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QUANTIFICATION OF NEUTRALIZING ANTIBODY FOR COVID-19 VACCINE DEVELOPMENT

Protocols for PRNT, MNA, and PNA assays codeveloped for SARS-CoV-2

INTRODUCTION

The release of a Public Health Emergency of International Concern by WHO Director General in January 2020 after the emergence of a number of SARS-CoV-2 clusters, rang the start of a race to find effective vaccines and therapeutics against the virus. In partnership with Public Health England (PHE) Porton Down, Nexelis decided to proactively initiate the development of assays that would be needed to evaluate the efficacy of vaccine candidates. The first step within a series of events that placed our company at the core of more than 60 vaccine development projects.

PREMISE

PHE Porton Down group formed in order to develop solutions protecting the British population against bacteriological threats. PHE has a world class reputation for developing BSL3/4 assays requiring the manipulation of highly contagious strains of infectious agents. The wave of SARS-CoV-2 development projects initiated in parallel created a demand that by far exceeded the capacity of all academic institutions and research laboratories with BSL-3/BSL-4 credentials. The industry needed a solution with the same robustness as the wild-type ELISA and neutralization assays. In record time, there needed to be ELISA and neutralization assays developed and qualified that would yield high throughput with precision and ideally, executed within BSL-2 laboratories to quantify immunoglobulin and neutralizing antibodies.

Ultimately, the assays developed by Nexelis and PHE, now published in Nature Protocols, were used in over 60 development projects and transferred to a network of laboratories all over the world.

SOLUTION

Nexelis' protein sciences group has an outstanding reputation. Scientists are capable of producing challenging virus-like particles or pseudo-particles that are molecules that closely resemble viruses but are non-infectious because they contain no viral replication genetic material. The advantage of generating pseudo-particles is that these tests could be performed in a BSL-2 facility. While the wild-type plaque reduction neutralization test (PRNT) is considered the reference method to measure antibody response for many viral diseases, micro-neutralization (MNA) and pseudotyped virus neutralization assays (PNA) carry some advantages over PRNT, as shown in the table below. Together, Nexelis and PHE developed protocols for all three assay types.[1]

The MNA reduces assay time, allows increased throughput, and reduces operator workload while remaining dependent upon the use of wild-type virus. This ensures that all SARS-CoV-2 antigens are present, but Biosafety Level 3 (BSL3-3) facilities are still required. PNA also offers greater efficiency than PRNT. Furthermore, once its neutralizing activity has been correlated with that of PRNT or MNA, PNA can be performed with less stringent biocontainment as it utilizes a pseudotyped virus rather than the wild type.

Comparison of Assay Types Developed for SARS-CoV-2 Vaccine R&D

	PRNT Plaque Reduction Neutralization Test	**MNA** Micro-Neutralization Assay	**PNA** Pseudotyped Virus Neutralization Assay
Speed	• Long turnaround time • Very low throughput	• Reduced assay time • Increased throughput	• Reduced assay time • Even higher throughput than MNA
Level of technical difficulty	• Technically demanding • Difficult to automate	• Reduced operator workload	• Reduced operator workload
Virus type used	• Wild-type virus	• Wild-type virus	• Pseudotyped virus
Implications of virus type used	• All SARS-CoV-2 antigens present	• All SARS-CoV-2 antigens present	• Not all SARS-CoV-2 antigens present • Must correlate neutralizing activity vs. PRNT or MNA
Biosafety requirement	• BSL-3	• BSL-3	• BSL-2
Suitability of data output for regulatory submission	• Problematic	• Good	• Good
Qualified assay	• No	• Yes	• Yes

The whole team was reallocated to SARS-CoV-2 work beginning in February 2020 with a charter to generate any and all immunological tools and reagents needed to develop these assays. In addition to developing a suitable assay, our team focused on ensuring that these assays could subsequently be scaled to handle higher sample numbers. In parallel, a team of 20 scientists and analysts (that has now grown to a team of 60 FTEs) collaborated to develop and qualify assays and test up to 50,000 samples per month, an unrivaled capacity.

