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RESEARCH HIGHLIGHT

Novel attempts launched toward universal Sarbecovirus vaccine

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The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and new coronaviruses raise the demand for universal vaccines. In recent *Science* and *Cell* papers, Martinez et al. and Nathan et al. reported two novel approaches for vaccine design based on structural analysis on the immunogens to achieve better elicitation of broad B cell or T cell responses against Sarbecoviruses, respectively.

The emerging SARS-CoV-2 variants are challenging the current COVID-19 vaccines. Sarbecoviruses (lineage B of genus *Betacoronavirus*) have caused two major outbreaks during the past two decades (SARS-CoV in 2003, and SARS-CoV-2 from 2019), and more SARS-like viruses are continuously found from nature reservoirs. Therefore, universal vaccines against Sarbecoviruses are key to ending the current pandemic, and to preventing additional emergent variations and future outbreaks.

SARS-CoV-2 spike is the major immunogen for current vaccines. Three structurally independent modules on a spike, i.e., receptor-binding domain (RBD), N-terminal domain (NTD), and the S2 subunit, can elicit neutralizing antibodies.[1] However, coronaviral spikes show considerable genetic diversity among different species and variants. Moreover, convalescent COVID-19 patients show little cross-neutralizing activity against SARS-CoV,[2] suggesting that the current immunogen may not elicit broad protection. A previous study discovered that nanoparticles displaying heterologous Sarbecovirus RBDs produced a broad humoral immune response.[3] In a new work published in Science, Martinez et al.[4] designed four chimeric spikes that fuse NTD, RBD, and the rest of spike from different Sarbecoviruses. For example, one of the four designs includes NTD from the bat HKU-3 coronavirus, RBD from SARS-CoV RBD, and the remainder of the spike from SARS-CoV-2 (Fig. 1a). They confirmed the successful fold and activity of each spike by successfully rescuing the corresponding infectious recombinant viruses and queried whether the trivalent immunogens would elicit broadly protective antibodies against Sarbecoviruses. For these immunization experiments, lipid nanoparticle-encapsulated, nucleoside-modified mRNA was chosen to express chimeric spikes, since this kind of mRNA vaccine potently activates B cell responses[5] and is comparable with the licensed SARS-CoV-2 mRNA vaccines. To determine the most effective combination, they performed four vaccination strategies in parallel, each in aged mice: (1) prime and boost with all four chimeric spikes; (2) prime with two chimeric spikes, and boost with the other two spikes; (3) prime and boost with one single chimeric spike; (4) prime and boost with prototype SARS-CoV-2 spike (representing the current monovalent vaccine). By binding and neutralization assays, strategy 1 elicited antibodies with the highest cross-reactivity (against SARS-CoV, SARS-CoV-2, HKU-1 and RsSHC014), whereas strategy 4 could only induce significant antibodies against spike of SARS-CoV-2 and two other viruses with high identity to SARS-CoV-2 (Pangolin GXP4L and bat RaTG13). Both strategies 1 and 4 elicited similar in vitro neutralizing potency against prototype SARS-CoV-2 and three variants (B.1.1.7, B.1.351, and mink "Cluster V"), but only strategies 1 and 2 conferred full protection in mice challenged with SARS-CoV, SARS-CoV-2, and B.1.351 variant, whereas strategy 4 could only protect mice infected with SARS-CoV-2 viruses. The broad protection provided by strategy 1 is probably due to its multiplexed formulation which includes the exact immunogenic domains from these Sarbecoviral species (Fig. 1a). To extend the application of the chimeric spike vaccine candidate, the authors also demonstrated that strategies 1 and 2 could confer protection against a heterologous Sarbecovirus, WIV-1.

Overall, this study proves the concept that immunization with multiplexed chimeric spikes confers broader protection against Sarbecoviruses, which is an important step for pan-Sarbecovirus vaccine development. The structure-based multivalent vaccine is well-designed, but more effort will be required to make it a universal Sarbecovirus vaccine. The cross-protection against SARS-CoV, SARS-CoV-2, HKU-1, and RsSHC014 is achieved by combining the immunogenic domains from these viruses. Although there is no WIV-1-derived immunogen in these chimeric spikes, WIV-1 and RsSHC014 are close in the phylogenetic tree and their spikes share high sequence similarity. Further, strategy 1 failed to exhibit better neutralization activity than strategy 4 against variant B.1.351. The next step would be to evaluate additional viruses and variants to confirm the protection breadth. Moreover, the chimeric immunogens could be further optimized via counterpart replacements and local, structure-directed epitope modifications to improve the cross-reactivity and simplify the formulation process.

