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COVID-19 Promise Fulfilled, But Where Next For mRNA Vaccines?

by Alex Shimmings

After a baptism of fire during the coronavirus pandemic, mRNA vaccine technology has earned its stripes. In less than a year, mRNA vaccines have been catapulted from interesting pipeline prospects to game-changers in the fight against COVID-19. But what does this success mean for the future of the technology?

Before the COVID-19 pandemic hit, messenger RNA (mRNA) vaccine technology was long on promise but short on evidence and there was no expectation of that changing in the near future.

Fast forward 12 months and what had been touted as the technology's advantages – nimbleness of response to a new threat, speed of manufacture, potent immunogenicity – have all been confirmed by the rapid development and approval of the first two COVID-19 vaccines from two of the field's leading players. Never before have vaccines been brought to market so swiftly.

Response rates of more than 90% to *BioNTech SE*/*Pfizer Inc.*'s Comirnaty and *Moderna, Inc.*'s COVID-19 vaccine were both a ringing endorsement for the technology's potential and a huge boost to the worldwide pandemic response. With proof of concept established in such a high-profile fashion, and with the successful manufacture and roll out of millions of doses now underway, surely the technology has the world, and not just that of infectious diseases, at its feet?

Its cheerleaders certainly believe so. "We get asked quite often 'How could a team of 1,000 people go from the novel virus sequence online to an authorized product with 94% efficacy for COVID-19 in just 11 months?'" Moderna CEO Stéphane Bancel told January's J.P. Morgan Healthcare meeting. "Before, we believed that mRNA might work and might deliver a safe medicine approved. Now, we know this is possible."

Franz-Werner Haas, CEO of the third leading mRNA company, *CureVac NV*, agrees. "The pioneering work in the mRNA technology that our founder Dr. Ingmar Hoerr has started more than 20 years ago has now reached a high level of maturity especially in the vaccine field," he said. "We are confident that this approach is an important contribution not only to the current situation, but also to global medical challenges of the future."

COVID-19 has undoubtedly been transformative for mRNA vaccine technology, and for its leading companies, which are now in the enviable position of deciding how to spend unexpected windfalls from vaccine sales and pandemic-propelled investments (Moderna alone is expecting $11.7bn in COVID vaccine revenues this year). Future plans involve expanding on its promise not only in infectious diseases but also in cancer immunotherapy and even autoimmune disease.

But, in parallel, the pandemic has laid bare some of the technology's drawbacks – the extremely cold conditions that the COVID-19 vaccines need for storage being the most well-known. Emergency use authorizations aside, clear regulatory paths to market are still needed and, most importantly, it is still to be seen how durable the immune responses will be to these first mRNA inoculations.

Companies Big And Small

The last year has wrought many changes in the field as a whole. R&D in mRNA vaccines intensified as more companies entered the field, but the three pioneer firms – BioNTech, Moderna and CureVac – still tower over the scene. New research by Pharmaprojects shows that the trio is involved in the development of half of the entire mRNA vaccine pipeline. The total number of companies now stands at 35, with 15 of these having more than one candidate in development (*see Exhibit 1*).

Many of the smaller outfits arrived with the coronavirus. "The 'plug-and-play' nature of mRNA vaccine production, which unlike traditional vaccines does not require unique infrastructure for each development program, means the technology is viable for smaller biotech players in the field to expand their presence," commented Pharmaprojects analyst Shardha Millington.

Of the big pharma firms currently in the game, most were early adopters having already invested in mRNA vaccines via collaborations with the biotech specialists. Pfizer leant on its existing 2018 mRNA flu vaccine deal with BioNTech when the two pivoted to COVID-19; *Sanofi* expanded its 2018 deal with TranslateBio last year; as did *GlaxoSmithKline plc* with CureVac in February 2021. These deals further emphasize the field's growing importance to companies with large vaccine franchises to protect. *Merck & Co., Inc.* and *Takeda Pharmaceutical Co. Ltd.* are two other big pharma names with mRNA vaccines research partnerships under way.

Exhibit 1.

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Therapeutic Spoils

The Pharmaprojects analysis shows that for all the mRNA vaccine technology's broad future potential, it is for now COVID-19's moment. "Despite COVID-19 only arriving on the scene at the end of 2019, 28% of mRNA vaccines across all stages of development are targeting SARS-CoV-2," noted Millington (*see Exhibit 2*).

Exhibit 2.

Click here to explore this interactive content online

With the past year's media focus, it is easy to forget how nascent this field is. Pharmaprojects shows that out of the 74 mRNA vaccine programs in the pipeline, 67% are still in preclinical development, and most of the rest are still at Phase I. Moderna's and Pfizer/BioNTech's COVID-19 vaccines truly leapfrogged to market.

