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Clinical Medicine EDITORIAL

The Innovation Medicine

From "undruggable" to controllable: Milestones in pancreatic cancer therapy

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Received: May 23, 2026; Accepted: August 21, 2026; Published Online: August 23, 2026; https://doi.org/10.59717/j.xinn-med.2027.100273

Citation: Qi H., Zhang S. and Liu M. (2027). From "undruggable" to controllable: Milestones in pancreatic cancer therapy. *The Innovation Medicine* **5**:100273.

Pancreatic cancer has long been characterized by a dismal prognosis and a lack of effective therapeutic options, posing a persistent challenge for patients, clinicians, and researchers alike. As one of the most lethal and treatment-resistant cancers, pancreatic cancer is typically diagnosed late and progresses rapidly, meaning that many patients are no longer candidates for surgical resection by the time of diagnosis. Chemotherapy, the cornerstone of systemic treatment, is further hampered by the emergence of drug resistance, while the profoundly immunosuppressive tumor microenvironment (TME) constrains the efficacy of immunotherapy, all of which contribute to a persistently dismal five-year survival rate of approximately 13%.[1] Importantly, these challenges may reflect not the inherent untreatability of pancreatic cancer, but rather the lack of clearly defined therapeutic targets. However, recent breakthroughs, including a Phase I clinical trial of a therapeutic mRNA cancer vaccine and a Phase III study of the pan-RAS inhibitor daraxonrasib, have marked a significant step forward, underscoring progress in both immunotherapy and RAS-targeted therapy and opening new therapeutic avenues for pancreatic cancer treatment.

A VACCINE-DRIVEN AWAKENING OF ANTITUMOR IMMUNITY

As an attractive immunotherapeutic strategy, tumor vaccines are relatively safe and exhibit high specificity compared with other immunotherapies. They aim to enhance antitumor immunity by eliciting tumor antigen–specific T cell responses that improve the recognition and killing of tumor cells. In particular, mRNA-based cancer vaccines offer unique advantages such as flexible antigen design, the capacity to encode multiple tumor antigens, and rapid manufacturing, positioning them as a promising platform for personalized immunotherapy. Despite these advantages, however, the clinical translation of mRNA vaccines has been hampered by several key challenges. Tumor heterogeneity significantly limits the identification of shared tumor antigens, while highly variable immune responses among patients further limit therapeutic efficacy. These limitations are particularly pronounced in pancreatic ductal adenocarcinoma (PDAC), a cancer characterized by a low mutational burden and an immunologically "cold" tumor microenvironment, which together make effective immunotherapy especially challenging.

Nevertheless, prior studies have shown that T-cell immunity is associated with improved survival. Importantly, robust T cell responses depend on the presence of high-quality tumor neoantigens. In this context, personalized mRNA vaccines have emerged as a promising strategy by introducing patient-specific neoantigens identified through genomic sequencing, thereby priming antitumor immune responses.[2]

In a recent phase I study led by Vinod Balachandran at Memorial Sloan Kettering Cancer Center, the personalized mRNA vaccine autogene cevumeran (BNT122, RO7198457) was evaluated in 16 patients with resected pancreatic cancer. The vaccine was individually designed based on patient-specific tumor DNA alterations. Notably, approximately half of the patients exhibited tumor-specific immune responses, and among these responders, the majority remained alive 4–6 years after surgery, whereas non-responders had a median survival of only 3.4 years. These findings suggest that autogene cevumeran can elicit durable, tumor-specific T cell immunity in a subset of patients with PDAC, potentially translating into meaningful long-term survival benefit. More importantly, these results suggest that the immunologically "cold" state of PDAC may be reversible through personalized vaccination. The observed long-term survival further indicates the establishment of sustained antitumor immune responses, thereby providing new insights into long-term disease control. These encouraging results have led to an ongoing phase II trial, sponsored by Genentech in collaboration with BioNTech, to evaluate this approach in larger patient cohorts. Collectively, neoantigen-based vaccines represent a promising therapeutic avenue, with the potential to deliver meaningful clinical benefit in a subset of patients.

