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Betting on Self-amplifying RNA Shots

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Minimising the dose of RNA required for vaccines will not only lessen side effects, but also the cost and time required to produce doses

India has recently approved its first mRNA vaccine against COVID-19, developed by Gennova Biopharmaceuticals, a subsidiary of Emcure Pharmaceuticals. GEMCOVAC-19 is the first mRNA vaccine developed in India and the third mRNA vaccine to be approved for COVID-19 in the world. The pandemic has undoubtedly brought tremendous momentum to the field of nucleic acid vaccines, in particular messenger RNA or mRNA vaccines, since it offers advantages such as rapid development. Because mRNA can be produced quickly and synthetically, this greatly minimises the time required to manufacture these vaccines.

Over the years, studies have focused heavily on developing DNA rather than RNA candidates, because there were concerns about stability of RNA-based therapeutics. But we saw that DNA vaccines have generally performed poorly in human clinical trials, which has led to a renewed interest in RNA vaccinology for infectious diseases.

However, a big hurdle in the field of the mRNA vaccines has been the efficient delivery of mRNA. While many delivery vehicles have been investigated, lipid nanoparticles (LNP) consisting of an ionisable lipid, phospholipid, cholesterol and PEGylated lipid are the most clinically advanced and are used in both the Pfizer/BioNTech and Moderna vaccines. The combination of these advances has enabled the approved COVID-19 vaccines and set the stage for future mRNA technologies.

Another challenge is lowering the dose of RNA in order to avoid side effects associated with high doses of RNA. The data from the clinical trial shows that approximately 50 per cent of participants had side effects even though the RNA was prepared with modified nucleotides in the vaccine. This is caused by innate sensing and detection of foreign RNA that humans have evolved to fight infections from RNA viruses. These side effects are directly proportional to the total administered dose of RNA. Therefore, minimising the dose of RNA required for vaccines will not only lessen side effects, but also the cost and time required to produce doses.

Another hurdle that is now coming into light is the limited protection being offered by the mRNA vaccines. To avoid loss of efficacy, periodically updated vaccine boosters that compensate for antibody waning and viral evolution will be needed, especially in high-risk groups. So, how to address this requirement?

Here comes the concept of self-amplifying RNA (saRNA) to the rescue. Since saRNA is a much larger molecule as it encodes four extra proteins in addition to the vaccine antigen or gene of interest.

It is a newer type of RNA vaccine with high immunogenicity. Derived from alphaviruses or flaviviruses, it contains the viral replicase enzyme that allows it to amplify itself. Since saRNA is already more immunogenic than other RNA molecules, activating several Toll-like receptors, for instance, this elevated expression of viral antigen in vivo causes extremely robust immune responses. The saRNA packaged in lipid nanoparticles expresses the antigen for much longer than mRNA.

The first-in-human clinical trial for a saRNA vaccine was performed in 2020 for a COVID-19 vaccine by a team at Imperial College London, which concluded the combined phase I/II clinical trial in January 2021. The doses used in the trial, much less in comparison to the Pfizer/BioNTech vaccine and Moderna vaccine, illustrate the benefits of this platform.

Also, COVID-19 is not the only pathogen that's been explored for this platform. Other applications have included infectious diseases such as influenza, rabies, HIV-1, malaria, Chlamydia trachomatis, Ebola, RSV and Zika viruses, as well as oncology applications such as melanoma and colon carcinoma.

Future research will likely include optimising both the molecular design of saRNA (sequence and structural elements), the delivery vehicle, as well as the manufacturing and quality control processes used for these vaccines. Self-amplifying RNAs have shown enhanced antigen expression at lower doses compared to conventional mRNA, suggesting this technology may improve immunisation in the future.

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