Research Strategy: Jon Moore

RNA-based therapeutics: present and future

The story of how messenger RNA technology rapidly delivered highly effective prophylactic vaccines in the SARS-CoV-2 pandemic is foundational. Programmes developed by BioNTech SE and Moderna Inc used nucleoside base modifications to develop vaccines that successfully protected against the virus. The base modification technology was developed by the scientists Katalin Karikó and Drew Weissman based on their insights into how synthetic mRNA interacted with the immune system – discoveries that led to their receipt of the Nobel Prize in Physiology or Medicine in 2023.

At the same time, the ability of the mRNA vaccines to curb the pandemic was only possible due to existing infrastructure at BioNTech and Moderna which had been created to support their long-standing plans to develop therapeutic mRNA-based vaccines for cancer. BioNTech's programme started in 2008 while Moderna's was underway by 2015 at the latest.

These mRNA cancer vaccine initiatives are now bearing fruit. In August, Moderna and its partner, Merck & Co Inc, announced positive results for a Phase 3 trial in more than 1,100 adjuvant melanoma patients. The results showed that a personalised cancer vaccine regimen added to pembrolizumab, the standard of care, benefitted patients. This followed results from a preceding Phase 2b study, where the addition of a personalised vaccine reduced recurrence or death by 49% up to five years out[1]. Moderna's success represents a spectacular demonstration of the power of an mRNA medicine beyond infectious diseases.

Moderna, BioNTech and their pharma partners have made significant investments in logistics and infrastructure to meet the challenge of building personalised mRNA cancer vaccines. In Moderna's case, these have been scaled for late-stage clinical trials. Manufacture commences with DNA and RNA sequencing of patient tumours, proceeds via selection of the most promising antigens (up to 34 in the Moderna cancer vaccines), and then follows by the synthesis of a DNA construct, *in vitro* transcription to produce mRNA and finally its encapsulation into, or complex formation with, defined lipids to form a nanoscale formulation for delivery to patients. The objective is to treat patients with their first dose of therapeutic vaccine within four weeks of accessing the tumour material. Currently this is typically achieved within six weeks.

It is universally acknowledged that cancer vaccines have generally disappointed in pivotal trials. Therefore, Moderna's positive results in randomised Phase 2 and Phase 3 trials will be attributed by many to either mutated neoantigens being more effective than those previously pursued by the field, or to LNP-pseudouridine-modified mRNA being a uniquely high-performing modality. However, it can equally be argued that the clinical success of the Moderna/ Merck partnership has been driven by selecting the right indication, setting and partners.

Deploying a fully individualised therapeutic cancer vaccine in an adjuvant setting is a demanding task which mRNA vaccines have shown they can meet. However, similar timelines from surgery/biopsy to first dose have been delivered by DNA vaccines (Geneos Therapeutics Inc) and viral vectors (e.g. Transgene SA and Nouscom AG).

A key, if not unique, advantage of lipid nanoparticles (LNPs) for the therapeutic vaccine role is the ability to re-dose with the same entity multiple times (typically nine doses are used in the BioNTech and Moderna clinical trials). There is no counterpart of the toggling between adenoviral vector mediated priming and vaccinia virus vector mediated boosting deployed by Nouscom. mRNA is also devoid of the theoretical possibility of DNA-based vectors integrating into patient cells. Finally, while adjuvanted peptide-based vaccines could be deployed quickly and at scale, the diverse peptides required for a personalised product will differ considerably in their physicochemical properties. This could encourage the prioritisation of manufacturability rather than antigen quality in the choice of agents taken forward.

BioNTech continues to use native uridine-containing mRNA in its cancer vaccine portfolio and while this platform currently lacks a clear Phase 2 victory in a randomised trial, it should not be discounted. Published data indicate that the BioNTech cancer vaccines can deliver very strong T cell responses. Peak levels of vaccine-induced T cell clones can reach 20% of total T cells[2]. Moreover vaccine induced T cell clones can be very persistent, which has been linked to long term control of pancreatic adenocarcinoma in early Phase 1 trials[3].

A pivot to off-the-shelf cancer vaccines

Despite all the progress in building logistical pipelines to deliver individualised RNA therapeutics in close to four weeks, this could still be too slow for some patients. There are strong scientific grounds to deploy cancer vaccines prior to surgery and given the desire of patients and clinicians to begin treatment as soon as possible after diagnosis, the typical six-week delay while an individualised therapy is manufactured is widely considered too long. Only an off-the-shelf vaccine can realistically access neoadjuvant opportunities.

