Design of a Universal SARS-CoV-2 Vaccine Effective Against Evolving Variants

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Overview

- Immune responses to SARS-CoV-2
- Conserved regions of coronaviruses
- GeoVax MVA-VLP technology
- MVA-VLP-COVID
- Designing a vaccine with broad protection

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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
- **Multifunction responses with memory:** required for optimal protection from infection and serious illness

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SARS-CoV-2 Antibody Responses

- Neutralizing antibodies, specific to the Spike (S) protein present in most sera of convalescent patients *Emerging Infectious Diseases* 2021: 27(issue 2)
- Neutralizing antibodies persist for months, long-term data is absent *Science* 2020: 370 (issue 6521)
- SARS-CoV-2 infection induces bone marrow resident plasma cells in humans *Nature* 2021: 595 (421–425)
- Memory B cell numbers readily detected 1-8 months after infection *Science* 2021: 371 (issue 6529)

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SARS-CoV-2 Antibody Responses

- The duration of neutralizing antibodies may be short-lived *Nature Micro* 2020: 5 (1598-1607)
- Non-protective antibodies may rarely be associated with antibody-mediated enhancement of disease *Immunity* 2020: 53 (248-263)
- Stabilized S protein is the antigenic target central to most of the 1st generation vaccines, focus on virus neutralization (Pfizer, Moderna, J&J, AZ, NovaVax)

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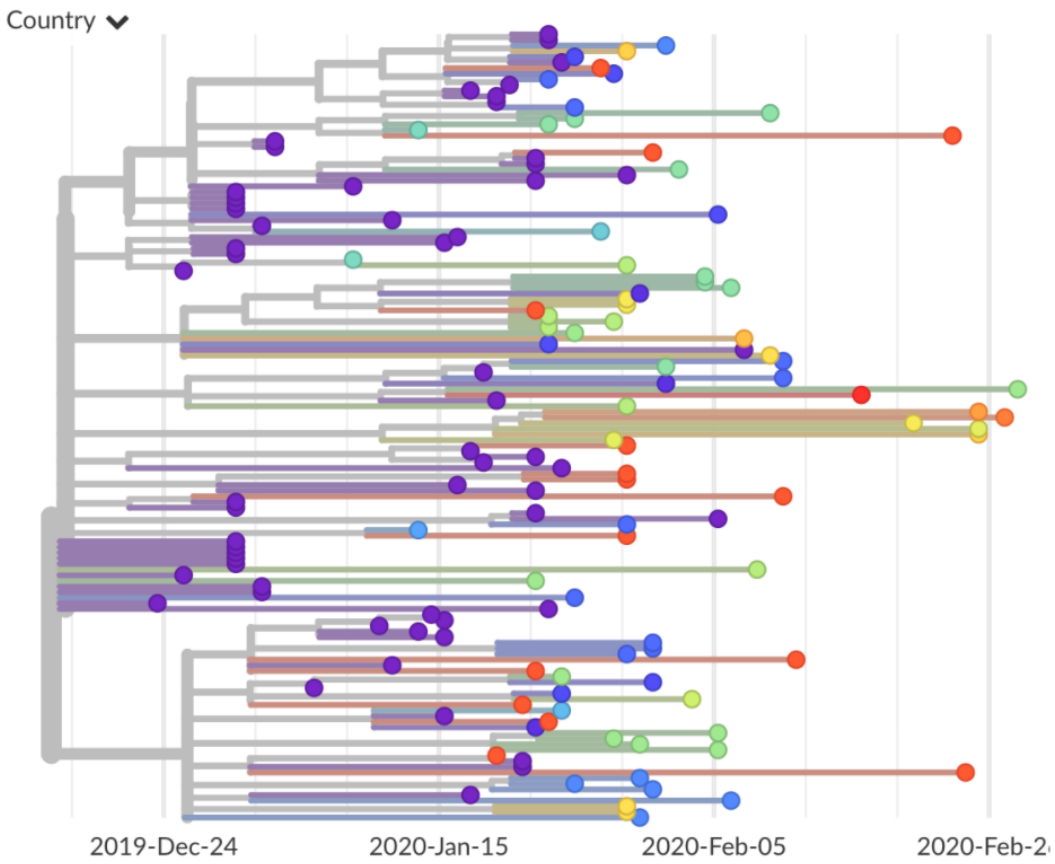
SARS-CoV-2 Vaccine Challenge is Emerging Variants