TARGETING THE CORE ONCOGENIC DRIVER: PAN-RAS INHIBITION

Oncogenic RAS, one of the most frequently mutated drivers across human cancers, promotes tumorigenesis by activating multiple downstream signaling pathways. Despite its central role in cancer progression, RAS was long considered undruggable. However, recent therapeutic advances have transformed RAS into a tractable target. The development of the first KRAS inhibitor, sotorasib (AMG-510), demonstrated the feasibility of selectively targeting the inactive KRAS(OFF) state and paved the way for next-generation strategies to engage the active RAS(ON) state.

In this context, Revolution Medicines has developed daraxonrasib (RMC-6236), a noncovalent tri-complex inhibitor targeting active pan-RAS(ON) proteins.[3] Mechanistically, daraxonrasib recruits cyclophilin A to form a tri-complex with active RAS, thereby generating a composite binding interface that sterically blocks effector interactions and suppresses downstream signaling. By targeting multiple RAS isoforms and mutant variants, this strategy enables more comprehensive suppression of oncogenic signaling and may overcome compensatory pathway activation that often limits the efficacy of mutation-specific inhibitors. Results from the phase 1–2 study demonstrated that daraxonrasib showed manageable safety and antitumor activity in previously treated RAS-mutant PDAC patients, supporting its potential as a promising therapeutic strategy.[4]

Recently, its phase III clinical trial RASolute 302 (NCT06625320) in pancreatic cancer has also demonstrated encouraging outcomes. RASolute 302 has shown that oral daraxonrasib significantly improves overall survival (OS) compared with standard chemotherapy in patients with metastatic PDAC. The median OS was 13.2 months in the daraxonrasib group versus 6.7 months in the standard chemotherapy group (HR = 0.40, $P < 0.0001$), representing a near doubling of OS and demonstrating meaningful clinical benefit. Moreover, daraxonrasib was generally well tolerated, with a manageable safety profile. As an oral pan-RAS inhibitor, it enables broad suppression of oncogenic RAS signaling in advanced pancreatic cancer. These findings may provide a promising therapeutic option for patients with RAS-addicted pancreatic cancer and could reshape current treatment strategies (Figure 1).

COMPLEMENTARY STRATEGIES: TOWARD A NEW THERAPEUTIC PARADIGM

Collectively, these advances may reshape current treatment paradigms and improve outcomes in PDAC. Mechanistically, these two therapeutic strategies are fundamentally distinct. Personalized mRNA vaccines primarily function by activating tumor-specific immune responses, thereby enhancing immune-mediated tumor cell killing. In contrast, pan-RAS inhibitors directly target oncogenic RAS signaling, suppressing pancreatic cancer cell growth and survival.

Given these differences, the two approaches may form a complementary and potentially synergistic therapeutic framework. Specifically, they could be integrated into a stage-specific treatment strategy with clearly defined roles: personalized mRNA vaccines may be suited for early-stage disease, particularly in the postoperative setting to prevent recurrence through immune activation, whereas daraxonrasib may be more effective in advanced disease by controlling tumor progression via direct inhibition of oncogenic signaling.

