Molecular Therapy
Editorial

Molecular therapies and vaccines face the challenges of emerging infectious diseases

Over the course of more than two centuries, vaccination has had a dramatic impact on improving human and animal health in a world filled with infectious diseases. Preventative vaccination has a significant impact on reducing morbidity and mortality, and we have witnessed the eradication of smallpox, wild-type poliovirus types 2 and 3, and rinderpest virus due to global immunization efforts. In the face of continuously evolving and newly emerging pathogens, additional approaches to conventional vaccine platforms (inactivated, live attenuated, subunit) are essential to induce protective immunity. *In vivo* gene delivery employing nucleic acids (DNA, mRNA) and vectored technologies (adenovirus [Ad], vesicular stromatitis virus [VSV], others) have moved beyond being experimental and are undoubtedly demonstrating potency as vaccine platforms capable of inducing protective humoral and cellular immune responses in people. This special issue of *Molecular Therapy* highlights the critical role that the gene-transfer field has in the global fight against emerging diseases.

More than any other infectious disease, coronavirus disease 2019 (COVID-19) is propelling significant advances in gene-encoded vaccine technologies.[1,2] mRNA-, DNA-, and Ad-based vaccines have received either full approval or emergency use authorization for use in people to reduce severe COVID-19 disease. In a world of almost 8 billion people, each vaccine platform affords benefits to different populations and is needed to cover diverse global needs. Nucleic-acid and vectored delivery are now poised to accelerate responses against other infectious-disease concerns. The response to COVID-19 also highlighted the potential of monoclonal antibodies as powerful therapeutics in the treatment of infectious disease. However, the pandemic also revealed the vulnerabilities and challenges for healthcare systems to deal with emerging diseases. All these aspects are covered in this special issue.

For more than 2 years, the world has been battling the pandemic outbreak of a respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, the pathogen that causes COVID-19. Worldwide, there have been >200 million confirmed cases, resulting in >4.5 million deaths. Zhang et al. explain how the innate immune system senses the SARS-CoV-2 virus, which results in the induction of expression of various anti-viral genes, including cytokines such as type I and III interferons, to restrict spreading of the virus in the body by interfering with parts of the viral life cycle.[3] At the same time, the virus has evolved multiple strategies for immune-evasion strategies to be able to replicate and escape from the host's immune-surveillance mechanisms. The authors explain what has been learned about the innate immune response to SARS-CoV-2 and the mechanisms by which the virus may evade the host's innate defences. Innate immunity provides activation signals for antigen-specific adaptive immunity, such as antibody formation. Vaccines aim to do just that in order to establish a pre-existing immune barrier and thus prevent viral or other pathogens from infecting humans or causing disease. To this end, new recombinant-vaccine platforms may accelerate vaccine development compared with more traditional approaches.

Adenovirus-based vaccines have seen global interest in the development of strategies to prevent the spread and disease severity associated with the COVID pandemic. This broader interest and knowledge in society relating to technologies used for vaccine implementation brings great interest in the utility and safety of adenoviruses at scale in the population. Yet, adenoviruses are a source of vaccine technology with a rich history of vector development, refinement, and testing in the last two decades. In a thorough and detailed review of the entire field, Coughlan, Kremer, and Shayakhmetov articulate the current state of the art from both a historical and future-looking perspective, setting out the existing obstacles and opportunities for further improvements that potentially mitigate safety concerns and maintain or even enhance their efficacy.[4]

The first two COVID-19 vaccines that received accelerated regulatory authorization were based on nucleoside-modified mRNA. These vaccines gave rise to greater than 90% protective efficacy against symptomatic SARS-CoV-2 infection as well as tolerable safety profiles in pivotal phase III trials. Real-world evidence generated following global vaccination campaigns with these vaccines has confirmed that this platform is safe and effective in combatting COVID-19. This success has underscored the broader potential of this new drug class, not only for other infectious diseases but also for cancer and inherited diseases. Szabó et al.[5] provide a brief history and the current status of development of four mRNA-vaccine platforms, nucleoside-modified and unmodified mRNA, circular RNA, and self-amplifying RNA, as well as an overview of the current status of COVID-19 mRNA vaccines.

Recently, the first vaccine has been licensed for malaria, and another one promises to provide even more significant protection against severe disease. Given the scale of malaria, the impact of these vaccines cannot be understated—large-scale implementation would save the equivalent number of children's lives as curing all childhood cancers. Yet, these vaccines will require yearly boosters that make them prone to program interruptions and rapid rebounds in disease. Moreover, no vaccine in the pipeline has come near the ~80% infection-blocking

protection needed in the field to drive malaria to long-term control. Monoclonals, although currently expensive and limited in the need for repeated administration, may be better poised to provide the high levels of infection-blocking protection needed and can overcome other issues plaguing malaria vaccines such as low immunogenicity in endemic areas. Aleshnick et al. discuss the promise and pitfalls for monoclonals and where they fit in the fight against malaria.[6]

Finally, Olliaro and Torreele provide valuable critical thought on the current global public-health response.[7] The ongoing COVID-19 pandemic and the increasing number of outbreaks in the past two decades bring attention to the many challenges faced by present efforts to tackle infectious diseases. The future landscape for preparedness and epidemic responses must take into consideration engagement at multiple levels for scientific, clinical, research and development (R&D), government, community, and individual health priorities. Importance must also be placed on education and developing equitable strategies for the prevention, treatment, and control of infectious diseases in all regions of the world. This review serves as a call for collective responsibility, transparency, and overall unity in the global response for improving accessibility to potentially life-saving products and healthcare resources.

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