CONFÉRENCE

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Structure-guided coronavirus vaccine design

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A few weeks after the release of the SARS-CoV-2 genome sequence in January 2020, my lab identified angiotensin-converting enzyme 2 (ACE2) as a *bona fide* receptor enabling entry into target cells of this newly emerged virus. We determined cryoEM structures of the SARS-CoV-2 spike trimer in two functionally relevant conformations, showing that this virus shares a conserved cell invasion mechanism with the one we had discovered for SARS-CoV-1 and MERS-CoV. These structures have been used by thousands of groups worldwide to map and understand the effect of emerging mutations in variants and to guide the design of vaccines and therapeutics.

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. One of these antibodies (S309) is currently used in the clinic worldwide as a variant-proof therapeutic.

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 is currently evaluated in phase 3 clinical trials and will help meet the global demand for doses needed to end the pandemic due to its scalability and high shelf-life stability.

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