CellPress

Cell
Leading Edge

Preview

mRNA-based monkeypox virus vaccine prevents disease in non-human primates

Adam N. Nitido[1] and Alejandro B. Balazs[1,*]
[1]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA 02139, USA
*Correspondence: abalazs@mgh.harvard.edu
https://doi.org/10.1016/j.cell.2024.02.011

The mpox outbreak in 2022 launched a vaccination campaign employing an existing vaccine with moderate protection, highlighting the lack of scalable Orthopoxvirus vaccines with optimal protection. In this issue of *Cell*, Zuiani et al. report pre-clinical findings of an mRNA-based mpox vaccine, paving the way for Phase I/II clinical trials.

Monkeypox virus (MPXV) infections have historically been restricted to densely forested regions of Africa and transmitted zoonotically. Recently, MPXV has emerged as a global public health threat following a large outbreak of human-to-human transmission among men who have sex with men (MSM) in non-endemic regions.[1] Mpox initially presents as fever, myalgia, and lymphadenopathy early in infection, with painful skin lesions erupting within days of symptom onset.[2] Two distinct clades of MPXV had been described previously, Clade I and Clade II, with estimated case fatality rates of 10% and <1%, respectively, and with up to one third of these deaths occurring in children.[3] However, viruses isolated from the recent 2022 outbreak have been proposed to form a novel Clade IIb[2] with a significantly lower case fatality rate (estimated at 0.08%).[4]

MPXV is a member of the Orthopoxvirus genus, which also includes variola virus (aka smallpox virus), vaccinia virus, and cowpox virus. In response to the 2022 outbreak, targeted vaccination campaigns using the previously FDA-approved Orthopoxvirus vaccine, JYNNEOS, were employed in patient populations at greatest risk for infection. Given the high homology between virus species in the Orthopoxvirus genus, vaccines developed against one Orthopoxvirus species can provide immunological cross-protection against other Orthopoxvirus species.[2] JYNNEOS is a live attenuated vaccine based on Modified Vaccinia Ankara (MVA) that is administered as two subcutaneous doses. It has a demonstrated efficacy of 66% against mpox caused by MPXV Clade IIb.[5] MVA is the product of extensive passaging in cultured chicken cells, resulting in a loss of viral replication in human cells while retaining sufficient immunogenicity to elicit immunity that prevents serious mpox without achieving sterilizing protection.[6] However, MVA-based vaccines only result in relatively low levels of MPXV-neutralizing antibodies,[7] suggesting that a more immunogenic vaccine might achieve higher efficacy.

The worldwide use of mRNA-based vaccination during the COVID-19 pandemic has stimulated the clinical development of mRNA vaccines targeting diverse infectious diseases, including Influenza, RSV, CMV, EBV, HSV, VZV, and HIV. In this issue of *Cell*, Zuiani and colleagues extend these efforts by evaluating the efficacy of an mRNA-based vaccine against mpox in animal models.[8] During natural infection, MPXV is found in two antigenically distinct forms: enveloped virion (EV) and mature virion (MV). Zuiani and colleagues test vaccines that encode two distinct EV antigens combined with either one or two MV antigens. They demonstrate the effectiveness of the 4-antigen vaccine (BNT166a) in a cynomolgus macaque lethal challenge model with Clade I MPXV (the field standard for evaluating vaccines against Orthopoxviruses), demonstrating complete protection from death and minimal lesion development in animals receiving BNT166a (Figure 1).[8] This is in contrast to previous MVA-based vaccines, which protected animals from lethal disease and reduced—but did not eliminate—lesion formation following viral challenge.[6] These findings support the continued clinical development of BNT166a, which is currently under evaluation in a Phase I/II clinical trial (NCT05988203) and is one of only two mRNA vaccines for MPXV to have reached this stage of clinical development.

Notably, previous mRNA vaccines targeting SARS-CoV-2 elicited long-lived immunity against severe COVID-19; however, antibody titers fell by more than 10-fold within 6 months of the two-dose regimen.[9] It will be important to determine whether two doses of BNT166a exhibit a similar outcome or if antibody titers, and more importantly, protection, will be sustained over time. Given what we have learned about the immune response to mRNA vaccines for SARS-CoV-2, it is likely that BNT166a can elicit sustained protection from severe disease, but clinical trials will be required to confirm these predictions.

Since the WHO declared smallpox eradicated in 1980, routine vaccination of people for smallpox has ceased. As a result, the accompanying cross-protection to other Orthopoxviruses (such as MPXV) has declined, leaving most people in the world vulnerable to emerging Orthopoxviruses.[10] Given the moderate clinical efficacy of the JYNNEOS vaccine against mpox and the high rate of adverse events associated with the earlier-generation smallpox vaccines such as ACAM2000, there remains a significant unmet need for safe and effective MXPV vaccines.

