Vaccine induction of broadly-specific antibody and T-cell responses to combat SARS-CoV-2 variation

Mark J. Newman, PhD

Chief Scientific Officer

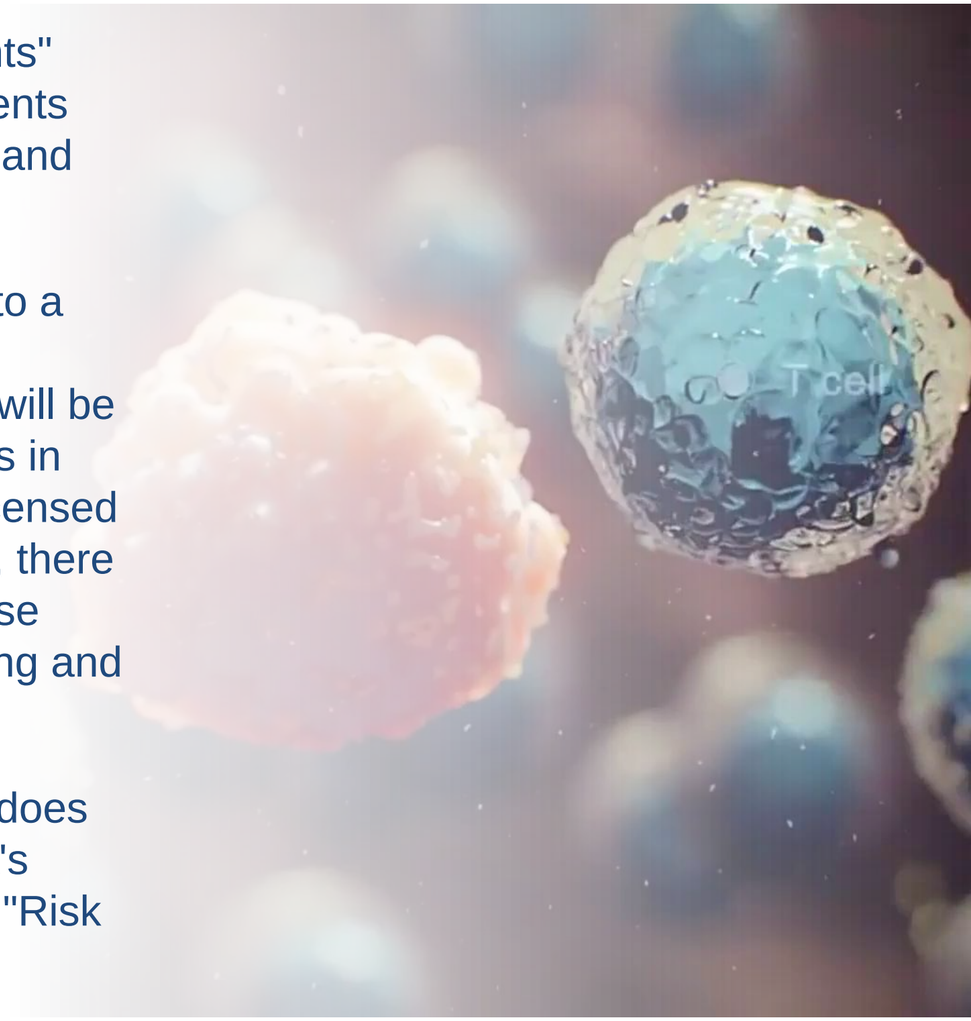
GeoVax®

Forward Looking Statements

Certain statements in this presentation may constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act. These statements are based on management's current expectations and are subject to uncertainty and changes in circumstances.

Actual results may differ materially from those included in these statements due to a variety of factors, including whether: GeoVax can develop and manufacture its vaccines with the desired characteristics in a timely manner, GeoVax's vaccines will be safe for human use, GeoVax's vaccines will effectively prevent targeted infections in humans, GeoVax’s vaccines will receive regulatory approvals necessary to be licensed and marketed, GeoVax raises required capital to complete vaccine development, there is development of competitive products that may be more effective or easier to use than GeoVax's products, GeoVax will be able to enter into favorable manufacturing and distribution agreements, and other factors, over which GeoVax has no control.

