Self-amplifying RNA as a tool to tackle emerging flavivirus outbreaks: lessons learned from the COVID-19 pandemic

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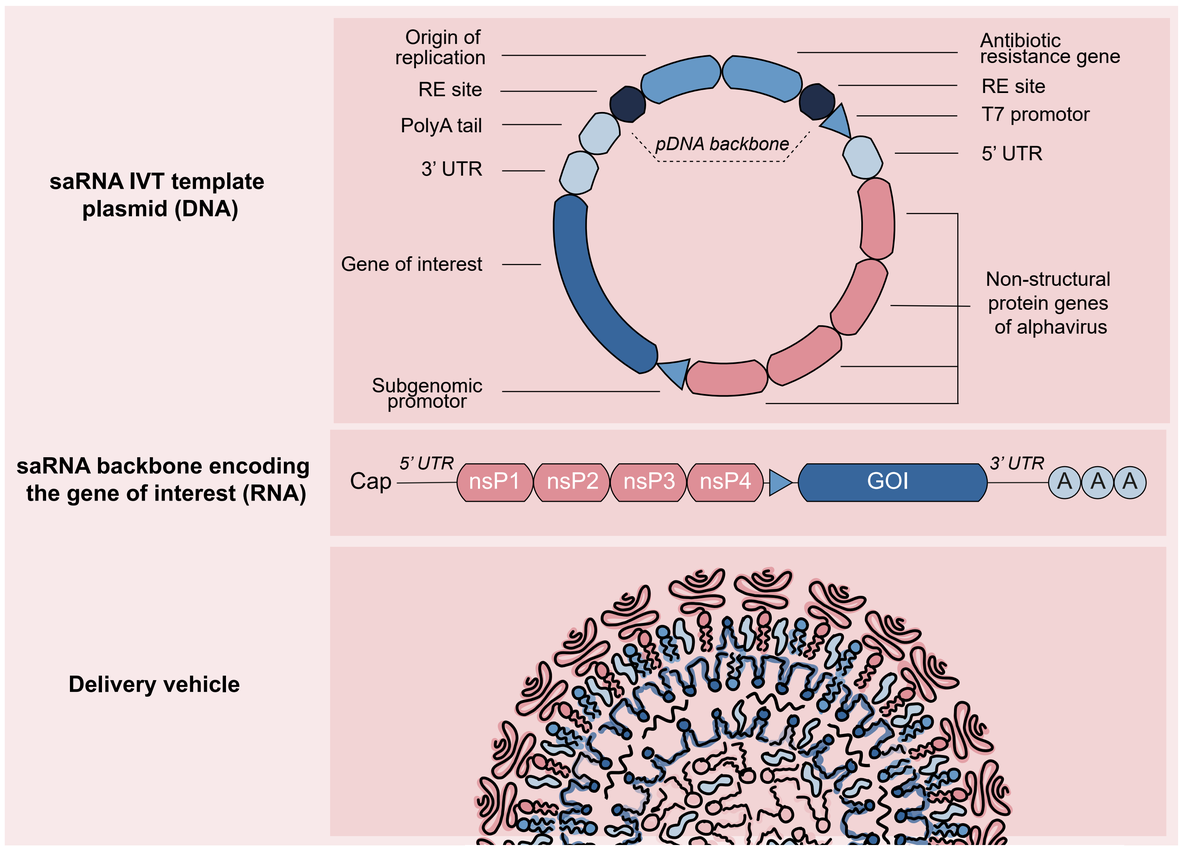
Background

Outbreaks of multiple Flaviviruses have afflicted humankind for centuries due to their rapid spread predominantly by arthropod vectors. Global warming has caused epidemics to emerge in previously unaffected regions. The SARS-CoV-2 outbreak and subsequent race in vaccine development can provide strategies to the scientific community to avoid a flavivirus pandemic.

The COVID-19 battle led to the first-time authorization of messenger ribonucleic acid (mRNA) based vaccines that employ in vitro transcribed (IVT) synthetic mRNA molecules to instruct host cells to produce the viral antigen in a natural way. The mRNA platform has proven to carry several advantages over other vaccination strategies, including its flexibility due to relatively easy sequence engineering and its inability to integrate into the host's genome. In recent years, mRNA vaccines have been generated against multiple flaviviruses, including tick-borne encephalitis virus (TBEV) and Dengue virus.

