Design Considerations for a Universal Coronavirus Vaccine

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Overview

- Immune responses to SARS-CoV-2
- Variable and conserved regions of coronaviruses
- GeoVax MVA-VLP technology
- MVA-VLP-COVID vaccine: preclinical evaluations
- Design features of a Pan-Coronavirus vaccine

Immune Responses to Viral Infections

- **Humoral immune response:** antibodies specific for the virus capture and neutralize virus, blocking infection and limiting cell-to-cell spread
- **Cellular immune response:** cytotoxic (CD8) and helper (CD4) T-cells limit viral replication and clear infection by killing virus-infected cells
- **Multifunctional responses with memory:** required for optimal protection from infection and serious illness

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SARS-CoV-2 Antibody Responses - Infection

- Neutralizing antibodies, specific to the Spike (S) protein present in most sera of convalescent patients

Emerging Infectious Diseases 2021:27 (issue 2)

- Neutralizing antibody levels wane rapidly in the absence of repeat exposure

Science 2020: 370 (issue 6521)

- Bone marrow resident plasma cells are detectable

Nature 2021: 595 (421–425)

- Memory B cells are induced

Science 2021: 371 (issue 6529)

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SARS-CoV-2 Antibody Responses - Vaccines

- Neutralizing antibody responses are induced readily by vaccination
- The duration of neutralizing antibodies is variable depending on vaccine format and often short-lived

Nature Micro 2020: 5 (1598-1607)

- S protein is the basis for most of the 1st generation vaccines
  - Focus is on the induction of neutralizing antibodies

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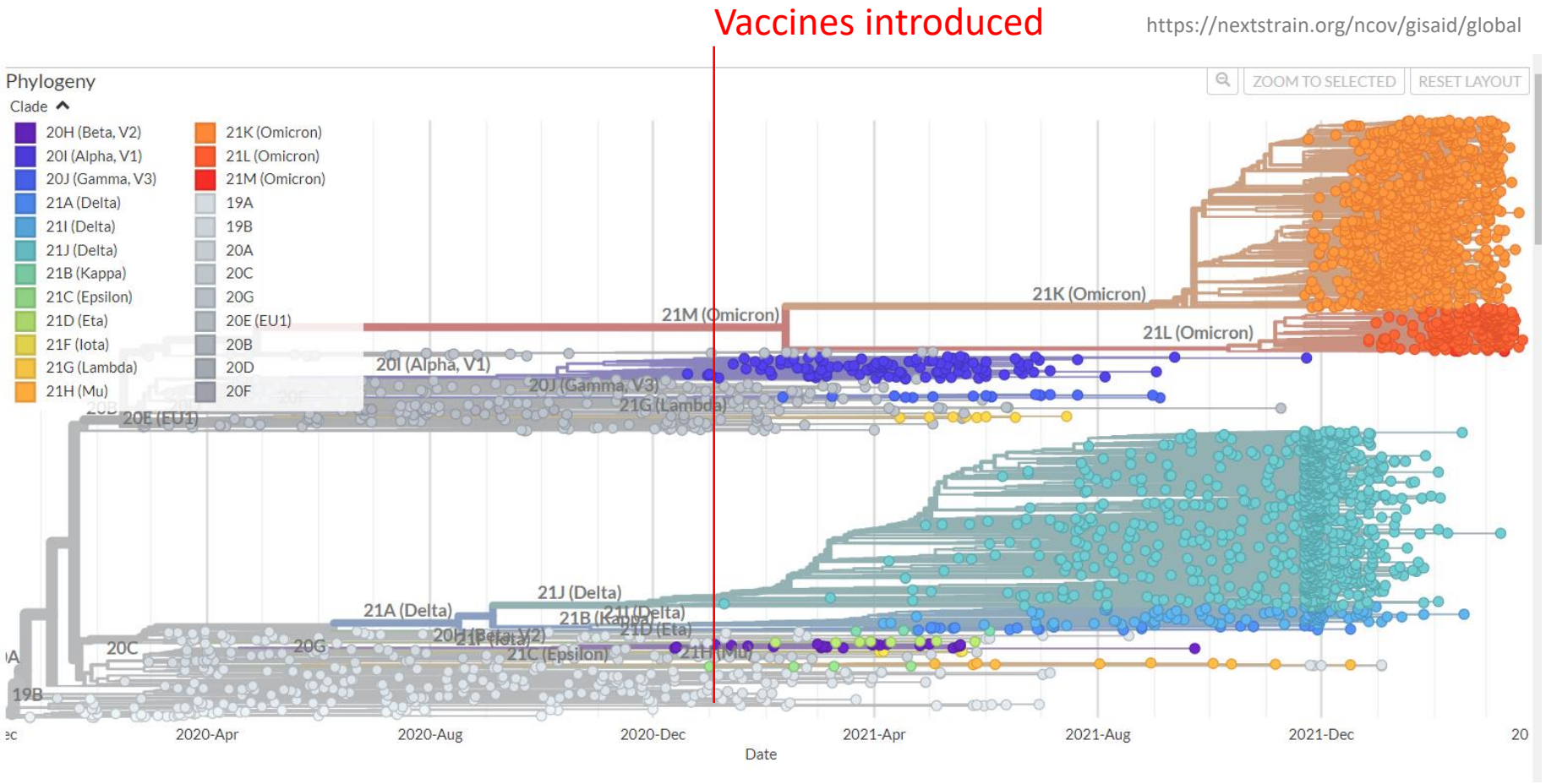
Vaccine Challenge: Evolving Variation



SARS-CoV-2 rapidly mutates and can “evolve” to generate variants that are more transmissible and/or resistant to antibody-mediated neutralization

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Variants of Concern (VOC)

Variant Designation	Initial Source	S-Protein Mutations	Pathogenesis	Antibody Resistance
α - Alpha (B1.1.7)	UK - Sept 2020	3, ↑ ACE binding	50% ↑ infection	±
β - Beta (B.1.351)	RSA – May 2020	8,↑ ACE binding Related to α	50% ↑ infection	↑, vaccines & monoclonals
γ - Gamma (P.1)	Brazil - Nov 2020	8,↑ ACE binding Related to α and β	50% ↑ infection ↑ VL	↑, vaccines & monoclonals
δ - Delta (B.1.617.2)	India – Oct 2020	8,↑ ACE binding	60% ↑ infection	↑ 30-40%, vaccines
ε - Eta (B.1.525)	Nigeria - Dec 2020	7,↑ ACE binding Related to α	50% ↑ infection	↑ 30%, vaccines & monoclonals
ι - Iota (B.1.526)	USA - Nov 2020	3, ↑ ACE binding	±	±
κ - Kappa (B.1.617.1)	India - Oct 2020	8,↑ ACE binding	±	↑ 30%, vaccines
λ - Lambda (C.37)	Peru – Aug 2020	7,↑ ACE binding	±	↑ 30%, vaccines
ο - Omicron (B.1.1.529)	RSA – Nov 2021	34, ↑ ACE binding	- Most transmissible	Undetectable without booster

