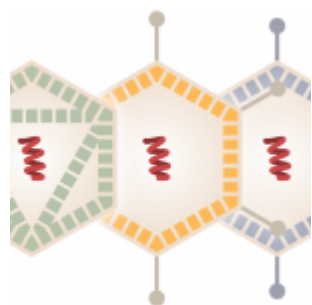
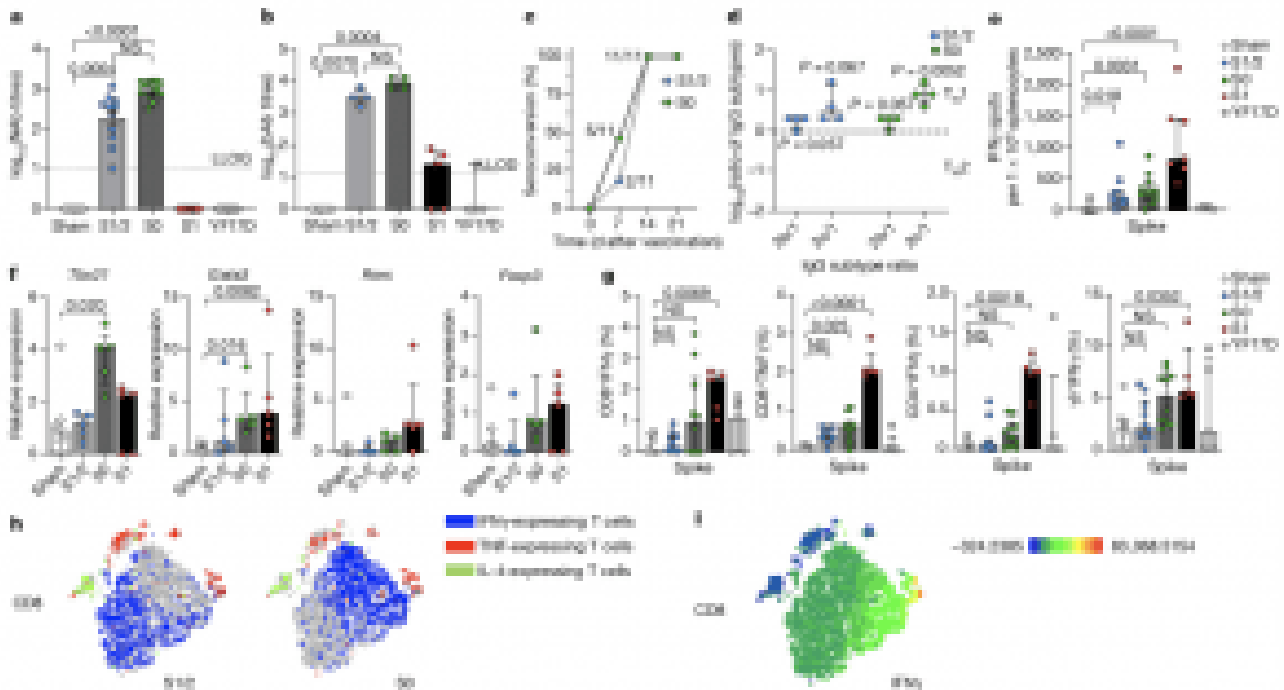


# Pre-clinical evaluation of a vaccine that induces both SARS-Cov-2 and yellow fever virus immunity.



Yellow fever vaccine is one of the most immunogenic and efficacious vaccines that induces life-long immunity after a single vaccine dose. Live-attenuated yellow fever 17D (YF17D) vaccine is a small positive-sense single-stranded RNA live-attenuated virus with limited vector capacity that can tolerate insertions of antigens in the viral polyprotein. This property has facilitated the use of YF17D as a vector for other vaccines *such as the Japanese encephalitis virus (for the Imojev vaccine) or dengue virus (for the Dengvaxia vaccine)*. Researchers thus *aimed to develop a candidate SARS-Cov-2 vaccine that uses the YF17D vaccine as a vector to express a non-cleavable prefusion form of the SARS-CoV-2 spike antigen (YF-S0)*. They then tested the vaccine candidate in 3 preclinical models (mice, hamsters and non-human primates).