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



Nextstrain via Bedford.io

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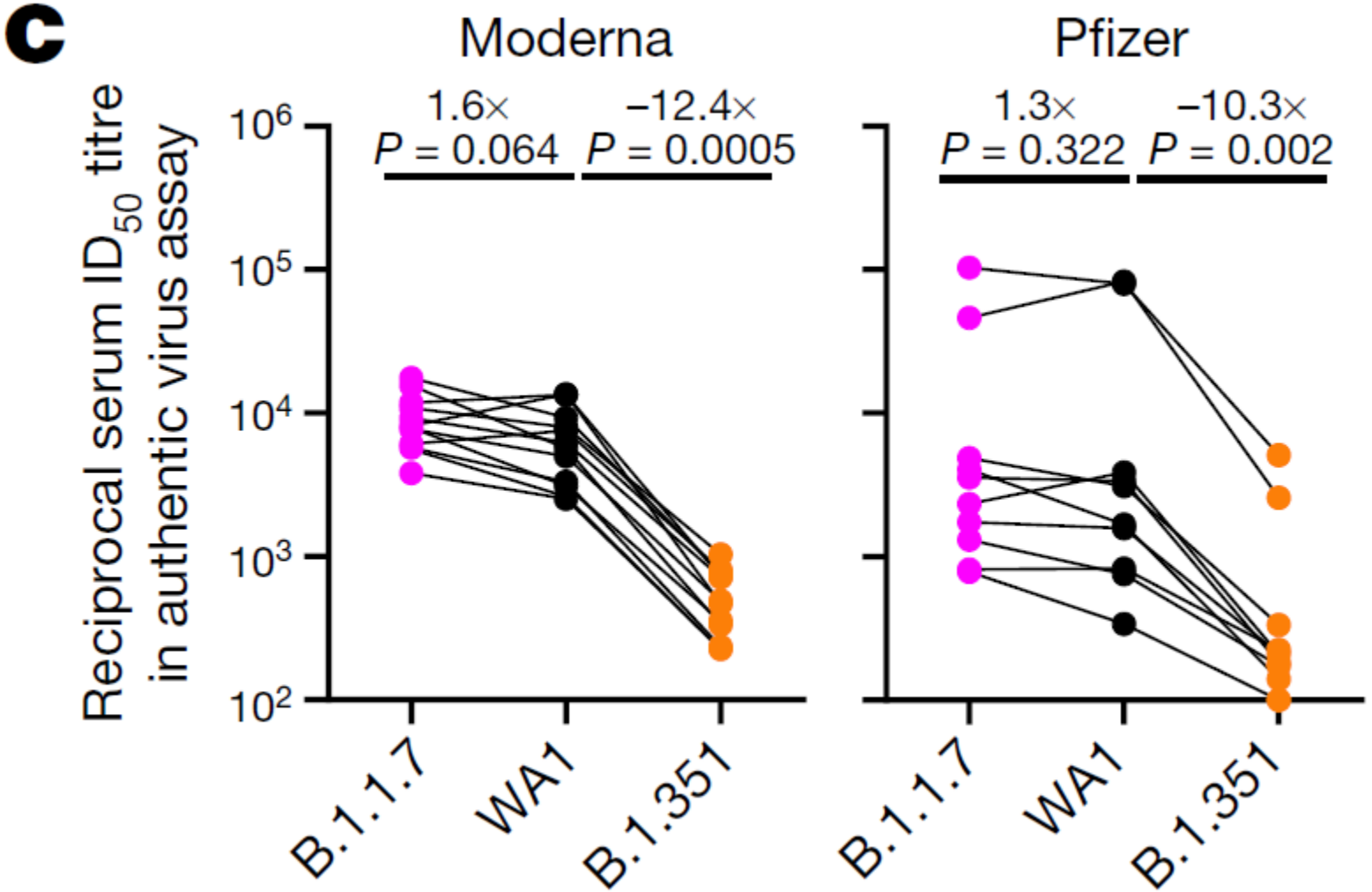
Reduction of Vaccine-Induced Antibody Activity



Nature 593, 130–135 (2021)

Variants of WHO Concern

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 Most transmissible	↑ 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

SARS-CoV-2 Cellular Immunity

- >90% of convalescent patients had detectable CD4+ T-cell responses *Science* 2021:371(issue 6529)
- Multi-specificity and functionality of T-cells are associated with accelerated viral clearance and with protection from severe COVID-19 *Oxford Open Immunol* 2021:2 (issue 1)
- Patients who recovered from SARS-CoV-1 infection possess long-lasting memory T-cells 17 years after the outbreak of SARS in 2003 *Nature* 2020:584 (457–462)

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SARS-CoV-2 Cellular Immunity

- T-cells in uninfected donors recognized epitopes in NSP7 and NSP13, suggesting cross-reactive recognition seasonal viruses and CoV-2 *Nature* 2020: 584 (457–462)
- NSP7 T-cell epitopes are conserved among animal beta-coronaviruses *Nature* 2020: 584 (457–462)
- Vaccine induction of T-cells is likely to be required for optimal and long-term efficacy against emerging SARS-CoV-2 variants