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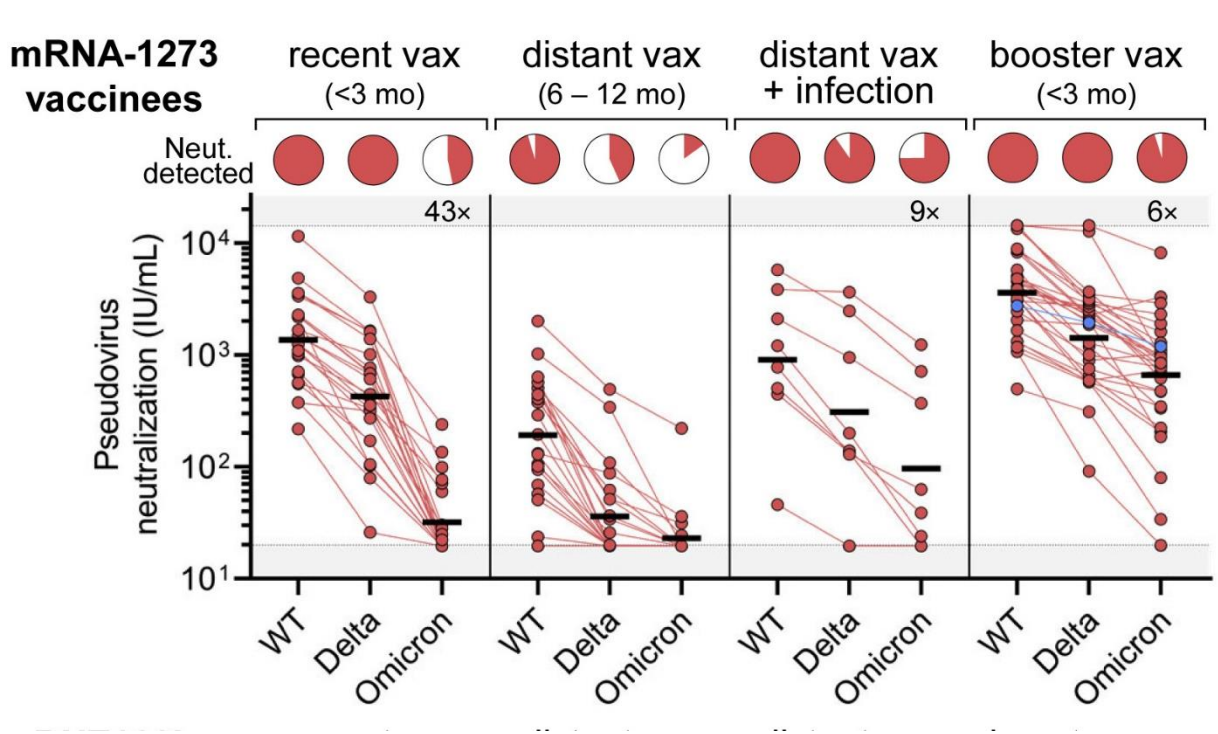
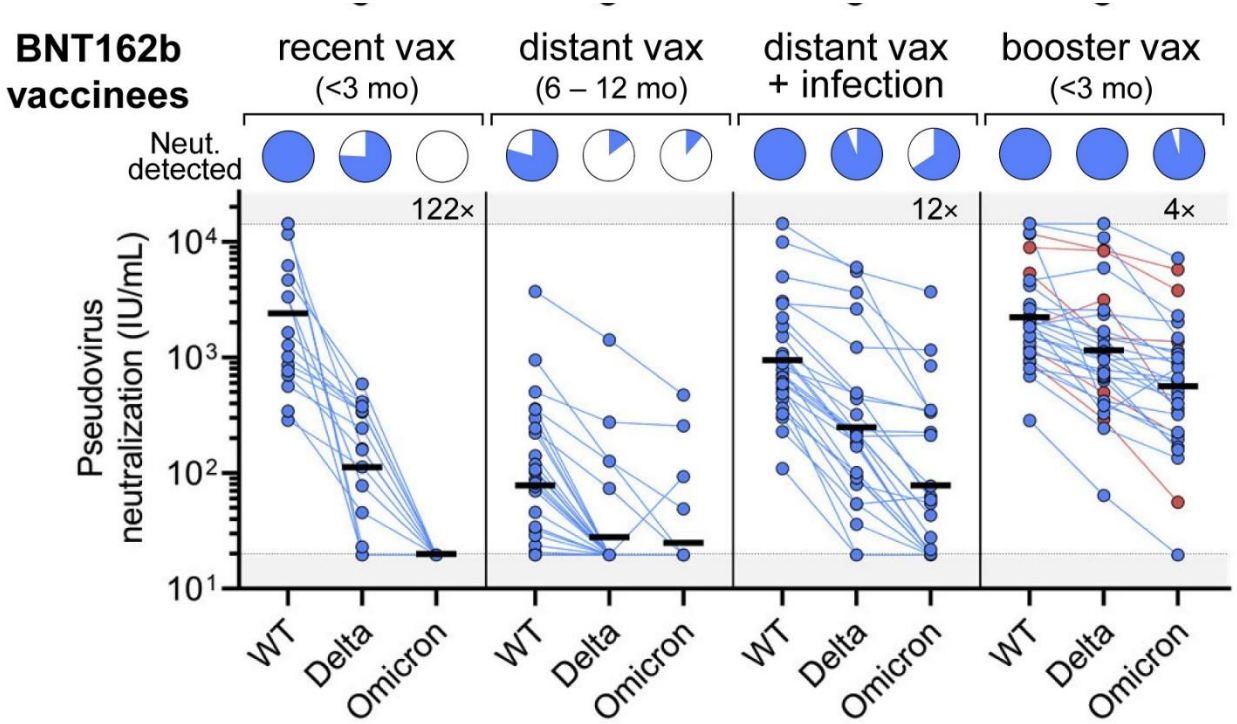
Reduction of Neutralizing Antibody Function Against VOC





Cell **185**, 457–466, February 3, 2022

SARS-CoV-2 Cellular Immunity (T-cells)

- >90% of convalescent patients had detectable CD4+ T-cell responses against epitopes in multiple viral proteins

Science 2021:371(issue 6529)

- Multi-specific and functional T-cell responses are associated with accelerated viral control, clearance and with protection from severe COVID illness

Oxford Open Immunol 2021:2 (issue 1)

- T-cells in uninfected donors recognized epitopes in multiple viral proteins, suggesting cross-reactive recognition seasonal viruses and SARS-CoV-2

Nature 2020: 584 (457–462)

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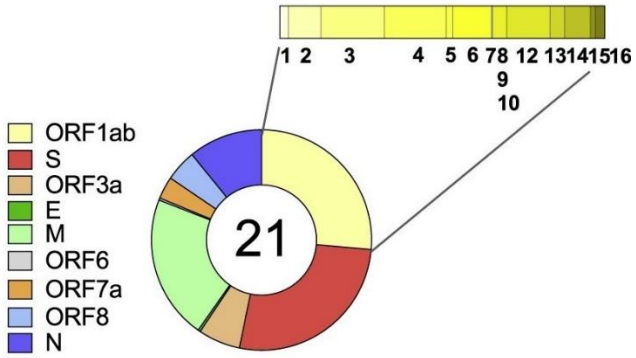
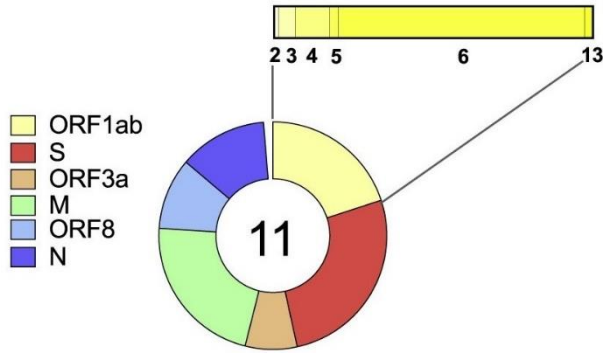
Detection of SARS-CoV-2 T-cell Responses in Uninfected Individuals