While they sit outside the spotlight, there are a large number of off-the-shelf cancer vaccine concepts in various stages of clinical testing. BioNTech has taken at least four off-the-shelf cancer vaccines into the clinic, most based on lineage specific antigens or cancer testis antigens. However the most advanced of the BioNTech products, BNT-113, which is in Phase 3, is based on the tumour specific and viral-infection derived E6 and E7 oncoproteins from HPV-16. Furthermore, Moderna's current pipeline contains four off-the-shelf cancer vaccine concepts: one is based on recurrent frameshift mutations observed in Lynch syndrome, one on the tumour microenvironment antigens PDL1 and

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IDO1, and two on, as yet undisclosed, tumour associated antigens. The antigen targets embedded in the last three products retread old ground from failed programmes. They represent a bet on the particular vaccine technology and the opportunity to run more vaccine modality-appropriate clinical trials.

An LNP-mRNA off-the-shelf vaccine based on differentiated tumour specific antigens (TSAs) is however about to enter the clinic. This is Epitopea Ltd's Cryptivax-1001 for high-grade serous ovarian cancer. This product is inspired by recent discoveries from unbiased surveys of the cancer specific immunopeptidome that couple advanced immunopeptidomics with computational biology. These studies have revealed that the great majority of TSAs are wild-type in sequence and the majority are derived from so-called non-coding DNA. These wild-type but aberrantly expressed peptides are highly immunogenic and their mouse counterparts can deliver superb tumour control in syngeneic mouse models. Helpfully, they are sufficiently shared within individual indications to make an off-the-shelf beads-on-a-string vaccine a compelling opportunity. Epitopea anticipates that the combination of highly tumour-specific novel antigens, optimally configured for presentation and delivered by a powerful T cell inducing modality, will deliver strong benefits for future patients.

Where mRNA technology is going next

Will mRNA-therapeutics make an impact beyond prophylactic vaccines for infectious diseases and therapeutic cancer vaccines? There were certainly more lofty ambitions for the technology in Moderna's early days, and Moderna and BioNTech have variously explored the technology for gene replacement and the *in vivo* generation of biologics. These other applications potentially require some retuning of the technology. Both infectious disease vaccines and cancer vaccines take advantage of the pronounced immunostimulatory properties of synthetic RNA administered in a lipid nanoparticle and based on ionisable lipids. Both native and pseudo-uridine modified mRNA appear able to deliver the kinds of T cell responses useful for immune system control of cancer. But pseudo-uridine modified mRNA has strong advantages if one wants to make a protein in the transduced cells. The approved SARS-CoV-2, RSV and influenza vaccines manufactured by Moderna all drive the synthesis of immunogenic virus-derived proteins that are targeted by strong antibody responses.

Gene and enzyme replacement applications, or the *in vivo* generation of antibodies and other biologics in patients, might in some cases demand a longer period of synthetic RNA-mediated protein production than conventional mRNA constructs can deliver. Two technologies that could deliver this are self-amplifying RNA (which includes and exploits some of the replication machinery of RNA viruses) and circular RNA (which avoids exonuclease-mediated degradation of the therapeutic mRNA inside cells and employs usually virally-derived internal ribosome entry sites for initiation of translation). For those interested, recent reviews on these technologies are cited in the references section[4,5].

Enzyme replacement

Moderna has a clinical programme to restore propionyl-CoA carboxylase expression to propionic acidaemia due to mutations in the PCCA or PCCB genes. This was recently partnered with the rare disease specialist company Recordati SpA. Propionic acidemia is a rare genetic disease affecting approximately 1/100,000 individuals. The Recordati/Moderna product, mRNA-3927, is based on two mRNAs encoding either the PCCA or PCCB genes delivered together by intravenous infusion with the PEG-containing formulation driving liver uptake and expression. Interim clinical data has been reported from 16 patients dosed with between 300 µg and 900 µg of product (by mRNA content) per kg body weight every two weeks. No dose limiting toxicities have been reported, and there is a 70% reduction in the risk of (potentially life threatening) metabolic decompensation events in the cohort of patients who reported these in the 12 month pre-treatment period.

Moderna's publication on the first in-human trial results does not discuss why an LNP-mRNA approach (Koeberl et al, 2024) is uniquely advantageous in this indication. The combined length of the PCCA and PCCB mRNAs (2500 and 1800 bp, respectively) is close to, but not beyond, the limit of what can be encoded in the classic vector for DNA-based gene therapy, AAV. While it is possible that circular RNA or self-amplifying RNA constructs would provide a route to a less intensive repeat treatment schedule, the repeat dosing of the conventional pseudouridine-modified mRNA-3927 appears well-tolerated. It is also worth noting that Moderna has a second mRNA-based enzyme replacement project in early clinical trials, mRNA-3705 for methylmalonic acidaemia (MMA).

