Revolutionizing cancer research with the power of mRNA

moderna

Innovation in the mRNA field allowed for rapid development of COVID-19 vaccines, which has enhanced interest in investigation of potential mRNA-based approaches for cancer therapy.

Previous attempts at developing cancer vaccines encountered significant challenges. Obstacles included heterogeneity of genetic mutations between individuals, effective identification of antigens to generate strong and lasting immune responses, and mechanisms of immune system evasion and other hurdles within suppressive tumour microenvironments. Improved mRNA technology, understanding of cancer biology and technological advances are informing how we address these challenges. Learnings from mRNA research and development related to manufacturing/stability and T-cell response data have helped researchers design and test novel cancer therapy modalities.

Moderna aims to use mRNA technology (**Fig. 1**) to instruct the immune system to detect and attack cancer cells, with the ultimate goal of clinically benefitting patients. This could include individualized therapies that target specific characteristics of each person's cancer, and "off-the-shelf" therapies designed to act on targets or pathways that apply to multiple patients with cancer.

A MULTIPRONGED APPROACH

The adaptability of mRNA technology means that Moderna can pursue a variety of strategies to combat cancer. With several oncology clinical trials underway across a variety of solid tumors, there is concerted effort to mobilize science into action. Moderna is embarking on a journey to evaluate the use of our mRNA platform and scientific learnings from research and clinical experiences to deliver the greatest possible impact to patients.

One approach is tailoring therapy to each patient's unique cancer mutational fingerprint. Cancerous cells develop mutations that may confer selective advantage, such as those that lead to uncontrolled growth or allow evasion of immune destruction; this unique set of cancer mutations in the patient's tumour generates neoantigens, which the immune system can recognize as abnormal. The majority of neoantigens and their antigen-presenting molecules are unique to each patient; however, past methods have used more commonly identified tumour-associated antigens to generate T-cell responses. An individualized approach enabled by technological advancements in next-generation sequencing may identify tumour centric mutations, and computational algorithms that consider the patient's neoantigen repertoire could predict those most likely to launch an immune response against the patient's cancer cells, potentially eliciting clinically meaningful T-cell responses. Early results have provided proof-of-concept for neoantigen targeting modalities and support the potential for an mRNA therapy to make an impact in oncology[1-3]. Clinical trials are ongoing to explore this novel approach (NCT05933577, NCT06077760, NCT03313778, NCT03897881).

While mRNA technology may provide an opportunity to tailor treatment to an individual patient, it may also be applied to address targets that are known to drive evasion of the normal immune response and are widely expressed in many cancers. This approach could target common oncogenic pathways or guide antigen presenting cells to target immune checkpoint proteins. T-cells may then recognize cancer cells that overexpress these checkpoint proteins, identifying and destroying tumour cells expressing them; T-cells may also recognize and destroy immunosuppressive T-regulatory cells displaying the same proteins. A clinical study exploring this investigational approach is underway (NCT05533697).

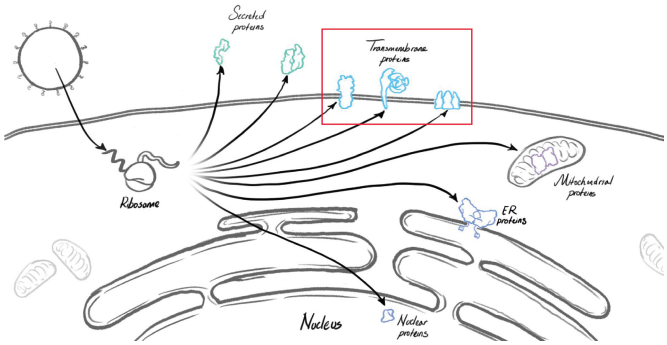

Figure 1. The promise of mRNA. mRNA therapies may enable diverse approaches to vaccine antigen design and cellular localization providing the potential to target a wide network of intra- and extracellular processes. ER, endoplasmic reticulum; mRNA, messenger RNA.

Advancements in mRNA science and the adaptability of the mRNA platform can be leveraged to assess an innovative and diverse portfolio of investigational cancer therapies, including individualized approaches, modalities targeting more broadly expressed antigens, as well as encoding immunomodulatory proteins.

ACCELERATE RESEARCH

Even with significant strides in oncology research, cancer continues to cast a wide shadow. In 2020, the International Agency for Research on Cancer estimated that the global impact of cancer escalated to >19 million new cases and 10 million deaths, representing millions of patients and families urgently needing treatments. Moderna's extensive research efforts and strategic collaborations (for example, Merck & Co., Inc., Rahway, NJ, USA) seek to increase our aspiration to improve treatment options.

mRNA has extraordinary potential and Moderna feels a strong sense of responsibility to explore how it can address unmet needs in cancer treatment and beyond. Moderna is extremely grateful to the trial participants, researchers, and staff who are vital to this progress. Moderna remains committed to accelerating discovery and development in the oncology space – this is just the beginning of our fight against cancer. With continued dedication to harness the power of mRNA, Moderna is striving to create transformative therapies and deliver hope to patients around the world.

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REFERENCES

1. Gainor, J. F., *et al. J. Immunother. Cancer.* **11** (2023). doi: 10.1136/jitc-2023-SITC2023.1530
2. Khattak, A., *et al. J. Clin. Oncol.* **41**, no. 17 suppl. (2023). doi: 10.1200/JCO.2023.41.17_suppl.LBA950
3. Rojas, L. A., *et al. Nature.* **618**, 144–150 (2023).