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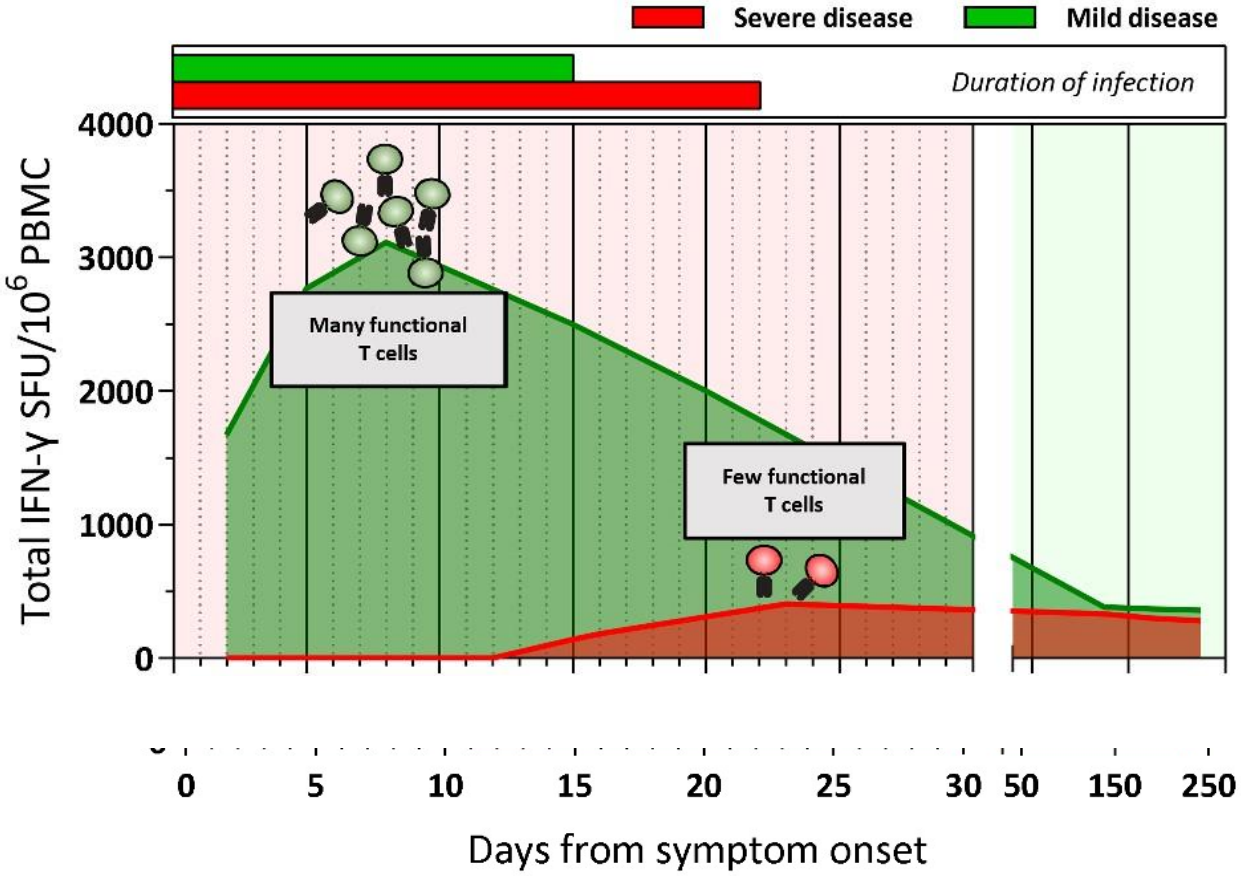
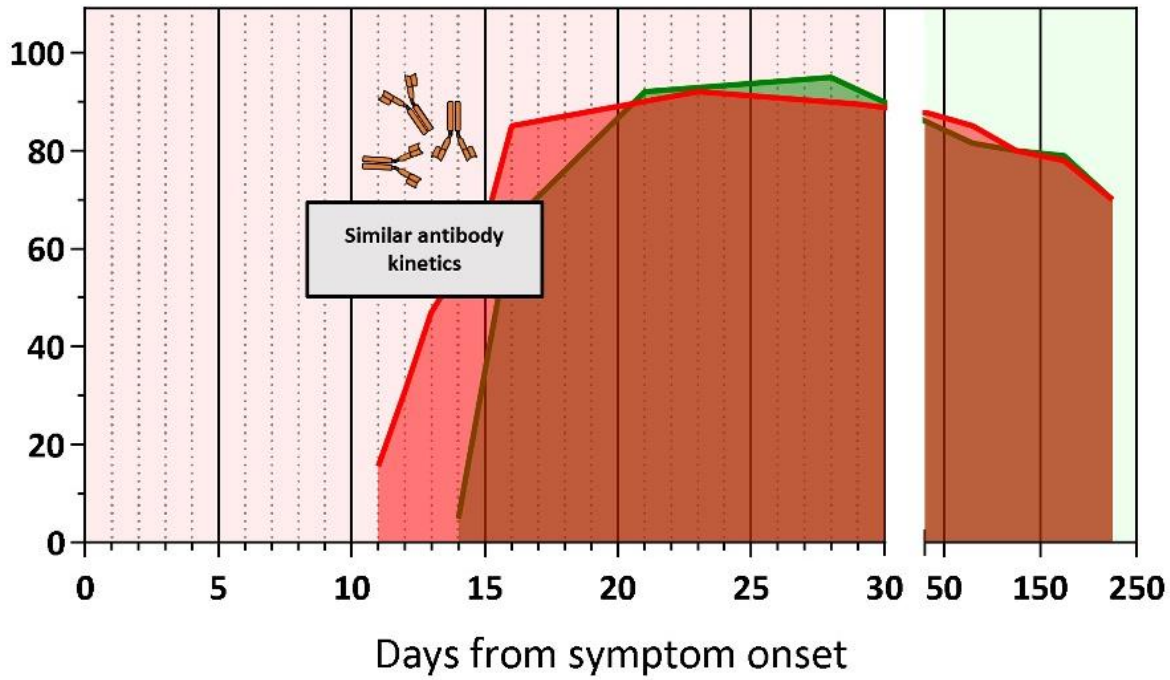
SARS-CoV-2 Disease Severity

