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Rapid delivery of antiviral antibodies is facilitated by in vivo electroporation

Newsletter by: Rachel A. Liberatore and Chasity D. Andrews, RenBio Inc., NY, USA
rachel.liberatore@renbio.com; chasity.andrews@renbio.com

In February of 2017, an agency within the United States Department of Defense that focuses on 'high risk, high reward' research, the Defense Advanced Research Projects Agency (DARPA), released an announcement for a new program focused on viral outbreak responses. This Pandemic Prevention Platform (P3) program called for an unprecedented acceleration of the existing capabilities to develop countermeasures to a novel viral outbreak with pandemic potential. Based on the response times needed to prevent a rapidly spreading virus from achieving that potential, the P3 program called for the development of such countermeasures in a seemingly unbelievable 60 days, rather than the multiple years typically required. Such an extreme shortening of timelines would obviously require significant innovation of the strategies and technologies currently used.

When thinking about the requirements for responding to a rapidly spreading, highly pathogenic virus, it becomes clear that the antiviral agent developed must be able to be manufactured quickly and provide near-immediate efficacy. Indeed, the P3 program stipulated that protection from infection must be achieved within as few as 3 days post administration. Because vaccines rely on complex host immune responses that can take weeks to fully develop, neutralizing antibodies (NAbs), which have the ability to immediately block viral infection, were the agent of choice. In order to deliver these NAbs, nucleic acid-based delivery technologies such as Adeno-Associated Virus (AAV) systems, lipid nanoparticle (LNP) formulations of mRNA, and electroporation (EP)-mediated delivery of plasmid DNA (DNA/EP), were clearly preferable over standard monoclonal antibody delivery. Monoclonal antibodies are typically delivered in protein form, either by intravenous infusion or subcutaneous injection, and take at a minimum several months to produce in large bioreactors.

A note from the Editor: European Commission in response to the emergency call launched in January to fight the COVID-19 outbreak selected 17 projects involving 136 research teams from across the EU and beyond, which will start working on developing vaccines, new treatments, diagnostic tests and medical systems aimed at preventing the spread of the Coronavirus. OpenCorona (one of the selected projects) aims at developing DNA vaccination that will be administered through electroporation. Read more at https://tinyurl.com/eu-corona19.

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The extra time required for in vitro protein production following the identification of a suitable NAb cannot be tolerated on the cusp of a pandemic, and thus a key component of the P3 program was that only nucleic acid-based antivirals would be used; all the platforms supported by the P3 program would end with the delivery of NAb-encoding DNA or RNA. By delivering a nucleic acid "bio-blueprint" directly to an individual, it enables that person's own body to become the bioreactor and produce the NAb protein. Each of these nucleic acid delivery systems, AAV, LNP-formulated RNA, and DNA/EP, vary in a number of respects, but some of the main differences between them are related to the average duration of expression and the peak levels of serum NAb achievable. There are also variable effects on the elicitation of immune responses directed against the delivered product and/or the expressed NAb itself.

Recent ground-breaking improvements in NAb identification and optimization combined with the shortened manufacturing timelines required for such nucleic acid-based systems have brought the previously unimaginable P3 demands into the realm of possibility. Indeed, in response to the current COVID-19 pandemic some of the groups funded by the P3 program have been asked to test their platforms using SARS-CoV-2, the virus that causes COVID-19. Hopefully, the technological advances developed as part of the P3 program can be successfully applied to this current crisis. Regardless, there can be little doubt that we will face another viral outbreak with pandemic potential in the future. Because the manufacture of plasmid DNA is faster than either AAV or LNP-formulated RNA, DNA/EP has the potential to provide the fastest route to antiviral NAb delivery. Given the pandemic we are in, and the likelihood of more to come, continued research and investment in this technology remains essential.

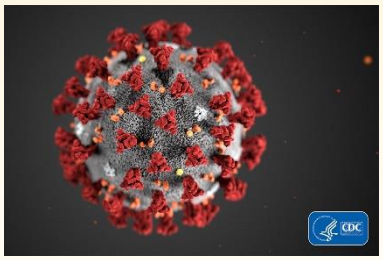
Forthcoming events

7th School on Pulsed Electric Field Applications in Food and Biotechnology
Zaragoza, **new dates**: September 7 – 11, 2020
http://pefschool2020.electroporation.net/

8th European Medical and Biological Engineering Conference – EMBEC 2020
Portorož, **new dates**: November 29 – December 3, 2020
http://embec2020.org/

Electroporation-Based Technologies and Treatments
Ljubljana, November 15 – 21, 2020
http://2020.ebtt.org

EU Commission secures 47.5 million EUR for COVID-19 vaccine-related research.



A strain of coronavirus named SARS-CoV-2 causes the disease Covid-19. (photo/illustration Courtesy CDC)

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