GeoVax assumes no obligation to update these forward-looking statements and does not intend to do so. More information about these factors is contained in GeoVax's filings with the Securities and Exchange Commission including those set forth at "Risk Factors" in GeoVax's Form 10-K.



Critical Importance of Both Antibodies & T cells for Protection

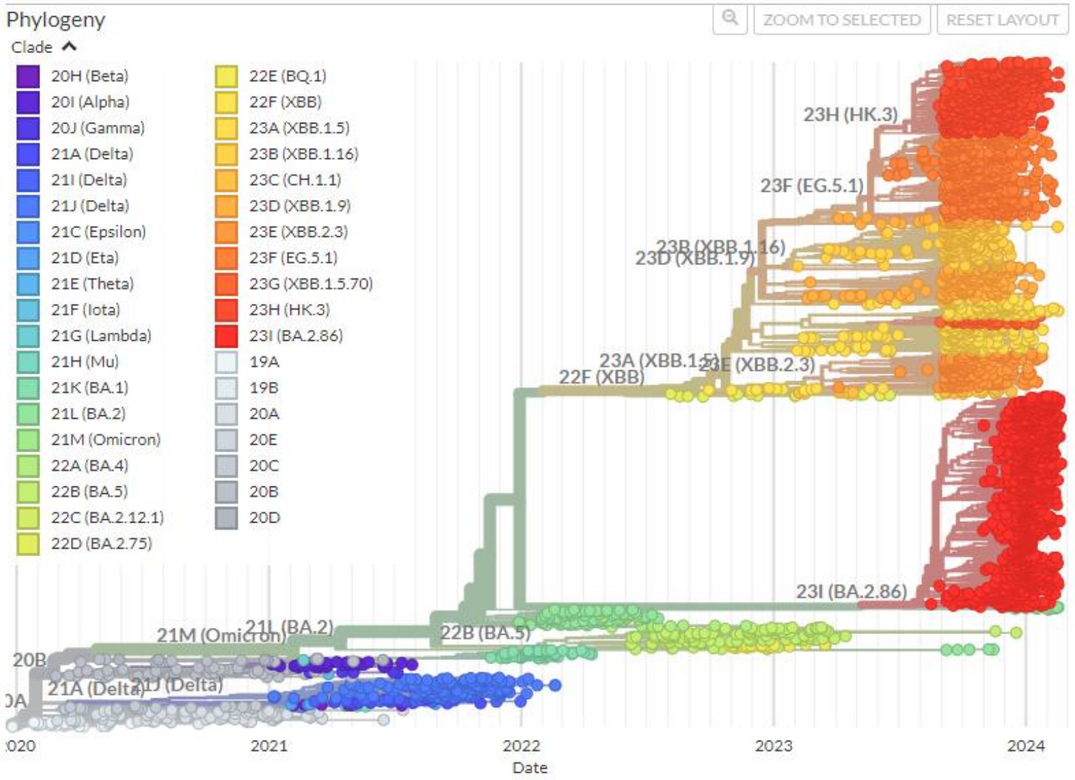
COVID-19 Disease Severity

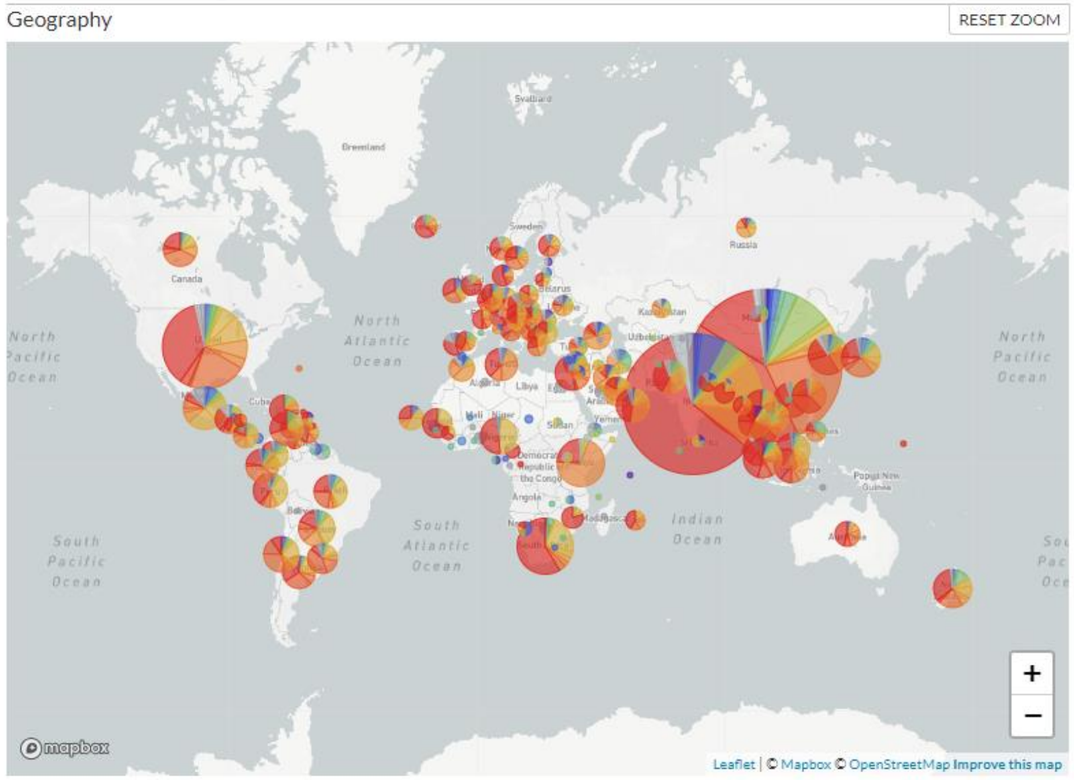
	Asymptomatic Infection	Symptomatic Infection	Severe Disease, Hospitalization	Death
