Vaccine and drug trials in the COVID-19 pandemic: lessons for India

Alok Bhattacharya, Sudha Bhattacharya and Viswa Mohan Katoch

The Coronavirus pandemic has caught most countries off guard, unprepared to handle a fast-spreading viral infection with a high rate of fatality and absence of any prophylactics and preventive agents. It has made it clear that a strong scientific base with access to novel technology platforms, trained scientific manpower and flexible regulatory systems are required to fight such infections and prevent future infections to go out of control. Developing the scientific and technology base could have a ripple effect in fighting several other incurable diseases, such as many forms of cancer and genetic disorders.

China alerted the World Health Organisation (WHO) on 31 December 2019 about the surge of pneumonia-like cases in Wuhan. By 9 January 2020, it was shown to be due to a novel virus, which was named severe acute respiratory syndrome Coronavirus 2. The sequence of the entire novel coronavirus genome was announced and was made available by 10 January 2020 (ref. 1). A potential vaccine for this virus was ready by 5 February 2020 and recruitment of volunteers was initiated for the study (trial accession no. NCT04283461, clinical trials.gov). This vaccine is based on mRNA platform technology developed by the biotech company Moderna, and the trial is being done in collaboration with NIAID, USA. Two other mRNA-based vaccine candidates for coronavirus are from the leading European companies BioNTech and CureVac[2], who are close to initiating human patient trials with their products. The speed (42 days) at which new potential vaccine candidates based on mRNA technology was developed requires special mention. The idea of using mRNA is conceptually simple. Since mRNAs code for proteins, the introduction of cognate mRNA coding for a target antigen allows synthesis of the antigen proteins *in situ*, stimulating an immune response. However, there are many hurdles in mRNA technology. RNA molecules are prone to degradation, stimulate the innate immune system and need to be delivered to the right cells in the body. The companies listed above have circumvented most of these problems as they have been developing their technology platforms over a period of time, enabling them to come out rapidly with a novel product.

Another potential vaccine candidate that has entered phase I trial in China is CanSino's Ad5-nCoV, which uses adenovirus-based viral vector vaccine platform (trial accession no. ChiCTR2000030906)[3]. The adenovirus-based platform is also being used by the Oxford Vaccine Group in collaboration with the Jenner Institute of Oxford University[4]. Recruitment for the trial has already started. Both the Chinese and Oxford groups have been developing this platform for the last few years and have been successful in developing an effective vaccine against Ebola.

Gene delivery platforms are being increasingly used to develop vaccines and new therapies[5,6]. Some of these viral and non-viral platforms are safe and effective. Among these, adeno-associated viruses have emerged a potential delivery system for vaccines as also genes and therapeutic molecules for genetic disorders. Gene editing systems also have high potential for therapeutics and diagnostics. These therapeutic platforms require well-standardized technologies, which include vectors with low toxicity and low immunogenicity, high stability and high level of expression in target tissues. There is a specific need for manufacturing facilities that can produce a large number of doses in a short time along with rapid mechanisms to test efficacy and toxicity for different batches. Once in place, these platforms can be used for other diseases including cancer and genetic disorders.

Vaccines using the conventional route through live-attenuated or killed viruses are also being developed[7], in addition to recombinantly expressed viral coat proteins as subunit vaccines. Conventional vaccines, generated by attenuating or inactivating the pathogen, have been used successfully in the past. However, there is a risk of reversion in the case of live attenuated vaccines. Moreover, the organisms must be characterized before embarking on such a venture. Inactivation may not always induce protective responses and could cause more damage. The examples are Ebola[8] and formalin-inactivated respiratory syncytial virus (RSV)[9]. Such vaccine production requires the cultivation of pathogen on a large scale. Not all pathogens are amenable for cultivation in large cultures. Hence, new and highly versatile approaches that are independent of whole pathogen cultivation are required to effectively and quickly combat outbreak situations[10]. Generating strong immune response is one desirable goal of a vaccine; however, hypersensitivity could lead to an aggravated response with or without cytokine storm. For example, the candidate vaccines for RSV infections were not successful in clinical studies[11]. Safety issues have also been associated with viral vaccines, such as influenza where vaccine-induced encephalitis has been seen in elderly patients[12]. It is also well known that many viruses evolve rapidly due to high rate of mutations and/or recombination. It is likely that vaccines and drugs developed at a given time may not be protective or efficacious during future pandemics[13,14].

Ab initio approaches for vaccine design are also being used for the Coronavirus. Mostly these use a 3D structural model of the virus and key viral proteins. Since experimental determination of structure may take a long time, vaccine developers are relying upon accurate computationally predicted structures. Recently DeepMind released the structure of the viral proteins to spur drug and vaccine development[15]. University of Cambridge and DiosynVax are working towards a structure-based targeted vaccine that will have very low side effects and could block entry of the virus[16].