However, most of these vaccines target structural protein epitopes to induce neutralizing antibody responses, which is complicated by the potential induction of antibody-dependent enhancement (ADE). ADE is a phenomenon in which sub-neutralizing concentrations of anti-viral IgGs enhance infection of Fc gamma receptor positive cells, thereby increasing the risk of an exacerbated pathogenesis upon infection after vaccination.

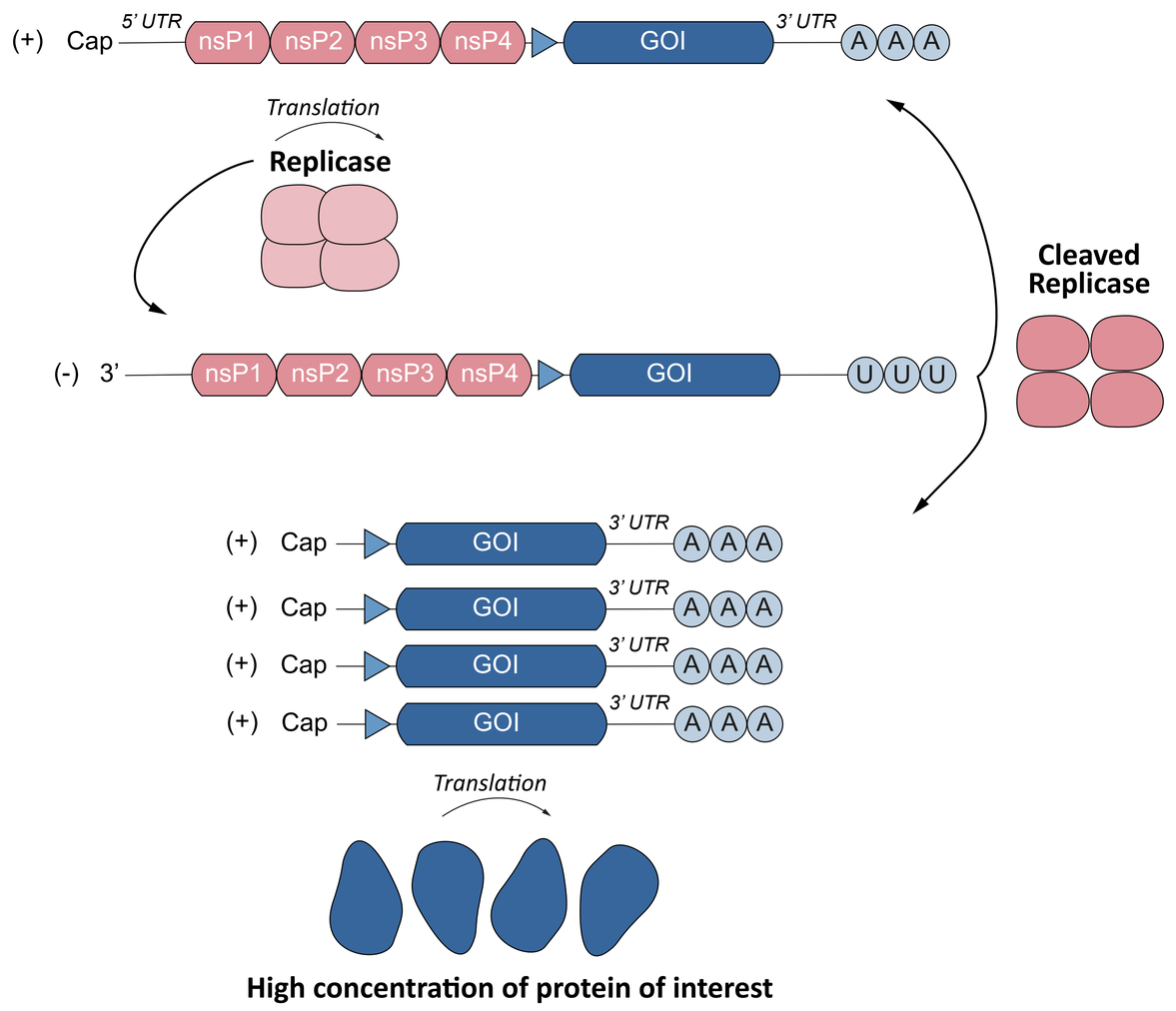


Methodology

To avoid vaccine-induced ADE, next-generation vaccination strategies should aim to stimulate T-cell-mediated immunity against multiple antigens, including flaviviral non-structural proteins. The self-amplifying (sa) RNA platform provides such opportunity, as it carries the option for single-vector delivery of multiple and/or complex polypeptides by incorporation of multiple subgenomic promotors.

