Column

Combating the pandemic with a potential cure: A thermostable mRNA vaccine emerges as a promising candidate against COVID-19

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Abstract

The ongoing global pandemic caused by the deadly SARS-CoV-2 (COVID-19) has initiated worldwide efforts to develop effective vaccines against the virus. Many promising strategies have been considered in developing vaccines. Among the various vaccine candidates, mRNA vaccine has emerged as a leading contender to contain COVID-19. We describe here some of the recent advances in thermostable mRNA vaccine and discuss its potential to neutralize the virus.

Keywords: COVID-19, SARS-CoV-2, Vaccines, mRNA, Thermostable

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To cite this article: Singh S; Combating the pandemic with a potential cure: A thermostable mRNA vaccine emerges as a promising candidate against COVID-19, Biotechnology Kiosk, Vol 2, Issue 9, PP: 20-25 (2020); DOI: https://doi.org/10.37756/bk.20.2.9.2

Introduction

As the COVID-19 pandemic continues to wreak havoc, the world is asking how close we are to a potential cure. All eyes are set upon the arrival of a vaccine. According to the World Health Organization a vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The rat race to develop the vaccine had begun the moment the novel virus strain was identified. However, it is not as easy as it seems. When we inject a foreign substance in a human body it is bound to elicit an immune response and this response needs to be tamed and well directed to avoid any deleterious side effects.

Development of a vaccine is a multiphase process which requires stringent testing and control at every step. The product has to pass through clinical trial phase before it can be made available to human beings. Classically speaking it takes almost ten to fifteen years to produce a potent vaccine against diseases. But keeping in mind the current state of pandemic with the death toll increasing every moment we cannot afford to wait so long. More than thirty-five companies and academic institutions had joined the race for the vaccine and more than four of them have successfully entered the clinical trial phases. In a couple of cases the animal testing stage was skipped to quickly enter the human trial phase. However, despite the expedited testing we cannot ignore the fact that a vaccine might prove useful against a particular disease but might cause some other serious side effects.

Various strategies have been employed to create the vaccine and among all approaches a messenger RNA (mRNA)-based vaccine has emerged as a versatile and rapid platform to quickly respond to this challenge. In our current article we shall discuss the salient findings of a research recently published in Cell by a team of researchers who have developed a thermostable mRNA Vaccine against COVID-19 (1).

The highlights of the research

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human corona virus closely related to SARS-CoV is responsible for the COVID 19 pandemic. The clinical manifestations caused by SARS-CoV-2 range from non-symptomatic infection to mild flu-like symptoms, severe acute respiratory distress syndrome, pneumonia and even death (2). The number of cases has crossed the 3.5 million mark with over 250,000 deaths (the numbers are increasing every moment).

Corona viruses belong to a class of enveloped positive-sense, single-stranded RNA viruses, and the virion is composed of a helical capsid formed by nucleocapsid (N) proteins bound to the RNA genome and an envelope made up of membrane (M) and envelope (E) proteins, coated with a ‘‘crown’’-like trimeric spike (S) protein.

Similar to other human coronaviruses, the full-length S protein of SARS-CoV-2 consists of S1 and S2 subunits. First, the S protein mediates viral entry into host cells by binding to its receptor, angiotensin-converting

enzyme 2 (ACE2), through the receptor-binding domain (RBD) at the C terminus of the S1 subunit, which subsequently causes fusion between the viral envelope and the host cell membrane through the S2 subunit. The full-length S protein, S1, and RBD are capable of inducing highly potent neutralizing antibodies and T cell-mediated immunity and, therefore, have been widely selected as promising targets for corona virus vaccine development. Figure 1is the summary of the research.

