Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Preclinical Evidence Supporting the Potential of Nanotechnology in Improving COVID-19 Vaccine

Dibya Sundar Panda*

Pharmaceutics Department, College of Pharmacy, Jazan University, Al Jazan 72388, Sakaka, Saudi Arabia

1. Introduction

The boon of biomedical research is vaccine. Vaccine is an economical means of protecting people’s life from infectious diseases. The vaccines must be safe, stable and effective in developing required level of immunity for a long period of time with minimum doses (Ada, 1991). Many approaches has been applied in developing vaccines for COVID-19, which are as follows:

- Attenuated virus devoid of virulence with sufficient antigenicity.
- Vaccines containing parts of protein or protein shell, simulating COVID-19 virus, and producing immune response safely.
- Viral vector vaccines, work as a stage for protein synthesis of coronavirus mediating immune response safely.
- RNA and DNA vaccines, genetically engineered nucleic acids, which synthesizes protein mediating quick immune response safely.

RNA and DNA vaccines are capable of developing immunity against specific pathogen with less chance of infection economically. Many challenges lies in delivering them to the site of action along with other immunogens as a part of vaccination regimen. They are like untimely destruction of molecules and failure in converting into working immunogen (Donnelly et al., 2005). Protein containing vaccines are effective against infectious caused by Haemophilus influenza type b, diphtheria, tetanus, acellular pertussis, meningococcus and pneumococcus (Skibinski et al., 2011) but need adjuvant to fortify their immunogenicity, and suffer from early destruction. The aforementioned drawbacks can be encountered with the use of effective delivery system, that can deliver the vaccine at the target site along with adjuvant if needed, protecting it from the degradation in hostile environment. The delivery system should produce lingering immunogenic effect without any side effects. Nano delivery systems could fulfill the above requirements and can exhibit sustained release of the vaccine molecules without getting harmed by proteases. Surface adsorption enables cognate surface receptor interaction (Means et al., 2003). Using nano carriers for vaccine molecules enhances cellular uptake leading to potentiation of innate, humoral, cellular and mucosal immune responses (Pati et al., 2018). Currently approved Covid-19 vaccine for use are given in Table 1.

Nano particle vaccine are effective, safe and easy to prepare. Attenuated virus vaccine are more effective in comparison to vaccines containing parts of virus but has a lengthy production time, needs storage at subzero temperature and has the risk of side effects. Nucleic acid (RNA and DNA) containing vaccines are quick to produce but costly and may need more than one dose.

There are earlier reports about the successful use of self-assembled nano carrier for delivery of m-RNA vaccine ensuring optimized cellular fate and immunity activation (Kim et al., 2021; Shin et al., 2020), have substantiated that nano carrier are ideal in delivering the antigen as they resemble the virus structure and the first m-RNA vaccine launched for clinical trial was encased in lipid nanoparticle. Nano technology can help in cellular delivery of mRNA vaccine bypassing many barriers including the endosomes (Wu and Li, 2021). DNA vaccines could be more efficient in terms of stability, solubility, immunogenicity upon delivering as nanoparticles (Lu et al., 2020). Nanotechnology intervened DNA and RNA vaccines could elicit both humoral and cell based immunity (Dong et al., 2020).

There are reports about the successful immune response of nanoparticle vaccines for COVID-19 in mice following a single dose. The researcher are making efforts to ease its storage condition by preparing them in freeze dried form, which will facilitate its transport (Stanford University, 2021).

2. Nano Particles of Spikes

SARS-CoV-2, spike protein is bigger in size, researchers are attempting to condense it which will be easy and convenient to use. The vaccine has been prepared by combining condensed spike with ferritin nanoparticles tested before in humans.

Researchers have tested the condensed spike nanoparticles along with another four candidates nanoparticles containing full spike, full or part spikes, part of the spike binding to cells during infection in the mouse.

Solo dose of two nanoparticle vaccines produced antibodies double of that seen in COVID-19 infected people, the condensed spike nanoparticle vaccine shown a significantly greater neutralizing reaction in contrast to the binding spike or the full spike containing vaccines. Following the subsequent dose, mice that got the condensed spike nanoparticles vaccine had the utmost levels of neutralizing antibodies (Powell et al., 2021).

3. Preclinical Progress

There is report of about twelve vaccine candidates which are on preclinical study phase, out of which one is based upon self-amplifying
RNA, three on DNA, one based upon glycoprotein nanoparticle for nasal delivery, one is based upon the plant producing viroid particles while rest are vector based or protein based (Soleimampour and Yaghoubi, 2021). Majority of the vaccine candidates in the preclinical trial are based upon recombinant protein subunits, DNA, RNA, others are based on inactivated/attenuated virus, vectors and ptein and T cell based. (Mishra and Tripathi, 2021).