Antibodies	++++	+++	++	++
T Cells	+	++	++++	++++

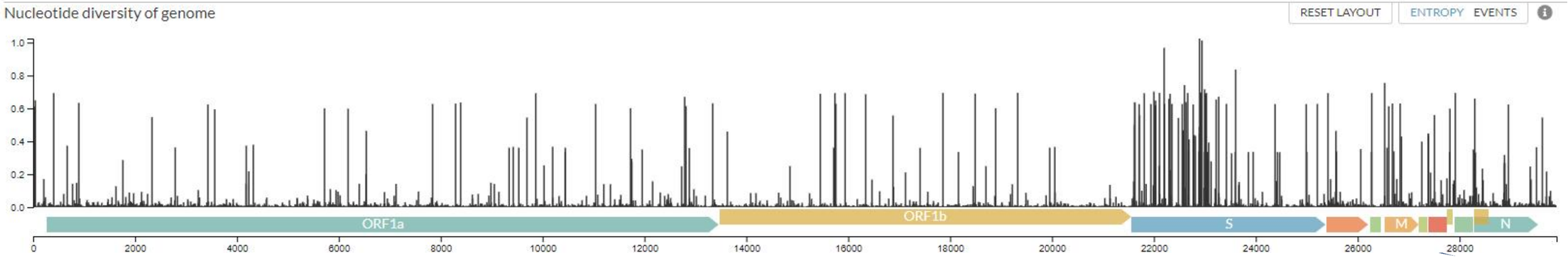
- Vaccine induced antibodies are highly effective but have limited a limited functional half-life
- Antibodies specific to the Spike protein are driving the emergence of variants
- Early/large T cell responses (cross-reactive) are associated with faster viral clearance and/or better clinical outcomes
- Lower levels of T cells are found in BAL of fatal or severe COVID-19 cases