Pending the results of ongoing clinical studies in patients, mRNA-based vaccines may be capable of eliciting a high level of protection against MXPV and

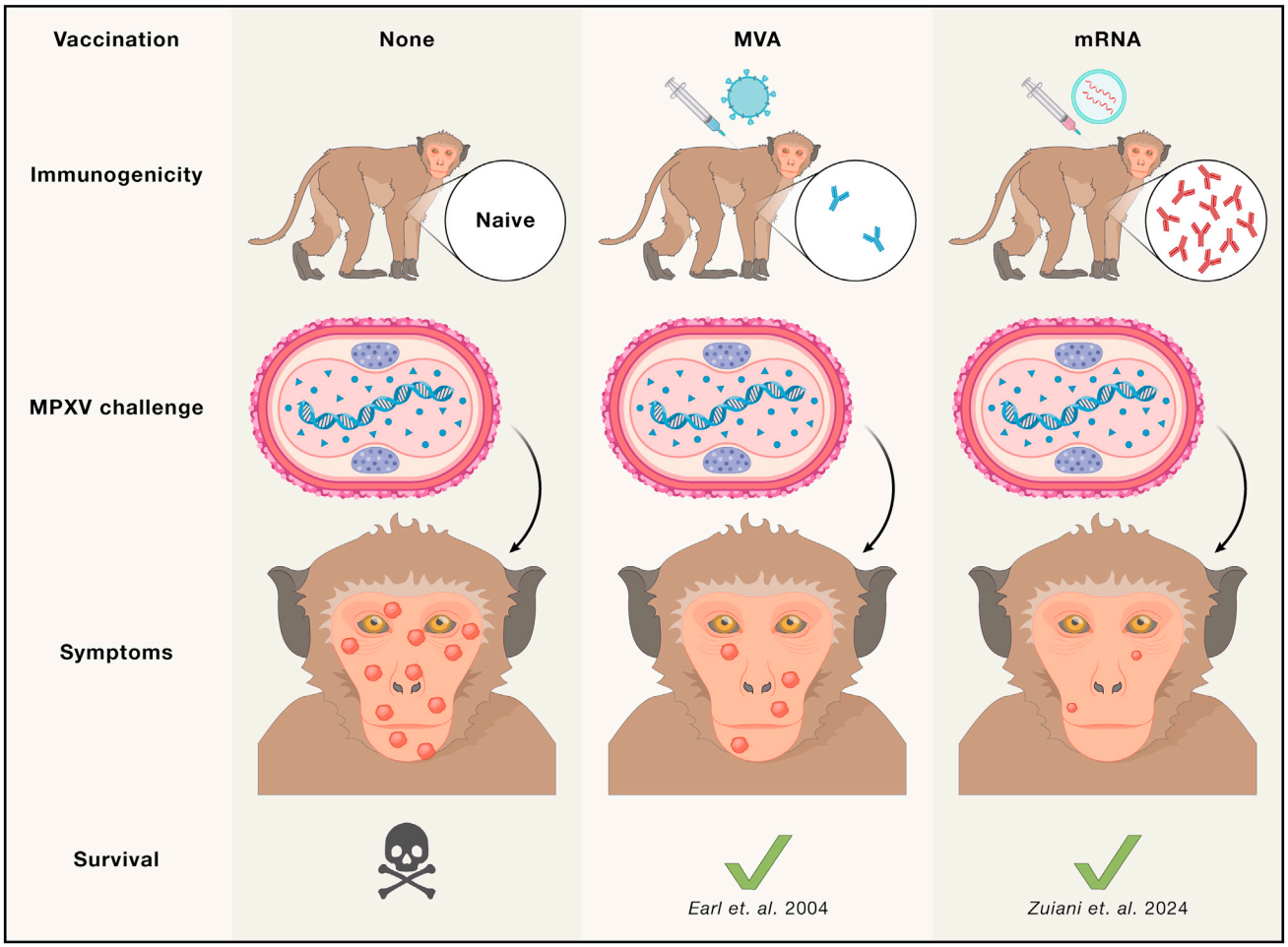

Figure 1. Comparison of MPXV vaccine efficacy in non-human primates

Overview of studies evaluating the efficacy of MVA- or mRNA-based vaccines against lethal challenge with Clade I MPXV. In each study, a group of vaccinated cynomolgus macaques was compared to a group of non-vaccinated (naive) cynomolgus macaques. Post-vaccination, the immunogenicity of each cynomolgus macaque was evaluated by measuring antibody titers against specific Orthopoxvirus antigens. The cynomolgus macaques were then challenged with a Clade I MPXV infection (the field standard for evaluating vaccines against Orthpoxviruses). While naive animals exhibit a high burden of lesions and do not survive challenge, animals receiving MVA vaccine produce low antibody titers, exhibit fewer lesions, and survive. In contrast, all animals receiving an mRNA-based vaccine demonstrate high antibody titers, have very few lesions, and survive virus challenge.