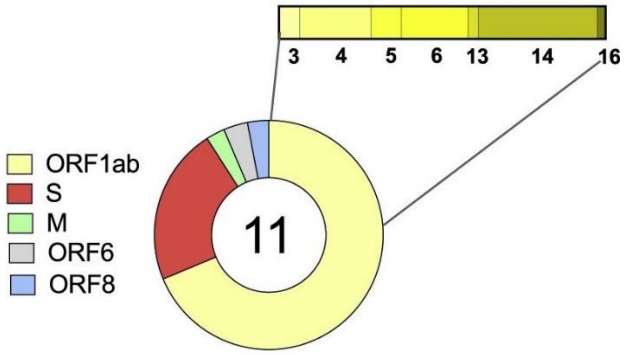
CD4+ T-cells



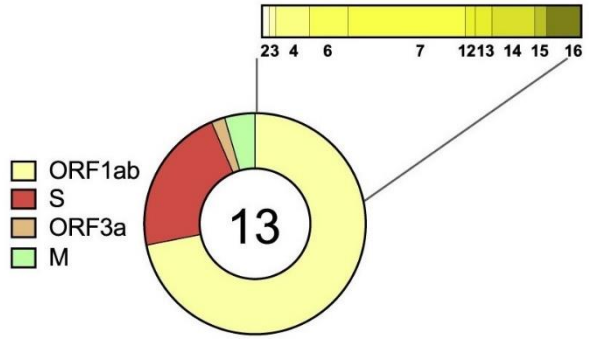
CD8+ T-cells



Exposed



Unexposed



Cell 2020:181(1489-1501)

SARS-CoV Conserved Sequences

- Sequences of phylogenetically related SARS-CoV vary in S, ORF3 and ORF8

Nature Rev Micro 2019:171(181–192)

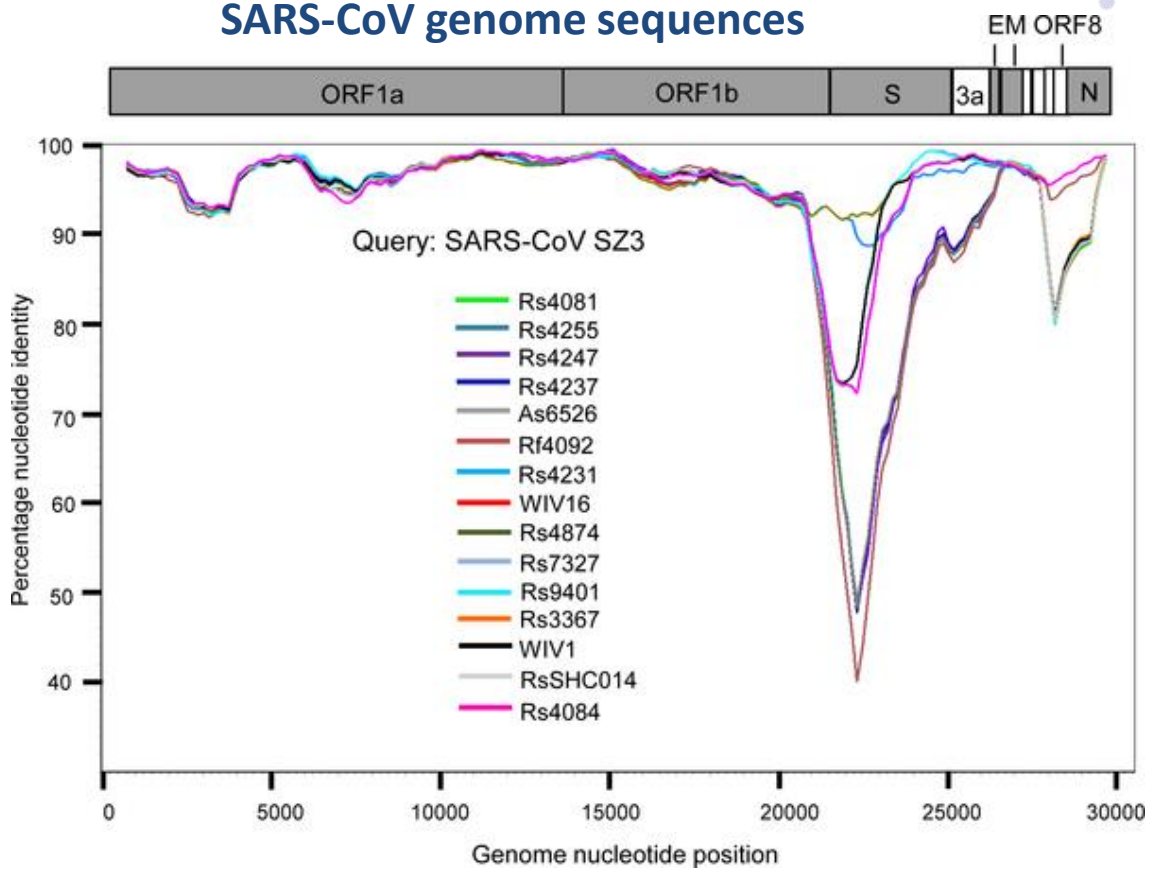
- Mutation in the S and ORF8 allowed for efficient spread SARS CoV-1 from bats to civets

PLOS Pathogens 2017:13(11)

- MERS-CoV, exhibits high sequence homology among the ORF1a/b genes but mutations in the S gene

PLOS Pathogens 2017: 13(11)

Similarity plot based on the full-length SARS-CoV genome sequences



PLOS Pathogens. 13(11). 2017

Addressing Evolving Variants or Novel Coronaviruses Through Vaccines

- Establish global surveillance
- Adjust vaccines using circulating variant S-protein sequences
  - Booster immunization campaigns, yearly, regionally, as needed
- Develop vaccines specific to viral proteins that are less subject to variation
  - Ancestral or matrix S-protein sequences, targeting conserved epitopes
  - Target conserved T-cell epitopes in other viral structural and nonstructural viral proteins