Functional T cells and not circulating antibody correlate with reduced disease severity



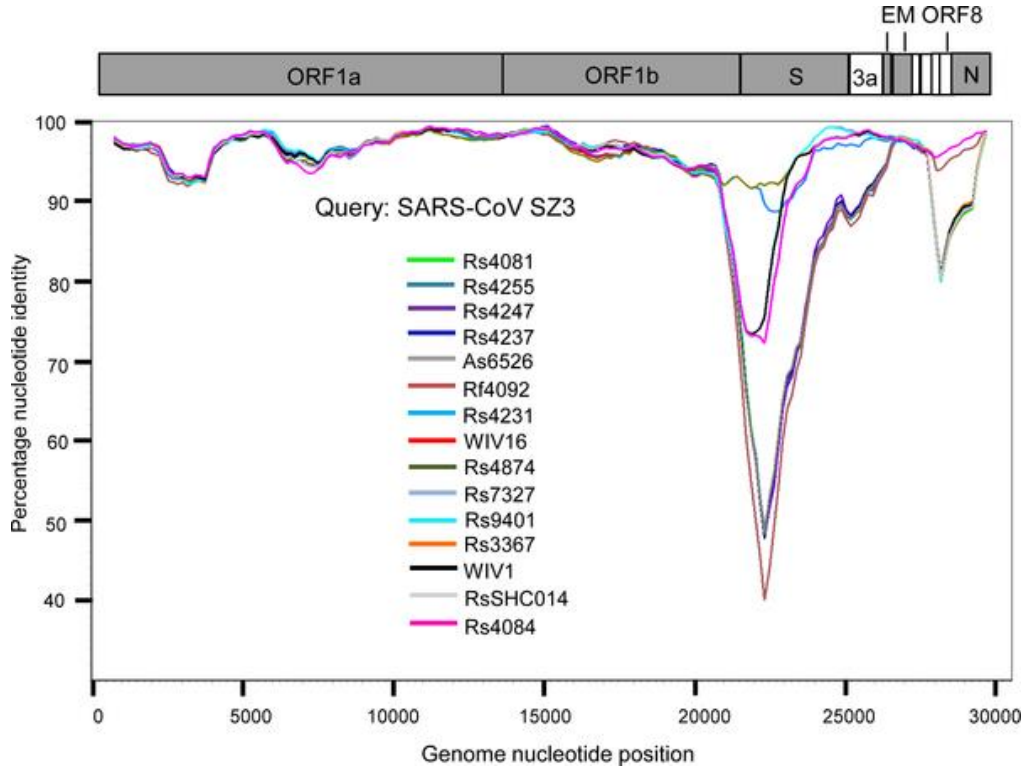


Science 05 Feb 2021:Vol. 371, Issue 6529

SARS-CoV Conserved Sequences

- Sequences of phylogenetically related SARS-CoV vary in Spike, ORF3 and ORF8 *Nature Rev Micro* 2019:171(181–192)
- Mutation in the S and ORF8 allowed for efficient spread 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)

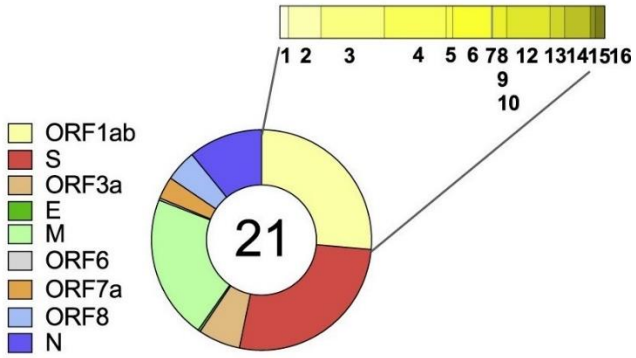
Similarity plot based on the full-length SARS-CoV genome sequences