**Fig. 1 | Humoral and cell-mediated immune responses in mice.** *Pfmr*<sup>-/-</sup> mice were vaccinated twice (at day 0 and day 7) intraperitoneally with 400 PFU of each construct. **a, b**, Titers of neutralizing and binding antibodies 14 days after vaccination. **c**, Seroconversion rates at the indicated days. **d**, Ratio of IgG2b or IgG2c to IgG1 compared to isotype control T<sub>H</sub>1 or T<sub>H</sub>2 cell response. **e**, **f**, Mice were vaccinated with YF-S12 (*n* = 11), YF-S0 (*n* = 11), YF-S1 (*n* = 11), sham (*n* = 11) or YF17D (*n* = 9); data from 3 independent experiments. For binding antibody quantification (**f**) antiIgG subtyping (a), serum minipools from two random mice are assayed. **g**, Number of IFN- $\gamma$ -secreting cells after 5dSIS-Cut-19 peptide pool stimulation. Mice were vaccinated with YF-S12 (*n* = 11), YF-S0 (*n* = 10), YF-S1 (*n* = 7), sham (*n* = 7) or YF17D (*n* = 5). YF-S1 and YF17D from sham, and YF-S1/2, YF-S0 and sham from sham, independent experiments. **h**, Normalized mRNA expression levels of *Pib2c*, *Ccr4b*, *Il6* and *Foxp3* quantified by RT-qPCR in 5-peptide-stimulated splenocytes. Data are expressed as fold change

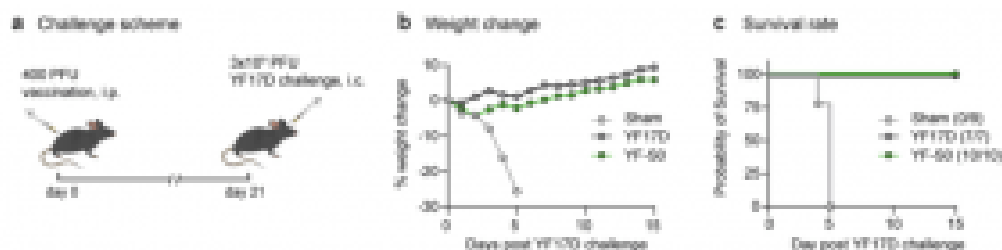
over median of uninfected controls = (YF-S1/2, YF-S0 and YF-S1) = 2 sham and = 1 uninfected control from a single experiment (s.g.). Percentage of IFN- $\gamma$ - and TNF-expressing CD8<sup>+</sup> cells, and IFN- $\gamma$ -expressing CD4<sup>+</sup> and  $\gamma$ H T cells, after 5 peptide stimulation. Mice were vaccinated with YF-S1/2 (*n* = 11), YF-S0 (*n* = 10), YF17D (*n* = 5) or sham (*n* = 6); YF-S1 and YF17D from single experiments; YF-S1/2, YF-S0 and sham from three independent experiments. **i, j**, FACS of IFN- $\gamma$ -specific CD8<sup>+</sup> T cells positive for at least one intracellular marker (IFN- $\gamma$ , TNF- $\alpha$ , IL-4) after 5-peptide stimulation (*n* = 6 for YF-S1/2 and YF-S0). **k**, Heatmap of IFN- $\gamma$  expression density of 5-specific CD8<sup>+</sup> T cells after YF-S1/2 and YF-S0 vaccination. Scale bar represents density with IFN- $\gamma$ -expressing cells; low expression, red; high expression, blue. Data in **h–k** are median  $\pm$  IQR. Two-sided two-tailed t-test (Student's *t*-test) and a one-sample *t*-test (if) was applied.

Source: Sanchez-Felipe et al., 2021

The pre-clinical hamster model showed that YF-S0 induces robust broadly neutralizing antibodies specific to the spike protein that is associated with a significant restriction of the SARS-CoV-2 upon intranasal challenge. Researchers observed similar YF-S0 immunogenicity and protection profiles in the murine and non-human primates model. Analysis of cellular immune responses demonstrated that YF-S0 also induces pro-inflammatory (IFN-g $\gamma$ ) antigen-specific CD4 and CD8 T cells. Lastly, they also demonstrated that YF-S0 also induces broadly neutralizing yellow fever virus-specific antibodies and cellular immunity in mice, and is potentially safer than YF17D.

In summary, findings by Sanchez-Felipe et al., demonstrated that yellow fever virus vectored SARS-CoV-2 vaccine in

immunogenic, safe and protective in pre-clinical studies. Further, this vaccine induces both SARS-Cov-2 and yellow fever virus-specific immunity and could be used as a YF17D boost in older individuals.



Protection from lethal YF17D. a, *Ifnar*<sup>-/-</sup> mice were vaccinated with either a single 400 PFU intraperitoneal (i.p.) dose of YF17D (black) (n = 7) or YF-S0 (green) (n = 10), or sham (grey, n = 9). After 21 days, mice were challenged by intracranial (i.c.) inoculation with a uniformly lethal dose of 3 × 10<sup>3</sup> PFU of YF17D and monitored for weight evolution (b) and survival (c). The number of surviving mice at study end point (day 15) is indicated. Data are from two independent experiments. (Source: Sanchez-Felipe et al., 2021)

**Journal Article: Sanchez-Felipe et al., 2021. [A single-dose live-attenuated YF17D- vectored SARS-CoV-2 vaccine candidate.](#) Nature.**

*Summary by Cheleka AM Mpande*