Structure-guided coronavirus vaccine design

David Veesler[1]

[1]*N/A*

dveesler@uw.edu

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019 resulted in the ongoing coronavirus disease 2019 (COVID-19) pandemic. To understand immunity elicited by SARS-CoV-2 infection or vaccination, we carried out structural and serological analysis of polyclonal and monoclonal antibody responses in hundreds of individuals as the pandemic evolved. We identified an antigenic supersite targeted by all potent neutralizing antibodies specific for the SARS-CoV-2 spike N-terminal domain (NTD) and showed that they protect hamsters against SARS-CoV-2 challenge in vivo. We found that NTD antibodies represent a key part of the immune response against SARS-CoV-2 and exert a selective pressure participating in the emergence of variants harboring NTD mutations enabling escape from neutralization by this type of antibodies. We delineated an antigenic map of the spike receptor-binding domain (RBD) and revealed that it is the main target of neutralizing antibodies in the plasma and memory B cells of infected individuals and that it entirely accounts for cross-variant plasma neutralizing activity. We discovered several RBD-specific, human broadly neutralizing sarbecovirus monoclonal antibodies and showed that they protect hamsters against challenge with SARS-CoV-2 variants of concern.

Based on our antibody studies, we designed a subunit vaccine multivalently displaying the SARS-CoV-2 RBD at the surface of a computationally designed proteinaceous nanoparticle (GBP510) to focus antibody responses on this key domain of vulnerability, an approach completely different from the one followed by major pharmaceutical companies. Our vaccine elicits neutralizing antibody responses that are an order of magnitude more potent than the prefusion-stabilized spike trimer, used for all 3 vaccines distributed in the US, and protects mice and non-human primates from SARS-CoV-2 challenge. This vaccine recently met the study endpoints in a phase 3 clinical trial and will help meet the global demand for doses needed to end the pandemic due to its scalability and high shelf-life stability.

Current SARS-CoV-2 vaccines do not protect against SARS-CoV-1 due to extensive genetic diversity among these related but distinct viruses belonging to the sarbecovirus subgenus. As a result, spillover of another sarbecovirus in humans could lead to a new pandemic. My group is therefore developing multivalent vaccines aiming to elicit broad immunity against sarbecoviruses, including SARS-CoV-2 variants, SARS-CoV-1 and SARS-CoV-X to ensure we are prepared for the future emergence of a novel sarbecovirus. We designed a mosaic sarbecovirus multivalent RBD-nanoparticle and showed it protects mice against SARS-CoV-1 challenge even in the absence of the SARS-CoV-1 RBD in the vaccine. This study provides proof-of-principle for elicitation of broadly protective sarbecovirus immunity, and will enable clinical advancement to curtail the emergence of variants and for future pandemic preparedness.