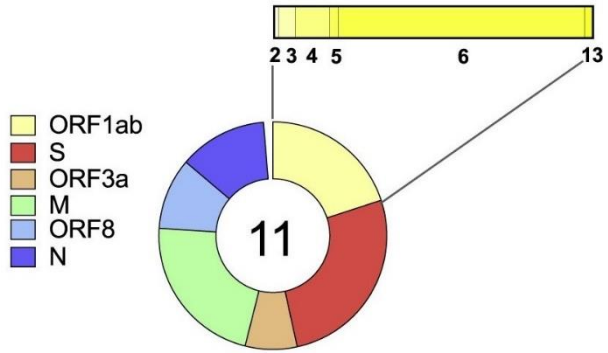
PLOS Pathogens. 13(11). 2017

Conserved SARS-2 T-cell Epitopes in ORF1a & 1b

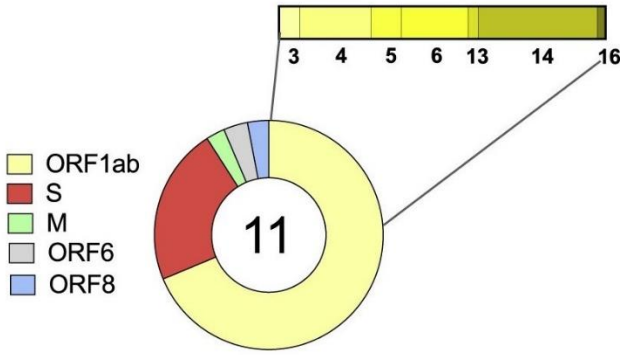
CD4+ T-cells



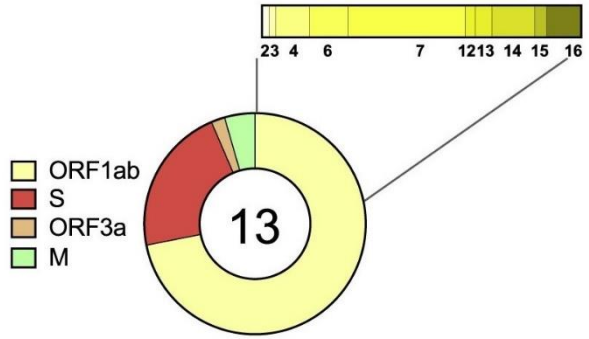
CD8+ T-cells



Exposed



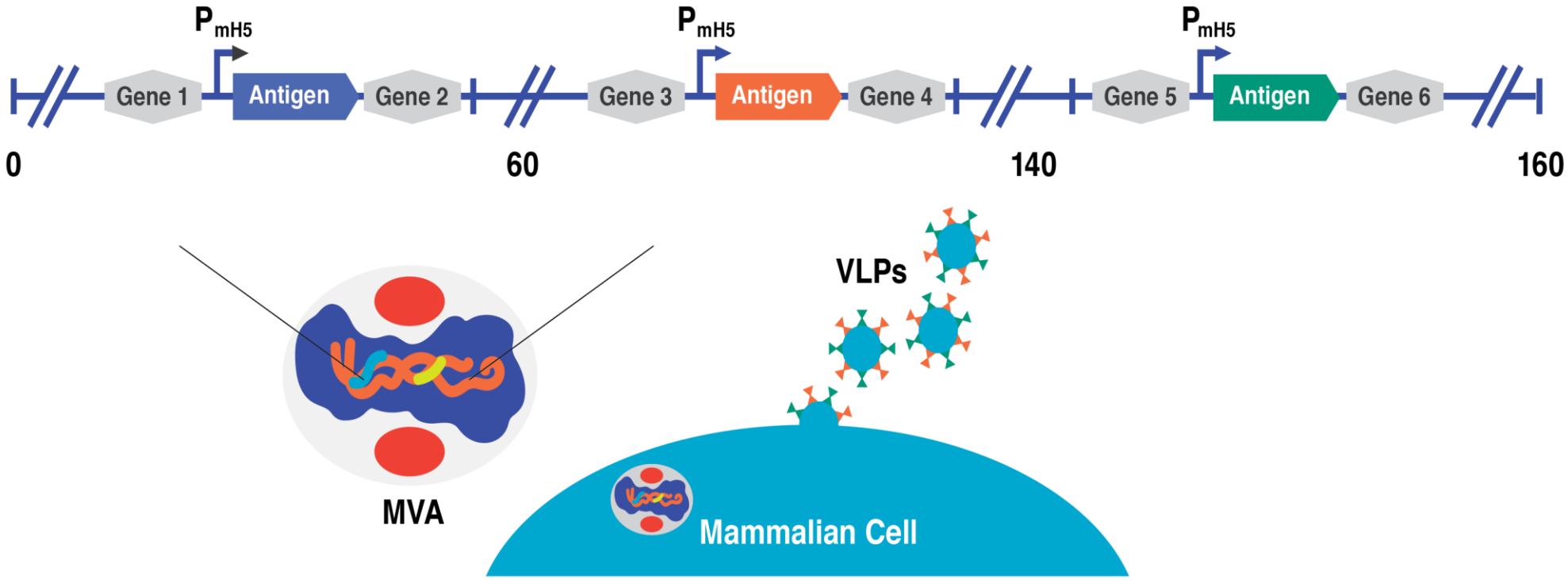
Unexposed



Cell 2020:181(1489-1501)

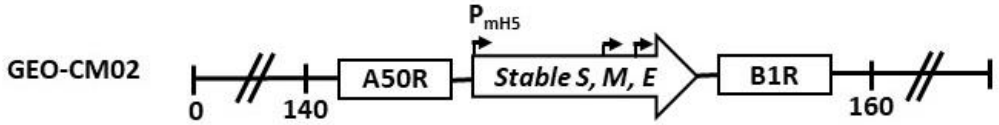
GeoVax MVA-VLP Vaccine Platform

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



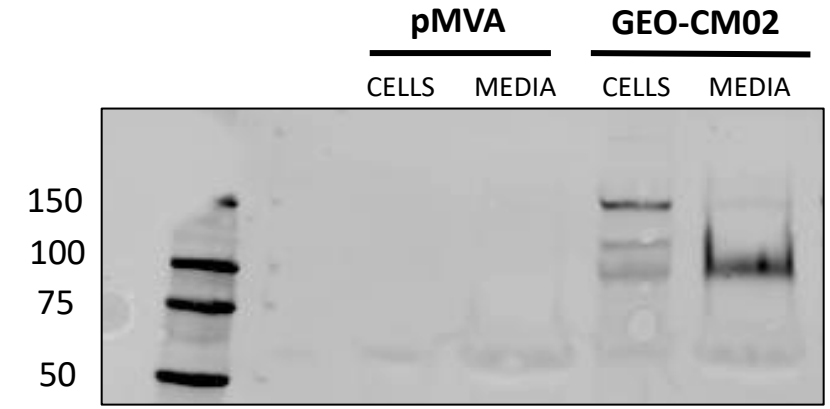
MVA-SARS-CoV-2 (GEO-CM02)

