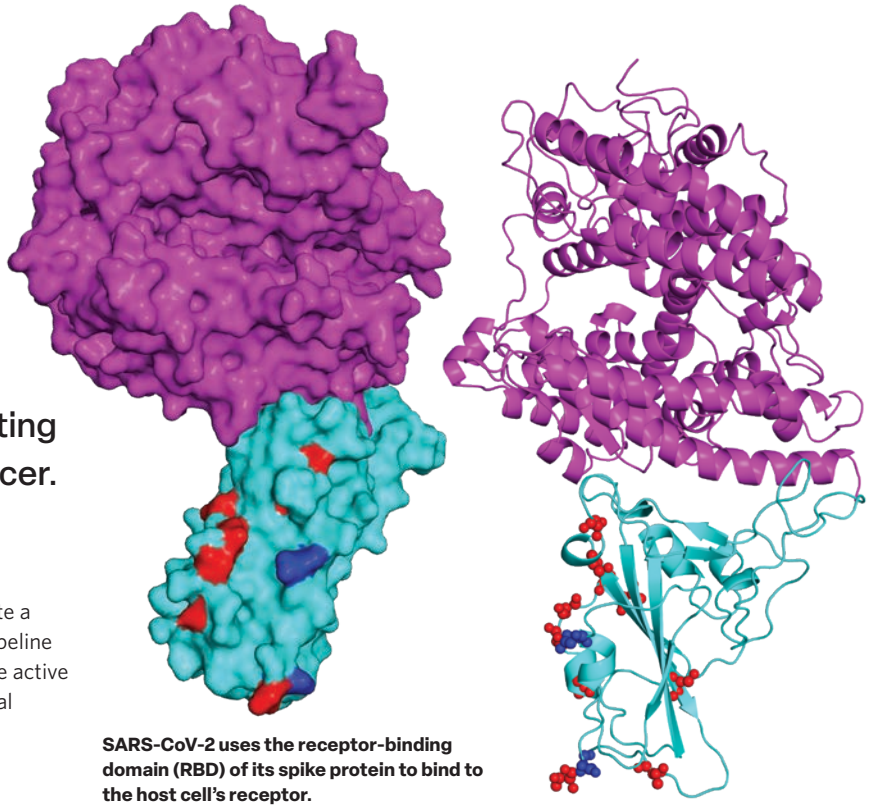
Exploring new frontiers in biotherapy

Biotherapies hold promise of combating transmissible diseases, and lung cancer.



SARS-CoV-2 uses the receptor-binding domain (RBD) of its spike protein to bind to the host cell's receptor.

Almost immediately after the outbreak of COVID-19 in China in early 2020, Yuquan Wei formed a team to begin research for a vaccine. Unlike those who took a chance on other novel approaches, they decided to focus on the recombinant protein vaccine — a type of vaccine that has repeatedly demonstrated its efficacy in preventing Hepatitis B, influenza and human papillomavirus.

Recombinant protein vaccines use the proteins of a virus to activate the immune system. "It's a safe and proven technology, with simple composition and few side effects," says Wei, director of the State Key Laboratory of Biotherapy and Cancer Centre, West China Hospital of Sichuan University. Wei adds that "long-established manufacturing and quality control systems can lead to vaccines with high quality at lower cost."

For decades, Wei's team has combined strengths in clinical, pharmaceutical and materials science to create a technology translation pipeline of biotherapies, which use active ingredients from biological sources to stimulate the immune system.

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SARS-CoV-2 uses the receptor-binding domain (RBD) of its spike protein to bind to the host cell's receptor and enter the cell. Based on computational analysis of the protein structure, they designed a recombinant protein targeting the RBD.

After six months of research, the team published the pre-clinical data in *Nature*[1] in July 2020. Animal studies show that as early as 7 days after a single dose of injection, the recombinant protein can elicit potent functional antibody responses in mice, rabbits and rhesus macaques.

They use the insect cell expression system, a well-known tool for the production of complex proteins, and have built a production site with an annual capacity of 100 million doses. "With our design and production platform, we can now develop effective vaccines against the new variants within three months," says Wei.

Phase III clinical trials of these RBD-based vaccines have been completed, and applications for conditional marketing authorization are underway in China and Japan. In addition, the team has finished *in vivo* studies of two inhibitors against the virus, published in *Science*[2], and is conducting pre-clinical studies of a drug candidate.

Therapeutic gene editing

Wei's colleague, You Lu, director of the Department of Thoracic Oncology, made yet another breakthrough in therapeutic gene editing. In 2016, Lu initiated the first-in-human phase I clinical trial of gene-edited T cell for advanced non-small-cell lung cancer treatment.

In this study, Lu's team used CRISPR-Cas9 based gene editing to disrupt the checkpoint inhibitor gene *PD-1* in T cells, before the modified T cells were transfused to patients. Based on earlier cell and animal studies, Lu hypothesized that this approach might assist in releasing the 'brake' of the immune system, increasing its ability to kill cancer cells. The results were published in *Nature Medicine*[3] in 2020.

Therapeutic gene editing still faces significant challenges before it can be widely used in clinical practice. Safety is a key concern, says Lu. "Efficiency, selection of target genes and prevention of potential adverse effects" are major considerations for the team.

The quest for more effective and safer biotherapies continues at West China Hospital. The researchers are working towards a more precise gene-editing approach, looking for better biomarkers and targets with a higher specificity, and exploring the integration of emerging biotherapies with conventional therapies for future cancer treatment. "Taking on such challenges will help biotherapies benefit more people," says Wei. ■

References

1. Yang, J., Wang, W., Chen, Z. *et al. Nature* **586**, 572–577 (2020)
2. Qiao, J., Li YS., Zeng R. *et al. Science* **371**, 1374–1378 (2021)
3. Lu, Y., Xue, J., Deng, T. *et al. Nat Med* **26**, 732–740 (2020)