Self-amplifying RNA vaccines against antigenically distinct SARS-CoV-2 variants

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Compared with conventional mRNA-based vaccines, self-amplifying RNA (saRNA) vaccines promise improved and longer-lived potency due to both the amplification of the RNA in vivo and the adjuvating properties of double-stranded RNA and its replication intermediates.[1] Inducing protective immune responses by delivering an RNA through a self-amplifying mechanism should therefore require lower doses than for mRNA-based vaccines.

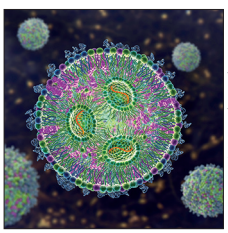
saRNA vaccines have now entered clinical trials. Arcturus Therapeutics previously reported the safety and immunogenicity of the COVID-19 vaccine ARCT-021 in a phase 1/2 trial[2] and is currently evaluating the immunogenicity and efficacy of an improved vaccine, ARCT-154, in an integrated phase 1/2/3a/3b, randomised, observer-blinded trial in adults with no pre-existing SARS-CoV-2-specific immunity.[3] The ARCT-154 vaccine comprises a replicon based on the Venezuelan equine encephalitis virus (VEEV), in which the VEEV structural proteins were replaced with the full-length ancestral spike protein of SARS-CoV-2 with stabilising mutations. In the integrated phase 1/2/3a/3b trial, which was conducted during the circulation of the delta (B.1.617.2) variant of SARS-CoV-2, two doses of ARCT-154 were well tolerated and immunogenic. The authors reported an efficacy of 56·6% against any form of COVID-19 and 95·3% against severe disease.

In *The Lancet Infectious Diseases*, Yoshiaki Oda and colleagues[4] conducted a side-by-side immunogenicity comparison of ARCT-154 with the mRNA-based vaccine BNT162b2 when given as fourth-dose boosters. In this double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial, which was conducted in adults who had previously received three doses of an mRNA vaccine, ARCT-154 was administered as a 5 µg dose, whereas BNT162b2 was given as a 30 µg dose. 4 weeks after the ARCT-154 booster dose, immune responses to the Wuhan-Hu-1 (ancestral) strain of SARS-CoV-2 were non-inferior compared with those in individuals who received a BNT162b2 booster dose. Notably, recipients of the ARCT-154 booster dose had superior immune responses against the antigenically distinct BA.5 variant to those who received the BNT162b2 booster dose, and the authors are in the process of assessing immunogenicity to currently circulating SARS-CoV-2 variants.

Taken together, these two studies show that the saRNA vaccine ARCT-154 is immunogenic as both a priming and a booster vaccine. As a priming vaccine, the efficacy was slightly lower than that initially reported with mRNA-based vaccines;[5,6] however, the booster dose induced broader responses than an mRNA-based vaccine. This finding could be crucial in the current phase of the ongoing COVID-19 outbreak, in which booster vaccine updates are required to combat antigenically distinct SARS-CoV-2 variants.[7–9]

The authors are cautious in discussing the need for vaccine updates if saRNA vaccines were to be implemented as booster vaccine doses, but it is tempting to speculate that, compared with mRNA-based vaccination, the broader neutralisation profile after saRNA vaccination correlates to better vaccine efficacy against antigenically distinct variants. If this is true, saRNA booster vaccines that do not completely match with novel emerging variants could give better clinically relevant protection than the updated mRNA-based booster vaccines. However, the authors do not discuss why saRNA vaccination leads to broader neutralisation profiles than mRNA-based vaccination in their study—after all, both vaccines encoded a stabilised version of the ancestral SARS-CoV-2 spike protein.

The importance of local immune responses in mucosal tissues to achieve protection against respiratory viruses is becoming increasingly clear; however, mucosal vaccines have not been used in the interruption of the COVID-19 pandemic outside of clinical trials. Recent advances in liposome formulation and lipid nanoparticle encapsulation for mRNA-based vaccines, and the propensity of these molecules to be taken up by mucosal tissues, have created novel opportunities for the application of saRNA vaccines as mucosal vaccines. In mice, a direct comparison between administration routes of an saRNA COVID-19 vaccine showed that intranasal vaccination induced robust respiratory mucosal immune responses, whereas intramuscular vaccination did not.[10] Even when used as a booster



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dose after intramuscular priming, intranasal saRNA vaccination elicited the development of mucosal SARS-CoV-2-specific T cells.

The study by Oda and colleagues,[4] in combination with other clinical trials of saRNA vaccines,[11] suggests that these vaccines are safe, well-tolerated, and immunogenic. In particular, the superior immune responses elicited by saRNA vaccines compared with mRNA vaccines against antigenically distinct SARS-CoV-2 variants are encouraging. Additionally, saRNA vaccines formulated on lipid nanoparticles were shown to be thermostable at room and refrigerated temperatures, in contrast to the early mRNA-based vaccines.[12] Finally, the application of saRNA vaccines as mucosal vaccines (eg, administration as nasal spray) could expand the potential of vaccines in reducing SARS-CoV-2 transmission. Taken together, saRNA technology could represent an improvement in RNA vaccine technology, but whether this leads to better and longer-lasting immunity warrants further investigation.

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