MVA Encoding Stabilized Spike, Membrane and Envelope



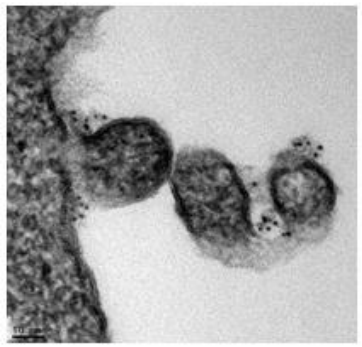
Insert Stability

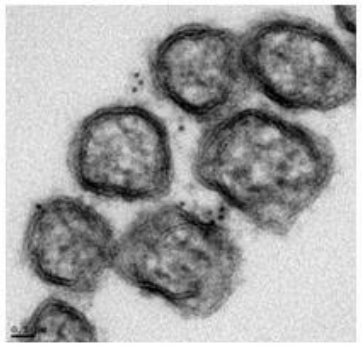
	Spike plaques	MVA plaques	Insert integrity
Seed virus	125	125	100%
Passage 15	399	399	100%
Passage 20	410	412	99.5%

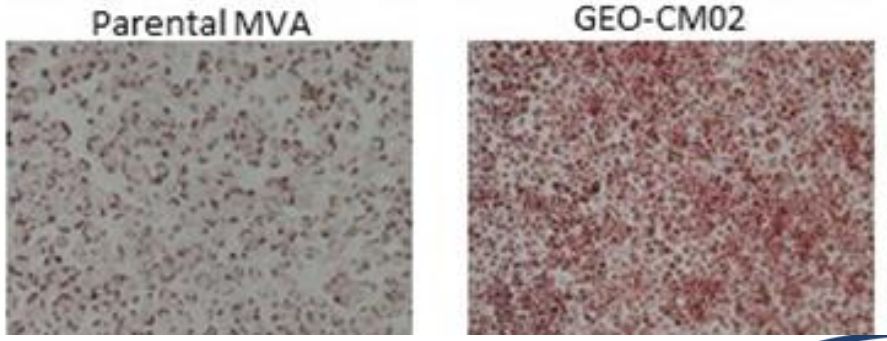