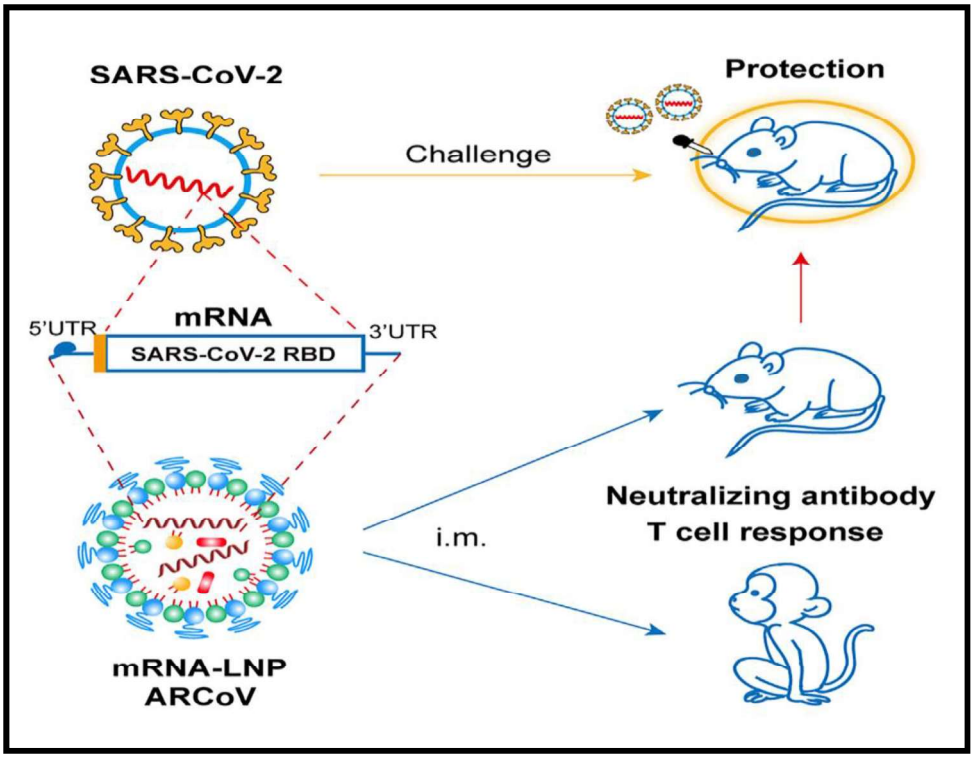

Figure 1: The diagrammatic summarization of the research highlighting the potential of the thermostable mRNA based ARCoV vaccine. (***Source:*** *Cell 2020 (1)*).

Messenger RNA (mRNA)-based therapy is one of the latest approaches for treating cancer and other infectious diseases (3). The mRNA vaccine field has developed rapidly in basic and clinical research owing to the technological advances in mRNA modification and delivery tools. It has been observed in preclinical studies that mRNA-based vaccines induce potent and protective Immune responses against various pathogens in small and large animals, with an acceptable safety profile. Clinical trials for mRNA vaccines against viral diseases such as influenza, Zika, Ebola, cytomegalovirus and rabies infection have been carried out in many countries successfully. The biggest advantage of the mRNA vaccine platform is its potential of scalable production within a very short period of time which makes it the preferred choice during times of this pandemic. Messenger RNA manufacturing avoids the lengthy process of cell culture and purification and the stringent biosafety measures for traditional virus vaccine

production. A clinical-scale mRNA vaccine can be designed and manufactured rapidly, within weeks, when the viral antigen sequence becomes available. It took only 42 days for Moderna's mRNA-1273 to enter the phase I clinical trials as the very first mRNA vaccine against COVID-19 in the United States in March 2020.

