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Synthetic Biology and the Boost of COVID-19 Vaccines Technology Development through International Alliances

Biología sintética y el impulso del desarrollo tecnológico de las vacunas COVID-19 mediante alianzas internacionales

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ABSTRACT

The importance of the development of the necessary technology to achieve the production of vaccines from a “synthetic biology” perspective is analyzed, as well as the essential articulation and financing through international cooperation to combat COVID-19, all the information on this topic is from the bibliographical research on topics focused on the development, cooperation, and international regulations involved in the synthesis of COVID-19 vaccines. A comprehensive vision on the recent development strategies on health and bioeconomy issues is proposed to face future eventualities and thus promote better health-oriented developments with the possibilities of immediate action.

KEYWORDS: synthetic biology, vaccines, COVID-19.

RESUMEN

Se analiza la importancia del desarrollo de la tecnología necesaria para lograr la producción de vacunas desde una perspectiva de “biología sintética”, así como la imprescindible articulación y financiación a través de la cooperación internacional para combatir la COVID-19, todo ello, a partir de la investigación bibliográfica sobre temas enfocados con el desarrollo, participación y regulaciones internacionales involucradas en la síntesis de vacunas COVID-19. Aquí se propone una visión integral sobre las recientes estrategias de desarrollo en temas de salud y bioeconomía para enfrentar futuras eventualidades y así propiciar mejores desarrollos encaminados a la salud con las posibilidades de una actuación inmediata.

PALABRAS CLAVE: biología sintética, vacunas, COVID-19.

INTRODUCTION

Synthetic biology aims to move quickly from idea to product, at a low cost, generating relevant and reliable results (Clarke, 2020). To achieve this goal, it is necessary to optimize each of the design-build-test (DBT) components that are part of the production paradigm of any biologic, device, or drug. Emerging technologies (such as CRISPR-Cas and data science) can trigger the evolution of automated production systems (National Academies of Sciences, Engineering, and Medicine, 2018).

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In the medical industry, one of the main bottlenecks is demand since the continuous synthesis of biological materials is required. Due to this need, the importance of streamlining processes and improving technology arises (Katz *et al.*, 2021; Kelwick *et al.*, 2020; Kohn, 2004). Since the H1N1 pandemic in 2009, and later, with the emergence of H7N9 avian influenza in 2013, scientists at the J. Craig Venter Institute in San Diego, CA. and Synthetic Genomics Inc. raised concerns about driving highly efficient and fully automated platforms in the production of biologics for the medical industry (Boles *et al.*, 2017; Dolgin, 2020, 2021).

The emergence of SARS-CoV-2 in Wuhan in China (December 2019) reactivated the development of devices and rapid tests to perform reliable diagnostics and search for effective treatments through drugs and therapies. In addition, the first attempts to immediately design and RNA, DNA, viral particle, or protein vaccine against COVID-19 were initiated (Brooks & Alper, 2021; Tan *et al.*, 2021). This paper aims to describe the importance of developing the technology necessary to automate the vaccine production process from a “synthetic biology” perspective and the articulation and funding needed through international cooperation to overcome the SARS-CoV-2 pandemic.

1. TECHNOLOGY DEVELOPMENT STRATEGY FOR COVID VACCINE DEVELOPMENT

Previous experience in the scientific field and the development and production of vaccines worldwide led to the decision to use mainly a portion of the SARS-CoV-2 mRNA that translates the S protein, which alerts the immune system and then introduces it intramuscularly as synthetic mRNA, with a carrier. Other delivery options were also contemplated, either within a viral particle or the delivery of viral DNA vectors (Forni *et al.*, 2021). On March 16, 2020, just 66 days after the SARS-CoV-2 viral genome was released, the first human trial was conducted by administering the first vaccine created by Moderna and the National Institute of Health (NIH) (Haynes, 2021; Rappuoli *et al.*, 2021).

