Applications of mRNA-Based Therapies in Oncology and Autoimmunity Beyond Vaccination

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In recent years, mRNA-based therapies have become a powerful approach, reshaping gene therapy and modern treatment methods.[1] Compared to recombinant proteins and plasmid DNA, mRNA therapeutics provide important benefits, such as a strong safety profile due to their non-integrating and non-mutagenic characteristics. First demonstrated *in vivo* by Wolff et al.[2], mRNA allows functional protein production without the risk of genomic insertion. The success of mRNA vaccines during the coronavirus disease-2019 pandemic accelerated the advancement of this technology, highlighting its rapid development, scalability, and safety. Current platforms make it possible to achieve fast, strong, and temporary protein expression, supporting the development of personalized cancer vaccines that target tumor antigens and new immune-modulating treatments for autoimmune disorders without causing widespread immunosuppression.[1]

For cancer therapy, mRNA-based treatments are showing significant promise by stimulating immune responses specifically tailored to individual tumors. Several delivery approaches, such as naked mRNA injections, lipid nanoparticles, and dendritic cell-based vaccines, are under investigation for cancers including melanoma, lung, and prostate cancer. Clinical trials like the IVAC MUTANOME trial in melanoma have shown neoepitope-specific T-cell responses in 60% of patients, with good tolerability and effectiveness (Table 1).[3] Moreover, mRNA-engineered immune cells, including chimeric antigen receptor T (CAR-T) cells, are being studied to improve results in solid tumors. Research on mRNA-2752 combined with durvalumab in advanced solid tumors such as head and neck squamous cell carcinoma, triple-negative breast cancer, melanoma, and non-small cell lung cancer has shown encouraging anti-tumor effects, with about half of head and neck cancer patients experiencing measurable tumor shrinkage (Table 1).[3] Combining these therapies with checkpoint inhibitors or anti-angiogenic agents is anticipated to further enhance their therapeutic impact, positioning mRNA as a highly adaptable option in cancer immunotherapy.[4] Moreover, personalized cancer vaccines using mRNA technology are proving to be a promising approach for custom treatments by encoding tumor-specific antigens to stimulate the immune system to find and destroy cancer cells. Lipid nanoparticles improve mRNA delivery, while engineered immune cells like CAR-T cells further strengthen treatment results. When these mRNA-based methods are combined with immune checkpoint inhibitors, they offer considerable potential to improve cancer treatment outcomes (Figure 1).[5] A clinical trial evaluating BNT112 and cemiplimab in advanced prostate cancer showed evidence of immune activation and PSA responses, suggesting biological activity even in advanced stages of the disease (Table 1).[3]

In autoimmune conditions, mRNA therapies take a different approach by retraining the immune system to recognize and tolerate the body's own antigens instead of provoking an immune response. Unlike conventional vaccines that target pathogens, these treatments aim to adjust the immune system so that it identifies and accepts self-antigens.[5] This is done by delivering mRNA encoding disease-specific autoantigens to dendritic cells, which then present these antigens to T cells in a non-inflammatory way. This mechanism encourages the growth of regulatory T cells (Tregs), which helps decrease the immune system's attacks on the body's own tissues.[6] Additionally, current studies are exploring mRNA-based treatments for autoimmune conditions like multiple sclerosis (MS) and type 1 diabetes (T1D). Research has demonstrated that mRNA vaccines carrying MS autoantigens can expand Tregs and suppress autoreactive T cells in mouse models, delaying disease progression without triggering broad immune suppression[6]. Likewise, in T1D, preclinical studies indicate that mRNA immunotherapies can encourage antigen-specific tolerance by precisely targeting autoreactive T cells under non-inflammatory conditions, supporting the preservation of remaining β-cell function without causing widespread immune suppression.[6] Table 1 summarizes the clinical performance of mRNA-based vaccines across various cancers, showcasing their ability to induce strong tumor-specific immune responses. Several candidates demonstrated safety, immunogenicity, and potential synergy with checkpoint inhibitors; underscoring mRNA vaccines' promise in overcoming immunotherapy resistance and advancing cancer treatment.