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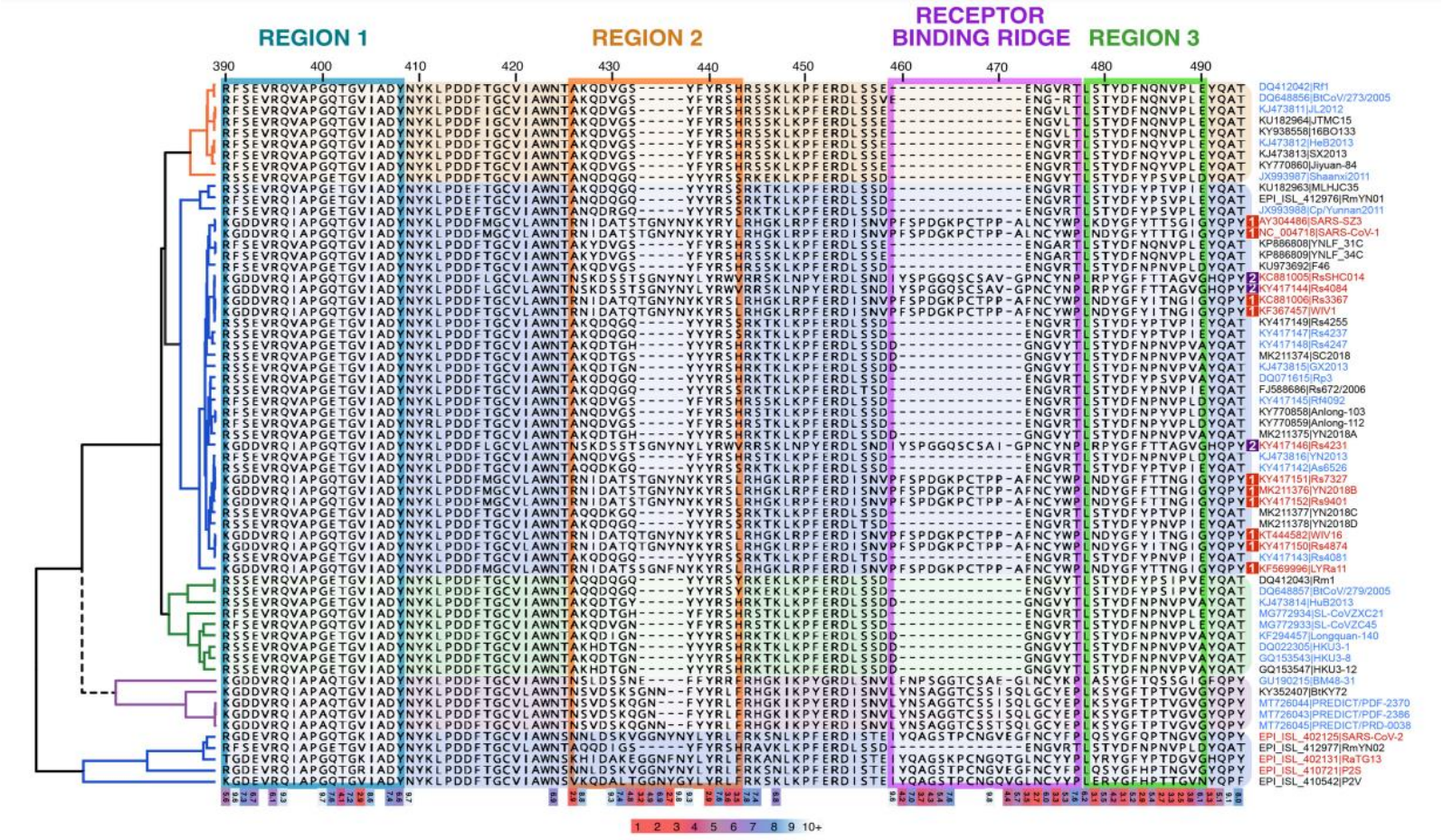
Variation of RBD is an Obstacle for Induction of Neutralizing Antibodies



- ACE2 is not a universal receptor for sabrecoviruses (Blue do not use ACE2)
- SARS-CoV S gene varies amongst viruses in the same clade
- Evolution of S is likely driven by selective immune pressure

Virus Evolution, 2021, 7(1): veab007

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Potential Value of T-cell Responses to Conserved Epitopes

- Nucleocapsid (N), Membrane (M) and Envelope (E) are highly conserved structural proteins
  - T-cell epitopes in N and M proteins are immunogenic and T-cells detectable in convalescent SARS-CoV-2 patients
- Nonstructural genes (NSP & ORF) are the most highly conserved amongst CoV-2 viruses
  - T-cell epitopes in NSP are immunogenic and induce cross-reactive T-cell responses
- **Hypothesis:** Targeting N, M and E using vaccination will protect against emerging S variants, targeting ORF1ab will approach universal protection

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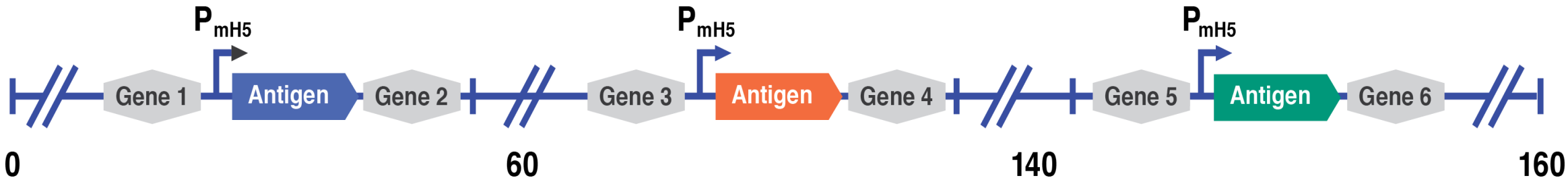
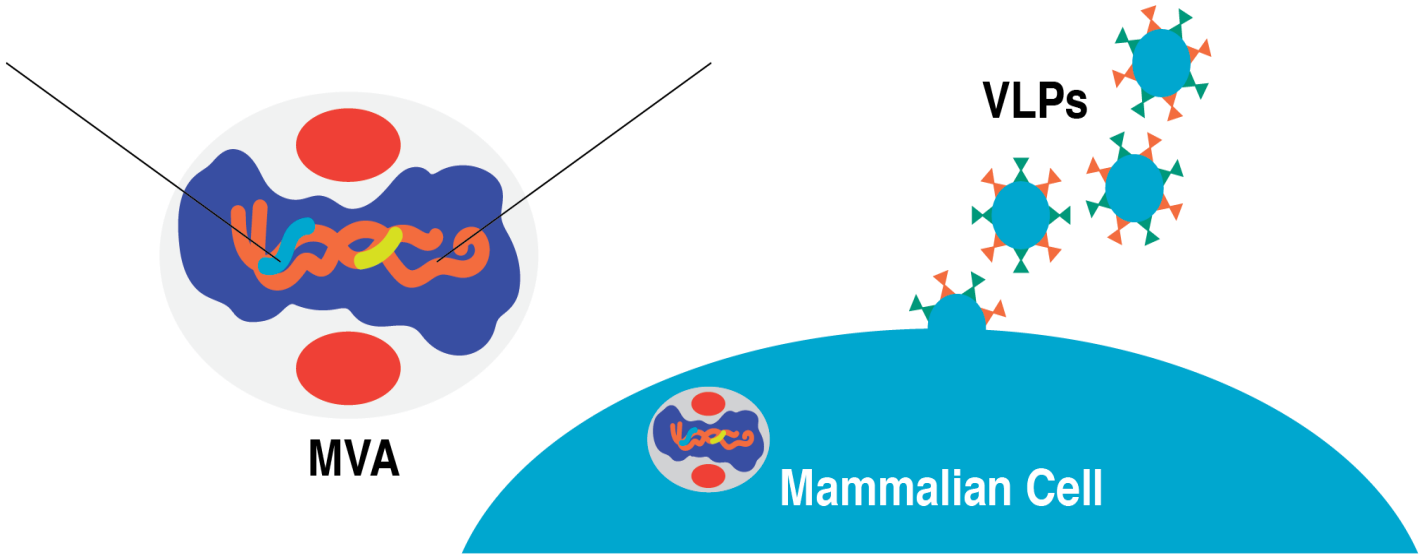
GeoVax MVA-VLP Vaccine Platform