Complementary to antibody-dependent protection, elicitation of broad T cell response is another critical aspect in vaccine design. This month in *Cell*,[6] Nathan et al. predicted and verified highly conserved $CD8^+$ T cell epitopes across the SARS-CoV-2 proteome by analyzing protein structural information. They assumed that a single residue in a protein would be less mutable during evolution if it has more interactions with other residues, because it may be crucial to maintain the local conformation. SARS-CoV-2 spike and other 14 proteins with high-quality structures were studied in a structure-based network analysis,[7] in which the mutationally constrained regions were identified and scored. Sequence alignment showed that the regions on a spike with high network scores are also

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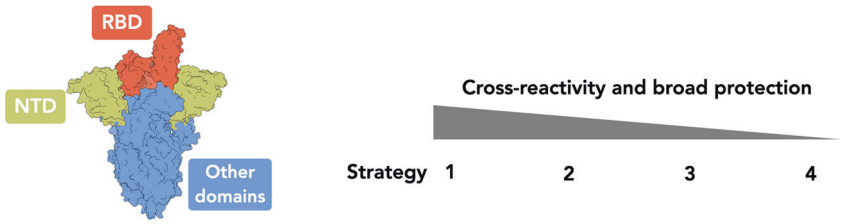
a

Chimeric spike design				Vaccination strategies			
Spike	NTD	RBD	Other domains	Strategy-1	Strategy-2	Strategy-3	Strategy-4
Chimera-1	HKU3-1	SARS-CoV	SARS-CoV-2	Prime/Boost	Prime	N/A	N/A
Chimera-2	SARS-CoV	SARS-CoV-2	SARS-CoV	Prime/Boost	Prime	N/A	N/A
Chimera-3	SARS-CoV-2	SARS-CoV	SARS-CoV-2	Prime/Boost	Boost	N/A	N/A
Chimera-4	SARS-CoV-2	RsSHC014	SARS-CoV-2	Prime/Boost	Boost	Prime/Boost	N/A
SARS-CoV-2	SARS-CoV-2			N/A	N/A	N/A	Prime/Boost



b

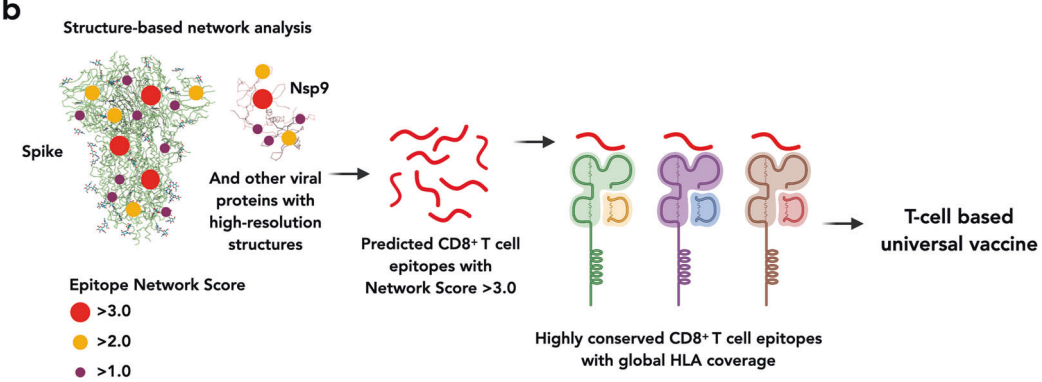


Fig. 1 Schematic summaries of novel approaches in pan-Sarbecovirus vaccine design. a Chimeric spikes recombined with heterologous domains from different Sarbecoviruses are designed as immunogen candidates. The results of different vaccination strategies demonstrate that a mixture of multivalent immunogens confer a higher level of cross-protection than monovalent immunogens. **b** Regions across SARS-CoV-2 proteome with high Network Score (>3.0) are identified by structure-based network analysis. Conserved $CD8^+$ T cell epitopes with global HLA coverage, which benefit universal vaccine design, are further discovered from the high-scored epitope pool.

conserved among Sarbecoviruses, and the mutation of these residues impaired pseudovirus infectivity, which verified the irreplaceable attribute of the residues. The authors further identified highly conserved $CD8^+$ T cell epitopes (8, 9, 10, or 11AA peptides from SARS-CoV-2 proteome with network scores > 3.0), and defined the putative binders for 18 globally dominant human leukocyte antigen (HLA) class I alleles by in silico prediction. The epitopes in the narrowed pool were characterized by wet-lab experiments, and 109 highly networked (conserved) $CD8^+$ T cell epitopes which could stably bind to 18 HLA class I alleles were finally found (Fig. 1b). These epitopes can be recognized by $CD8^+$ T cells from both convalescent COVID-19 patients and people vaccinated with mRNA vaccines.

The authors creatively utilized 3D structure information to find highly conserved T cell epitopes, reaching beyond sequence conservation towards structural constraint. This study represents a promising direction for T cell-based universal vaccine design.

Learning from the vaccine development against other pathogens (e.g., HIV[8] and Lassa virus[9]) has demonstrated that the two arms of adaptive immunity, B cell and T cell responses, need to be considered together during vaccine design. The elicitation of broad B and T cell responses, and consideration of conserved epitopes and thoughtful display of multivalent and/or chimeric antigens would be the final answer against the next coronavirus pandemic.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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