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TABLE 1. Clinical Efficacy of mRNA Vaccines in Various Cancers.[1]

mRNA vaccine	Targeted cancer(s)	Key clinical outcomes
IVAC_M_uID	Triple-negative breast cancer (TNBC)	Strong poly-epitopic T-cell responses in post-neoadjuvant settings.
mRNA-2752 + durvalumab	Advanced solid tumors (HNSCC, TNBC, melanoma, NSCLC, etc.)	Promising antitumor activity, with ~50% of head and neck cancer patients demonstrating objective tumor regression. Synergy with checkpoint inhibition noted.
CV9103	Hormone-refractory prostate cancer	Elicited potent antitumor immunity in both prophylactic and therapeutic settings, supporting its potential as a versatile vaccine platform.
CV9104	Metastatic castration-resistant prostate cancer (mCRPC)	Elicited antigen-specific immune responses, but clinical efficacy (e.g., survival benefit) needs further confirmation.
BNT112 + cemiplimab	Advanced prostate cancer	Measurable immune activation and PSA responses in advanced disease.
Lipo-MERIT	Checkpoint inhibitor-refractory melanoma	Sustained CD4+/CD8+ T-cell responses against tumor antigens, supporting its role in overcoming immunotherapy resistance.
IVAC MUTANOME	Melanoma	Neoepitope-specific T-cell responses (60% of patients); well-tolerated. Highlights feasibility of personalized mRNA vaccines.
mRNA-2416	Ovarian cancer/refractory solid tumors	Well-tolerated with evidence of immunomodulation (↑OX40L/PD-L1 in tumors), indicating potential for combination with immune therapies.
NCI-4650	Melanoma, GI, GU, and hepatocellular cancers	Safe and immunogenic, with mutation-specific T-cell expansion seen in all tumor types.
TriMixDC-MEL	Stage III/IV melanoma	Durable tumor control and robust CD8+ T-cell activation.
TriMix-DC + ipilimumab	Advanced melanoma	Enhanced CD8+ T-cell responses were associated with clinical benefit, highlighting synergy between mRNA vaccines and CTLA-4 blockade.
ECI-006	Melanoma	Favorable safety profile with measurable immunogenicity.
Dendritic cell vaccines	Prostate cancer, melanoma, breast cancer	Variable results: some trials reported prolonged survival (prostate) or complete responses (melanoma), while others emphasized safety (breast). Antigen selection had a critical influence on efficacy.

HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer.

Despite their promising potential, mRNA therapies still face several obstacles that limit their broad clinical application. One significant challenge is the natural instability of mRNA molecules, which are easily degraded by nucleases. To address this, protective delivery systems like lipid nanoparticles (LNPs) are required for effective transport.[7] This issue is being tackled with encapsulation techniques and chemical modifications, such as incorporating pseudouridine, to boost protection and improve cellular uptake.[8] Additional strategies to enhance mRNA stability and translation efficiency include 5′ cap modifications (e.g., ARCA and CleanCap), optimization of the open reading frame through codon selection and GC content enrichment, and engineering of untranslated regions (UTRs) to remove destabilizing elements and extend 3′ UTRs-all aimed at achieving effective and sustained protein production.[9] New methods like self-amplifying mRNA (saRNA), which replicates within cells to increase antigen expression with smaller doses, and circular mRNA (circRNA), designed to improve stability and extend protein expression, are also under investigation to tackle these challenges.[9]