Barouch DH, N Engl J Med 2022; 387:1011-1020 & Goldblatt et al., 2022. Immun. Rev

SARS-CoV-2 Genomic Variation – A Significant Hurdle







T-cell Responses to SARS-CoV-2 Proteins

- Nucleocapsid (N), Membrane (M) and Spike (S) structural proteins are very immunogenic
  - T-cells are readily detectable in convalescent SARS-CoV-2 patients
  - Numerous T-cell epitopes are present in S, N and M proteins
  - T-cell epitopes tend to be highly conserved, small and linear peptides

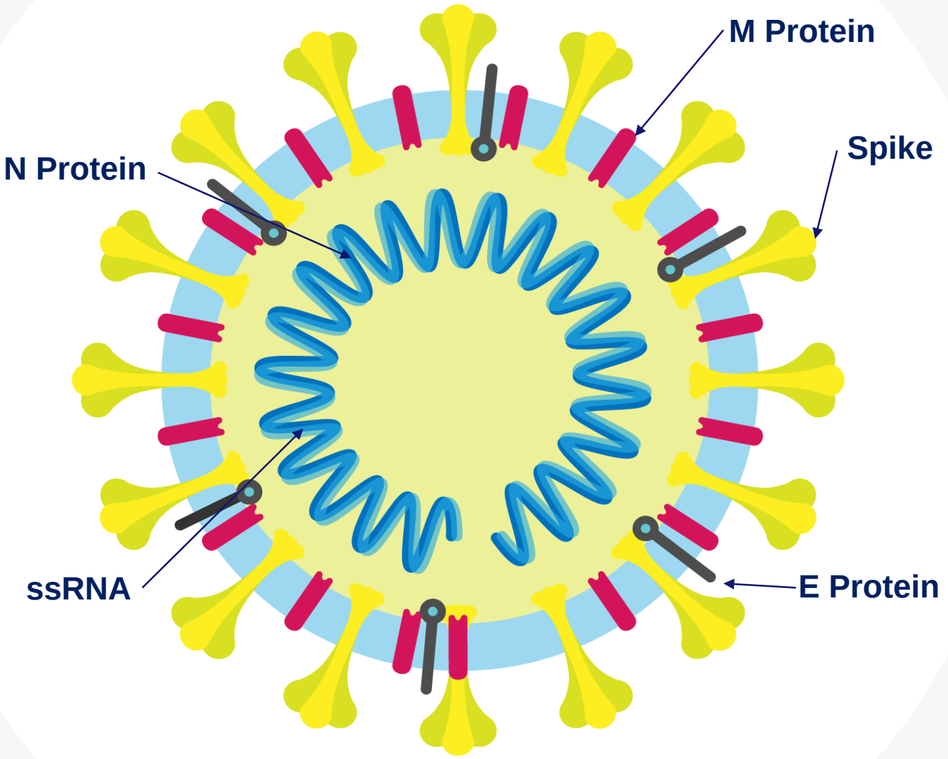
- Nonstructural genes (ORF/NSP) are highly conserved and immunogenic
  - T-cell epitopes in NSP known to induce “cross-reactive T-cell responses”
  - Coronavirus-specific beyond SARS-CoV-2

- **Hypothesis:** Targeting structural proteins and NSP using vaccination to induce T-cell responses will increase protection against a rapidly evolving virus
  - Contributions of immune responses to individual viral proteins can be tested using the hACE-2 mouse model

GeoVax Multi-Antigen Vaccine Design

GEO-CM04S1

- S+N co-expressed
- Wuhan sequence
- Native S



SARS-CoV-2

GEO-CM01/02

- S+M+E co-expressed
- MVA-VLP platform (in vivo)
- Wuhan sequence
- P2 stabilized and native S

