COVID-19 may become nanomedicine's finest hour yet

The nanotechnology-enabled mRNA-based vaccine platform recently approved against COVID-19 bears hope for improved vaccine development and trialling capacities in low- and middle-income countries as part of a broader global public health agenda.

Steffi Friedrichs and Diana M. Bowman

For over a year now, the COVID-19 pandemic has caused havoc the world over, killing thousands of people every day, and threatening the lives and livelihoods of millions of others. At the time of writing this commentary, over 2.7 million COVID-19 deaths had been recorded globally[1], with an estimated 4.5% shrinkage in global gross domestic product[2]. If there ever was a silver lining, it is the unique demonstration of responsible research and innovation around the globe that has enabled the rapid scientific assessment of the virus, its characteristics, epidemiology and its pathobiological effects, and the open sharing of the respective results, as well as the rapid development, authorization and manufacture of numerous vaccines at unprecedented speed, marking an unparalleled hand-in-hand collaboration in the "triple helix of government–industry–university interactions"[3].

It would, however, be wrong to pretend that this formidable showcasing of mission-oriented research and development (R&D) of COVID-19 vaccines, which to this date provided 15 vaccines to the World Health Organization Emergency Use Listing/Prequalification evaluation process was anything else than an empirical exercise in itself[4]. Indeed, the R&D of those vaccines has been as unpredictable as the specifics of the SARS-CoV-2 virus and its spread around the world; while public health officials and others had been warning of a forthcoming global pandemic, nobody was able to foresee the exact details and timeline of either the virus or a vaccine against it.

Predictions based on reasoning and pragmatism

In April 2020, an editorial published in this journal listed five companies and organizations that had announced that they were actively working on potential COVID-19 vaccine candidates, noting that 'it may still take a year to 18 months to achieve the production and distribution of vaccines (the race against COVID-19)'[5]. Of these, however, only two have by now made it onto the World Health Organization Emergency Use Listing/Prequalification list[4]. By August 2020, a *Nature Nanotechnology* Editorial highlighted the role of nanotechnology in the development of COVID-19 vaccines[6], pointing out that the biomimetic capabilities (that is, the ability to design and synthesize virus-like particles for targeted drug delivery and advanced biotechnology applications, such as cancer nanovaccines, immunoengineering and rapid-response sensors) afforded nanotechnology a unique position in pre-clinical and clinical COVID-19 research. In the same Issue, Shin et al. found that of the 16 vaccine candidates known to be in clinical development at the time only 4 were using nucleic acid-based functionality (that is, DNA or messenger RNA (mRNA) vaccines)[7]. The authors predicted that "[w]hile these platforms are attractive in terms of safety, speed, stability and scalability, they carry a significantly higher risk of failure in clinical development as seen previously with other novel technologies"[7].

The innovative underdogs are first past the post

In November 2020, the first two tailor-made COVID-19 vaccines by Moderna/National Institutes of Health (NIH) and Pfizer–BioNTech reported their successful (preliminary) results of phase III clinical trials with 94.5% and 95% efficacy, respectively. These vaccine candidates were not based on the well-known and widely employed live-attenuated vaccine or inactivated vaccine design, but rather on the new class of mRNA-based technology. The subsequent approval of the Pfizer–BioTech vaccine in December by the United Kingdom's Medicines and Healthcare Products Regulatory Agency represented a significant milestone for the mRNA-based vaccine platform, as it had never before been approved for use in vaccines[6,8]. The significance of this 'first' cannot be understated and has not been lost on those in the nanomedicine community.

While some commentators and public health experts may have been surprised by this 'first' in terms of regulatory approval, vaccine developers had recognized mRNA-based technologies as an advent to 'a new era in vaccinology' for some time[9]. Despite the technology's novelty, there was a growing body of evidence that mRNA vaccines could be designed to exhibit enhanced safety, efficacy and effectiveness, specificity and long-lasting antiviral response, compared to conventional vaccines[9,10], supported by an increasing number of authorizations for their clinical trials by both the European Medicines Agency and the US Food and Drug Administration[9]. Indeed, in May 2020, the Coalition for Epidemic Preparedness Innovation described that an ideal platform technology to address "a newly emerging epidemic disease, such as COVID-19 […] would support development from viral sequencing to clinical trials in less than 16 weeks" and found that RNA platforms were among those with the greatest potential to reach this speed (https://cepi.net)[11].

