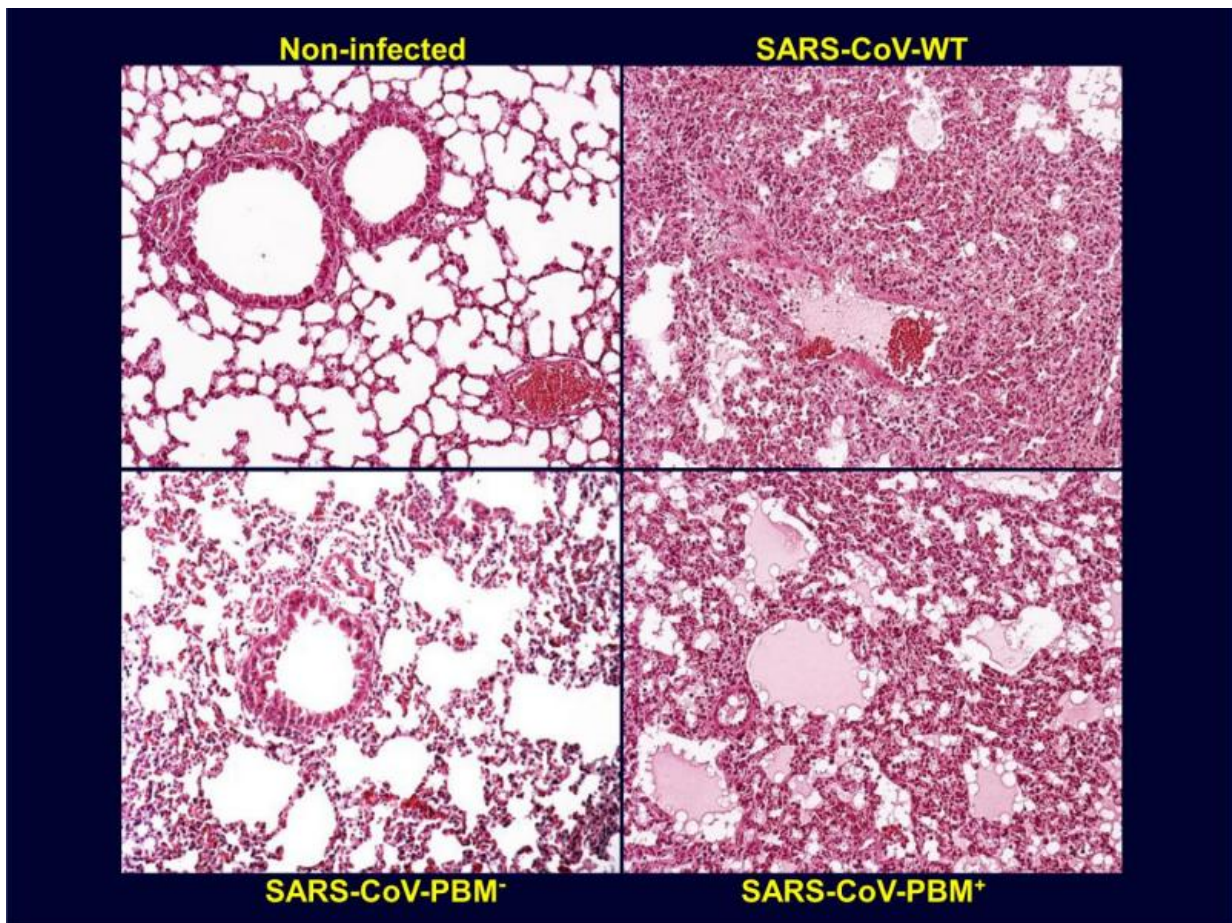


# Towards a safe and efficient SARS-coronavirus vaccine

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Representative tissue sections of lungs from non-infected mice, or mice infected with wild-type SARS-CoV (WT), with an engineered SARS-CoV including an E protein with a functional PDZ-Binding-Motif (PBM<sup>+</sup>) or with E protein PBM motif knocked out (PBM<sup>-</sup>). Non infected mice and mice infected with a SARS-CoV mutant lacking E protein PBM (PBM<sup>-</sup>) showed clear airways which were functional, whereas mice infected with viruses with E protein PBM (WT and

PBM+) showed collapsed airways with lung edema, which led to lung failure and death. Credit: Enjuanes et al, CC-BY

Live attenuated (weakened) viral vaccines are considered safe so long as their "reversal" to a virulent (or disease-causing) virus is prevented. A study published on October 29th in *PLOS Pathogens* reports on how to rationally modify an effective live attenuated SARS vaccine to make it genetically stable.

Luis Enjuanes, from the Centro Nacional de Biotecnología in Madrid, Spain, and colleagues had previously introduced a SARS-CoV lacking the envelope (or E) gene as a promising [vaccine](#) candidate. The researchers had shown that this vaccine, which they called SARS-CoV-ΔE, was attenuated in different animal models, indicating that the E protein is necessary for the [virus](#)' ability to cause disease. They had also demonstrated that vaccination with SARS-CoV-ΔE fully protected mice against challenge with virulent SARS-CoV that is lethal in unvaccinated mice, suggesting that it is an efficient vaccine.

In this study, the researchers addressed the question of stability of the vaccine candidate. To do this, they propagated the SARS-CoV-ΔE virus for a number of generations in cell lines and in mice and found that—over time—the virus accumulates mutations and reverts to a virulent phenotype.

Studying a collection of mutants, they were able to reveal the molecular basis of the reversion: The E protein contains a motif called a PDZ binding motif or PBM, a protein-protein recognition sequence that modulates cellular pathways important for viral replication, dissemination in the host, and pathogenesis. And all the reverted viruses had incorporated in the genome a functional PBM, apparently to

compensate for removal of this motif with deletion of the E protein.

To avoid such compensation and reversal to virulence, instead of deleting the entire gene, the researchers introduced small deletions in the E gene that did not destroy its PBM. Such mutants are still attenuated but appear to no longer select for the incorporation of novel protein domains into the virus genome and so avoid the reversion to virulence.

To create an additional safeguard, the researchers introduced mutations into another SARS-CoV gene called nsp1. Nsp1 was chosen as a second attenuation target because this gene is located at a distant site from that of the E gene in the viral genome, making it very unlikely that a single mutational event can restore both the E gene and the nsp1 gene to their un-attenuated sequences and thereby restore virulence.

The researchers found that small deletions within the nsp1 gene alone resulted in an [attenuated virus](#) that was unable to cause disease but protected vaccinated mice against challenge with the virulent parental virus. And when they tested the new vaccine that includes small attenuating mutations in both the E and nsp1 [genes](#), they saw that it maintains its attenuation after prolonged propagation in vitro and in vivo and provided full-protection of mice against the challenge with the virulent original SARS-CoV.

The researchers conclude that "understanding the molecular mechanisms leading to pathogenicity and the in vivo evaluation of vaccine genetic stability contributed to a rational design of a promising SARS-CoV vaccine". They also suggest that "understanding how an attenuated SARS-CoV reverted to virulence could also be useful for vaccine development against other relevant coronaviruses, such as the MERS-CoV".

**More information:** Jimenez-Guardeño JM, Regla-Nava JA, Nieto-Torres JL, DeDiego ML, Castaño-Rodríguez C, Fernandez-Delgado R,

et al. (2015) Identification of the Mechanisms Causing Reversion to Virulence in an Attenuated SARS-CoV for the Design of a Genetically Stable Vaccine. *PLoS Pathog* 11(10): e1005215. [DOI: 10.1371/journal.ppat.1005215](https://doi.org/10.1371/journal.ppat.1005215)

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