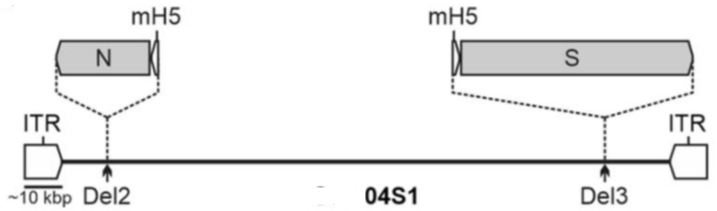
Astuti &Ysrafil. *Diabetes Metab Syndr*. 2020 Apr 18

Modified Vaccinia Virus Ankara (MVA) as a Vaccine Vector

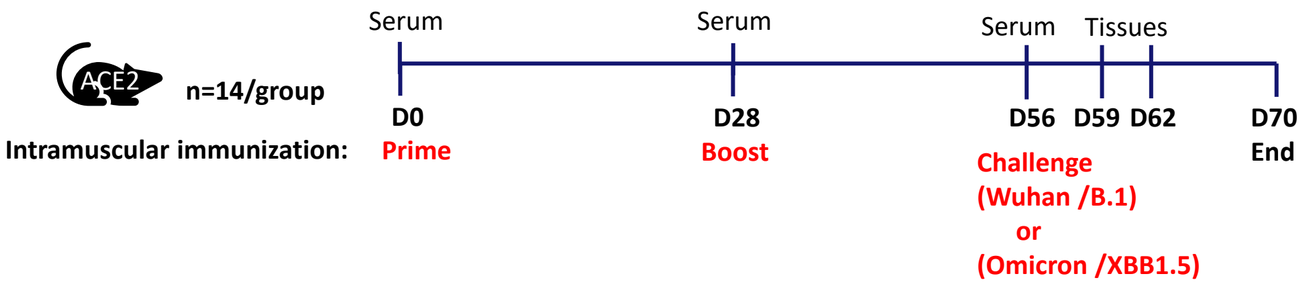
1. Large and available genetic **coding capacity** allowing for the insertion of multiple genes into different sites, supporting the simultaneous expression of multiple immunogenic proteins.
2. Preferentially **targets antigen presenting cells** in vivo, in particular cells of the dendritic cell lineage, of particular importance for the induction of CD8+ T cells.
3. Presents antigens through the **cross-presentation** pathway, which is highly effective for the induction of antibody and CD4+ T cell responses.
4. It lacks critical immune evasion genes present in vaccinia and allows for the induction of innate immune responses which provide an **adjuvant effect**.
5. **Vector Immunity does not impact MVA** infection of cells and the subsequent expression of encoded genes and induction of associated humoral immunity.
6. MVA can be **safely and effectively used** as a vaccine vector in people of all ages, including **immunocompromised** individuals.