LNP-mRNA technology also provides a route to deliver the gene editing or base editing machinery to execute 'one-and-done' modifications to the genome of target cell types. The technology is deployed in several of the programmes of both Intellia Therapeutics Inc (e.g. NTLA-2002/ lonvoguran ziclumeran) and Beam Therapeutics Inc (e.g. BEAM-302) for liver targeting of mRNA encoded editing machinery and the targeting guide RNA. For gene editing, LNP-mRNA generally competes with AAV-based viral vectors. As the gene editing machinery itself is likely to provoke T cell responses limiting repeat dosing the re-dosability of an LNP-mRNA product provides little benefit in this parameter. However, pre-existing anti-AAV antibodies are an issue for viral-vector based gene therapy and gene editing, so LNP-mRNA platforms do have an advantage. More important, however, is tissue tropism, with LNP-mRNAs being ideal for liver delivery. Significant effort is being applied to alter the tissue tropism of LNP-mRNA approaches.

The liver tropism of current clinical LNPs can also be exploited for the *in vivo* production of biologics via a nucleic acid modality that is not subject to the genome integration and hence potential host cell transformation risks of DNA-based vectors.

AstraZeneca Plc has been exploring routes to express antibodies vs. hospital acquired infections such as Staphylococcus aureus *in vivo*[5]. Published work indicates that mice can be protected against bacteria challenge by

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the administration of LNP-mRNA formulations encoding relevant antibodies. Larger animal studies indicate that peak concentrations of ~ 10 µg/ml can be achieved, which are comparable to the steady state doses achieved in patients treated with therapeutic antibodies such as pembrolizumab.

By encoding mutant antibodies benefitting from half-life extension technology it would appear feasible to protect long-term hospital patients from infection by potentially drug-resistant bacteria for several months. Moreover, in a pandemic situation comparable to the Covid pandemic with mortality enhanced in immune-suppressed individuals, a rapidly deployable technology such as LNP-mRNA affords the possibility of *in vivo* generation of passive immunity that can evolve with the epitope shifts driven by vaccines and host immunity in the wider population.

Returning to oncology, LNP-mRNA technology is also being used for the multiplexed *in vivo* production of T cell engagers recruiting T cells to three different surface targets relevant to multiple myeloma in Moderna's mRNA-2808. This product has recently entered a phase 1/2a trial in relapsed refractory multiple myeloma. A second mRNA-encoded T cell engager programme for ovarian cancer is in the works. Recent disclosures from Moderna reveal an aspiration to encode soluble TCRs as LNP-mRNA allowing the targeting of intracellular targets revealed by peptide presentation on MHC[7].

Once better established, LNP-mRNA technology may also provide a work around to the CMC issues that can limit productivity in biologics discovery by facilitating *in vivo* production of certain complex biologics that may have non-ideal properties for efficient fermentation or formulation as an infusion product in protein form.

The final LNP-mRNA products covered by this article are *in vivo* CAR-Ts. Many former oncology-focused cell therapy companies are pivoting to auto-immunity, aiming to use lentiviral vectors to transduce patient T cells *in vivo* to recognise the CD19 surface antigen, depleting B cells in the hope of inducing an immune reset. Clearly, lentiviral transduction is a permanent modification, providing a patient's immune system with an ongoing ability to delete B cells, which may last six months to many years. If a short duration B cell depletion is sufficient for an immune reset, then *in vivo* delivery of LNP-mRNA encoded CD19-CAR-T constructs may have a significant advantage. Moderna's mRNA-6007 is one of several products exploring this area.

It should be noted, however, that sufficient B cell depletion for an immune reset can be achieved by delivering an LNP-mRNA encoded CD19 targeted T cell engager xCD3 to the liver and driving secretion of the recombinant protein. This approach is being explored by Abogen Therapeutic's ABO2203 which recently reported data from three refractory secondary immune thrombocytopenia patients, who were treated with no more than four doses of the product. Abogen reported rapid and complete peripheral B cell depletion (and sustained B-cell depletion in bone marrow), which allowed durable platelet recovery[8].

Summary

LNP-mRNA technology is now being deployed beyond its initial clinical breakthrough in infectious disease vaccines, to various vaccine approaches in oncology and now to the *in vivo* generation of biologics and cell therapies. It's not yet clear where the technology will deliver the biggest benefits to patients over other modalities, but its potential speed to the clinic is going to enable it to compete in many of the next decade's races to deliver approved therapeutics for unmet needs in multiple therapeutic areas.

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