2. INTERNATIONAL COOPERATION AND PROMOTION OF COVID VACCINE TECHNOLOGY DEVELOPMENT

The expertise acquired during the production and development of vaccines during the H1N1 pandemic contemplated the need to articulate international cooperation. The Coalition for Epidemic Preparedness Innovations (CEPI) is a global partnership to develop vaccines to overcome future epidemics, to which Mexico belongs and was founded in 2017 in Davos, Switzerland. Interestingly, in September 2017 and before the release of COVID-19, CEPI funded three technology platforms: an mRNA vaccine printer (RNA Printer™), a molecular clamp platform, and a self-amplifying RNA vaccine platform. The RNA Printer™ was a prototype developed by CEPI and CureVac AG for small-scale, fully automated, and portable (mRNA) printing. Viral surface proteins are molecularly unstable and change shape; this instability results in an immune response that produces antibodies that do not effectively bind to viruses and therefore are unable to prevent infection. Therefore, the molecular clamp platform is crucial for developing protein-based vaccines; this project is underway at The University of Queensland. A self-amplifying RNA vaccine platform aims to harness the body's cellular machinery to produce an antigen (i. e., a foreign substance that induces an immune response) rather than injecting the antigen directly. This technology is under development by Imperial College London (CEPI, 2021b).

In 2018, CEPI and Imperial College London formally agreed on developing a self-amplifying RNA vaccine (saRNA) platform. By February 2019, CEPI and CureVac AG reiterated the continued development of the prototype of the RNA Printer™ for small-scale, fully automated, and portable mRNA printing. Interestingly, in 2013-2017, Kent Boles and collaborators published and patented the prototype of a system capable of producing biomolecules, developing a platform that merged the advances obtained up to that moment, under a “synthetic biology” perspective, with cutting-edge vaccine manufacturing technologies which employ RNA or DNA. This system has recently come on the market under name BioXp™ 3250 platform. Currently, two companies are producing an automated mRNA printer in series: Tesla Inc., which was implemented for CureVac AG, and the BioXp™ 3250 system from CODEX DNA (CEPI, 2021a; Christodoulou, 2018; Codex DNA, 2020).

3. ACCELERATING THE COVID-19 VACCINE DEVELOPMENT

CEPI, the Gavi Vaccine Alliance (Gavi), and the World Health Organization (WHO) have launched the “ACT Accelerator” for vaccines to accelerate the development of an effective vaccine for all countries. Thus, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) joins the global public-private partnership, ACT Accelerator. IFPMA finally published vaccine policy principles guiding its work with ACT Accelerator Vaccines Partnership (COVAX). Several IFPMA members, associations, and consortia have joined different initiatives such as COVID-19 Therapeutics Accelerator (ACT), Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), and Corona Accelerated R&D in Europe (CARE). In March 2021, Chatham House, IFPMA, Biotechnology Innovation Organization (BIO), Developing Countries Vaccine Manufacturers Network (DCVMN), and CEPI assessed the urgency for COVID-19 vaccine production to reach its full potential. In this meeting, it was noted that vaccine manufacturing processes are very complex, involving cutting-edge science and technology, and addressed manufacturing capacity issues, complex technology transfer management, and international supply chain management. Issues related to manufacturing capacity, raw material availability, policy, regulation, production improvement, supply-demand, and forecasting-visibility were also assessed, considering the potential impacts on production for both COVID-19 and non-COVID-19 materials (IFPMA, 2020; WHO, 2021).

4. INTERNATIONAL REGULATIONS TO BE FOLLOWED TO COMBAT COVID-19

Due to the imminent deployment of COVID-19 drugs and vaccines, it became necessary to articulate a rigorous global regulatory harmonization based on scientific evidence. On November 6, 2020, the World Health Organization and the International Coalition of Medicines Regulatory Authorities issued a joint statement (WHO-ICMRA). As in other areas of the pandemic response, multilateral cooperation among regulatory agencies has been crucial to ensuring that COVID-19 vaccines and drugs are safe, effective, and quality assured, benefiting all countries equally and simultaneously. At the same time, the scientific community in both public and private sectors have responded immediately and responsibly to develop vaccines worldwide, receiving millions of dollars in contributions to encourage technological platforms for diagnostics, vaccines, antibody therapy, drugs, and others to combat COVID-19 (WHO, 2020).