GEO-CM04S1 Efficacy Testing in Transgenic hACE2 Mice

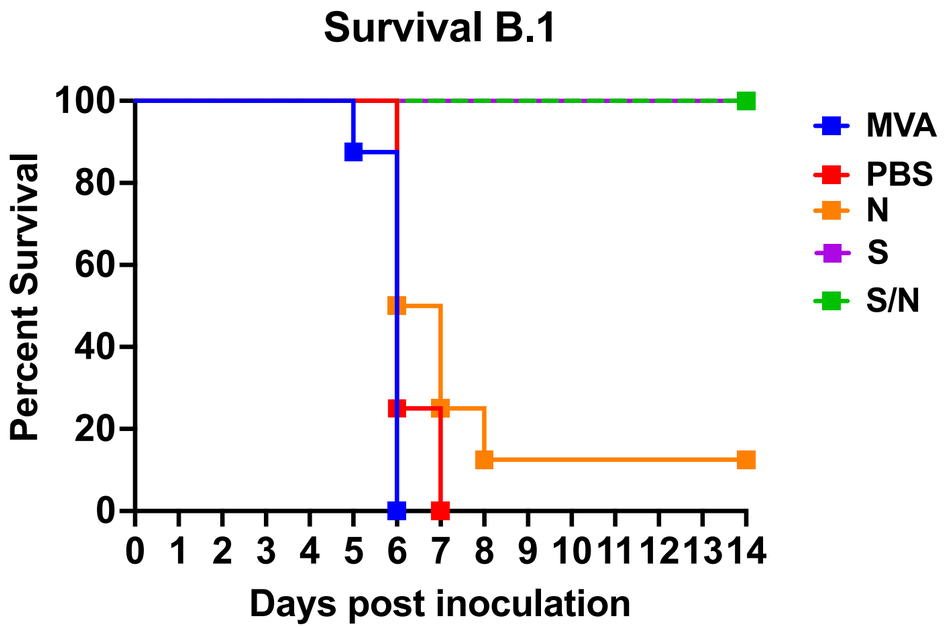
Vaccine Design:

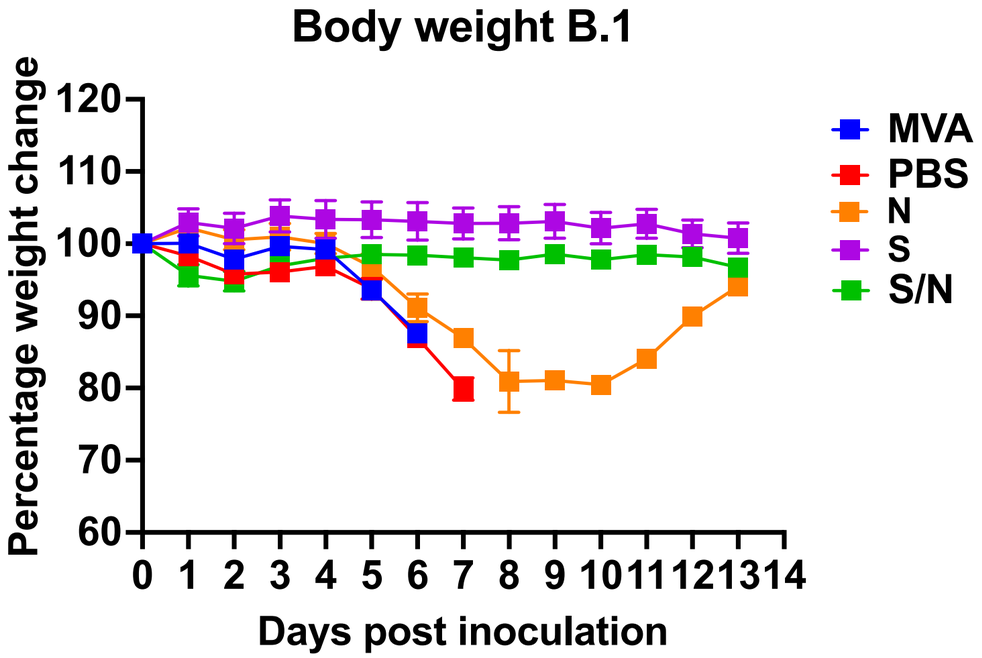


Study Design:

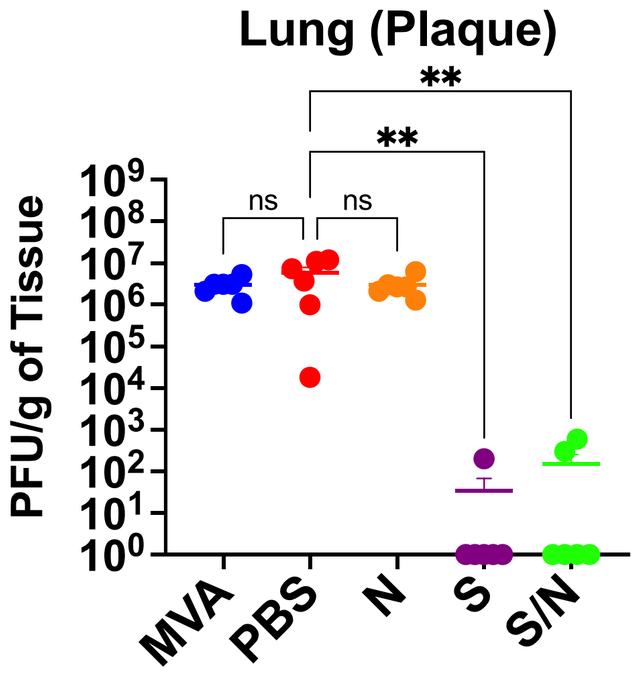


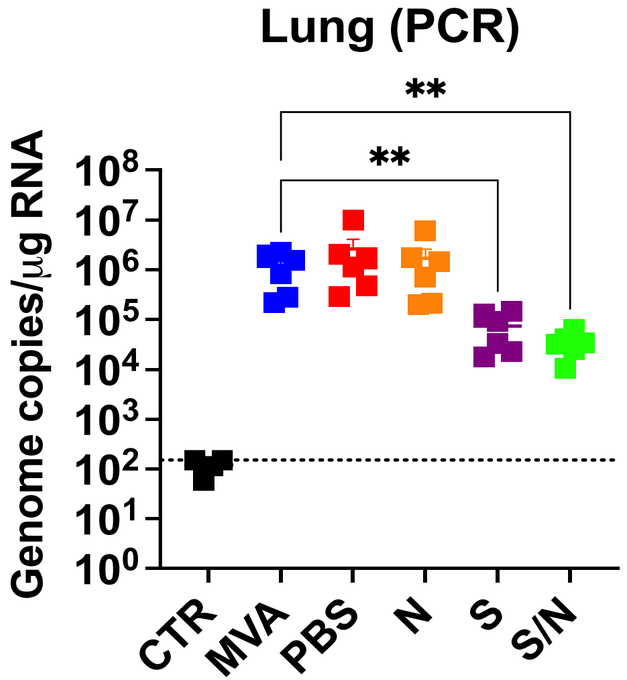
GEO-CM04S1 Efficacy against Wuhan (B.1) in hACE2 Mice