Another issue is immunogenicity, where the immune system may detect foreign mRNA or its delivery system, resulting in inflammation.[7] This is addressed through nucleotide modifications-such as substituting with pseudouridine or 1-methyl pseudouridine, as done in nucleoside-modified mRNA-and purification techniques like high-performance liquid chromatography, which help lower innate immune responses, remove contaminants, and improve the safety profile of mRNA treatments.[9] Off-target effects and precise tissue targeting are further challenges since current delivery methods often lack specificity, causing non-specific buildup, particularly in the liver.[10] To improve targeting, researchers are developing better delivery systems through high-throughput screening, optimizing LNPs for specific tissues, and exploring alternative carriers like polypex complexes and peptide-based platforms.[9] Advances in nanomedicine are also contributing to overcoming these barriers, offering more precise and tailored delivery solutions.[11]

In oncology, tumor heterogeneity poses a unique challenge by enabling tumors to mutate quickly and create immunosuppressive environments that reduce the effectiveness of treatments. Overcoming this requires approaches such as multipoint tumor sampling, targeting multiple antigens, and combining with other immunotherapies like immune checkpoint inhibitors or adoptive T-cell therapies.[9] mRNA cancer vaccines, with their rapid production timelines, natural adjuvant properties, and safety benefits, are well suited to address this complexity.[12] Another obstacle is the manufacturing complexity and high costs, which continue to restrict the scalability of mRNA therapies. Potential solutions include improving production systems, fostering collaborations

