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Revisiting RNA in immunity: SARS-CoV-2 mRNA vaccine-based strategy for cancer immune response

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ICI therapy revolutionizes oncology by reinvigorating systemic immunity, acting not only locally within the tumor microenvironment but also peripherally in lymph nodes and blood. The coordinated immune activation is crucial for clinical efficacy, but the primary or acquired resistance remains major hurdles, spurring the investigation of cancer vaccines. The concept of therapeutic vaccination, first proven in principle by treating established infections, found a parallel and early forerunner in oncology with the pioneering work of Coley and Old.[1] By providing tumor-associated antigens or tumor-specific antigens, cancer vaccines can potentially transform immunologically 'cold' tumors into 'hot' ones, creating a fertile ground for ICIs to then exert their effects. Thus, the combination of cancer vaccines to "step on the gas" and ICIs to "release the brakes" represents a powerful synergistic strategy to overcome cancer therapy resistance.

Based on the antigen specificity, patient applicability, and the method of antigen-presenting cell (APC) loading,[2] cancer vaccines could be categorized into two major types: predefined vaccines targeting shared-antigen/ personalized neoantigen and anonymous antigen vaccines loaded ex vivo/in situ. Predefined shared-antigen vaccines (e.g., targeting WT1) offer an off-the-shelf advantage but are often limited by heterogeneous antigen expression and suboptimal immunogenicity, yielding marginal survival benefits in large trials. In contrast, the predefined personalized neoantigen vaccines elicit highly specific T-cell responses against patient-specific mutations, effectively countering tumor heterogeneity; however, their complex, resource-intensive production process hinders broad clinical application. As for the anonymous antigen vaccines, they leverage the full tumor antigen repertoire without prior antigen identification. This is achieved via ex vivo loading onto APCs or in situ delivery of immunostimulants (e.g., radiotherapy). Although in situ vaccines present a practical, "off-the-shelf" approach, their efficacy is constrained by the need for robust APC recruitment and activation within the tumor microenvironment. Overcoming these challenges, such as through combinatorial approaches with immune modulators or advances in rapid neoantigen identification and vaccine production, may enable more effective