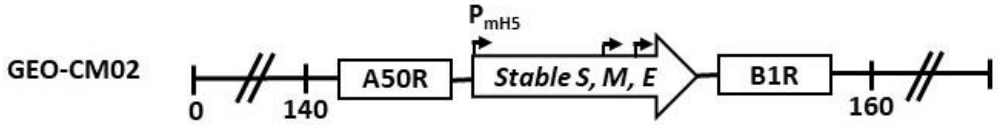
Non-infectious virus-like particles (VLP) generated *in vivo*





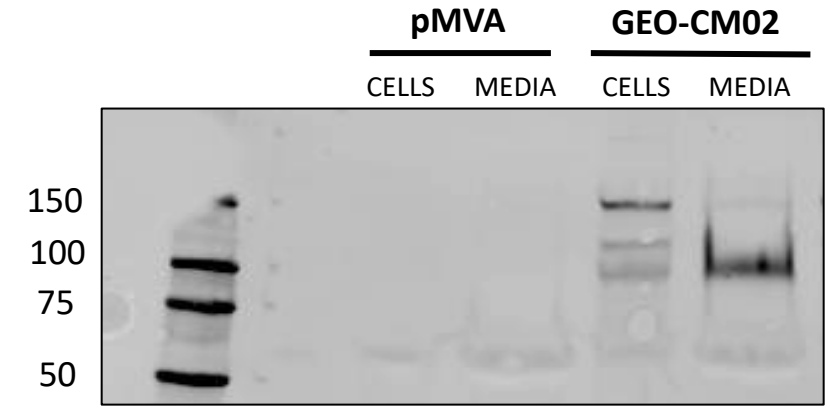
MVA-SARS-CoV-2 (GEO-CM02)

MVA Encoding Stabilized Spike, Membrane and Envelope



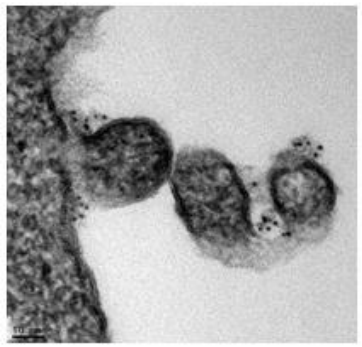
Insert Stability

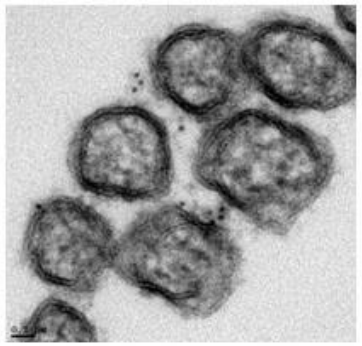
	Spike plaques	MVA plaques	Insert integrity
Seed virus	125	125	100%
Passage 15	399	399	100%
Passage 20	410	412	99.5%

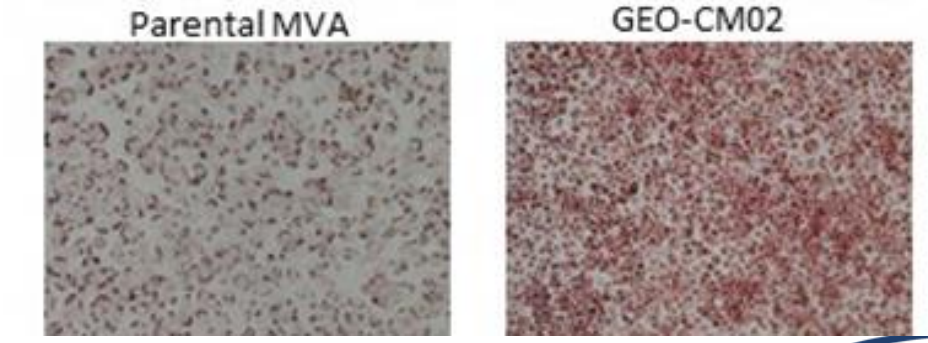


Spike protein expression

VLP formation







Membrane protein expression

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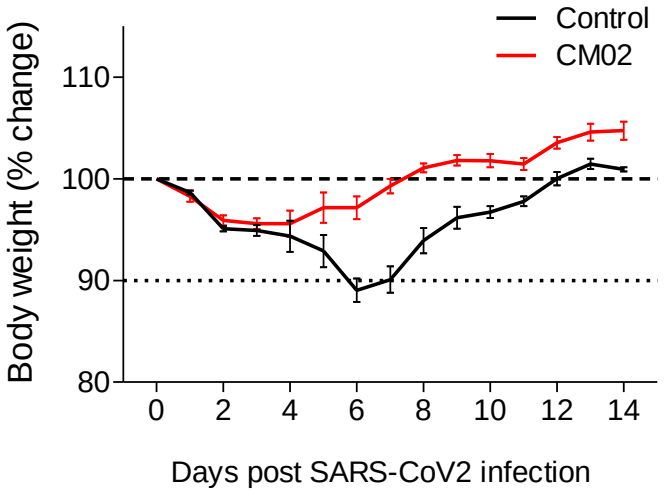
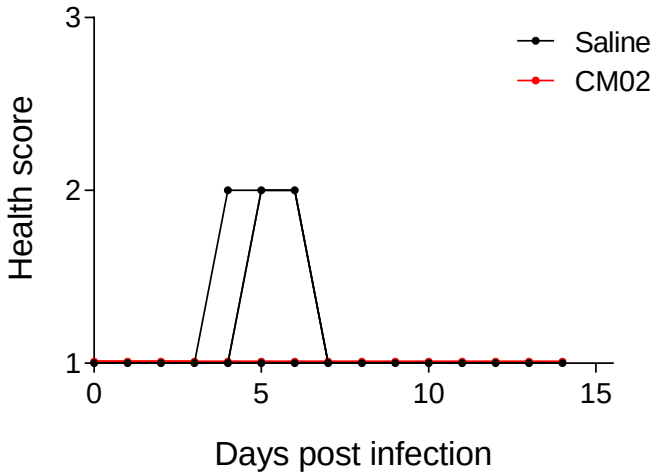
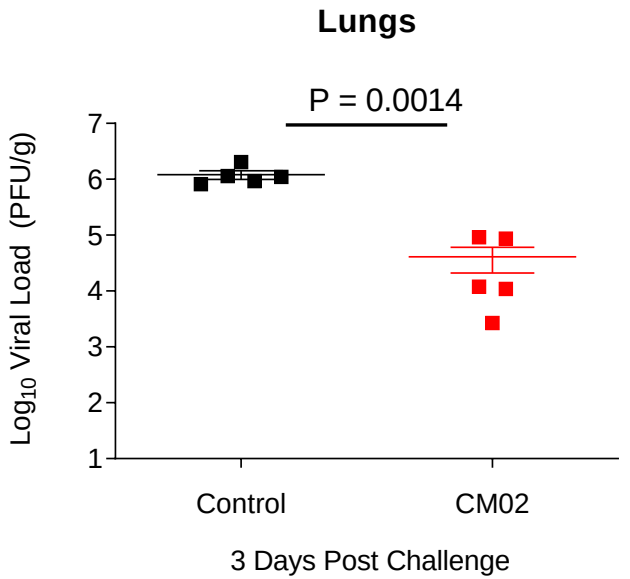
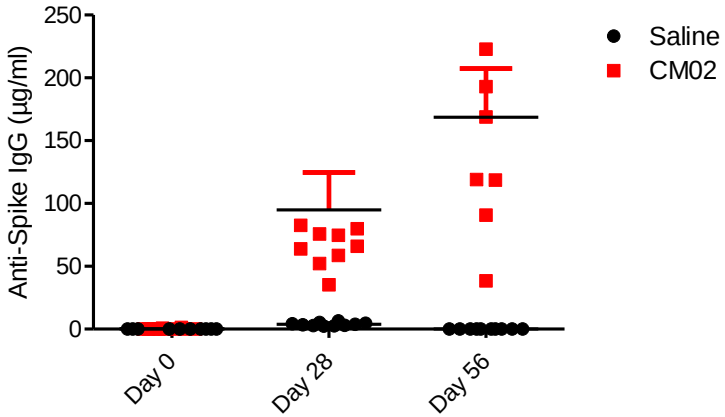
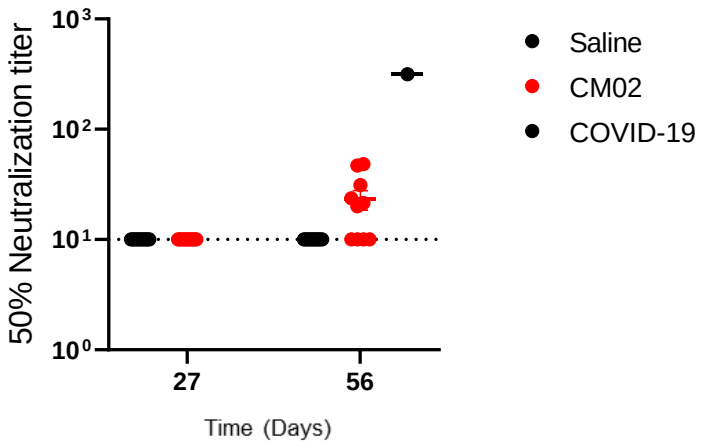
GEO-CM02 Efficacy in Hamsters

