A promising vaccine approach to induce longer-lasting protective immunity against COVID-19

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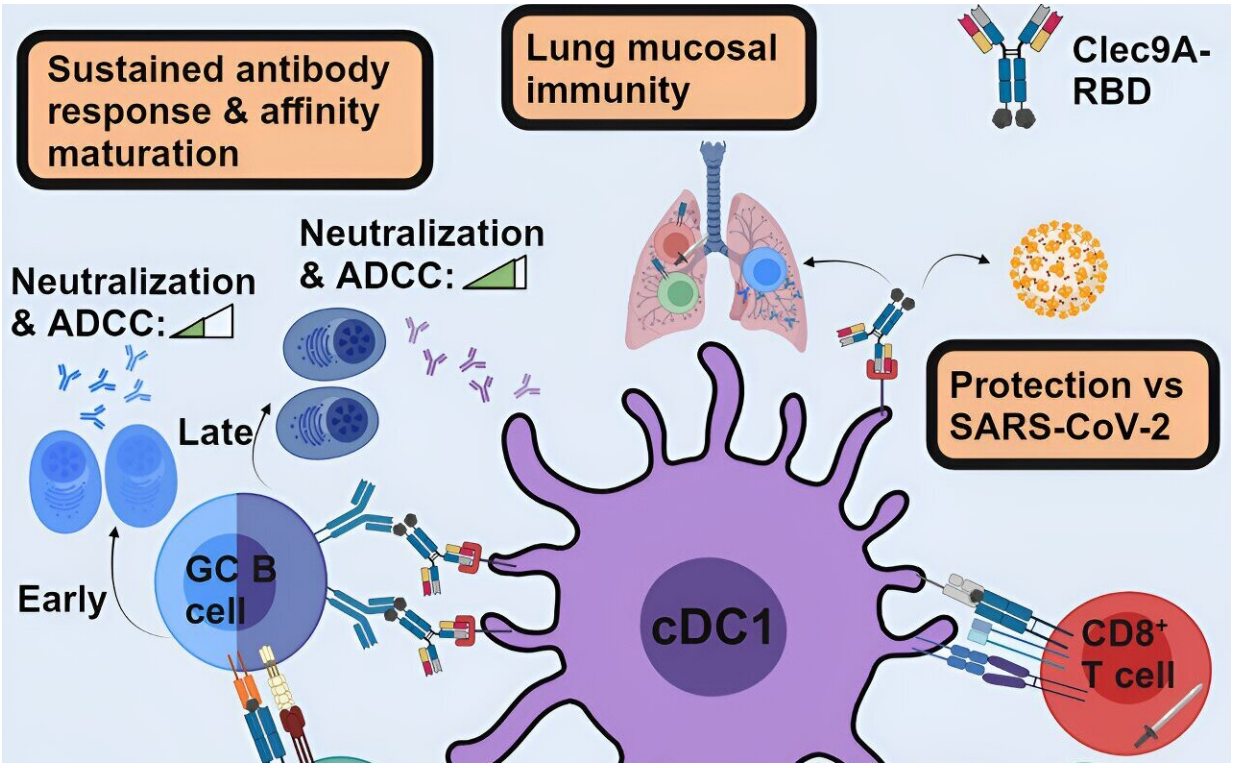

Graphical abstract. Credit: *Molecular Therapy* (2024). DOI: 10.1016/j.ymthe.2024.05.003

A team from the Yong Loo Lin School of Medicine at the National University of Singapore (NUS Medicine) and Monash University has

engineered a COVID-19 vaccine that induced—in pre-clinical models—very long-lasting, protective immunity against SARS-CoV-2 virus with a single-shot immunization.

In an ongoing, four-year collaboration, the team leveraged a novel vaccine platform to fuse the receptor-binding domain (RBD) from the spike protein of the SARS-CoV-2 virus to the Clec9A antibody. The Clec9A antibody targets a specific subset of dendritic cells, a specialized type of immune cells found in tissues such as the skin, which are responsible for initiating immune responses in our body.

Upon a single shot immunization of the Clec9A-RBD antibody construct, the team monitored the immune responses in pre-clinical models over 21 months, and found no signs of declined immunity. In contrast, it observed that the quality of the immune response (the neutralizing antibody response, in particular), was associated with increased protection over time.

The study, titled "Single-shot dendritic cell targeting SARS-CoV-2 vaccine candidate induces broad, durable and protective systemic and mucosal immunity in mice," is published in *Molecular Therapy*,

This new Clec9A targeting technology may potentially address the issue of waning COVID-19 vaccine immunity, and eliminate the need for repeated booster jabs, particularly for people aged 60 and over, medically vulnerable individuals and their caregivers.

"The results that we see in this study are very promising, and we are confident that the work performed in pre-clinical models is highly translatable to humans," said Associate Professor Sylvie Alonso, Principal Investigator of this study. "Indeed, a human equivalent of this immune cell subset exists, and our collaborator, Associate Professor Mireille Lahoud, at Monash University is developing this approach

towards future human application."

Associate Professor Lahoud said, "This study demonstrates the strength of our platform targeting specialized immune cells for vaccine improvement, and exemplifies the power of international research collaborations spanning basic discoveries to translational studies."

"There remain many diseases where effective vaccines have proven difficult to generate. Validation of this platform provides strong proof-of-concept for application to such challenges," she said.

Current Messenger RNA (mRNA) COVID-19 vaccines have been reported to demonstrate peak effectiveness of 62% after three weeks, post-jab, before declining to 9% after nine months. Protection from booster doses has been reported to wane, dropping from 60% one month after the booster dose to 13% at nine months.

"Our teams in NUS Medicine and Monash University foresee that the exceptional durability of the immune responses induced by the Clec9A targeting technology, when used as a booster vaccine strategy, may address the shortcoming of current mRNA vaccines, chief of which is the rapid waning of immune responses," Associate Professor Alonso, who is also co-Director of the Infectious Diseases Translational Research Programme at NUS Medicine said.

"We are now evaluating our vaccine candidate as a booster vaccine in mRNA-vaccinated pre-clinical models. We hope to demonstrate that this booster approach will induce long-term protective immunity, and avoid the need of multiple (annual) booster shots.

"Beyond COVID19, this versatile, rapidly-deployable vaccine platform shows promising potential to be part of the pandemic response against diseases caused by unknown pathogens in the future."

This latest breakthrough follows closely on the heels of the team's 2022 research, published in the *Proceedings of the National Academy of Sciences* of the United States of America. Back then, it leveraged on the Clec9A targeting vaccine platform to deliver the universal influenza vaccine candidate M2e.

M2e is notoriously known to be unable to induce strong and durable immune responses. The team demonstrated that a single-shot immunization of the Clec9A-M2e construct triggered long-lasting immune responses to effectively protect against multiple strains of the flu. It effectively removes a major bottleneck in the clinical development of M2e-based vaccine candidates.

More information: Nicholas You Zhi Cheang et al, Single-shot dendritic cell targeting SARS-CoV-2 vaccine candidate induces broad, durable and protective systemic and mucosal immunity in mice, *Molecular Therapy* (2024). DOI: 10.1016/j.ymthe.2024.05.003

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