In a recent study published in Cell, Afkhami and colleagues systematically compared different routes of vaccine delivery, origin of the vaccine platform as well as valence of the vaccine and demonstrated that the respiratory mucosal delivery of a trivalent chimpanzee’s adenovirus (Ad)-vectored vaccine is superior to any other of the tested conditions in inducing broadly-acting immunity and protection against current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and possibly future variants of concern (VOC). The ongoing global coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has forced an uniquely fast development of novel mRNA- and vector-based vaccines. While these vaccines have proven effective for the control of COVID-19 caused by the ancestral SARS-CoV-2 strain, different VOC escape vaccine-induced immunity and demonstrated a failure in limiting protection efficacy against mild to moderate COVID-19. Therefore, there is an urgent need for the development of improved next-generation vaccines.

Afkhami and colleagues developed trivalent vaccine candidates expressing the SARS-CoV-2 antigens spike protein 1 (S1), nucleocapsid and the RNA-dependent RNA polymerase (RdRp) protein in adenoviral vectors of human (Tri:HuAd) or chimpanzee (Tri:ChAd) origin (Fig. 1a). Interestingly, both the quantity and quality of the humoral and cellular immune response induced upon vaccination clearly depends on the delivery route. More specifically, a single-dose intranasal immunization with Tri:HuAd or Tri:ChAd was clearly superior in inducing systemic (serum IgG) and mucosal (airway IgG, IgA) neutralizing antibodies compared to the Ad-vector of human origin (Tri:HuAd). Thus, the authors unequivocally demonstrated the outperforming nature of the mucosal delivery route in combination with the chimpanzee-derived Ad-vector vaccine platform.

To ultimately prove that the multilayered immune response induced by mucosal delivery of Tri:ChAd would confer highest protection against fatal SARS-CoV-2 infection, Afkhami and colleagues vaccinated mice either intranasal or intramuscular with a single-dose Tri:HuAd or Tri:ChAd, respectively, followed by a lethal challenge with a mouse-adapted SARS-CoV-2 virus. Indeed, in line with the superior induction of humoral, cellular and trained innate immunity, the outstanding features of the mucosal, but not systemic, applied Tri:ChAd vaccine translated into full protection against an otherwise lethal infection. Importantly, in contrast to first-generation COVID-19 vaccines which were less effective against immune-escape VOC, mucosal vaccination with the Tri:ChAd vaccine conferred potent protection not only against lethal challenge with the wild-type ancestral SARS-CoV-2 strain, but also as well against the VOC B1.1.7 and B.1.351.

Next to the delivery route and the origin of the Ad-vector vaccine, the valence of the vaccine might be decisive for vaccine efficacy. To experimentally prove this, the authors constructed in addition to the trivalent vaccine the bivalent vaccine Bi:ChAd (nucleocapsid and RdRp) and the monovalent vaccine Mono:ChAd (S1) (Fig. 1c). Mucosal immunization with mono-, bi- and trivalent chimpanzee-derived Ad-vector vaccine and subsequent lethal SARS-CoV-2 challenge revealed morbidity and extensive lung pathology in mice vaccinated with Mono:ChAd. In contrast, Bi:ChAd vaccinated animals appeared clinically stable, but the trivalent vaccine proved the most effective in conferring protection against a severe course of SARS-CoV-2 infection (Fig. 1d). The fact that the Bi:ChAd vaccine was superior than the S1-expressing Mono:ChAd might be simply the consequence of a wider T cell immunity induced by Bi:ChAd against the virus or it might reflect that antigens other than S1 are more effective in inducing SARS-CoV-2-specific cellular immunity. Nevertheless, the study lacks a comparison between different Bi:ChAd vaccines including the S1 antigen that would allow answering this question.

In conclusion, considering many different facets of vaccine design, Afkhami and coworkers made several important key conclusions and recommendations needed for the development of improved next-generation vaccines.

**Funding Information**

Julia Volckmar1,2, Lars Melcher2 and Dunja Bruder1,2✉

1Infection Immunology Group, Institute of Medical Microbiology, Infection Prevention and Control, Health Campus Immunology, Infectiology and Inflammation, Otto-von-Guericke University Magdeburg, Magdeburg, Germany and 2Immune Regulation Group, Helmholtz Centre for Infection Research, Braunschweig, Germany

Correspondence: Dunja Bruder (dunja.bruder@med.ovgu.de)

Received: 2 May 2022 Revised: 23 May 2022 Accepted: 5 June 2022

Published online: 15 June 2022
findings that should be considered as blueprint for the development of sophisticated next-generation vaccines. They identified mucosal delivery of a trivalent vaccine incorporated in a chimpanzee-derived Ad-vector as the ideal tool for the stimulation of systemic and, even more important, mucosal antibody and T cell responses together conferring protection against an otherwise devastating SARS-CoV-2 infection. Without any doubt, the worldwide concerted effort that resulted in the incredibly fast development of first-generation SARS-CoV-2 vaccines was a great success in containing the global pandemics. However, since we...
are facing the problem that the virus is continuously evolving and thereby capable of escaping immunity induced by current vaccines, the development of improved next-generation vaccines taking into account recent research data is imperative. Notably, authorized first-generation SARS-CoV-2 vaccines (i.e. mRNA and vector vaccines) clearly differ from the ideal vaccine described by Afkhami et al. as they are generally applied intramuscular and are monovalent. While e.g. the ChAdOx1nCoV-19 vaccine from AstraZeneca actually is based on a vector system of chimpanzee origin, it is still monovalent and delivered intramuscular, thus offering potential for further optimization. Indeed, there is growing effort in probing the applicability of first-generation COVID-19 vaccines for respiratory mucosal delivery. However, most of the studies published so far did not distinguish between mucosal and systemic delivery routes, nor did they include different VOC. Therefore, the study by Afkhami et al. highlighted here should be considered as a milestone for future vaccine development since it unequivocally demonstrates the superiority of mucosal delivery of a trivalent ChAd-vectored vaccine in protection against ancestral SARS-CoV-2 and VOC.

**FUNDING**

Open Access funding enabled and organized by Projekt DEAL.

**ADDITIONAL INFORMATION**

**Competing interests:** The authors declare no competing interests.

**REFERENCES**

1. Afkhami, S. et al. Respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. *Cell* **185**, 896–915 (2022).
2. He, Q. et al. COVID-19 vaccines: current understanding on immunogenicity, safety, and further considerations. *Front. Immunol.* **12**, 669339 (2021).
3. Fiolet, T., Kherabi, Y., MacDonald, C. J., Ghosn, J. & Peiffer-Smadja, N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clin. Microbiol. Infect.* **28**, 202–221 (2022).
4. Bricker, T. L. et al. A single intranasal or intramuscular immunization with chimpanzee adenovirus-vectored SARS-CoV-2 vaccine protects against pneumonia in hamsters. *Cell Rep.* **36**, 109400 (2021).
5. Van Doremalen, N. et al. Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models. *Sci. Transl. Med.*, [https://doi.org/10.1126/scitranslmed.abh0755](https://doi.org/10.1126/scitranslmed.abh0755) (2021).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).