specific T cell responses after vaccination, suggesting that one reason earlier cancer vaccines showed limited efficacy is that many did not target antigens that were sufficiently tumor-specific, immunogenic, and effectively presented to T cells.⁸

The effectiveness of this vaccine relies on its ability to generate a targeted T cell response against tumor-specific neoantigens. After administration, the mRNA vaccine is taken up by antigen-presenting cells, where the encoded neoantigens are translated into proteins and processed into peptide fragments. These peptides are then presented on MHC molecules, particularly MHC class I, which activates CD8⁺ cytotoxic T cells. Rojas *et al.* showed that their vaccine induced strong *de novo* T cell responses, meaning these responses were newly generated rather than pre-existing. In responding to patients, multiple T cell clones expanded significantly, in some cases making up a large proportion of circulating T

cells. These cells also displayed functional markers such as interferon- γ , granzyme B, and perforin, which are all associated with cytotoxic activity and tumor cell killing. Together, these findings suggest that the vaccine is not only capable of activating T cells but also generating a functional and sustained anti-tumor immune response.⁸

To further characterize the immune response, Rojas *et al.* analyzed the expansion of functionality found in vaccine-induced T cell population. T cell analysis showed that vaccine-expanded T cell clones increased from undetectable pre-vaccination levels to as much as 10% of all circulating blood T cells in responding patients. This expansion was not limited to a single clone, but rather a true polyclonal immune response. This finding is consistent with earlier work showing that mRNA neoantigen vaccines can induce broad, multi-specific T cell responses against tumors.¹³ In addition, these expanded T cells displayed a strong cytotoxic phenotype. Single-cell sequencing revealed that they were primarily CD8⁺ T cells expressing key effector molecules such as perforin, granzyme B, and interferon- γ , all of which are associated with direct tumor cell killing.⁸ Functional assays further confirmed that these cells produced cytokines and degranulated upon antigen re-exposure, demonstrating that they were not only present, but functionally active against the vaccine-targeted neoantigens. Importantly, these T cell populations were also shown to persist over time and expand following booster vaccinations, suggesting the formation of long-term immune memory, a feature that was also observed in other neoantigen vaccine studies.¹⁴

Beyond immune activation, the study also evaluated whether this T cell response was translated into meaningful clinical outcomes. At a median follow-up of 18 months, patients who developed vaccine-induced T cell responses showed improved recurrence-free survival compared to those who did not respond. Specifically, responders had not yet reached a median recurrence time, while non-responders experienced recurrence at a median of 13.4 months. This suggests that the immune response generated by the vaccine plays a role in controlling residual disease after surgery, supporting findings from other neoantigen vaccine studies that link T cell response to improved clinical outcomes.^{13,14} A particularly notable example involved a patient who developed a small liver lesion after



vaccination that was initially suspected to be metastatic disease. However, biopsy revealed a dense infiltration of vaccine-induced T cells, and the lesion later resolved, suggesting that these immune cells may have actively eliminated metastatic tumor cells.⁸

The findings represent an important shift in cancer immunotherapy, demonstrating that even tumors traditionally considered immunologically unresponsive can be targeted through precise selection of the correct tumor-specific antigen targets and personalized vaccine design. Rather than demonstrating that mRNA vaccines can activate the immune system, Rojas *et al.* provide evidence that precise neoantigen targets can overcome the fundamental limitations that have historically constrained cancer vaccine efficacy.⁸ This distinction is critical, as it shifts the focus of immunotherapy from generalized immune stimulation to targeted immune recognition. As sequencing technologies and predictive algorithms improve, the ability to identify and prioritize immunogenic neoantigens will likely determine the success of future therapeutic strategies. In this context, personalized mRNA vaccines represent not simply a new treatment modality, but a broader framework for integrating tumor genomics into immune-based cancer therapy.

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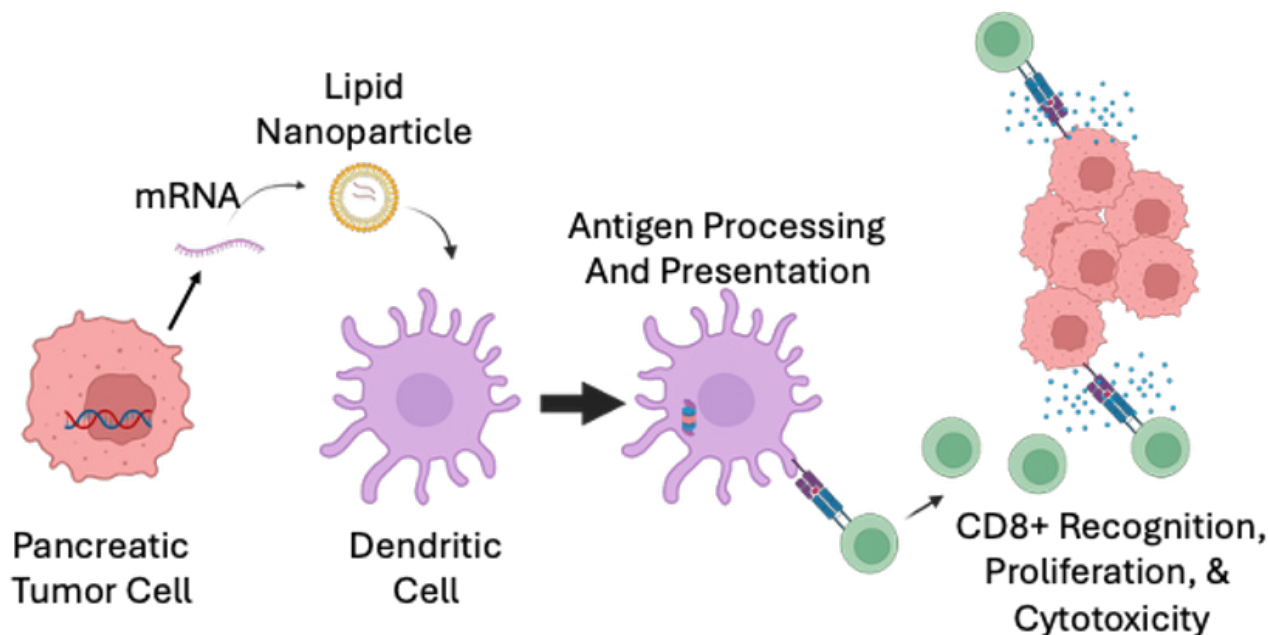


Figure 1. Mechanism of personalized mRNA neoantigen vaccination in PDAC. Tumor-specific neoantigens are encoded into mRNA, delivered to antigen-presenting cells via lipid nanoparticles, and presented on MHC class I to activate CD8⁺ T cells. This induces clonal expansion and tumor cell killing by granzyme B and perforin. Created in BioRender. Stewert, C. & Treml, J. (2026) <https://BioRender.com/hpस्पam>