India is one of the largest vaccine producers (both animal and human) in the world with facilities to manufacture both conventional and subunit vaccines. A

novel rotavirus vaccine was developed and produced here after decades of work[17]. Currently there are two attempts to make anti-COVID-19 vaccine in India, one from Zydus-Cadilla and the other from Serum Institute in collaboration with the US-based Codagenix. Based on available reports it appears that clinical trials for these vaccine candidates could be months away. In a pandemic situation being faced currently, we need to have technology already in place so that a quick response is possible. We can consider this situation similar to war for which the country is kept ready to mount a quick response at all times. There is dire need to form multidisciplinary scientific teams quickly with rapid fund mobilization and administrative approvals so that work can start immediately to find scientific solutions. Overall a major investment through budgetary and administrative support for science is required so that our scientists can prepare us for any eventuality. The funding required is miniscule compared to the economic and human losses that we are going through. In addition, once the pandemic subsides, the infrastructure created can be utilized to tackle major unsolved problems that are currently in the background. Some of these are consequences of climate change, food security, clean energy and water that require our urgent attention. Moreover, there are several other diseases (genetic disorders, some forms of cancer, drug-resistant tuberculosis) for which there are no treatments. We should not forget about these patients who are facing death and disability every day. Once this pandemic is over and the country has spent some funds on COVID-19 research, we should not go back to a lull and wake up when there is another pandemic. Scientific and technologic preparedness can only come through continuous and ongoing commitment.

1. Holmes, E., http://virological.org/t/initial-genome-release-of-novel-coronavirus/319
2. https://www.statnews.com/2020/03/19/an-updated-guide-to-the-coronavirus-drugs-and-vaccines-in-development/
3. https://www.fiercepharma.com/vaccines/china-s-cansino-pushes-coronavirus-vaccine-into-clinical-testing-as-moderna-doses-1st
4. https://economictimes.indiatimes.com/news/international/world-news/oxford-university-begins-enrolling-over-500-volunteers-for-coronavirus-vaccine-trial/articleshow/74864754.cms?from=mdr
5. Saroja, Ch., Lakshmi, P. and Bhaskaran, S., *Int. J. Pharm. Investig.*, 2011, **1**, 64–74.
6. Dubensky Jr, T. W., Liu, M. A. and Ulmer, J. B., *Mol. Med.*, 2000, **6**, 723–732.
7. https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf?ua=1
8. Richardson, J. S., Dekker, J. D., Croyle, M. A. and Kobinger, G. P., *Hum. Vaccin.*, 2010, **6**, 439–449.
9. Acosta, P. L., Caballero, M. T. and Polack, F. P., *Clin. Vaccine Immunol.*, 2015, **23**, 189–195.
10. Rauch, S., Jasny, E., Schmidt, K. E. and Petsch, B., *Front Immunol.*, 2018, **9**, 1963.
11. Neuzil, K. M., *Clin. Vaccine Immunol.*, 2016, **23**, 186–188.
12. Machicado, J. D., Bhagya-Rao, B., Davogustto, G. and McKelvy, B. J., *Clin. Vaccine Immunol.*, 2013, **20**, 1485–1486.
13. Thor, S. W., Hilt, D. A., Kissinger, J. C., Paterson, A. H. and Jackwood, M. W., *Viruses*, 2011, **3**, 1777–1799.
14. Shi, M. *et al.*, *Nature*, 2018, **556**, 197–202.
15. https://deepmind.com/research/open-source/computational-predictions-of-protein-structures-associated-with-COVID-19
16. http://diosvax.com/covidresponse
17. Nair, N. P. *et al.*, *BMJ Open*, 2019, **9**, e024840.

ACKNOWLEDGEMENT. S.B. and V.M.K. thank INSA and NASI for fellowships respectively. A.B. thanks Ashoka University for support.

Alok Bhattacharya and Sudha Bhattacharya are in the Ashoka University, Sonepat 131 029, India; Viswa Mohan Katoch is in the NASI-ICMR Chair on Public Health Research at Rajasthan University of Health Sciences, Jaipur 302 004, India.*
**e-mail: alok.bhattacharya@gmail.com*

Can sulphated polysaccharides from seaweed provide prophylactic and/or therapeutic solution to COVID-19 pandemic?

Ashish Kumar Jha, Suseela Mathew and C. N. Ravishankar

The novel Coronavirus or severe acute respiratory syndrome virus or SARS-CoV-2 has spread throughout the world in a very short period. Till date, there is no approved medicine or pharmaceuticals product found to be effective against COVID-19. Sulphated polysaccharides from seaweed possess antiviral, anti-inflammatory, anticoagulant, antinociception, antitumor, antiallergic and immunological activities which can be useful to fight Coronavirus COVID-19 pandemic.

Coronavirus is an enveloped virus with a positive sense single stranded RNA as its genetic material. The name corona comes from peculiar crown-like spikes over its outer surface. The novel Coronavirus or severe acute respiratory syndrome Coronavirus or SARS-CoV-2 is a new Coronavirus that originated in Wuhan, China in December 2019 and has soon spread throughout the world. As it is an etiological agent for Corona Virus Disease-19 (COVID-19), a contagious disease which can spread from person to person, the World Health Organization declared it as pandemic and a public health emergency. COVID-19 is characterized by mild to a severe disorder of the upper respiratory tract which can even manifest severe interstitial pneumonia and acute respiratory distress syndrome (ARDS)[1]. Though it is believed