There are several reports about nanotechnology based covid-19 vaccines which are at various stages of clinical trial. Lipid nanoparticles containing mRNA by Moderna has been approved for emergency use in several countries (Jain et al., 2020). ARCoV S1 with receptor binding domain (RBD 319–541) which is also based upon lipid nanoparticles is at phase 1 of clinical trial (Huang et al., 2021). LUNAR-COV19 (ARCT-021) Self-replicating mRNA prefusion spike protein; Lipid-enabled and Unlocked Nucleosomomer Agent modified RNA is in phase 1,2 of clinical trial (Campus et al., 2020). CvnCoV Spike mRNA and NVx-CoV2373 (Novavax) Full-length recombinant S protein of SARS-CoV-2 combined with saponin-based Matrix-M™ adjuvant Virus-like nanoparticle vaccine with saponin-based Matrix-M™ adjuvant are in phase 3 of clinical trial (Lundstorm, 2020). DNA INO-4800 (Inovio) plasmid pGX9501 expressing a synthetic, optimized sequence of the SARS-CoV-2 full length spike glycoprotein DNA coated-poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles by Inovio Pharmaceuticals, International Vaccine Institute, Coalition for Epidemic Preparedness Innovations (CEPI) Phase 2 trial is on hold due to required electroporation device clarifications (Krammer, 2020). CovigineX DNA plasmid with gene for SARS-CoV-2 nucleocapsid P FusogenixTM is formulated with neutral lipids and FAST proteins (fusion-associated small transmembrane) Entos Pharmaceutical Inc., Canadian Institutes of Health Research (CIHR), Research Nova Scotia (RNS), and the Institute for Ageing is in phase IA (Zimmer et al., 2020).

4. Conclusion

Preparation of nanoparticle vaccine can offer many solution to overcome the associated problems of currently approved COVID-19 vaccine.

Acknowledgements

Sincerely acknowledge the librarian for his help.

ORCID

Dibya Sundar Panda, 0000-0002-8986-1100.

