COVID-19 Mass Spectrometry Coalition – Action to Accelerate Diagnostics and Treatment

The novel coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, was declared a pandemic by the World Health Organisation on 12th March 2020 following its emergence in Wuhan China.[1] As of the 4th April 2020 there were over 1.2M confirmed cases of COVID-19 in 175 countries, with over 65,000 fatalities.[2] SARS-CoV-2 is one of three new pathogenic coronaviruses which have jumped from animal to human hosts over the past 20 years, and the current pandemic sends warning signs about need for preparedness and associated research.

Today's ability to undertake rapid and comprehensive genetic sequencing has shed light on the virus' origin from animal reservoirs. This has been matched by the rapid development and implementation of PCR tests to determine the presence of viral RNA in infected individuals, as well as the ongoing deployment of serological assays to detect antibodies that recognize the SARS-CoV-2 antigen[3,4]. The successful deployment of these tests relies on accurate descriptors of the viral antigens and of the host response. All tests require comprehensive validation and must be done on many clinical samples with community-wide standards for the required reagents as well as for the adopted methodologies.

Despite the considerable insight gained into SARS-CoV-2 at the genetic level, structural information continues to emerge and, as it does, our understanding of molecular descriptors that contribute to disease progression become less well defined, especially when we consider spread across different populations.[3,5] The provision of rapid, precise and reproducible diagnostic information that complements genomic information, at the proteomic and metabolomic level through the power of mass spectrometry therefore needs to be deployed now in an internationally coordinated effort to accelerate our understanding of COVID-19 disease.

The questions that can be answered by mass spectrometry-based analysis broadly fall into three categories. The first concerns profiling the host response, where serological testing relies on immunochemical approaches to understand signalling and immune responses during various stages of infection, and correlate prognosis with disease severity. Other biomarkers of host response will further our understanding of disease mechanisms and the susceptibility of certain groups.[6] In this context, the most valuable markers will be those indicating the transition from a beneficial immune response to a harmful inflammatory response and respiratory distress. Such data will allow us to screen high-risk populations, recognize high risk patients, track disease progression and identify sources of vulnerability that will help treat and prevent future coronavirus pandemics.

The second question, and arguably the most urgent, concerns the SARS-CoV-2 viral spike glycoprotein, as it is not only key for host-cell attachment but also as a target for neutralizing antibodies elicited through vaccination. Whilst RNA sequencing is extraordinary informative with regards to viral mutation or adaptation via immune selective pressure, it cannot inform on a critical feature among enveloped viruses, specifically viral spike glycosylation.

Many viruses exploit the glycosylation machinery, using host glycans for immune evasion, for example HIV-1 hiding immunological epitopes behind a "glycan shield". The functional role of SARS-CoV-2 spike glycans, of which there are 66 per trimer[7], is presently undetermined and yet is key for structure-based vaccine design, receptor (ACE2) binding and associated conformational dynamics which influence binding efficacy.[8] Measuring spike glycosylation and plasticity is crucial for the production of vaccine candidates which mimic circulating viruses and for drug development efforts to block receptor attachment and subsequent infection.

The final area, which is critical for policy decision and guidance, concerns *in-situ* analyses. It is still unclear how stable and infectious is SARS-CoV-2 on surfaces, and underlines the need for a robust

diagnostic for viral material as well as for RNA. SARS-CoV-2 RNA has been detected on various surfaces several weeks after they were last touched[9], and also in sewage[10], whether either source also has an infectious protein complement is unknown. Identification of the viral antigen and other biomarkers with mass spectrometry from various contaminated sources at defined time points, could fill this gap in knowledge and help to adopt caution and protective measures.

This collective mass spectrometry effort will provide molecular level information of SARS-CoV-2 in the human host. We propose an international and a comprehensive mass spectrometry-based omics and native approach that will reveal pathophysiological and structural information to treat COVID-19. Working to community standards[11,12], we will report all datasets, to complement genomic data. We need to act now by repurposing mass spectrometry resources in university labs and research institutes across the world that are routinely used for disease diagnosis, characterisation of complex biopharmaceuticals and drug discovery, to help tackle this and potential future pandemics. It is essential that mass spectrometry is now used collectively to quantify the viral antigens used in serological diagnostics and protein-based antigens.

Working with clinical colleagues, our efforts will allow the sharing of methods for sample collection, processing and data formatting. Open datasets will allow the computational community access to valuable information to determine the mechanisms behind antigen response and inform vaccine development, *in-silico* and *in-vitro* antiviral drug development. As countries across the world ramp up testing along with widespread sampling to confirm SARS-CoV-2 exposure and measure immunity, mass spectrometry has a significant role to play, and through these collaborative actions we will benefit all.

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