**Freie Universität Berlin**

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# Intranasal Droplets and Sprays Could Help Tackle SARS-CoV-2

## Researchers from Freie Universität Berlin and the University of Bern have published the results of a groundbreaking study

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**Scientists at Freie Universität Berlin (Germany) and the University of Bern (Switzerland) have developed highly effective SARS-CoV-2 preclinical vaccine candidates that can be administered in the form of nasal drops or sprays. Preclinical studies in hamsters demonstrated that the vaccine candidates induce robust neutralizing antibodies and prevent SARS-CoV-2 replication as well as signs of Covid-19. The findings were recently published in an article titled "Development of Safe and Highly Protective Live-Attenuated SARS-CoV-2 Vaccine Candidates by Genome Recoding" in the journal *Cell Reports*.**

Scientists have produced attenuated SARS-CoV-2 vaccine candidates by recoding the genetic information of SARS-CoV-2. To do this, they replaced original sequences in the genome of the pathogenic SARS-CoV-2 with synthetic, codon pair deoptimized sequences. The inserted, deoptimized sequences contain suboptimal codon pairs (a codon being a sequence of three nucleotides with genetic information that corresponds with a specific amino acid) and cause attenuation of the recoded viruses. The recoded viruses exhibit considerable replication defects in cultured cells and infected animals, and their pathogenic properties are significantly reduced. The crucial, new finding here, the research team says, is that the lead vaccine candidate is virtually apathogenic in two different hamster species but elicits strong neutralizing antibody responses. A single intranasal droplet vaccination completely protected hamsters from disease caused by SARS-CoV-2 infection.

The researchers say that genomic recoding did not affect the protein buildup of the virus. Therefore, the parental pathogenic SARS-CoV-2 virus and the recoded attenuated vaccine candidates produce exactly the same proteins. The live-attenuated virus vaccines, which are based on weakened pathogens, replicate in vaccinated individuals and thus stimulate the immune system to mount a response not just against the major surface glycoprotein spike, but the entire ensemble of virus antigens. Thus, modified live virus vaccines producing a wide range of immune responses may protect better against a variety of virus variants that differ mostly in the spike protein, such as the recently emerged variants alpha, beta, gamma, and delta. The authors say that this could have a significant advantage over the mRNA or vector-based vaccines, as these exclusively induce an immune response against the viral spike protein. In addition, live-attenuated virus vaccines can be administered intranasally and thus induce mucosal immune response directly at the site of virus entry. The researchers believe that this may offer better protection of target tissues from infection and could further limit disease severity and virus shedding.

SARS-CoV-2 vaccine candidates developed in this project offer three important advantages over most licensed vaccines and others still in development. First, vaccine candidates contain the entire viral buildup and are not limited to the viral spike protein. Second, vaccine administration is needle-free. Third, vaccines could be administered intranasally to induce immune responses at the site of infection.

"Our research paves the way for the development of sprayable intranasal vaccines," says Dr. Dusan Kunec, of Freie Universität Berlin, senior author of the published study. He added, "The intranasal vaccines tailored based on prevalent SARS-CoV-2 variants could be used in the future as vaccine boosters to refresh and broaden immune responses after primary immunization with other vaccines."

"Especially in the light of the continuing evolution toward new SARS-CoV-2 variants, live-attenuated vaccines may have great advantages over subunit vaccines such as the currently used mRNA or vector-based vaccines" says Dr. Jakob Trimpert, a virologist at Freie Universität Berlin and lead author of the study.

The first prototypes of the live-attenuated vaccines were developed at the University of Bern and the Institute of Virology and Immunology (IVI). The study was conducted as part of the Swiss National Science Foundation's project NRP78 "Recoding the SARS-CoV-2 Genome – A Multidisciplinary Approach to Generate Live-Attenuated Coronavirus Vaccines." The project has brought researchers from Switzerland and Germany together to evaluate different approaches to recoding the SARS-CoV-2 genome in developing vaccines. Alongside Freie Universität Berlin, project partners include the Institute of Virology and Immunology (IVI) headed by Professor Volker Thiel, the University of Bern led by Professor Sebastian Leidel, the University of

Geneva whose research team is managed by Professor Ramesh Pillai, and the Friedrich Loeffler Institute on the island of Riems directed by Professor Martin Beer.

## FURTHER INFORMATION

### Publication

Jakob Trimpert, Kristina Dietert, Theresa C. Firsching, Nadine Ebert, Tran Thi Nhu Thao, Daria Vladimirova, Susanne Kaufer, Fabien Labroussaa, Azza Abdelgawad, Andelé Conradie, Thomas Höfler, Julia M. Adler, Luca D. Bertzbach, Joerg Jores, Achim D. Gruber, Volker Thiel, Nikolaus Osterrieder, and Dusan Kunec: Development of safe and highly protective live-attenuated SARS-CoV-2 vaccine candidates by genome recoding. *Cell Reports 36*, 109493 (2021)
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