Are Genetic Vaccines the Right Weapon against COVID-19?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus disease (COVID-19), emerged in China in December 2019. Investigators have made rapid efforts to design therapeutic strategies targeting this rapidly spreading pathogen. Although not as lethal as SARS-CoV or Middle East respiratory syndrome (MERS)-CoV, the virus is highly transmissible, often without symptoms, with an estimated reproductive number (R_0) of 2.2.[1] On March 12, 2020, a mere 2 months since the outbreak was detected, World Health Organization (WHO) announced that COVID-19 had reached pandemic status. As a consequence, containment strategies have been implemented to slow viral transmission, but control of the infection will be challenging without a vaccine. The global scientific community and the vaccine industry, supported by international organizations such as Coalition for Epidemic Preparedness Innovations (CEPI) and the European Commission, have committed to developing a safe vaccine able to elicit a potent and long-lasting virus-specific immune response against SARS-CoV-2. The ideal target vaccine product profile should comprise some key elements. It should be consistently immunogenic with minimal side effects, such as undesired immunopotentiation in the form of increased infectivity.[2] Vaccine production should be implemented in a timely and efficient manner and be relatively inexpensive and suitable for large-scale good manufacturing practice (GMP) manufacturing. Moreover, as requested by regulatory agencies during the first regulatory workshop on COVID-19 held in March 2020 under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA), vaccine design should include a careful assessment of possible immune complications, such as the possibility of antibody-dependent-enhancement (ADE) of infection, before being released to the public.

To this aim, diverse platforms have been set up, but only a few can address these requirements. Conventional vaccines, such as inactivated, attenuated, or subunit vaccines, have been successful but have drawbacks, such as their strain specificity, and consequently are potentially associated with risks of viral interference and cross-immunity[3] and can be allergenic in some patient groups. Furthermore, vaccines based on viral proteins tend to elicit immune responses that are limited to the CD4+ T cell response or antibody-dependent mechanisms and lack a CD8+ T cell response. Besides this, the production of conventional vaccines can be expensive and time-consuming. Safety concerns, commonly associated with the use of whole virus as a vaccine platform, have been overcome by the development of replication-defective recombinant adenoviruses, which have proven safe for administration in humans and effective in inducing robust innate and adaptive immune responses. Third-generation adenoviral vectors have been employed to prevent or treat life-threatening infectious diseases such as Ebola, Zika, malaria, hepatitis C virus (HCV), and HIV[4,5] and tested in clinical trials for anticancer immunotherapy.[6] However, this vaccination strategy is hampered by issues such as pre-existing immunity in humans and challenges in construction. Therefore, newer vaccination approaches, such as genetic vaccines based on naked DNA or RNA, have emerged as promising alternatives owing to several beneficial features. First, they have a highly satisfactory safety profile without potential risk of integration or pathogenicity, and for this reason they are considered an ideal therapeutic strategy in cancer immunotherapy or for vaccinating immunocompromised people. Second, genetic vaccination can elicit both T cell activation and antibody production in response to even small amounts of expressed protein and, unlike whole virus vectors, can be more easily administered in multi-dose regimens without generating pre-existing immunity. Finally, the manufacturing process confers some advantages: both DNA and RNA are inexpensively and easily constructed directly from the genetic sequence of the desired antigen.

Once established, the production process can be easily adjusted according to the histocompatibility leukocyte antigen (HLA) diversity in the field in order to include the most immunogenic antigens and modulators for a specific population. Hence, the use of nucleic acids in vaccine development programs is growing in a wide range of traditional pharmaceutical markets, such as cancers and allergies, as well as infectious diseases, and it is increasingly demonstrating its safety and efficacy in early and mid-stage human clinical trials.[7,8] Nevertheless, these vaccination strategies still present some drawbacks, and differences between DNA and RNA must be taken into account. As for immunogenicity, a number of factors can increase DNA potency, such as the use of immunostimulants (cytokines and immunostimulatory molecules), tailored delivery routes and devices (with intramuscular injection followed by electroporation having been found to be the most effective in inducing strong immune responses), and different combination strategies (e.g., DNA prime followed by viral vector, peptide, or recombinant protein heterologous boosts). Conversely, over the past decade, vaccine developers have striven to increase RNA stability, improve its cellular delivery through encapsulation into nanoparticles, and reduce its constitutive reactogenicity by using modified nucleosides and controlling the onset of eventual toxicities. Challenges remain for RNA-based strategies, such as further improving stability, reducing toxicity (due to intrinsic inflammatory activity), and increasing protein translation, necessitating additional clinical studies. Additionally, in order to avoid the use of any animal or cellular materials, researchers are exploring alternative manufacturing strategies, such as the use of PCR-generated linear DNA fragments.[9] As shown in Table 1, genetic vaccines, DNA-based ones in particular, are an ideal vaccination platform for infectious diseases: both DNA and RNA can be developed and manufactured rapidly, ensuring a reproducible and standard production process, whatever the target disease or gene insert, but still with some intrinsic limitations to overcome, such as lower immunogenicity, in comparison to protein- and viral-based conventional vaccines.[10]

Table 1. Some Candidate Viral-Based and Genetic Vaccines against COVID-19 in Clinical/Preclinical Evaluation

Platform	Type of Candidate Vaccine	Developer	Current Stage of Clinical Evaluation/ Regulatory Status
DNA	DNA electroporation	Inovio Pharmaceuticals	phase 1 (NCT04336410)
RNA	LNP-encapsulated mRNA	Moderna/NIAID	phase 2 (IND submission) phase 1 (NCT04283461)
RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	phase 1/2 (2020-001038-36)
Non-replicating viral vector	adenovirus type 5 vector	CanSino Biological/Beijing Institute of Biotechnology	phase 2 (ChiCTR2000031781) phase 1 (ChiCTR2000030906)
Non-replicating viral vector	ChAdOx1	University of Oxford	phase 1/2 (NCT04324606)
DNA	DNA/PCR electroporation	Takis/Applied DNA Sciences/Evvivax	preclinical evaluation
DNA	DNA electroporation	Karolinska Institute/Cobra Biologics (OPENCORONA Project)	preclinical evaluation
RNA	mRNA	Curevac	preclinical evaluation
Non-replicating viral vector	Ad26	Janssen Pharmaceutical Companies	preclinical evaluation
Non-replicating viral vector	replication defective simian adenovirus	ReiThera/LEUKOCARE/Univercells	preclinical evaluation
Non-replicating viral vector	oral vaccine platform	Vaxart	preclinical evaluation
From WHO,[11] updated on May 5, 2020.			

The last decade has witnessed the outbreak of several new human pathogens, including Ebola, Chikungunya, Zika, SARS-CoV, MERS-CoV, and more recently the novel coronavirus (SARS-CoV-2). The continuous spread of such diseases at regular intervals poses a significant threat to human health and the economy, and there is an urgent need for a vaccine technology that is able to protect against rapidly arising or mutating pathogens. Genetic vaccination represents an ideal vaccine target product profile to be developed in response to an unexpected pandemic outbreak, so, in the future, every effort must be addressed to develop a vaccine platform that can be designed and produced in large scale in a timely fashion to be ready for a "disease X."

CONFLICTS OF INTEREST

A.C., E.M., G.R., F.P., and L.A. have an interest in developing vaccines and therapeutics to treat SARS-CoV-2. A patent has been filed at Takis for a genetic vaccine under development. G.C. declares no conflict of interest.

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