Before COVID-19, another pandemic threat – influenza – was the most popular viral target for mRNA-based vaccines, and by some way. Other viruses are in the mix: the most advanced candidate is a cytomegalovirus (CMV) prophylaxis program from Moderna, which is poised to enter Phase III.

Infectious diseases overall remain the main focus of mRNA vaccine development, accounting for 76% of all candidates, and non-viral pathogens are also in the technology's sights: CureVac has a preclinical-stage mRNA vaccine project for malaria, and Translate Bio has a preclinical program in collaboration with Sanofi directed at bacterial infections.

> ***Another attraction is the improved prospect of success in developing mRNA vaccines against the many diseases that have long held out against more traditional technologies, such as CMV and EBV.***

Moderna especially sees a lot of potential in infectious diseases, particularly now that the technology has been de-risked to a large extent.

“Because mRNA is an information molecule, we believe there'd be a much higher probability of technical success of a drug starting in the clinic to getting approved,” said Bancel. “For example, our CMV vaccine uses exactly the same chemistry, the same formulation, the same manufacturing processes as our COVID-19 vaccine which got authorized, same thing for the flu vaccine and so on.”

Determining the genomic sequence of a virus is quick and cheap to do and so a new mRNA-based product can be turned around very quickly, Bancel added. “Because we had nine vaccines in humans before COVID-19, we were able in only 48 hours to optimize the product, design the product, and then start making the product at GMP scale. And then, if you do it for one modality, you can replicate the same model for many more modalities over time.”

Another attraction is the improved prospect of success in developing mRNA vaccines against the many diseases that have long held out against more traditional technologies, such as CMV and the Epstein Barr virus (EBV, the cause of mononucleosis).

Indeed, companies in the field have little interest in the traditional pediatric vaccine market, eyeing up instead areas of unmet need. More than 80 viruses have been identified in the past 40 years but only 4% have a licensed vaccine, providing much scope.

Moderna is developing four first-in-class vaccines against respiratory diseases that include more than one mRNA strand to really prime the immune system response. Its CMV vaccine includes six mRNAs, the EBV vaccine has five and its combination vaccine against the common childhood respiratory tract infections, human metapneumovirus (hMPV) and parainfluenza virus 3 (PIV3), targets two distinct viruses.

BioNTech’s CEO Ugur Sahin told the 2021 J.P. Morgan meeting that his firm was working on HIV and tuberculosis vaccines with Pfizer, and had six undisclosed infectious disease programs, due to enter clinical testing in the next year or two.

The sales potential here could be significant. “What is the real size of the total addressable market for vaccines if one was able, thanks to a technology like mRNA, to develop a lot of vaccines for high unmet medical need?” asked Bancel. “In 2019, the worldwide vaccine revenues was $35bn. How big do you think that market could be five, 10 years from now if one was able to develop a lot of infectious disease vaccines?” Moderna believes its CMV vaccine alone could peak at $2bn-$5bn in annual sales.

Influenza is the exception to the new virus rule, and analysts say this makes sense – mRNA vaccines could well prove disruptive to this $5bn/year industry. Current products have low efficacy levels (around 50%) mainly because the long manufacturing lead times for current egg-based production leave too much room for antigenic drift to occur. Moving to an mRNA vaccine

technology would mean a faster response to new strains and, if the experience with coronavirus is anything to go by, could also provide higher response rates in the elderly who are most at risk from the disease. Moderna, BioNTech and TranslateBio each have flu vaccines in their pipelines.

Cancer Calling

One of the beauties of the mRNA vaccine technology is that it can be pitted against more than just microbes, and cancer is the other big area of promise.

mRNA vaccines can set a cancer patient's own cells to work in producing tumor (rather than pathogen) antigens, which again are presented to the immune system on the cell surface. In cancer, where the disease's *modus operandi* is to evade the immune system, this is expected to be useful in boosting the body's ability to recognize and kill tumor cells. Moreover, an mRNA vaccine can also be made to produce more than one antigen at a time.

At the moment, mRNA vaccines are being tested against 11 specific cancer types, although high-prevalence tumors like lung and colorectal cancers predominate (*see Exhibit 2*).

In most of these, the vaccine's mRNA codes for epitopes from known tumor-associated antigens. BioNTech's FixVac platform, for example, uses selected combinations of mRNA to encode cancer-specific shared antigens in melanoma, prostate and breast cancer, and also has one candidate where cancer and viruses overlap – HPV16-positive head and neck cancer.