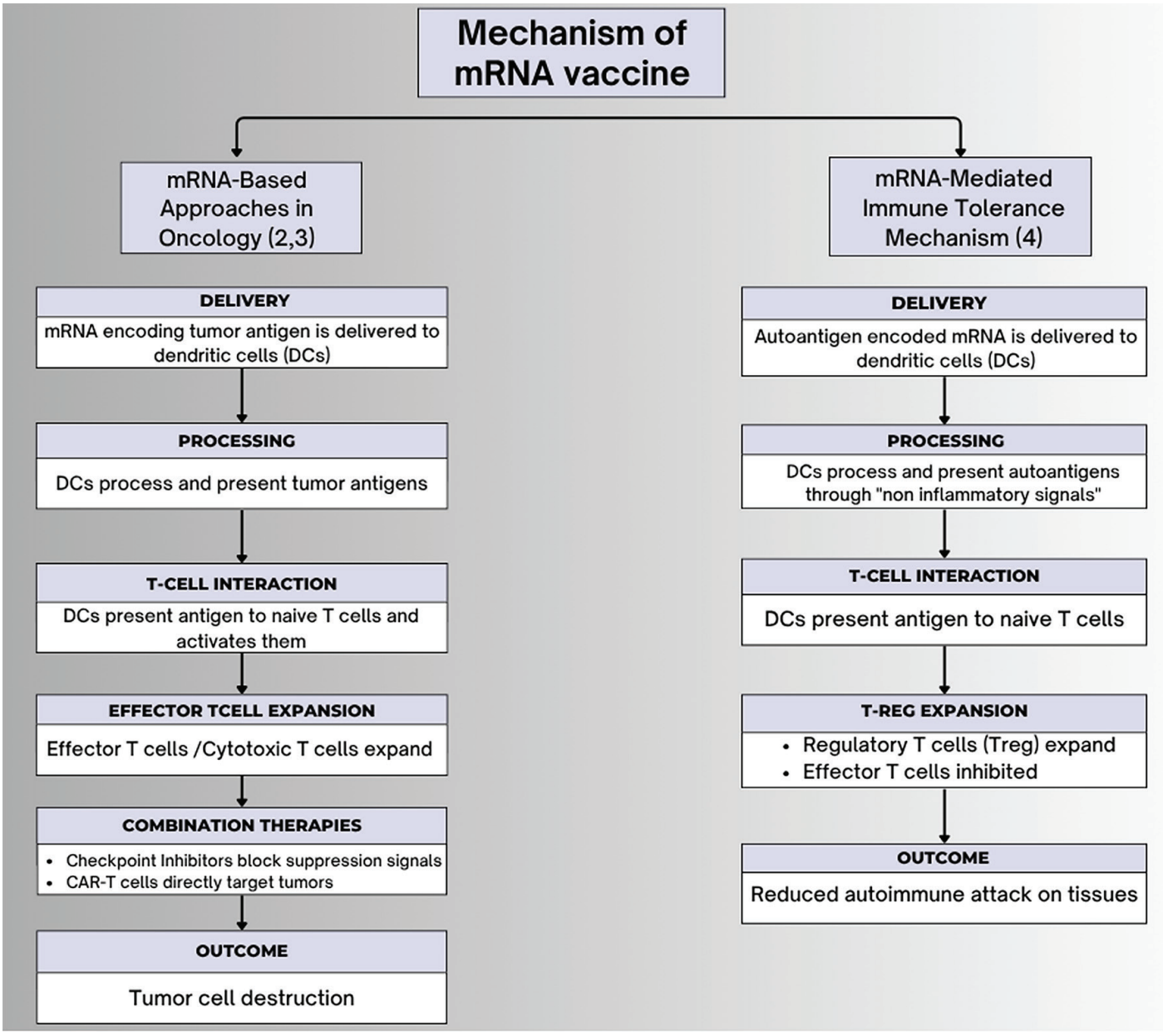

FIG. 1. mRNA-based approaches in oncology and their mechanisms.

between public and private sectors, and refining manufacturing methods to lower costs and shorten production times.[9] Notably, mRNA platforms support faster and more personalized treatment development compared to many traditional methods, offering the possibility of long-term cost-effectiveness in clinical practice.[11]

Looking ahead, new mRNA and vesicle-based technologies-such as programmable macrophage vesicle vaccines, immunoadjuvant-functionalized systems, and lentiviral gene therapies-present fresh immunomodulatory options for infectious diseases, oncology, and gene therapy. For example, a programmable macrophage vesicle-based vaccine (AM@AEvs-PB) has been created for the monkeypox virus, showing improved immune activation by delivering both intracellular and extracellular viral antigens with self-adjuvanting effects.[13] Engineered macrophage vesicles also hold promise in oncology by converting tumor-associated macrophages from an immunosuppressive M2 state to a pro-inflammatory M1 state, which boosts immune surveillance and promotes tumor elimination.[13,14] Different vesicle-based nanoparticles-including exosomes, microvesicles, and liposomes-are under study for their ability to deliver tumor antigens and adjust immune activity within the tumor microenvironment. Programmed nanovesicles, equipped with membrane-bound ligands, enable targeted immune modulation and dual-direction macrophage polarization.[14] Additionally, lentiviral vectors have become important tools in vaccine research, allowing for the genetic alteration of tumor and immune cells to improve antigen presentation and strengthen

immune responses.[15] Immunoadjuvant-functionalized systems, using extracellular vesicles or bacterial outer membrane vesicles, are also emerging as new approaches to boost tumor immunity by delivering antigens and adjuvants to activate dendritic cells and reprogram innate immune cells for stronger antitumor effects.[15]

In conclusion, mRNA-based therapies have shown significant transformative potential beyond vaccines, presenting promising uses in oncology and autoimmune diseases through personalized immune modulation, targeted antigen delivery, and enhanced safety profiles. Recent developments-including personalized cancer vaccines, CAR-T cells engineered with mRNA, and tolerogenic vaccines for autoimmune disorders-demonstrate the flexibility of mRNA platforms to both active immune responses and promote immune tolerance. Existing challenges such as instability, immune reactions, off-target effects, and complex manufacturing are being tackled with advances in lipid nanoparticles, nucleotide modifications, and improved delivery technologies, while new strategies like saRNA and circRNA further expand their therapeutic promise. Looking ahead, innovations such as programmable macrophage vesicle vaccines, immunoadjuvant-functionalized systems, and lentiviral gene therapies reflect a move toward more precise, flexible, and combined treatment options across infectious diseases, oncology, and gene therapy. The authors believe these developments signal the beginning of a new era in personalized medicine, where mRNA technologies will keep advancing as safe, effective, and customized therapies, provided that continued research and interdisciplinary cooperation drive this progress forward.

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