Spike protein expression

VLP formation







Membrane protein expression

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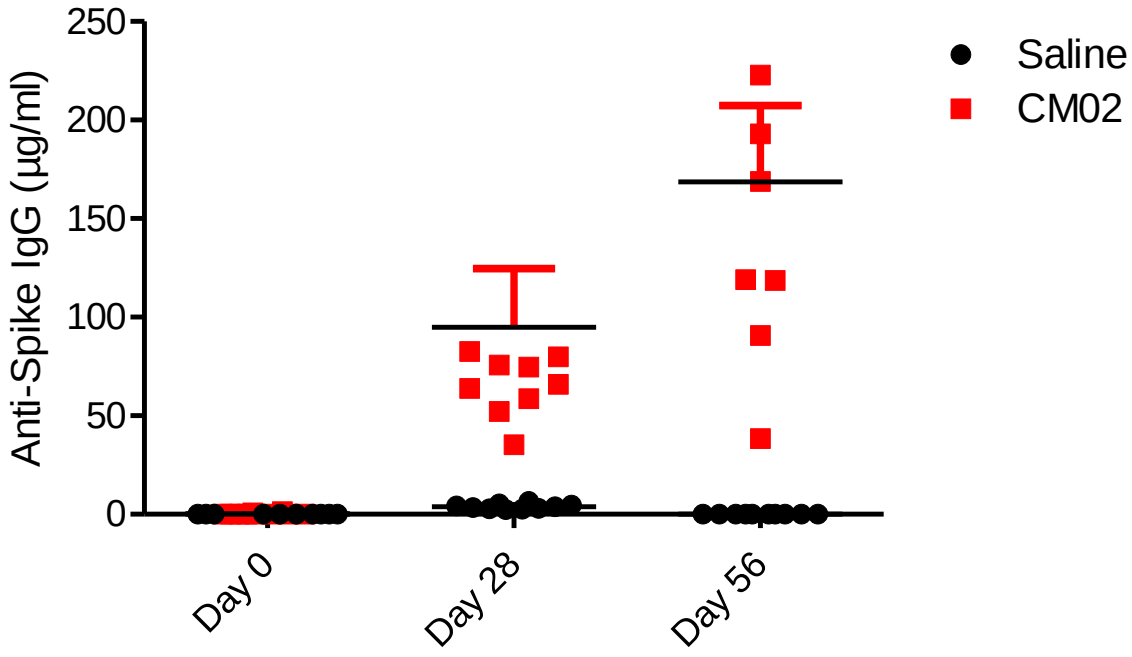
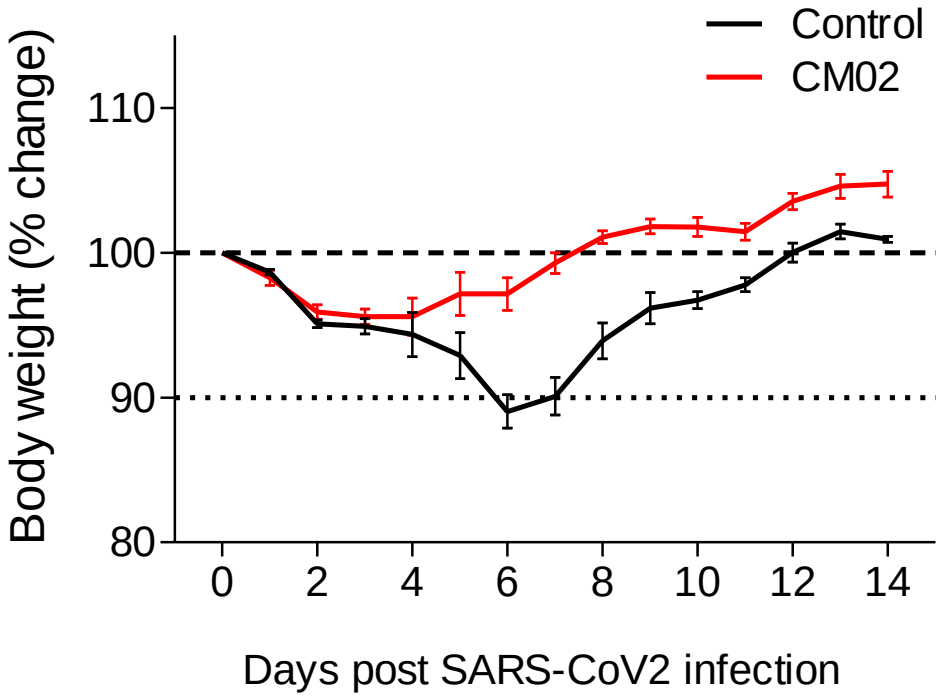
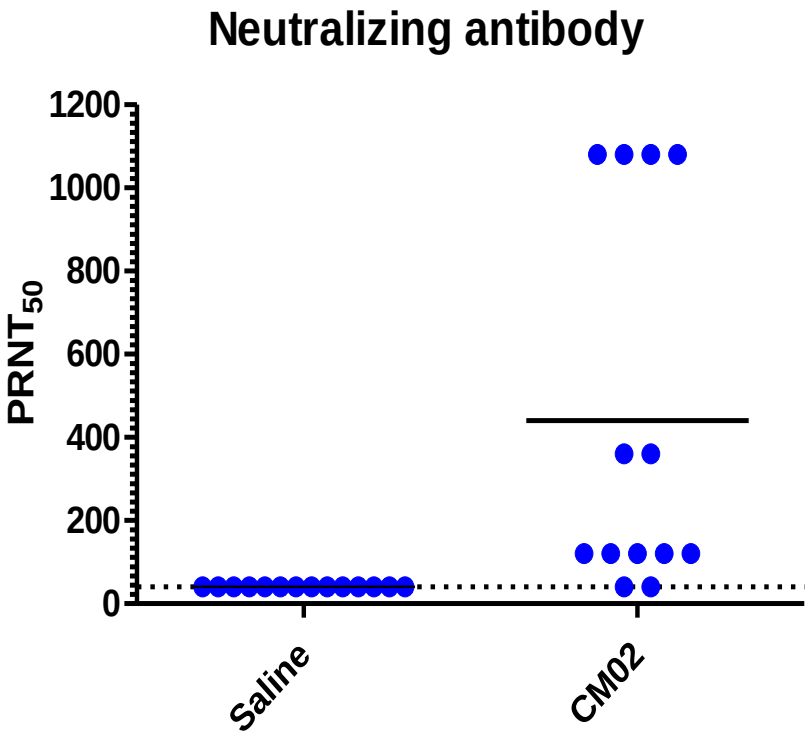
GEO-CM02 Efficacy in Hamsters