But there is scope to make bespoke vaccines. "The particularly exciting prospect here is that this nucleic acid-based tool lends itself well to highly personalized therapeutics, potentially to the level of individual patients," said Pharmaprojects' Millington.

Another of BioNTech's platform technologies, iNeST (or individualized neoantigen-specific immunotherapy) being developed in collaboration with *Roche Holding AG*/Genentech, uses the unique mutational profile of each patient to predict the resulting neoantigens, thus producing tailored, optimized mRNA as an immuno-oncology vaccine.

"Here, the targets are individual mutations," BioNTech's Sahin said. "So that means this is a fully individualized vaccine approach. The vaccine is customized to each individual patient and targets up to 20 neo-antigens per patient."

Technical Issues

The novel technology is not without its issues, however. The main one highlighted during the pandemic was the need for mRNA vaccines to be kept at very cold temperatures placing a high logistical barrier to their distribution. Moderna's vaccine requirement for storage at -20°C where it can be kept for up to six months (equal to most home freezers) is a big improvement on the -70°C needed for Pfizer/BioNTech's Comirnaty stated analysts at Bernstein in a 18 January

research note “but still not ideal for emerging economies.”

Companies are already working on enhancements. Moderna’s other vaccine candidates (CMV, Zika, hMPV/PIV3) can be stored at 5°C for 18 months and have lyophilized formulations – “significant for their commercial potential beyond the pandemic, especially in remote locations,” the analysts added, meaning that their logistical profiles are manageable and unlikely to be a major problem in future.

The storage problem could prove more of an issue for BioNTech (and the other mRNA players), but the analysts said that “If Moderna can solve the problem then we expect others to follow … In fact we would emphasize that COVID has advanced BioNTech's ability to commercialize such treatments given the world will have become far more accustomed to dealing with cold chain issues and will have better infrastructure in place than would have been the case otherwise.” The cold-chain issue will be less of a problem for cancer indications, where BioNTech is most focused.

Sahin said BioNTech was continuing to optimize its formulation, with “ongoing stability testing to update our current formulation and to provide longer stability times. We are working on an improved thermostable formulation which will most likely be available in the second half of 2021. And we are also evaluating other formulations which do not contain PEG.”

Key to solving the problem are new delivery platforms but work still needs to be done to prove them. Lipid nanoparticles are commonly used but novel twists on this are emerging, says Millington. One mechanism in development by pHion Therapeutics uses positively charged proprietary RALA peptides that interact with the negatively charged mRNA load to form highly stable nanoparticles with the additional benefit of low toxicity and immunogenicity. Similarly, Gennova Bio has a proprietary lipid organic nanoparticle (LION) technology which is able to act as an adjuvant.

Regulatory Requirements

Another area where mRNA vaccine technology is in its infancy is regulation. No specific guidance from the US Food and Drug Administration or the European Medicines Agency for mRNA vaccines exists as yet, although the products are clearly deemed safe enough for large clinical trials.

Bernstein analysts believe that the guiding principles that already exist for DNA vaccines and gene therapy vectors are likely to be applied to mRNA as these molecules fall into the broad vaccine category of genetic immunogens; many of these will probably be adapted for mRNA as development of these products continues. “In short, [this is] not a major issue in our minds.”

One hope for the pandemic is that the validation of the vaccine technology so far will mean that

it may be possible to develop and approve vaccines for virus variants without the need for Phase III clinical trials.

Here, Bancel is optimistic. "Regulators have approved a very clear path for flu for example, whereby once you demonstrate Phase III data, the next variant you simply put that in and you show some data for accepted surrogates of protection. My anticipation is that … should the need emerge, the regulatory framework will follow closely behind that."

But Bernstein analysts warned not to expect the rapid development times seen for COVID-19 vaccines to be repeated on the whole. "Though regulators are likely to be more comfortable with mRNA after COVID-19 (as long as nothing untoward occurs), we expect trial timelines to revert closer to normal and thus, all of the candidates are still several years away from reaching the market – even CMV, that is the most advanced, is unlikely to be licensed before 2024."

Durability of response

Perhaps the question that most haunts the field is that of duration of the immune response elicited by mRNA vaccines. As the Bernstein analysts point out: "It is one thing to have strong efficacy soon after dosing, it is another two to three years later." And as yet, these vaccines simply have not had the time to prove themselves long term.

Data from earlier studies by Moderna in flu and CureVac in rabies offer little help in this regard but there will be plenty of clinical and real-world data coming from the COVID-19 vaccines that should put some of this uncertainty to rest. The next few years should give a clearer picture of where exactly the field is going.

Find more information on the Pharmaprojects research