Enter nanomedicine

While the advent of this new era in vaccinology is the result of the directed, gradual progress of multiple advanced technologies, nanotechnologies play a significant part in several crucial steps of the development and application of both mRNA-based medicine in general, and the ideal vaccination technology platforms described by the Coalition for Epidemic Preparedness Innovation in particular: as advanced biotechnologies enable rapid genome sequencing and targeted genome editing, bioinformatics capabilities build an understanding of biological matter and an interdisciplinary language to copy and mimic it, nanotechnologies provide the ultimate translational tools to both analyse

and assemble matter of the required shape and nanoscale size to provide tailor-made, benign vehicles for advanced vaccines and therapeutics. This biomimetic capacity of nanotechnologies helped overcome the problems of the low stability, the tendency to trigger immune responses, and the lack of efficient delivery systems of the initial mRNA-based medicines[12]. In the case of mRNA vaccines for COVID-19, the functional mRNA molecule is protected and transported by a lipid nanoparticle shell consisting of the same sort of molecules that form the human cell, into which it needs to enter, in order to trigger the response that creates an immune response[13].

Nanomedicine's coming of age as a global health tool

While we are not suggesting that nanotechnology-based vaccines are the panacea for eliminating all viruses, whether it be Ebola or the seasonal flu, the rapid development processes by the vaccine developers and the fast-track approval by the regulatory agencies that we have seen over the past year in response to COVID-19 suggest that nanomedicine has the potential to play a significant role in addressing some of the most pressing population health challenges faced by low-income countries. Importantly, these solutions will not just be vaccines powered by nanotechnology but rather applications that range from drug delivery platforms through to robust lab-on-a chip devices[14].

In addition to the advantages that nanotechnology platforms provide to the design and rapid implementation of modern disease prophylaxes, nanomedicine also harbours immense value for early detection of the virus and discovery and development of therapeutics to treat the resulting infectious diseases[15]. For example, the anti-inflammatory corticosteroid dexamethasone, which had originally been formulated as a nano-based drug for the treatment of multiple myeloma[16] has recently been shown to reduce "death by up to one third in hospitalized patients with severe respiratory complications of COVID-19"[17].

One of the biggest advantages of RNA nanomedicine platforms in addressing pressing global health challenges is their inherent short set-up and delivery time, flexibility and affordability by virtue of being based on chemical processes, rendering the development (and adaptation) of a vaccine (to mutations) and the scale-up of its production significantly faster than that of the traditional vaccines that rely on the isolation and culturing of the respective virus. But while recombinant protein productions can be carried in a variety of platforms[7], it is the manufacturing step of the vaccines that now provides a major bottleneck to the scale-up of vaccinations in those countries where the currently approved 10 vaccines have received approval, because the building of manufacturing capacity of novel vaccine technology platforms requires both bespoke design and investment that can be shouldered by some high-income countries (or through sophisticated consortium approaches) only. This scale-up planning and implementation, however, needs to be done with the requirements of low- and medium-income countries in mind, in order to obtain both the best short-term response to the current pandemic, as well as the best proactive preparation for the (zoonotic) pandemics that are predicted to follow.

Emergency authorizations are used with the upmost discretion, and the regulatory threshold is high: most commonly the declaration of a public health emergency and then they only apply to the jurisdiction in which the declaration is made. As such, we are unlikely to see regulators using this tool on a more regular basis for more localized, and less deadly outbreaks of disease, despite what we have witnessed in response to COVID-19. But the experiences that have been gained are nevertheless a formidable pointer to both the needs and possibilities in fast-tracking vaccine R&D and authorization, especially with a view to more localized outbreaks of diseases in low- and middle-income countries, in which regulators now have familiarity with the new platform. Now that the more versatile and affordable nanomedicine platform has seen its first approvals, efforts to sustainably vaccinate the world against this current pandemic and simultaneously strengthen resilience against similar future crises is needed.

It may be expected that vaccine developments in less urgent cases may dedicate a more targeted approach to reaching the best possible distribution and administration route[7] especially with regard to vaccination needs in low-income countries, in which individuals are "far more likely to die of communicable disease than a noncommunicable disease"[18]. For mRNA nanomedicine vaccines to be successfully adopted in these countries, the vaccines must be improved to be more robust and less dependent on cold-chains. This would also benefit the distribution and administration logistics in high-income countries, where the approved Moderna/NIH and Pfizer–BioNTech vaccines, which require storage at −20°C and −70°C, respectively, threw governments around the world into a new a life-or-death race to not only secure millions of doses of vaccines, but to also put in place the necessary public health infrastructure to vaccinate their citizens en masse.

