A cell-based spike protein binding assay highlights differences in antibody neutralising capacity for SARS-CoV-2 variants

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The ongoing SARS-CoV-2 pandemic necessitates the development of tools that can support the development of therapeutics that are efficacious against both current and future viral variants. The engagement of the SARS-CoV-2 spike protein with the ACE2 receptor is a critical step in viral entry and its blockade a major determinant of the efficacy of monoclonal antibody therapeutics and vaccine-elicited serum antibodies.We quantified the binding of a range of SARS-CoV-2 recombinant spike proteins to A549-ACE2 cells by detecting the bound spike protein with secondary detection antibodies, followed by high-content confocal imaging. This system allowed quantification of antibody impact on spike protein binding, including against Delta and Omicron variants. Imaging-based methods for quantification of SARS-CoV-2 infection were also established and used to characterise phenotypic differences between viral variants. Anti-spike receptor binding domain (RBD) antibodies that reduced spike protein binding were identified, and concentration-dependent blocking activity characterised. Blocking activity of these antibodies correlated with their ability to neutralise replicating SARS-CoV-2 infection. Correlation between anti-spike protein antibody levels in plasma and spike blocking activity were also established. Whilst three tested monoclonal antibodies effectively reduced binding of the Delta spike protein, only one of these antibodies displayed a comparable reduction in binding of the Omicron spike protein. Phenotypic differences in expression of viral components and fusogenicity between 'Wuhan', 'Delta' and 'Omicron' viral variants were also characterised. We have developed a bioassay that quantifies the activity of spike protein blocking antibodies. The assay highlights how blocking activity of antibodies varies between SARS-CoV-2 spike protein variants.

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