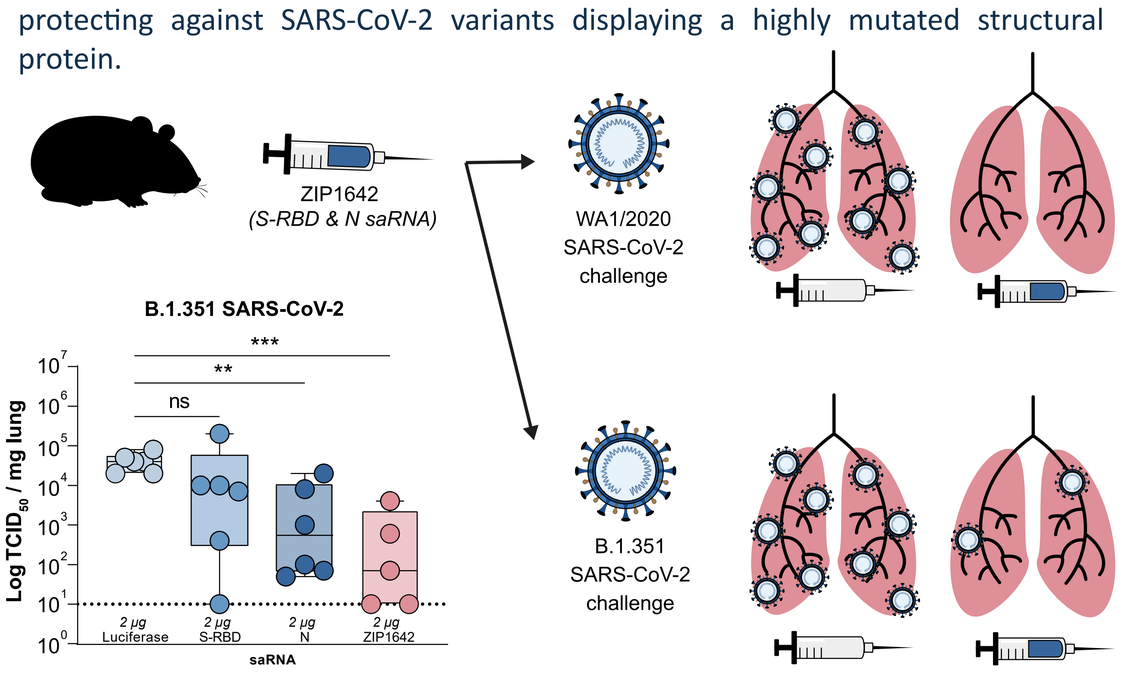
saRNA vaccines also encode for components of an alpha-viral derived RNA-dependent RNA polymerase (RDRP). Upon cytoplasmic delivery of the saRNA, the RDRP is capable of amplifying the original RNA strand and generating high levels of sub-genomic RNA encoding for the viral antigen(s).

This mechanism leads to higher antigen abundance inside the host cell for longer periods of time, which can drive equivalent or more potent immune responses at lower doses compared to those achieved by non-replicating mRNA vaccines.



Results - Proof of concept

Ziphius recently demonstrated that its saRNA platform can induce T-cell mediated immunity following a low dose of a dual-antigen anti-SARS-CoV-2 saRNA vaccine, thereby protecting against SARS-CoV-2 variants displaying a highly mutated structural Spike protein.



Conclusion

As only few research groups have characterized saRNA vaccines against flaviviruses (i.e. Zika virus and TBEV), Ziphius advocates the further acceleration of the development of new multi-antigenic saRNA vaccines with reduced risk for ADE to avoid flavivirus outbreaks.