may generate additional cross-protective immunity against diverse Orthopoxviruses, including other clades of MPXV and vaccinia virus (smallpox virus). If these ambitious goals are met, mRNA-based Orthopoxvirus vaccines may prove invaluable during a future public health emergency given their capacity for rapid scaling of production.

ACKNOWLEDGMENTS

A.D.N. and A.B.B. were supported by NIH/NIAID grants R01AI174875 and R01AI174276, NIH/NIDA grant DP2DA040254, and CDC subcontract 200-2016-91773-T.O.2. BioRender was used to create the draft of the figure.

DECLARATION OF INTERESTS

A.B.B. is a founder of Cure Systems LLC.

REFERENCES

1. Nuzzo, J.B., Borio, L.L., and Gostin, L.O. (2022). The WHO Declaration of Monkeypox as a Global Public Health Emergency. JAMA *328*, 615–617. https://doi.org/10.1001/jama.2022.12513.
2. Harapan, H., Ophinni, Y., Megawati, D., Frediansyah, A., Mamada, S.S., Salampe, M., Bin Emran, T., Winardi, W., Fathima, R., Sirinam, S., et al. (2022). Monkeypox: A Comprehensive Review. Viruses *14*, 2155. https://doi.org/10.3390/v14102155.
3. Vogel, L. (2022). Making sense of monkeypox death rates. CMAJ (Can. Med. Assoc. J.) *194*, E1097–E1097. https://doi.org/10.1503/cmaj.1096012.
4. Keikha, M., Zandhaghighi, M., and Shahraki Zahedani, S. (2023). Death-associated with human monkeypox outbreak 2022: the current perspectives – correspondence. Int. J. Surg. *109*, 1806–1807. https://doi.org/10.1097/JS9.0000000000000123.
5. Deputy, N.P., Deckert, J., Chard, A.N., Sandberg, N., Moulia, D.L., Barkley, E., Dalton, A.F., Sweet, C., Cohn, A.C., Little, D.R., et al. (2023). Vaccine Effectiveness of JYNNEOS against Mpox Disease in the United States. N. Engl. J. Med. *388*, 2434–2443. https://doi.org/10.1056/NEJMoa2215201.
6. Earl, P.L., Americo, J.L., Wyatt, L.S., Eller, L.A., Whitbeck, J.C., Cohen, G.H., Eisenberg, R.J.,

Hartmann, C.J., Jackson, D.L., Kulesh, D.A., et al. (2004). Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. Nature *428*, 182–185. https://doi.org/10.1038/nature02331.

7. Zaeck, L.M., Lamers, M.M., Verstrepen, B.E., Bestebroer, T.M., Van Royen, M.E., Götz, H., Shamier, M.C., Van Leeuwen, L.P.M., Schmitz, K.S., Alblas, K., et al. (2023). Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat. Med. *29*, 270–278. https://doi.org/10.1038/s41591-022-02090-w.
8. Zuiani, A., Dulberger, C.L., De Silva, N.S., Marquette, M., Lu, Y.J., Palowitch, G.M., Dokic, A., Sanchez-Velazquez, R., Schlatterer, K., Sarkar, S., et al. (2024). A multivalent mRNA monkeypox virus vaccine (BNT166) protects mice and macaques from orthopoxvirus disease. Cell *187*, 1363–1373.
9. Canaday, D.H., Oyebanji, O.A., Keresztesy, D., Payne, M., Wilk, D., Carias, L., Aung, H., St. Denis, K., Lam, E.C., Rowley, C.F., et al. (2022). Significant Reduction in Vaccine-Induced Antibody Levels and Neutralization Activity Among Healthcare Workers and Nursing Home Residents 6 Months Following Coronavirus Disease 2019 BNT162b2 mRNA Vaccination. Clin. Infect. Dis. *75*, e884–e887. https://doi.org/10.1093/cid/ciab963.
10. Rimoin, A.W., Mulembakani, P.M., Johnston, S.C., Lloyd Smith, J.O., Kisalu, N.K., Kinkela, T.L., Blumberg, S., Thomassen, H.A., Pike, B.L., Fair, J.N., et al. (2010). Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. Proc. Natl. Acad. Sci. USA *107*, 16262–16267. https://doi.org/10.1073/pnas.1005769107.