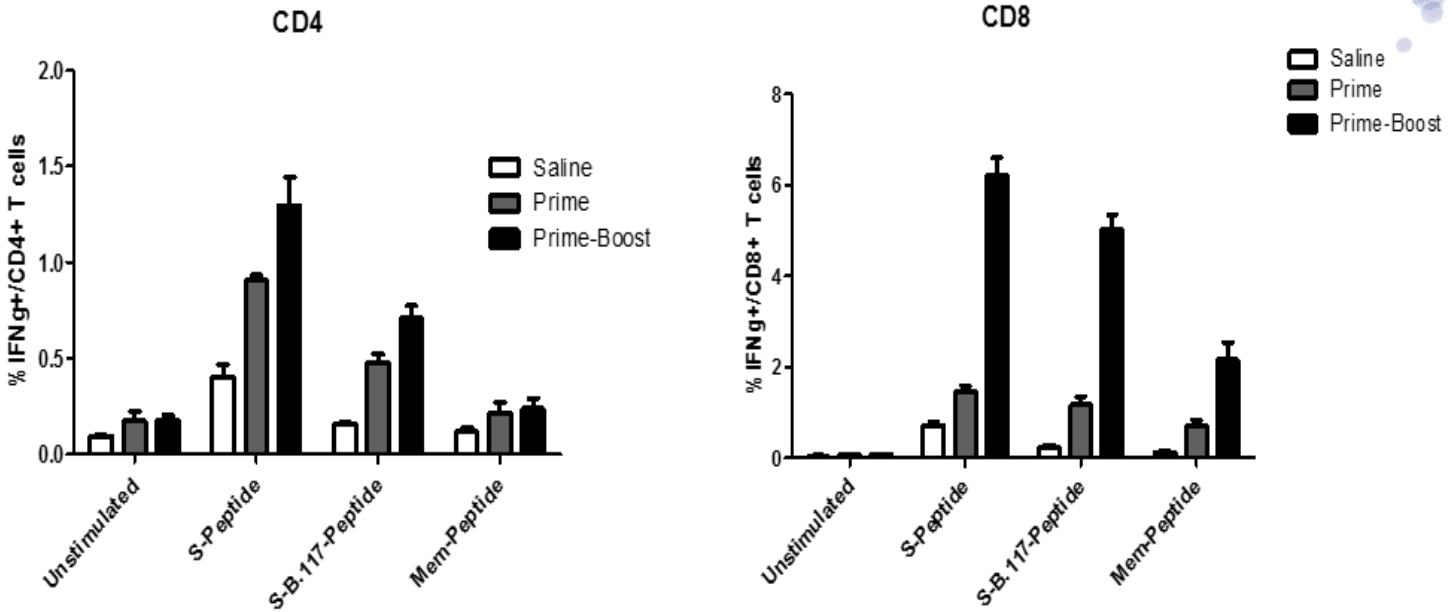


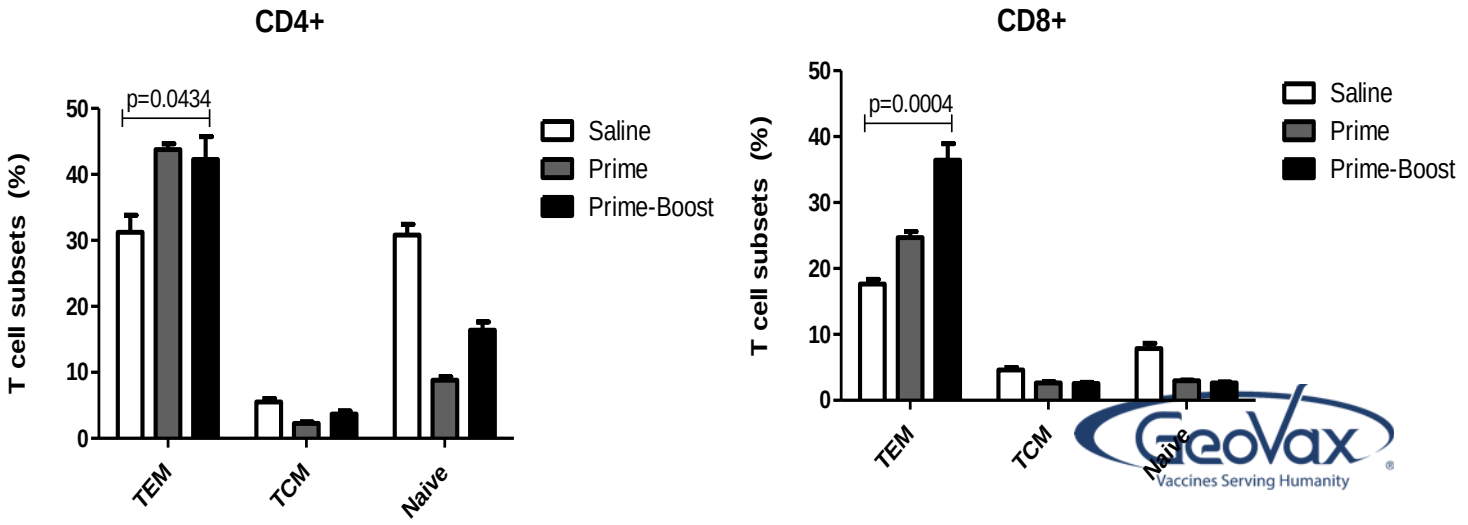


GEO-CM02 induces high titered antibody responses and protects animals from morbidity

GEO-CM02 Immunogenicity hACE2 Transgenic Mice







GEO-CM02 elicits neutralizing antibody and polyfunctional and memory T cell responses

Data Interpretation

- The use of MVA as a vector supports the design and production of “next-gen” vaccines encoding multiple viral proteins
  - S protein as the 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

Future Designs

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

Acknowledgements

- GeoVax team
  - Arban Domi
  - Sreenivasa Oruganti
  - Mary Hauser
  - Kevin Silva
- NIH SBIR funding
  - 1R43AI157578-01
- University Texas MB
  - Alex Bukreyev
  - Delphine Malherbe

Thank You

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