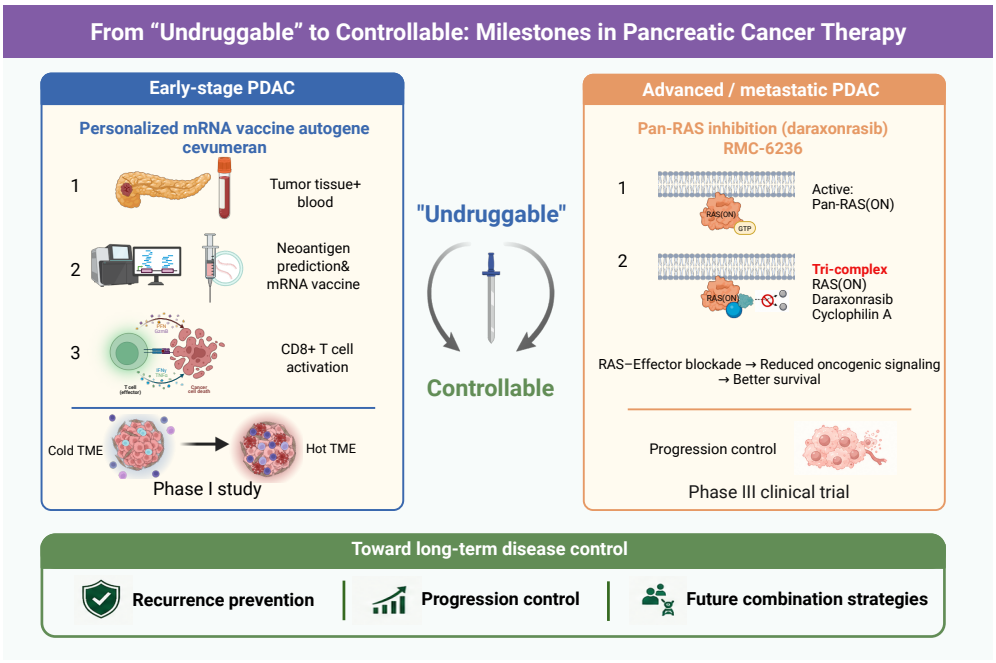

Figure 1. From "undruggable" to controllable PDAC: mRNA vaccination and pan-RAS targeting The left panel illustrates PDAC immunotherapy based on personalized mRNA vaccination (autogene cevumeran), leading to $CD8^+$ T cell activation and conversion of the tumor microenvironment from "cold" to "hot" (Phase I study). The right panel depicts PDAC therapy targeting pan-RAS signaling (daraxonrasib/RMC-6236), where a RAS–drug–cyclophilin A tri-complex blocks RAS–effector interactions, suppresses downstream oncogenic signaling, and achieves disease control in Phase III evaluation. The central arrow highlights the shift from "undruggable" to clinically actionable disease control. The bottom panel summarizes long-term management goals, including recurrence prevention, progression control, and future combination strategies.

Importantly, the potential synergy between these approaches also raises the prospect of combination strategies, which warrant systematic evaluation in future clinical trials.

Such a framework not only provides a conceptual basis for optimizing treatment across different disease stages but also holds promise for improving survival outcomes, offering renewed hope for both the medical community and patients.

REMAINING CHALLENGES AND UNRESOLVED QUESTIONS

For mRNA vaccines, response heterogeneity remains a key issue. Although the phase I trial demonstrated encouraging overall results, approximately half of the patients still failed to elicit a detectable immune response, highlighting the current limitations in identifying high-quality, patient-specific neoantigens. Future efforts should focus on improving the accuracy of neoantigen identification while reducing the cost and complexity of vaccine design. AI-driven immunoinformatics may further facilitate this process by accelerating epitope prioritization, antigenicity and safety assessment, and in silico evaluation of pan-RAS vaccine candidates, although such predictions will require rigorous experimental and clinical validation.[5] Clinically, personalized vaccination will require integrated workflows involving tumor sequencing, HLA assessment, neoantigen prediction, vaccine manufacturing, and timely therapeutic integration.

For daraxonrasib, despite its success in phase III clinical trials, long-term safety, durability of response, and the emergence of resistance will require continued evaluation. In addition, extending its potential application to earlier stages of PDAC may represent an important next step. Importantly, combination strategies and biomarker-guided approaches will be essential to optimize therapeutic efficacy and overcome resistance.

FROM BREAKTHROUGHS TO LONG-TERM DISEASE CONTROL

Taken together, recent advances in personalized mRNA vaccination and pan-RAS-targeted therapies mark a turning point in the treatment of pancreatic cancer. As breakthroughs in immunotherapy and molecularly targeted therapies continue to emerge and integrate, the traditional view of pancreatic cancer as an "undruggable" disease is being gradually reshaped.

Future efforts should focus on improving response rates, overcoming resistance, and systematically exploring synergistic therapeutic strategies, with the goal of transforming pancreatic cancer into a more controllable and potentially manageable disease. For clinicians, it will be essential to closely follow emerging advances and guidelines to inform clinical decision-making. For patients, a diagnosis of pancreatic cancer should not lead to a loss of hope, as the prospect of long-term disease control is increasingly within reach. Overall, these two recent breakthroughs represent important milestones in pancreatic cancer therapy, advancing the field from an undruggable disease toward a more controllable one and underscoring the need for further clinical validation.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (nos. 82541004 to M.Liu). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The figure in this article was created with Biorender.

AUTHOR CONTRIBUTIONS

Haoran Qi: Writing – original draft, Conceptualization. Shaobo Zhang: Data curation, Visualization. Mingyang Liu: Supervision, Project administration. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.