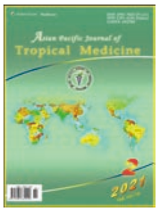

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Perspective

Asian Pacific Journal of Tropical Medicine

doi: 10.4103/1995−7645.306736

Impact Factor: 1.94

Addressing demand for recombinant biopharmaceuticals in the COVID−19 era

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1. COVID−19 pandemic

The emergence and re-emergence of infectious diseases in recent years demand national health care systems to develop effective surveillance mechanisms, diagnostic, treatment, and preventive strategies. The last two decades witnessed the outbreak of several viral infections with epidemic and pandemic potentials, most of which are zoonotic. These include severe acute respiratory syndrome-coronavirus (SARS-CoV), avian and swine-origin influenza viruses, Middle East respiratory syndrome-coronavirus, Ebola, Chikungunya, Zika, Nipah, and, more recently, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)[1]. SARS-CoV-2 represents family Coronaviridae, subfamily Orthocoronavirinae, and genus *Betacoronavirus*. By early November 2020, there have been more than 50 million confirmed cases of COVID-19 globally, with over 1 million reported deaths[2]. The ability of the virus to spread from person to person and the mortality associated with the infection pose serious threats to public health globally. The outbreak also had a major impact on global economy and lifestyle of human populations. The pathogenesis and transmission cycle of SARS-CoV-2 has not been elucidated completely, which hampers the development of effective treatment and preventive measures.

2. Need for affordable biopharmaceuticals

Currently, the global priority is to develop effective vaccines to control this pandemic[3]. Several candidates have been evaluated to develop effective vaccines, therapeutic or rapid diagnostic tests against SARS-CoV-2. More than 100 vaccine candidates are in different stages of testing *viz*., pre-clinical and clinical trials. Although developing a rapid diagnostic kit, vaccine or therapeutics is critical during the pandemic, the major challenge is to guarantee the distribution, accessibility, and availability of the vaccine/therapeutics to everyone around the world at an affordable price. Now the biggest challenge for all the governments and international organizations is to provide and ensure equal access to medical care for their citizens.

Today, most of the recombinant pharmaceutical proteins are produced by using mammalian, bacteria, and yeast cell cultures, which is often expensive to maintain and requires high capital investment. In middle-income and low-income countries, the demand for vaccine antigens, therapeutic antibodies, or other high-value molecules is often higher than the available production capacity, which hinders the accessibility of vaccines by the poor[4]. Furthermore, the obstacles such as limited budget, poor healthcare services, non-affordability of vaccine, drugs and other biopharmaceuticals or lack of investment for developing new vaccine results in an increased burden of infectious diseases in such countries.

3. Plant expression platform

In recent years, plants have been considered as a potential alternative to produce "high-value" foreign proteins rapidly at an affordable cost. The production of high-value recombinant proteins in plants is termed as "plant molecular farming". The history of

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How to cite this article: Shanmugaraj B, Phoolcharoen W. Addressing demand for recombinant biopharmaceuticals in the COVID-19 era. Asian Pac J Trop Med 2021; 14(2): 49-51.

Article history: Received 15 July 2020 Revision 11 September 2020
Accepted 20 October 2020 Available online 20 January 2021

plant molecular farming started back in the late 1980s after the report on successful expression of recombinant antibodies in plants[5]. Since then, several proteins have been produced and many are close to commercialization. The unique advantages of plant platform over other conventional production systems include increased protein yield, lower risk of contamination, sterility is not issue during production, reduced production cost, post-translational modifications of recombinant proteins with minor differences in glycosylation, safety, flexibility, speed of production and scalability[6–8]. A vast amount of literature has shown the potential of plant-based systems for the production of recombinant biopharmaceuticals. The proofs of concept and efficacy of many vaccine candidates and therapeutics expressed in plants have been reported (see reviews[9–13]).

4. Rapid acceleration and scalability

The currently available plant-based technologies for recombinant protein production include stable nuclear expression, stable chloroplast expression, transient expression, and suspension cultures. The stable transformation in nucleus or chloroplast can be achieved by *Agrobacterium*-mediated transformation or particle-bombardment whereas transient expression may be achieved by agroinfiltration or by using plant viruses. The stable plant suspension cultures can also be used for protein production by dispersing undifferentiated clusters of plant callus in a liquid medium that can be quickly propagated in bioreactors[14]. Each method has its own advantages and can be selected based on the nature of the target molecule. In the present scenario, the production of recombinant biopharmaceutical proteins through plant expression system seems to be reliable to deal with the pandemic situation. Cost and scalability are considered as the major advantages during the early stages of plant molecular farming technology, but now the rapid protein production by transient expression offers a faster vaccine production system. Transient expression system mediated by infiltration with *Agrobacterium tumefaciens* or with viral vectors is the method of choice especially during epidemic situations to produce adequate quantities of recombinant proteins rapidly in less than a month. The latest advances in transient expression results in a high-level accumulation of recombinant proteins, that can meet the industrial-level protein production[15,16]. The manufacturing of biopharmaceuticals in plants could be a low-tech option that presents an unprecedented opportunity to address the demand for recombinant proteins in low and middle-income countries in the area of diagnostics as well as biologics[17]. The potential of commercial application of plant molecular farming and its importance to benefit the poor in developing countries has been reviewed here[18,19].

5. Future perspective

The importance and the role of plant-made biopharmaceuticals in the fight against COVID-19 has been extensively commented elsewhere[20–22]. The existing concept of producing effective immunogenic vaccine candidates in plants is boosting the plant molecular farming community towards COVID-19 vaccine development. Our group is currently investigating the potential of plant expression systems in making SARS-CoV-2 vaccines and therapeutic monoclonal antibodies by expressing recombinant chimeric proteins, sub-unit proteins, virus-like particles, and other biologics[23]. We are also evaluating the possibility of using plant-produced SARS-CoV-2 recombinant protein as a diagnostic reagent for developing a rapid diagnostic test kit in Thailand. Moreover, the plant-based pharma companies such as Medicago (Canada), Kentucky BioProcessing (USA), and iBio (USA) have proposed virus-like particle and subunit-based vaccine production in plants[20]. Further research in this direction is highly needed to accelerate the fight against this pandemic. If plant-produced vaccine candidates or monoclonal antibodies are shown to be efficacious, the substantial investments along with the well-directed regulatory framework would be helpful to realize the benefits of plant expression system in addressing the demand for recombinant biopharmaceuticals, especially during an infectious disease outbreak. We believe that the plant production system can be more attractive to the resource poor or developing countries who can utilize the cost-effective production of commercially viable recombinant proteins. Further, the plant-based technology is easy to transfer and promote regional manufacturing of protein products at relatively low-cost.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgements

The financial support of Second Century Fund (C2F), Chulalongkorn University is greatly acknowledged.

Authors' contributions

Conceptualization, B.S. and W.P.; literature review, B.S.; writing-original draft preparation, B.S.; writing-review and editing, B.S. and W.P.; funding acquisition, W.P. All authors have read and agreed to the published version of the manuscript.

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