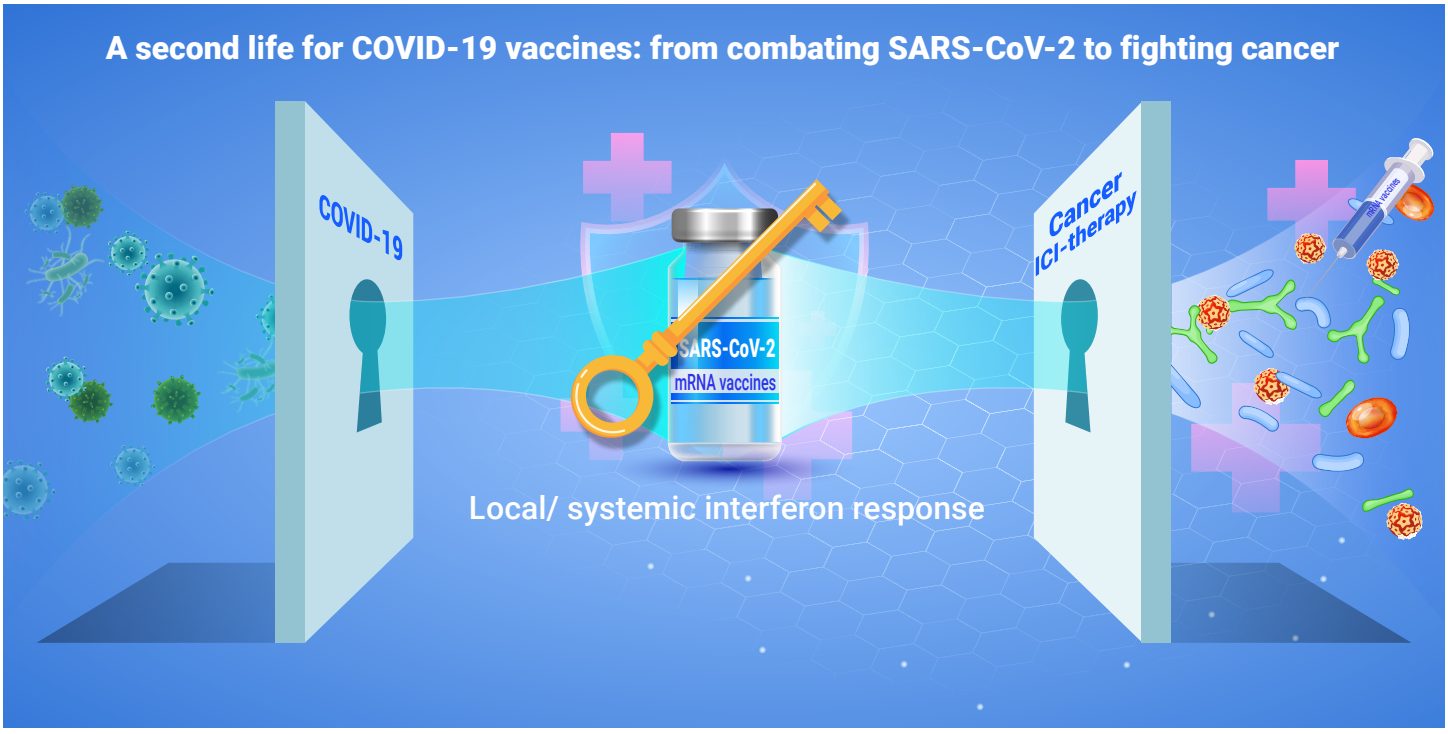

Figure 1. A second life for COVID-19 vaccines: from combating SARS-CoV-2 to fighting cancer.

and broadly applicable cancer vaccine strategies.

The monumental success of COVID-19 mRNA vaccines has unequivocally validated the platform's potential. The potent efficacy of COVID-19 mRNA vaccines arises from the synergistic combination of nucleoside-modified mRNA and the ionizable lipid nanoparticle (LNP) carrier.[3] The incorporation of modified nucleosides like N1-methylpseudouridine minimizes innate immune recognition, enabling high-level, sustained production of the encoded antigen. Simultaneously, the LNP itself acts as a powerful adjuvant, triggering a local inflammatory response and the production of key cytokines such as IL-6 and type I interferons. This immune stimulation, coupled with systemic repro-

gramming of the immune landscape, positions mRNA as an ideal platform for cancer immunotherapy. mRNA cancer vaccines uniquely enable scalable personalization by decoupling customized antigen design from a standardized production pipeline. Collectively, cancer mRNA vaccines offer a transformative platform for immunotherapy by uniquely combining scalable personalization, self-adjuvanting immunogenicity driving robust innate and adaptive immunity, and a favorable safety profile without genomic integration risks.

Recently, Adam J. Grippin et al. from the University of Texas MD Anderson Cancer Center reported a groundbreaking study, which demonstrated the clinically availability of SARS-CoV-2 mRNA vaccines as effective modulator of immune checkpoint blockade (ICI) in cancer patients.[4] Based on results from the large retrospective cohorts of patients with non-small cell lung cancer (NSCLC) and metastatic melanoma, they observed that receiving an mRNA vaccine within 100 days of starting ICI was associated with dramatically improved overall and progression-free survival. Interestingly, this benefit was specific to ICI therapy and not observed with chemotherapy or other vaccines like influenza, highlighting a unique synergistic effect. Then through extensive preclinical studies, researchers found that the mRNA-lipid nanoparticles (LNPs), regardless of the encoded antigen (spike or cytomegalovirus pp65), triggered a potent surge in type I interferon (IFN-I), blockade of which completely abrogated the antitumor effect. Besides, the mRNA vaccines encoding viral spike protein systemically activated antigen-presenting cells in lymphoid organs and primed the expansion of tumor-reactive and- infiltrating CD8+ T cells. Moreover, the infiltrating T cells induced a significant upregulation of PD-L1 and therefore, rendered the tumors, including previously immunologically "cold" ones with low baseline PD-L1, exquisitely sensitive to subsequent ICI treatment. Consequently, administration of the mRNA vaccine blocked the PD-1/PD-L1 axis and allowed for effective tumor cell killing. Corroborating these mechanisms in humans, researchers also observed that healthy volunteers receiving COVID-19 mRNA vaccines exhibited a robust early IFN-α response and activation of innate and adaptive immune cells, mirroring the pathways identified in mice. Furthermore, analysis of patient biopsies confirmed that recent mRNA vaccination was associated with higher tumor PD-L1 expression, effectively converting immunologically "cold" tumors into "hot" ones susceptible to immunotherapy. In addition, SARS-CoV-2 mRNA vaccination demonstrated a favorable safety profile in ICI-treated patients, without exacerbating immune-related toxicities. It induced a transient, self-limited type I interferon response that activated dendritic cells and upregulated tumor PD-L1. This synergy enhanced antitumor immunity while maintaining a controlled balance between immune activation and inflammatory tolerance. Lastly, this study identified a beneficial timing window, showing that mRNA vaccination within 100 days of ICI initiation improves survival in NSCLC and melanoma, including immunologically cold tumors, with consistent effects across vaccine platforms and regardless of prior vaccination. However, the evidence remained retrospective and subject to bias, lacking prospective randomized validation. Key parameters such as optimal vaccine dose, schedule, and sequencing relative to ICI remained unoptimized. Subgroup analyses by tumor genotype and immune phenotype are insufficient, and long-term efficacy, safety, and the impact of booster vaccinations are yet to be established. Herein, their work established that mRNA vaccines targeting non-tumor antigens are potent immune modulators capable of sensitizing tumors to ICI by resetting the systemic immune milieu via an IFN-I-dependent mechanism, which provides a novel, widely available, safe, and low-cost strategy to overcome intrinsic resistance to cancer immunotherapy.

