Developing Approaches for mRNA Vaccines in Oncology

A key challenge in developing therapeutic vaccines against cancer is getting the correct vaccine target delivered to the correct immune cells in the correct cellular context. A variety of mRNA-based approaches are showing great promise in achieving these goals. mRNA vaccines can be integrated into flexible and modular immunotherapeutic strategies designed to address the specific needs of persons with cancer. Flexible approaches make mRNA vaccines ideal for the development of personalised precision approaches to drive immune responses to neoantigens from the patient's own tumour.

Every form of cancer originates from a healthy cell. The developing immune system is educated to tolerate protein antigens expressed by healthy cells as "self" antigens. Cancer occurs when healthy cells start to break free from multiple layers of genetic mechanisms that restrict and suppress cellular replication, leading to uncontrolled and inappropriate proliferation. As a tumour develops, the malignant cells often begin to express proteins that serve as potential anti-tumour immune targets, or Tumour Associated Antigens (TAAs).

As part of this process, malignant cells generally lose the quality control mechanisms that ensure high-fidelity DNA replication, such that growing tumours can express increasing quantities of proteins representing genetic mutations. These mutations often encode peptide sequences or "neoantigens" that are different enough from the self-sequence that the immune system may recognise them as "non-self." Aside from neoantigens, TAAs may include unmutated self-proteins expressed in an inappropriate context.

Immune responses to neoantigens play a significant role in preventing malignant disease in humans. Indeed, many healthy people have circulating memory T cells specific for potential neoantigens, indicating a likely previous immune response to cancerous or precancerous cells that were successfully eliminated. A clinical diagnosis of cancer indicates that the natural antitumour immune response has failed, and a key goal of immunotherapy and vaccine development in oncology is finding ways to induce or restore those protective immune responses.

One mechanism for generating these protective immune responses is to express neoantigen sequences in a context that activates and stimulates the immune system. Another mechanism is to block suppressive factors expressed by tumours that turn off the immune system; for example, blockade of immune "checkpoints" represented by the PD-1 and CTLA-4 pathways has led to monumental success in the field of immunotherapy, with drugs such as Nivolumab and Ipilimumab. As a general strategy, there are obvious benefits for engaging both mechanisms at once, such as priming of neoantigen responses and de-suppression of the immune system. mRNA-based approaches are showing significant promise by engaging one or both mechanisms of action.

Neoantigens can be divided into two categories, "public" and "private," with public neoantigens being frequently found in a significant percentage of cancer patients, and private neoantigens being unique to the respective tumour of one individual. Immune responses to both public and private antigens are capable of suppressing tumours and even curing cancer in some individuals.

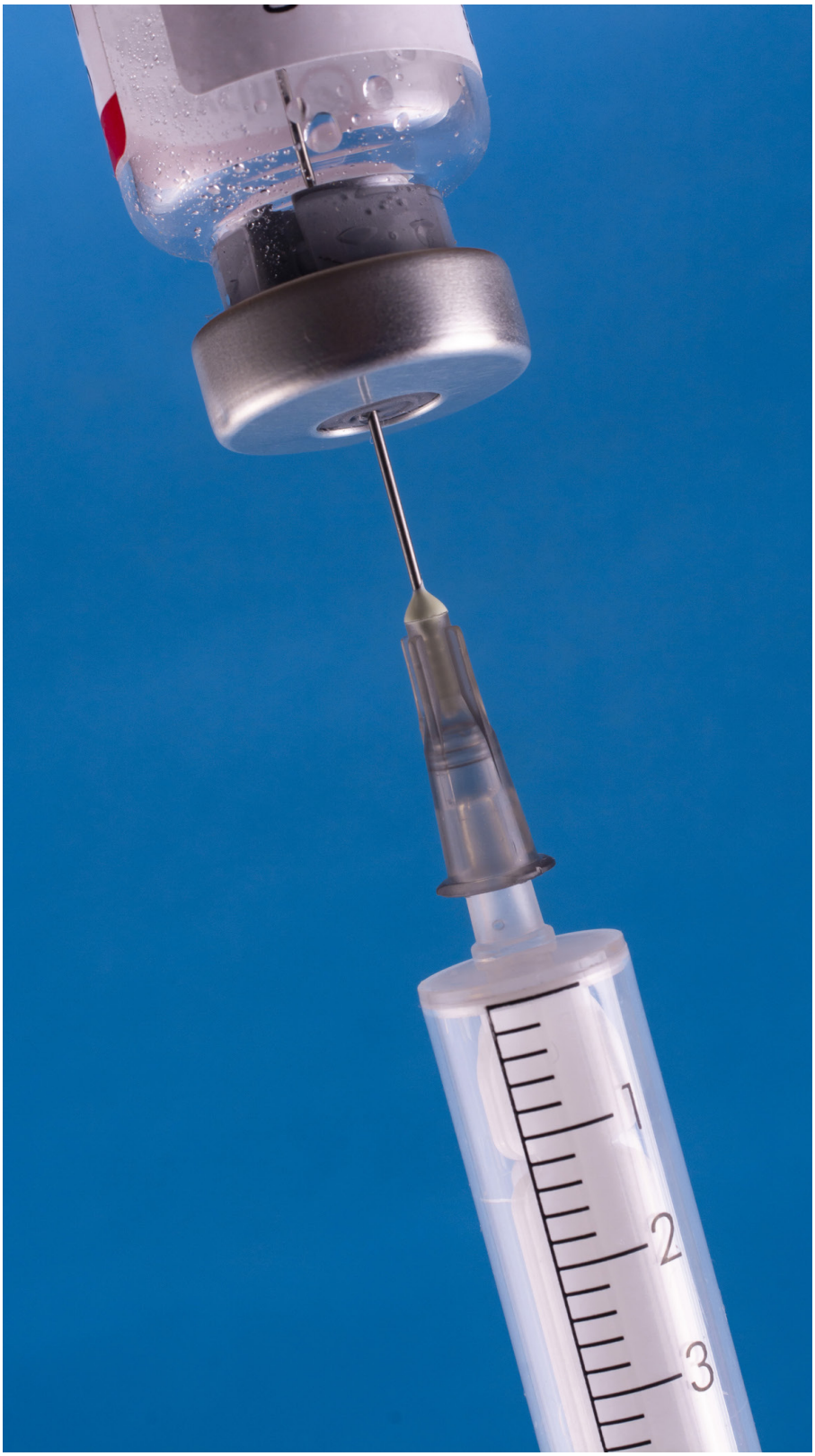
mRNA is an essential part of the most basic biological process in all living cells. In every human cell, natural mRNA carries genetic messages encoded in DNA from the nucleus and supports translation of that message into a protein in the cytoplasm. With current synthetic biology techniques synthetic mRNA can be routinely engineered to encode any arbitrary protein sequence. For immuno-oncology, this creates an opportunity to express any public or private antigenic sequence in cells transfected with the desired mRNA sequence.