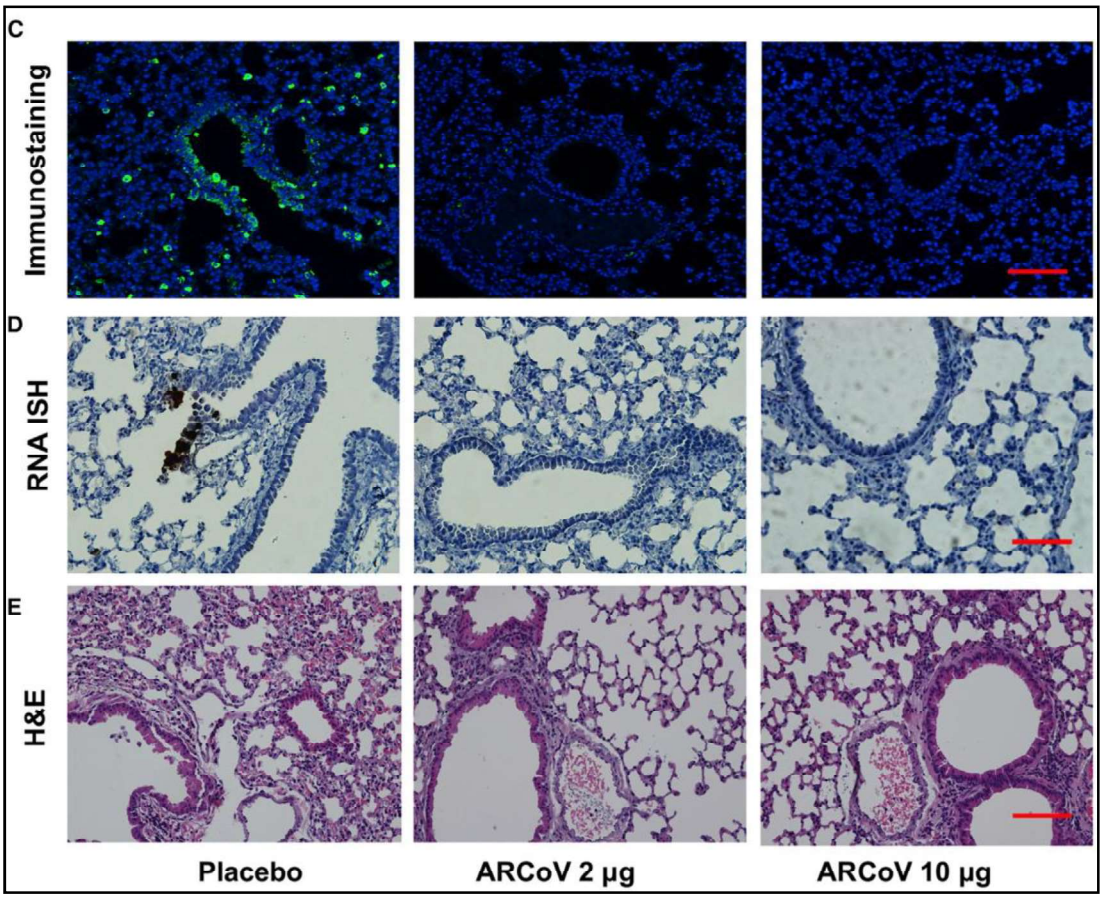

Figure 2: The immunostaining results showing protection of ARCoV against SARS-CoV-2 Challenge in Mice. (***Source:*** *Cell 2020 (1)*).

In the current study the researchers developed a lipid nanoparticle-encapsulated mRNA (mRNA-LNP) encoding the receptor binding domain (RBD) of SARS-CoV-2 as a vaccine candidate (called ARCoV). Lipid nanoparticles (LNPs) are one of the most attractive and commonly used mRNA delivery tools (4). The RBD of SARS-CoV-2 (amino acids [aa] 319–541) was chosen as the target antigen for the mRNA coding sequence. When the the RBD-encoding mRNA was transfected in multiple cell lines such as HEK293T, HeLa, Huh7 and Vero it resulted in high expression of recombinant RBD in culture supernatants. RBD protein expressed from mRNA retained high affinity for recombinant human ACE2 and functionally inhibited entry of a vesicular stomatitis virus (VSV)-based pseudovirus expressing the SARS-CoV-2 S protein. Immunostaining further demonstrated that this RBD protein can be recognized by a

panel of monoclonal antibodies (mAbs) against SARS-CoV-2 RBD as well as convalescent sera from three COVID-19 patients. It was further observed that the Intramuscular immunization of ARCoV mRNA-LNP elicited robust neutralizing antibodies against SARS-CoV-2 as well as a Th1-biased cellular response in mice and non-human primates. Two doses of ARCoV immunization in mice conferred complete protection against the challenge of a SARS-CoV-2 mouse-adapted strain (1). Figure 2 shows the immunostaining results showing protection of ARCoV against SARS-CoV-2 Challenge in Mice.

The scalability and accessibility of COVID-19 vaccines are major challenges to expediting delivery and massive immunization worldwide; therefore, a thermostable and ready-to-use vaccine is the need of the hour. The current ARCoV mRNA-LNP vaccine is manufactured in a liquid formulation without the need of thawing or reconstitution before injection, and a single-dose vaccine is prepared in a prefilled syringe for quick self-administration. The vaccine was tested for its stability and it was observed that the formulation maintained in vivo delivery efficiency at 40C and 250C for at least 1 week (1). However, the long-term stability of the ARCoV vaccine is still under evaluation. ARCoV is currently being evaluated in phase 1 clinical trials.

Concluding remarks

As the medical and scientific fraternity is battling against time to produce a potential cure in the form of a vaccine this thermostable mRNA vaccine candidate has shown promising results. The major advantages of the product are its simple route of administration i.e. the intra muscular route, its liquid formulation which requires no reconstitution, its thermostabilty and efficacy to name a few. The vaccine ARCoV has provided first-line evidence of immunogenicity and efficacy in multiple animal models can thus prove to be a potential vaccine candidate in near future with global accessibility and universal availability. This recent development has made us hopeful once again that after much anticipation we might finally have a potential cure and we are optimistic that soon we shall win this battle against COVID19 pandemic.

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