While the retrospective assessment of nanomedicine's moment of glory in times of a pandemic that mobilized unprecedented global efforts in science, technology and innovation can hardly be regarded as a universal performance indicator, it is more than reasonable to assume that the success of nanomedicine in both prophylaxes and treatment of infectious diseases will have numerous spill-over effects that establish nanomedical alongside biotechnological approaches as core capabilities in the fight against infectious diseases.

For many, this 'coming of age' story has been decades in the writing and is very different to what they were expecting: when Doxil, the first nanodrug was approved by the Food and Drug Administration in 1995, many commentators believe that nanomedicine would revolutionize the detection and treatment of many cancers[19]. While the list of approved nanotechnology-based cancer drugs grows, it continues to be described as being "largely still in the development phase"[20]. Developing safe and effective cancer treatments is expensive and time consuming, with a complex pathology and an ever-moving target, which is made even more difficult with proof of efficacy over an incumbent protocol needing to be shown. This is a hurdle that neither Moderna nor Pfizer–BioNTech had to clear, as they raced to get emergency authorizations for their vaccines.

While there is much uncertainty about how this next generation of nanotechnology-enabled vaccines may be deployed in the future, the advances made over the past year suggest that the field of nanomedicine has now come into its own, and with it comes significant promise for addressing other leading causes of morbidity and mortality globally. Nanotechnology and nanomedicine, in particular, have rightly earned their place in the spotlight, suggesting that nanotechnology-enabled vaccines may provide the cornerstone for addressing other pressing global health challenges going forward. ❐

Steffi Friedrichs[1]✉ and Diana M. Bowman[2]
[1]*AcumenIST, Brussels, Belgium.* [2]*Sandra Day O'Connor College of Law, Arizona State University, Phoenix, AZ, USA.*
✉*e-mail: steffi@acumenist.com*

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References

1. Covid-19 data in motion: Thursday, 4 March. *John Hopkins Coronavirus Resource Center* https://coronavirus.jhu.edu (2021).
2. Impact of the coronavirus pandemic on the global economy - statistics & facts. *Stastista Research Department* https://www.statista.com/topics/6139/covid-19-impact-on-the-global-economy/ (2021).
3. Owen, R. & Pansera, M. in *Handbook on Science and Public Policy* (eds Simon, D. et al.) 20–48 (Edward Elgar Publishing, 2019).
4. *World Health Organization Status Of COVID-19 Vaccines Within WHO EUL/PQ Evaluation Process* Guidance document (WHO, 2021); https://go.nature.com/38KrFiR
5. *Nat. Nanotechnol.* **15**, 239–240 (2020).
6. *Nat. Nanotechnol.* **15**, 617 (2020).
7. Shin, M. D. et al. *Nat. Nanotechnol.* **15**, 646–655 (2020).
8. *Nat. Nanotechnol.* **15**, 963 (2020).
9. Pardi, N. et al. *Nat Rev Drug Discov* **17**, 261–279 (2018).
10. Huang, L. et al. *Asian J. Pharm. Sci.* https://doi.org/10.1016/j.ajps.2020.08.001 (2020).
11. Lurie, N., Saville, M., Hatchett, R. & Halton, J. *N Engl. J. Med.* **382**, 1969–1973 (2020).
12. Xiong, Q. et al. *Nano Res.* **11**, 5281–5309 (2018).
13. Jones, R. Nanomacines come of age with mRNA vaccine. *Soft Machines* http://go.nature.com/3cGud2F (2020).
14. Li, J., Zeng, M., Shan, H. & Tong, C. *Curr Med Chem.* **24**, 2413–2422 (2017).
15. Moitra, P., Alafeef, M., Dighe, K., Frieman, M. B. & Pan, D. *ACS Nano* (2020).
16. An evaluation of the safety of Oncocort IV pegylated liposomal dexamethasone phosphate in patients with progressive multiple myeloma (AMETHYST). *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03033316 (2017).
17. *Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19* (University of Oxford, 2020); https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf (2020).
18. The top 10 causes of death. *World Health Organization* https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (2020).
19. Kawasaki, E. S. & Player, A. *Nanomedicine* **1**, 101–109 (2005).
20. Current nanotechnology treatments. *National Cancer Institute* https://www.cancer.gov/nano/cancer-nanotechnology/current-treatments (2017).

Competing interests

The authors declare no competing interests.