A variety of vaccine technologies can be used to deliver TAAs to the immune system.[1] Aside from mRNA, these can include engineered viral vectors and adjuvanted recombinant protein vaccines. A specific advantage of the mRNA approach is that unlike with viral vectors, there is usually minimal off-target immune response to non-TAA vaccine components. Unlike most protein-based vaccines, mRNA-encoded TAAs are expressed within the cytoplasm or secretory pathway of transfected cells, resulting in the processing and presentation of the TAA components to the immune system in a manner that mimics natural TAA processing in the tumour.

A "naked" RNA molecule will usually be rapidly broken down in the environment or the human body by ubiquitous RNA-degrading ribonuclease (RNase) enzymes. Therefore, mRNA vaccines and therapeutics are generally packaged in nanoparticles that protect and deliver mRNA cargo to target cells. The most commonly used nanoparticles are lipid nanoparticles, or LNPs, that can encapsulate mRNA for protection from RNases and facilitate delivery across a cellular membrane into the cytoplasm. After arrival in the cytoplasm, an mRNA molecule can immediately serve as a translational template for protein production. TAAs expressed in the cytoplasm are processed via the Class I endogenous pathway for stimulation of CD8+ T cells, often known as "killer T cells." TAAs expressed in the secretory pathway can be processed via the Class II exogenous pathway for stimulation of CD4+ T cells, often known as "helper T cells." Cooperative engagement of CD4+ and CD8+ T cells usually leads to an optimally effective immune response.

Important considerations for using mRNA to fight cancer can include selecting the best TAA sequence to include in the vaccine, creating a mechanism for delivery of antigenic mRNA to the cytoplasm of the optimal target cells, and reversing immune suppression associated with many cancers to enable induced immune responses to drive robust antitumour effects.

For the selection of TAA, mRNA vaccines have a distinct advantage in that RNA products encoding any novel sequence can be manufactured relatively quickly (within weeks). This makes mRNA vaccines especially suited for developing individualised vaccines



against private neoantigens. Several promising approaches use genetic sequences derived from a person's own resected tumour DNA for generating a personalised TAA vaccine.

A challenge of LNP-mediated delivery is the tendency of LNPs to transfect liver cells, generally not considered an optimal target. A variety of approaches are being tested for delivery to professional antigen-presenting cells (APCs) of the immune system.[2] The most important type of APC for priming novel immune responses is the dendritic cell (DC). New lipid formulations are showing promise for enhanced DC delivery of LNPs. In some experimental approaches, LNPs are coated with antibodies specific for DC surface markers, potentially leading to TAA delivery directly to the most potent immunostimulatory cell types.

In many clinical contexts, presenting antigens to T cells is insufficient to generate a robust antitumour response. This is because proliferating tumours generally create an immunosuppressive environment, through the expression of cell-surface "checkpoint" molecules such as PD-1 ligand (PD-L1) or soluble anti-inflammatory cytokines. To counter these effects, an mRNA vaccine may be delivered in conjunction with a checkpoint inhibitor monoclonal antibody, such as pembrolizumab, which binds to and blocks the inhibitory PD-1 receptor on T cells. Aside from a recombinant protein antibody product, an mRNA formulation may include mRNA that actually encodes a checkpoint inhibitor and/or a pro-inflammatory cytokine such as IL-12. If these mRNA therapeutics can be effectively delivered to the tumour microenvironment, this approach has the potential to be efficient and cost-effective, while minimising potential adverse side-effects of systemic delivery of checkpoint inhibitors and cytokines.

Due to relative simplicity, flexibility, and potential combinatorial use, mRNA-based immunotherapies are a promising avenue for future cancer vaccine treatments.

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