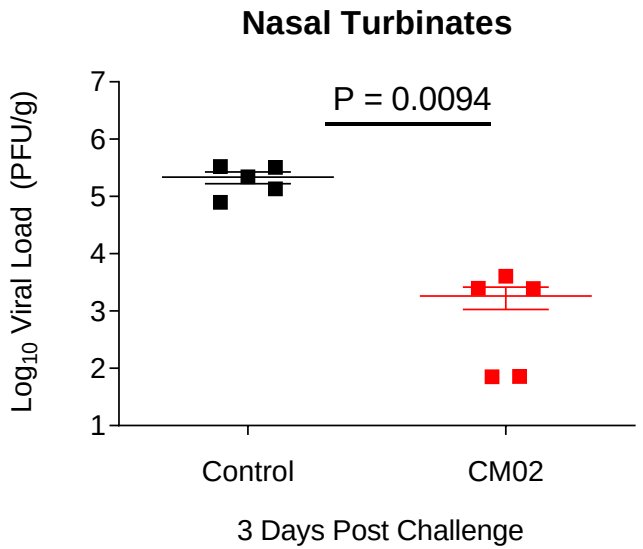








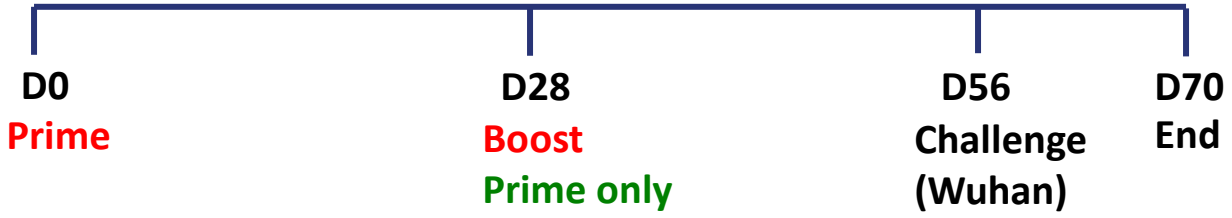




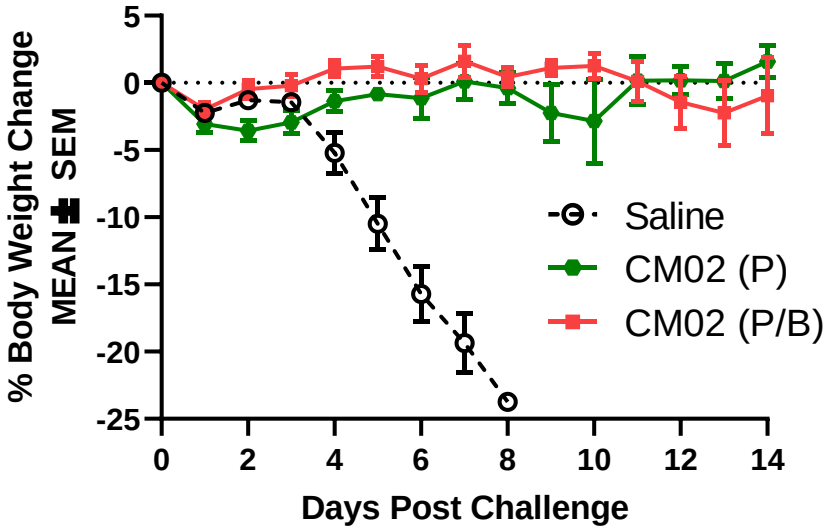
GEO-CM02: 100% protection against lethal SARS-CoV-2 challenge in a single dose

n=6/group

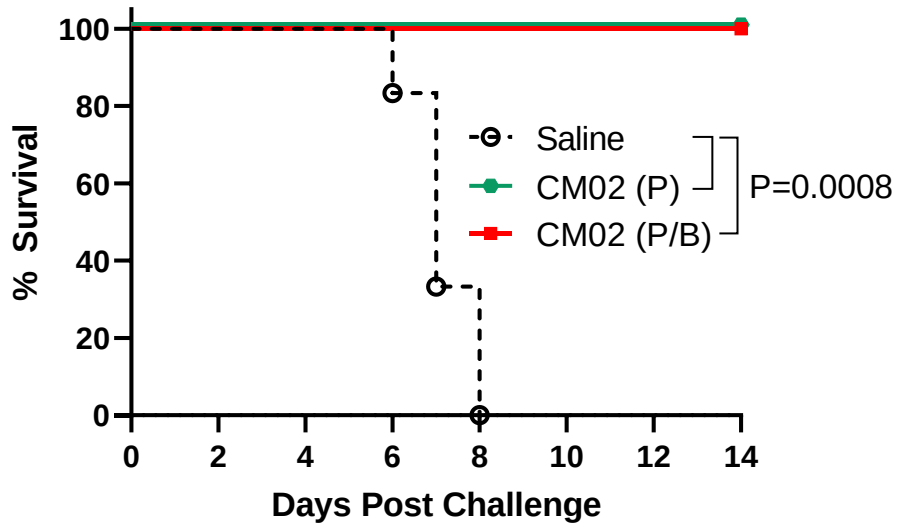
Intramuscular immunization:



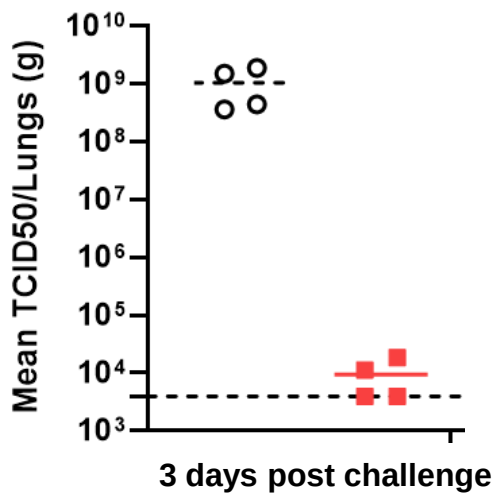
Body Weight



Survival



Viral Load



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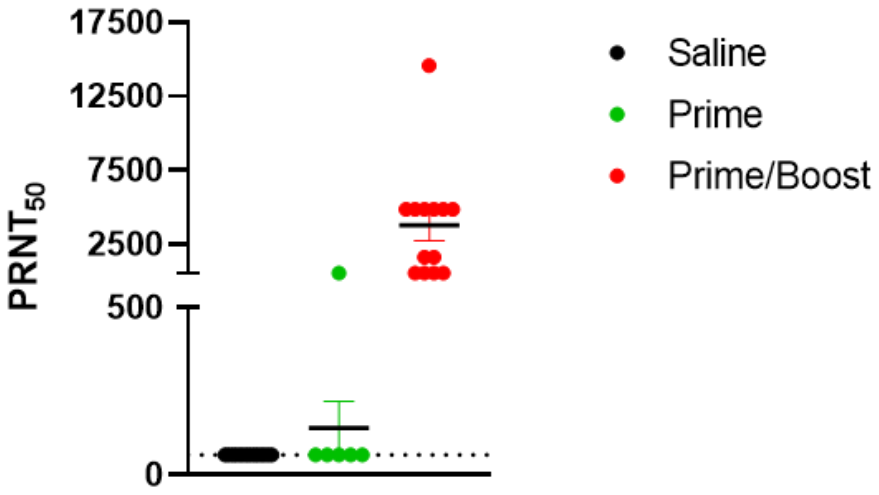
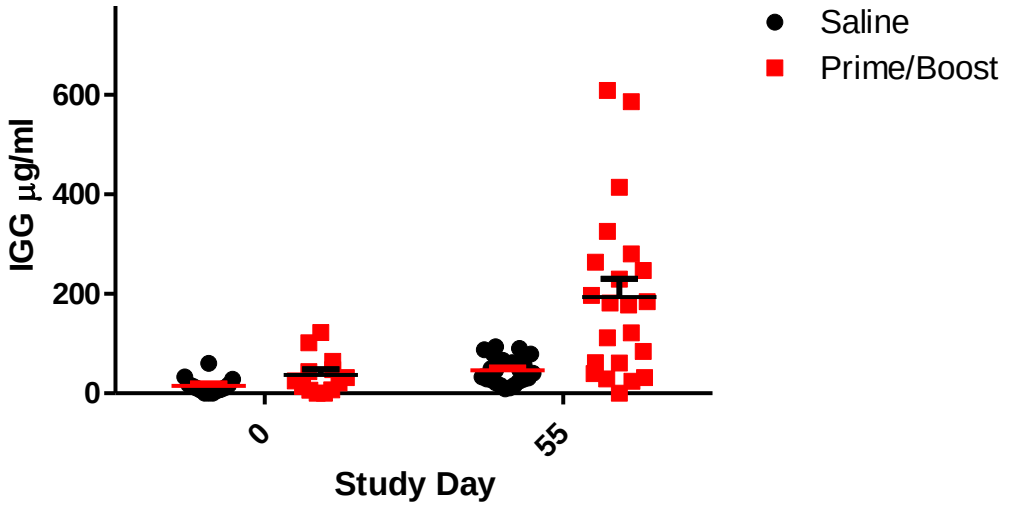
GEO-CM02 Immunogenicity hACE2 Tg Mice