5. COMPANIES WITH A “SYNTHETIC BIOLOGY” PROFILE INVOLVED IN THE DEVELOPMENT OF VACCINES, DEVICES, AND DRUGS AGAINST COVID-19

Companies such as Concentric (by Ginko) have focused on innovation, developing *in situ* tests for schools and companies. Mammoth Biosciences has developed detection platforms for SARS-CoV-2 through CRISPR technology. Sarah Ives of Distributed Bio developed the broad-spectrum Centivax flu vaccine technology in December 2020. On December 31, 2020, Charles River Laboratories International, Inc. announced the acquisition of Distributed Bio, Inc. (Cumbers, 2020).

A brief list of diagnostic technologies, drugs, and therapies, as well as vaccines so far developed for SARS-CoV-2 diagnosis, are the followings: Portable detection devices based on electrochemical or optical biosensors, surface plasmon resonance and field-effect transistor biosensors, as well as rapid molecular tests based on loop-mediated isothermal amplification (LAMP), Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and SARS-CoV-2 antigen rapid tests (Dinnes *et al.*, 2021; Sadighbayan & Ghafar-Zadeh, 2021). For patients with COVID-19, the treatments are newly developed molecules and new uses for those already authorized for other conditions (Rastogi *et al.*, 2020).

Current COVID vaccine synthesis platforms are mainly based on attenuated SARS-CoV-2 virus, inactivated SARS-CoV-2 virus, SARS-CoV-2 viral proteins, naked DNA or mRNA, and others under development (Puspharajah *et al.*, 2021). On the other hand, the development of other automated technology platforms continues to produce “multivalent” vaccines that include protection against influenza, MERS, SARS, and SARS-CoV and are also based on DNA templates, RNA molecules, proteins, and viral particles (Li *et al.*, 2021). Due to the pandemic caused by SARS-CoV-2, vaccine synthesis platforms have evolved exponentially, in such a way that this experience will be applied to develop vaccines in order to prevent or eradicate other infectious diseases such as: Retroviral enteritis, hepatitis, parotitis, etc. The next generation of vaccine manufacturing will include not only the well-known technologies of attenuated viruses, inactivated viruses, and viral proteins, but also toxoids, synthetic viral particles, synthetic peptides, polysaccharides, conjugated polysaccharides, bacterial vectors/synthetic antigen-presenting cells, etc. (Ghattas *et al.*, 2021). Therefore, if vaccine synthesis platforms evolve rapidly, delivery technologies for biomolecules, drugs and viral particles must be innovative, so that vaccine delivery devices such as: skin patch, nanoneedles, mucosal or inhaled dispensers, oral dispensers, tablets and more, are currently being developed (Abdellatif *et al.*, 2021; Ulmer *et al.*, 2015).

Established and emerging companies (created under the concept of “synthetic biology”) have a significant opportunity niche. Today, in the spotlight, there are ten companies ranked at the top of the world which have been created with the “synthetic biology” vision: *a*) public companies: Codexis, Ginko Bioworks, Twist Bioscience, Precigen, and Amyris; and *b*) private companies: Apeel Sciences, Insitro, ElevateBio, National Resilience, Impossible Foods. Also mentioned are promising companies such as Anthenia, Beam Therapeutics, Berkeley Lights, Codex DNA, Sana Biotechnology, Synlogic, Synthego, and Zymergen (Philippidis, 2021).

PROSPECTIVE

The pandemic caused by SARS-CoV-2 highlighted the enormous need to improve the processes involved in developing biosensors, drugs, and vaccine manufacturing. In general, the market for biomaterials is vast and rapidly expanding. It is a reality that automated systems to produce medical supplies are the formula to respond quickly to any health contingency. Synthetic biology, through continuous optimization and the DBT paradigm or model, is a compelling promise for responding to future pandemics. Due articulation in international cooperation and regulations has already taken essential steps that lay the foundation for the following actions to respond to pandemics. It is evidently a necessity that each country is willing to develop or install technologies to stop today's dependency in terms of technology and research for the production of biomaterials.

CONCLUSIONS

Due to the global outlook exerted by the appearance of SARS-CoV-2, the development of technology-based on a “synthetic biology” vision is crucial for the fight against emerging diseases. Since “synthetic biology” is supported by essential disciplines such as systems biology, computational biology, biotechnology, robotics, molecular biology, and many more, its use will be crucial to the DBT paradigm in the design of biomaterial production systems. We can assure we are living a moment of great opportunity for this new vision of technological development in the global bioeconomy.

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