Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an airborne virus that has rapidly spread across the world since the beginning of 2020. SARS-CoV-2 infection causes a spectrum of disease from asymptomatic to severe complications, including pneumonia, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), cytokine storm syndrome (CSS) and death. Increasingly contagious variants of concern (VOC) have fueled recurring global infection waves.

Design of effective vaccines must consider the divergent and rapidly mutating nature of coronavirus spike protein. While a high level of viral escape from neutralizing antibodies exist among the VOCs, the T cell epitopes to spike have remained largely conserved, suggesting the current vaccines may not be rendered completely effective. Our modified vaccinia Ankara (MVA)-VLP vaccine platform combines the safety of a non-replicating virus vector with enhanced immunogenicity of vaccine antigens displayed on the surface of VLPs in vivo following immunization. Herein, utilizing the MVA-VLP platform, we tested efficacy of multi-antigen vaccines expressing SARS-CoV-2 S (targeting B.1.1.7, B.1.351 and BA.1.1.529), and M and envelope (E) in preclinical animal challenge models.

METHODS

1. Vaccine development: SARS-CoV-2 genes were inserted into one site between two essential MVA genes, ASR and A6L, under direction of MVA promoter modified HS (PhnHS).

2. Vaccination: 6-week-old K18-BACE2 mice were vaccinated intramuscularly with 105 PFU of GEO-CM02 vaccine.

3. Challenge: Mice were challenged with 105 PFU of SARS-CoV-2 (B.1, B1.351, or BA.1.1.529) by intranasal route on day 56.

4. Tissue collection: At days 3 and 6 post infection, the mice were euthanized by cardiac puncture with profusion of 1X PBS. Lungs and brains were collected and flash frozen for further analysis.

RESULTS

1. MVA-vectored multi-antigen SARS-CoV-2 vaccines induce protective immunity against VoC

- Mice vaccinated with GEO-CM02 vaccine induced binding antibodies to Spike protein derived from B.1, B1.351, or BA.1.529 variants at day 43 or 55 post vaccination.

- Mice vaccinated with GEO-CM02 vaccine with prime and boost developed neutralizing antibodies against B.1, B1.351 and BA.1.529 variants, while the prime vaccine resulted in little neutralizing precipitation.

2. GEO-CM02 vaccine induces protective cellular immunity against VoC

- GEO-CM02 vaccine is capable of producing functional CD4+ and CD8+ T cells while maintaining a Th1 rather than Th2 phenotype.
- Vaccination led to an increase in IFN-γ and IL-2 producing CD4+ and CD8+ T cells specific for spike protein.

3. Characteristics of K18-hACE2 mice following vaccination and B.1 SARS-CoV-2 challenge

- Vaccinated mice remained healthy with slight weight loss at day 1 post challenge, with recovery, as opposed to saline mice.
- Higher virus titers were observed in lungs of saline mice than the vaccinated mice.

4. Characteristics of K18-hACE2 mice following vaccination and BA.1.1.529 SARS-CoV-2 challenge

- Vaccinated mice remained healthy with slight weight loss at day 1 post challenge, with recovery, as opposed to saline mice.
- Higher virus titers were observed in lungs of saline mice than the vaccinated mice.

5. Decreased viral nucleoprotein and leukocytes infiltration in vaccinated mice following BA.1.1.529 challenge

- Mice vaccinated with both prime and boost showed a decrease in the viral RNA levels at days 3 and 6 post challenge in the lungs, brain, nasal turbinates and olfactory bulb compared to the saline mice post challenge.

6. Reduced virus titers in vaccinated mice compared to saline mice

- Mice vaccinated with GEO-CM02 demonstrated significant decreased protein amounts of IL-6, IP10, MCP1, MPIF1 and MPIFβ compared to the saline mice post challenge.
- Mice vaccinated with GEO-CM02 resulted in increased amounts of RANTES compared to the saline mice post challenge.

7. Cytokine and chemokine levels in mice following BA.1.1.529 challenge

- Mice vaccinated with GEO-CM02 demonstrated significant decreased cytokine levels of IL-6, TNF, MCP1, and IFNγ compared to the saline mice post challenge.
- Mice vaccinated with GEO-CM02 expressed lower viral loads and an altered immune response compared to the saline mice.

CONCLUSION

- Utilizing the MVA-VLP platform, we tested efficacy of multi-antigen vaccines expressing SARS-CoV-2 S, M and E in preclinical animal challenge models.
- GEO-CM02 vaccine induce protective immunity against mice from SARS-CoV-2 variants spanning Alpha to Omicron.
- Vaccinated mice remained healthy and expressed lower viral loads and an altered immune response compared to the saline mice.

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