Pancreatic cancer RNA vaccine shows durable T cell immunity

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Memorial Sloan Kettering Cancer Center researchers have found RNA neoantigen vaccines that generate long-lived, functional $CD8^+$ T cells in patients with pancreatic ductal adenocarcinoma (PDAC), potentially delaying disease recurrence.

PDAC is a lethal cancer with limited treatment options and a low mutational burden. T cells defend the body by destroying harmful outside pathogens and mutated body cells, such as cancer.

Mutations in tumor cells can create neoantigens, novel proteins not present in normal cells. Finding these (via MHC molecules) alerts T cells that the tumor cell is no longer part of the body's normal self. The low mutational burden of PDAC produces few neoantigens, making tumors difficult for T cells to distinguish from self cells.

Traditional cancer vaccines have struggled to produce durable tumor-specific T cell responses. This study aimed to determine if an RNA neoantigen vaccine could induce long-term functional T cells that correlate with delayed PDAC recurrence.

In the Phase I trial, "RNA neoantigen vaccines prime long-lived $CD8^+$ T cells in pancreatic cancer," published in *Nature*, the team evaluated the effects of autogene cevumeran, an individualized mRNA–lipoplex vaccine encoding up to 20 neoantigens, combined with surgery, atezolizumab, and chemotherapy (mFOLFIRINOX).

Sixteen patients with resectable PDAC received autogene cevumeran following surgery and a single dose of atezolizumab, succeeded by 12 cycles of modified FOLFIRINOX chemotherapy and a vaccine boost. Investigators assessed vaccine-induced T cell responses using ex vivo IFNγ ELISpot assays, T cell receptor (TCR) sequencing, and longitudinal blood and tissue analyses over a median follow-up of 3.2 years.

Eight of the sixteen vaccinated patients developed strong neoantigen-specific $CD8^+$ T cell responses following vaccination. These patients, referred to as responders, experienced fewer cancer recurrences during the study period.

A median time to recurrence for the responders could not be determined since the majority had not relapsed by the study's end. Highly favorable survival outcomes of the responders were compared to a median of 13.4 months in non-responders.

CloneTrack, a sequencing-based tool, identified 79 vaccine-induced $CD8^+$ T cell clones in responders. Clones induced during priming doses reached peak expansion after six or fewer doses, with an average 100-fold expansion.

Vaccine-induced $CD8^+$ T cell clones demonstrated long-term persistence, with a projected average lifespan of 7.7 years post-boost. 86% of clones persisted at substantial frequencies for ~3 years post-vaccination. Approximately 20% of these clones could persist for decades, potentially outliving the host.

Vaccine-induced T cells transitioned from proliferative to effector states and stabilized as tissue-resident memory-like (TRM-like) cells, retaining cytotoxic functions for years. Persistent $CD8^+$ T cells maintained neoantigen-specific effector function upon in vitro rechallenge, even up to 3.6 years post-vaccination.

Tumors from patients who recurred showed a selective loss of vaccine-targeted cancer clones, indicating the need to address tumor heterogeneity and clonal escape mechanisms.

The potential of adjuvant mRNA–lipoplex neoantigen vaccines to induce durable, functional immunity (after surgery) in one of the most treatment-resistant cancers is clearly established (for a Phase I trial) with potential applications to cancers beyond PDAC.

Larger trials are needed to confirm efficacy and further research on increasing responder rates and reducing clonal escape.

More information: Zachary Sethna et al, RNA neoantigen vaccines prime long-lived CD8+ T cells in pancreatic cancer, *Nature* (2025). DOI: 10.1038/s41586-024-08508-4

Bespoke vaccines can elicit long-lived immune activity against pancreatic cancer, *Nature* (2025). DOI: 10.1038/d41586-025-00470-z

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