References

Powell, Abigail E., Zhang, Kaiming, Sanjal, Mrinmoy, Tang, Shaogeng, Weiden, Payton A., Li, Shanshan, Pham, Tho D., Pak, John E., Chiu, Wah, Kim, Peter S., 2021. A single immunization with spike-functionalized ferritin vaccines elicits neutralizing antibody responses against SARS-CoV-2 in mice. ACS Cent. Sci. doi: 10.1021/acscentsci.0c04165.
Ade G.L., 1991. The ideal vaccine. World J. Microbiol. Biotechnol. 7, 105–109. doi:10.1007/BF00328978.
Campus, E.V.R., Pereira, A.E.S, de Oliveira, J.L., et al., 2020. How can nanotechnology help to combat COVID-19? Opportunities and urgent need. J. Nanobiotechnol. 18, 125. doi:10.1186/s12951-020-00685-4.
Dong, Y., Dai, T., Wei, Y., et al., 2020. A systematic review of SARS-CoV-2 vaccine candidates. Sig. Transduct, Target Ther. 5 237. doi:10.1038/s41392-020-00352-z.
Dowmelly, J.J., Wahren, B., Liu, M.A., 2005. DNA vaccines: progress and challenges. J. Immunol. 175, 633–639. doi:10.4049/jimmunol.175.2.633.
Ilan Jones, Polly Roy, Spurtzik V. COVID-19 vaccine candidate appears safe and effective, January 29, 2021 https://doi.org/10.1016/j.ijid.2020.11.024, Epub 2019 Oct 8. PMID: 31753340.
Jain, S., Batra, H., Yadav, P., Chaud, S., COVID-19 vaccines under current preclinical and clinical studies, and associated antiviral immune response. Vaccines (Basel) 8 doi:10.3390/80601257.
Kim, J., Négier, Y., Gupta, M., Sabah, G., 2021. Self-assembled mRNA vaccines. Adv. Drug. Deliv. Rev. 170, 83–112. doi:10.1016/j.addr.2020.12.014, Mar Epub 2021 Jan 2 PMID: 33400957; PMCID: PMC8733707.
Krammer, F., 2020. SARS-CoV-2 vaccines in development. Nature 586, 516–527. doi:10.1038/s41586-020-2798-3.
Huang, Lanxiang, Rong, Yuan, Pan, Qin, Yi, Krehen, Tang, Xuan, Zhang, Qian, Wang, Wei, Wu, Jiayuan, Wang, Fubing. 2021. SARS-CoV-2 vaccine research and development: conventional vaccines and biomimetic nanotechnology strategies. Asian J. Pharm. Sci. 16 (2), 136–146.
Lu, Y., Wu, F., Duan, W., Mu, X., Fang, S., Lu, N., Zhou, X., Kong, W., 2020. Engineering a “PEG-g-PCL/DNA nanoparticle-in-PLGA microparticle” hybrid controlled release system to enhance immunogenicity of DNA vaccine. Mater. Sci. Eng. C Mater. Biol. Appl. 106, 110294. doi:10.1016/j.msec.2019.11.024, Epub 2019 Oct 8. PMID: 31753340.
Lundstrom, K., 2020. The current status of COVID-19 vaccines. Front. Genome Editing 2. doi:10.3389/fgen.2020.579297.
Means, T.K., Hayashi, F., Smith, K.D., Aderem, A., Luster, A.D., 2003. The Toll-like receptor 5 stimulus bacterial flagellin induces maturation and chemokine production in human dendritic cells. J. Immunol. 170, 5165–5175. doi:10.4049/jimmunol.170.10.5165.
Mishra, S.K., Tripathi, T., 2021. One year update on the COVID-19 pandemic: where are we now? Acta Tropica 214, 105778. doi:10.1016/j.actatropica.2020.105778, Epub 2020 Nov 28. PMID: 32325366; PMCID: PMC7695590.
Pati, R., Shvetsov, M., Sonawane, A., 2018. Nanoparticle vaccines against infectious diseases. Front. Immunol. 9, 2224. doi:10.3389/fimmu.2018.02224.
Shin, M.D., Shukla, S., Chung, Y.H., Bevis, V., Chan, S.K., Ortega-Rivera, O.A., Wirth, D.M., Chen, A., Sack, M., Fukorski, J.K., Steinmetz, N.F., 2020. COVID-19 vaccine development and a potential nanomaterial path forward. Nat. Nanotechnol. 15 (8), 646–655. doi:10.1038/s41565-020-0737-y, Epub 2020 Jul 15. PMID: 32669664.
Skibinski, D.A., Baudner, B.C., Singh, M., O’Hagan, D.T., 2011. Combination vaccines. J. Glob. Infect. Dis. 3, 63–72. doi:10.1007/978-3-77928.
Soleimampour, S., Yaghoubi, A., 2021. COVID-19 vaccine: where are we now and where should we go? Expert Rev. Vaccines 20 (1), 23–44. doi:10.1080/14760584.2021.1875824, Epub 2021 Feb 17. PMID: 33435774; PMCID: PMC7898300.
Stanford University, 2021. ‘Nanoparticle vaccine for COVID-19’. ScienceDaily. ScienceDaily. www.sciencedaily.com/releases/2021/01/210108142138.htm, vaccines8040649 (2020).
Wu, Z., Li, T., 2021. Nanoparticle-mediated cytoplasmic delivery of messenger RNA vaccines: challenges and future perspectives. Pharm. Res. 38 (3), 473–478. doi:10.1007/s11095-021-03015-x, Epub 2021 Mar 3. PMID: 33660201; PMCID: PMC7928182.
Zimmer C., Corum J., Wei, S.L. Coronavirus Vaccine Tracker, https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine

Table 1

| Manufacturer | Vaccine | Type | Number of dose | Time interval | Efficiency% |
|--------------|---------|------|----------------|--------------|-------------|
| Pfizer | BNT162b2 | mRNA | 2 | 21 days | 95 |
| Moderna | COVID-19 Vaccine | mRNA | 2 | 28 days | 94.1 |
| AstaZeneca/SKBio | ChAdOx1S [recombinant] | Chimp panzee adenovirus | 2 | 12 weeks | 82 |
| Serum Institute of India Pvt Ltd | ChAdOx1S [recombinant] | Chimp panzee adenovirus | 2 | 12 weeks | 82 |
| Johnson & Johnson | Ad26 | adenovirus | – | – | 66 |
| Gamaleyka National Research Centre for Epidemiology and Microbiology | (Gam-COVID-Vac) | Heterologous | – | – | 91.6 |
| Beijing Institute of Biotechnology | CanSinoBiO Ad5 | recombinant adenovirus | – | – | 90.07 |

4. Conclusion

Preparation of nanoparticle vaccine can offer many solution to overcome the associated problems of currently approved COVID-19 vaccine.

Ethical approval

Not applicable.

Credit authorship contribution statement

Concept, collection of data, compilation of manuscript solely done by the corresponding author.

Declaration of Competing Interest

Nil.