The seminal study establishes a paradigm in which the SARS-CoV-2 mRNA-LNP vaccine, functioning as an integrated unit, systemically reprograms the innate immune landscape to potentiate checkpoint blockade (Figure 1). The core mechanism is initiated by the sensing of the mRNA-facilitated by its intrinsic sequence features (e.g., unmodified uridine) and/or LNP-induced higher-order structures-by pattern recognition receptors (e.g., the melanoma differentiation-associated protein 5, MDA5), triggering a robust type I interferon response.[5] While this model is compelling, it unveils several fertile grounds for groundbreaking investigation to fully harness this phenomenon for oncology:

First, at the mechanistic level, it is imperative to systematically decode the immunostimulatory signature of the mRNA itself. Defining a consensus sequence "code"—including specific motifs, nucleotide composition, and secondary structures—that maximizes IFN-driven immunity while minimizing hyperinflammation represents the most direct path to improving safety and efficacy. Concurrently, exploring potential crosstalk with cytosolic DNA-sensing pathways (e.g., the cyclic GMP-AMP synthase, cGAS) could reveal hidden layers of immunogenicity and further amplify anti-tumor responses.

Second, translating these mechanistic insights will enable the re-engineering of mRNA-LNPs for novel delivery strategies. A transformative goal is to optimize formulations for local intratumoral administration, aiming to create a potent in situ vaccine capable of generating robust abscopal effects (the phenomenon where localized radiotherapy leads to the regression of metastatic tumors at distant, non-irradiated sites) against metastases.

Finally, at the clinical integration level, future work should explore the synergy between exogenous RNA-LNPs and standard tumor-destructive therapies like radiotherapy. A key question is to what extent the sensing of endogenous tumor-derived RNA, augmented by exogenous RNA, can synergize with or dominate established pathways (e.g., STING) to achieve superior systemic immunity. And future studies are required to delineate the role of non-canonical RNA sensing mechanisms, particularly those involving ribonucleoproteins, in the overall immunogenicity of mRNA.

Ultimately, this paradigm-shifting work provides the seminal insight that clinically approved mRNA-LNPs systemically reprogram antitumor immunity independently of antigen specificity, a conceptual advance that fundamentally decouples immune modulation from traditional antigen-centric vaccine design. By demonstrating that mRNA-LNPs function as versatile "immune context modifiers" this study transcends not only the conventional boundary between infectious disease and oncology vaccines, but also moves beyond the historical constraint of patient- or tumor-specific antigens. The resulting strategy establishes a new class of off-the-shelf, non-antigen-specific immunotherapeutics capable of reshaping the TME and potentiating adaptive immune responses across a broad spectrum of cancers. Looking forward, resolving the remaining mechanistic questions will propel the rational design of next-generation in situ mRNA vaccines. Early clinical development paths may include combining these modular mRNA immunomodulators with established therapies or sequencing them with antigen-specific vaccines in multimodal regimens. By offering a universally applicable, scalable, and readily deployable platform, this approach heralds a new era of accessible and effective cancer immunotherapy.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.