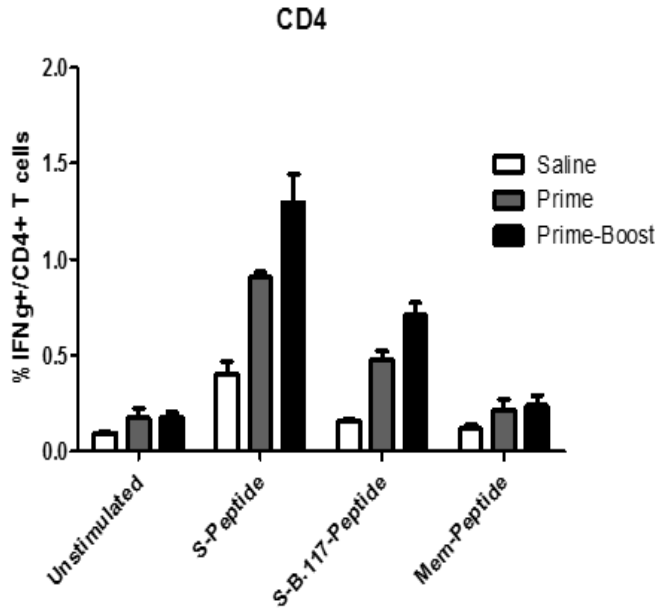
Neutralizing antibody

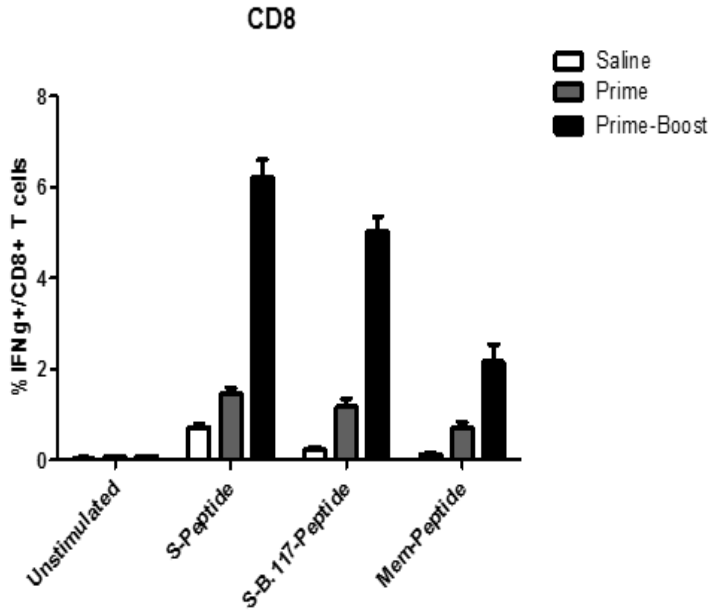


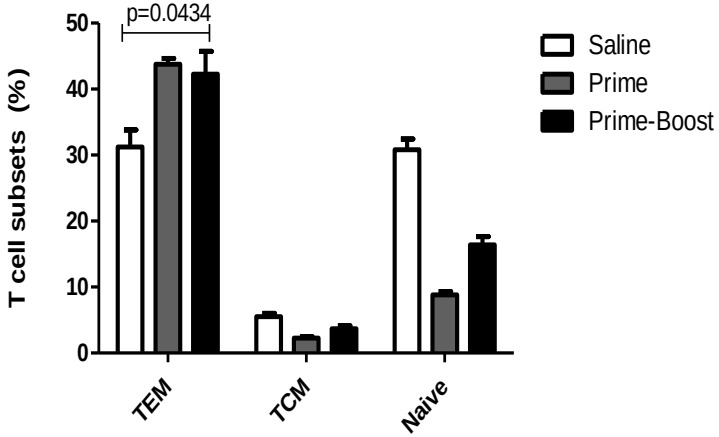
Binding antibody

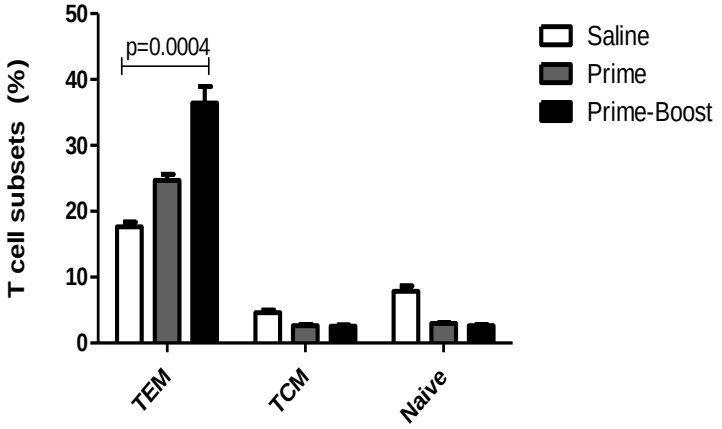


GEO-CM02 Immunogenicity hACE2 Tg Mice





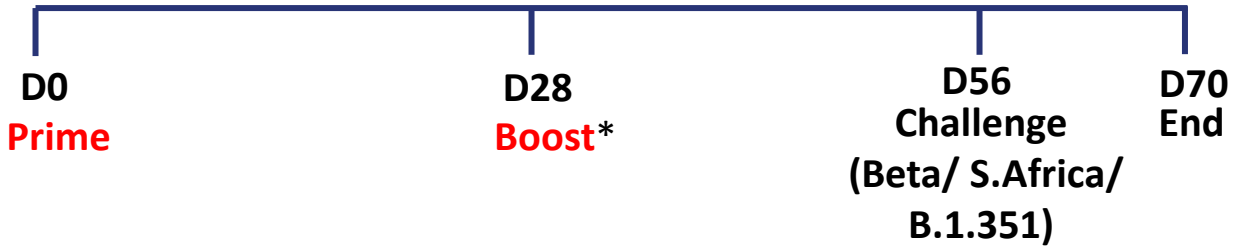


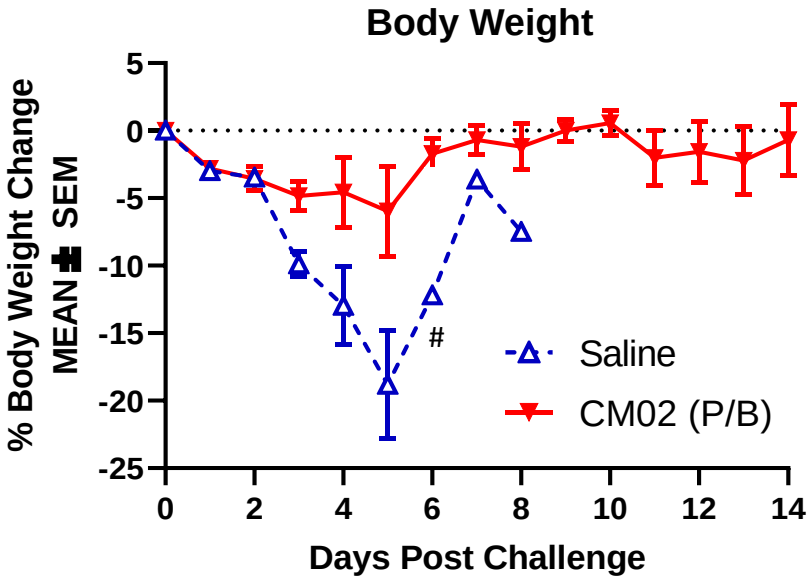


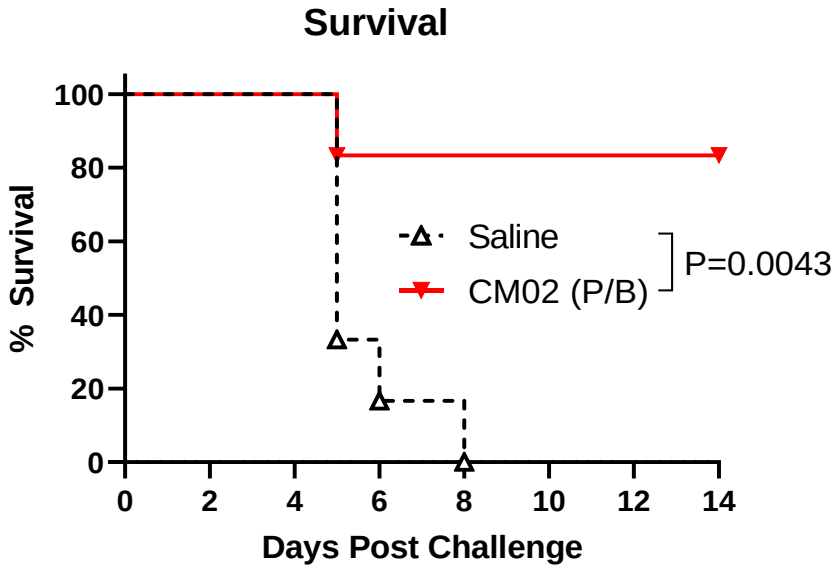
GEO-CM02 Protects Against Beta Variant SARS-CoV-2

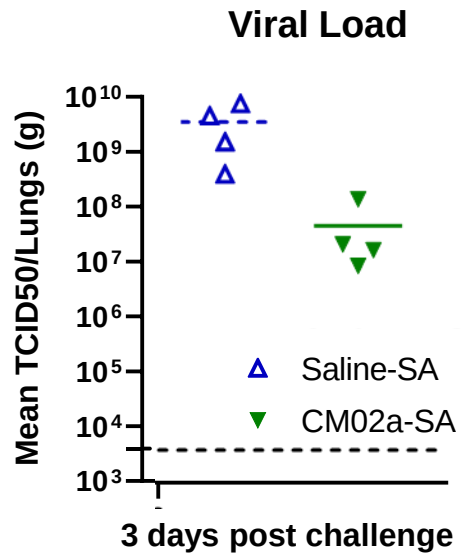
n=6/group

Intramuscular immunization:









- two mice remaining

Data Interpretation: Efficacy against VOC

- The use of MVA as a vector supports the design and production of “next-generation” vaccines encoding multiple viral proteins
  - S protein as the primary antibody target
  - M and E as T-cell targets
- The combination of S, M and E protein expression supports VLP formation, optimal immunogenicity
- Functional antibodies and T-cell responses are induced that mediate protection from infection and pathogenesis
- GEO-CM02 protects animals from morbidity and mortality against SARS-CoV-2 and the Beta variant

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Future Designs: Pan-Coronavirus Vaccines

- Express additional viral genes encoding conserved proteins as antigens to increase the breadth of T-cell responses
  - >60% of the viral genome (ORF) encodes NSP that are sequence conserved and immunogenic in humans
- Build on existing MVA-SME (GEO-CM-02) vaccine construct
  - Encode NSP under different promoters
  - Expression not part of the VLP structure

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Thank You

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