RESULTS

As of April 2021, PHE and Nexelis teams published in peer-reviewed Nature Protocols "Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays."

In 18 months, Nexelis and PHE Porton Down supported more than 60 SARS-CoV-2 related development projects by multiple multinational pharmaceutical companies, innovative biotechnology companies, governmental and non-governmental bodies including BMGF, CEPI, and BARDA, and are still currently testing more than 50,000 samples per month in their BSL-2 and BSL-3 laboratories.

Nexelis and PHE team's deep expertise in vaccine development were instrumental in our ability to excel in this partnership and achieve method development, qualification, and validation in a period three times faster than previously thought possible.

The team obtained funding and support from BMGF and CEPI, who were expecting to give their grantees access to the same "universal" assays. This initiative facilitated regulatory agencies' clinical data review and allowed for comparisons amongst different trials. CEPI announced the creation of a global network of clinical samples testing laboratories to reliably assess the immunological responses to SARS-CoV-2 vaccine candidates in October. In doing so, CEPI established an agreement with Nexelis to transfer its technology and reagents with its central laboratory network.

NEXELIS RECOGNIZED FOR SARS-COV-2 WORK WORLDWIDE

- Operation Warp Speed: Nexelis is a BARDA COVID-19 Medical Countermeasure Support Service Partner for high-throughput SARS-CoV-2 assay development and testing of human serum samples.
- The Coalition for Epidemic Preparedness Innovations (CEPI) has partnered with Nexelis to lead its centralized global network of clinical sample testing labs in assessing and comparing the immunological responses generated by SARS-CoV-2 vaccine candidates.
- The Bill & Melinda Gates Foundation awarded Nexelis a grant to provide centralized assays to support studies of over 20 vaccine candidates and approximately 200 monoclonal antibody candidates.
- In May 2021, Nexelis obtained the prestigious Vaccine Industry Excellence best central/specialty laboratory award in recognition for its contribution to the development of lifesaving vaccines.
- Nexelis proudly contributed to over 60 SARS-CoV-2 development projects including four of the first five vaccines reaching the commercial stage.

Nexelis' neutralization assay robustness was tested on a panel of samples against assays developed by 48 other laboratories in the world (18 wild-type virus and 30 PNAs). The results demonstrated the excellent precision and accuracy of our assays. A blind version of the survey was shared by principal investigator David Montefiori at Duke University.

14th Annual ViE Vaccine Industry Excellence AWARDS

Best Central/Speciality Laboratory Award

In May 2021, Nexelis proudly obtained the prestigious Vaccine Industry Excellence best central/specialty laboratory award in recognition for its contribution to the development of lifesaving vaccines.

The succession of events showcases our unique position within the industry, world class immunology sciences, agility and ingenuity, a translational broad scope of services, and collaborative mindset making Nexelis a company tailored for strategic partnerships.

For what's next in immunology and vaccine testing and development, choose Nexelis.

[1] Kevin R. Bewley, Naomi S. Coombes, Luc Gagnon, Lorna McInroy, Natalie Baker, Imam Shaik, Julien R. St-Jean, Natalie St-Amant, Karen R. Buttigieg, Holly E. Humphries, Kerry J. Godwin, Emily Brunt, Lauren Allen, Stephanie Leung, Phillip J. Brown, Elizabeth J. Penn, Kelly Thomas, Greg Kulnis, Bassam Hallis, Miles Carroll, Simon Funnell, and Sue Charlton. "Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays." Nature Protocols. April 23, 2021. https://www.nature.com/articles/s41596-021-00536-y?

ABOUT NEXELIS

With unrivaled expertise in immunology, 5 operating sites in North America and Europe, and a translational offer of services covering the needs of the pharmaceutical industry from the lead selection to the late clinical stage, Nexelis is a leading provider of assay development and advanced laboratory testing services in the infectious, metabolic and oncologic fields. Our versatile team of scientists, working with state of the art technology platforms, were instrumental in the development, qualification, validation, and large-scale sample testing of assays that supported the FDA filing of almost 100 new molecular entities, including blockbuster vaccines and biologics, anti-viral drugs, immunotherapy, gene and cell therapy products.

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