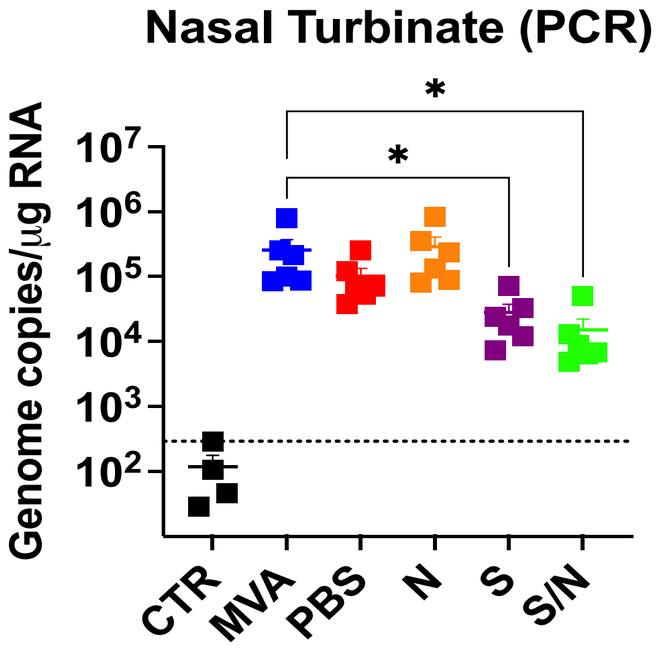




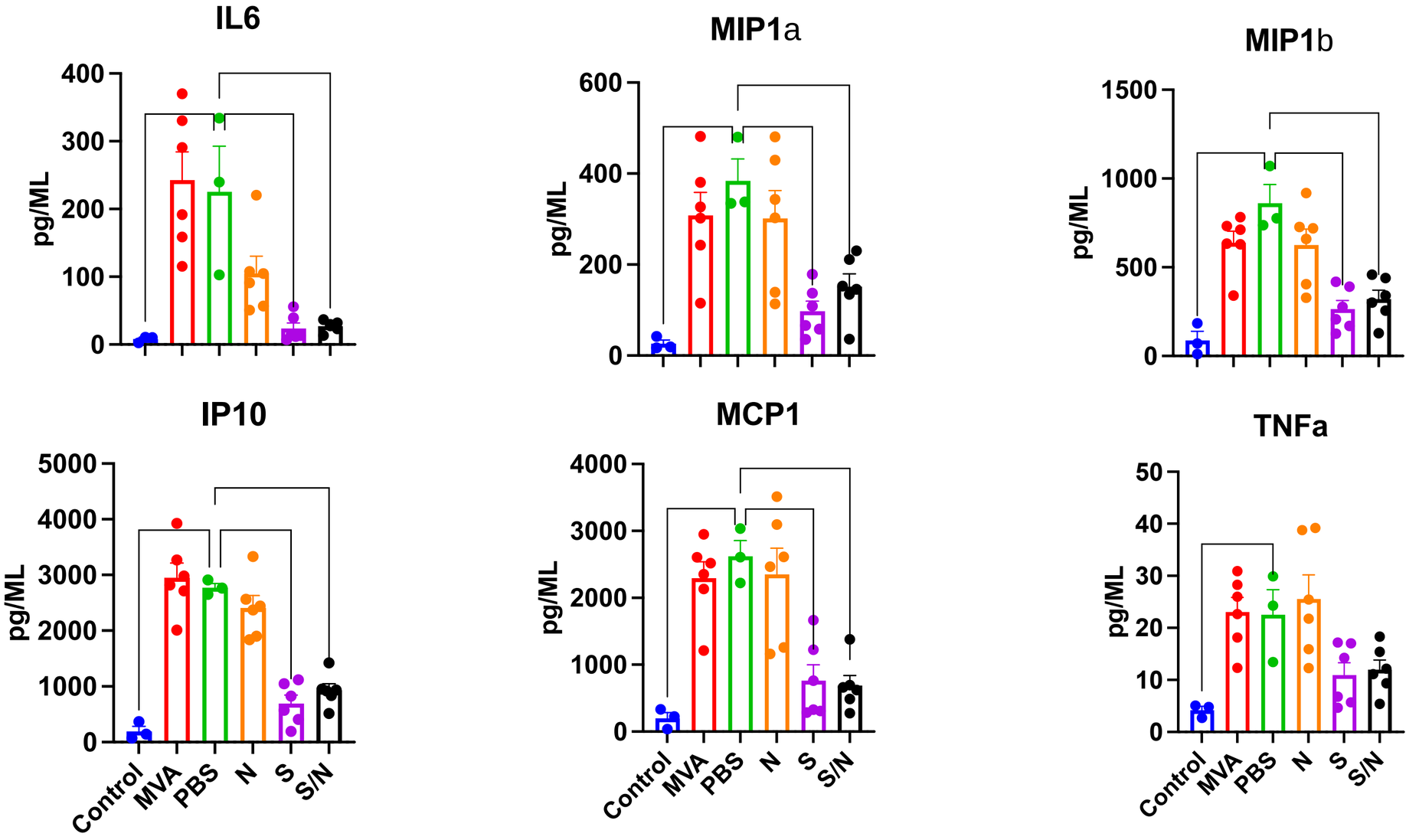
GEO-CM04S1 Efficacy against Wuhan (B.1) in hACE2 Mice







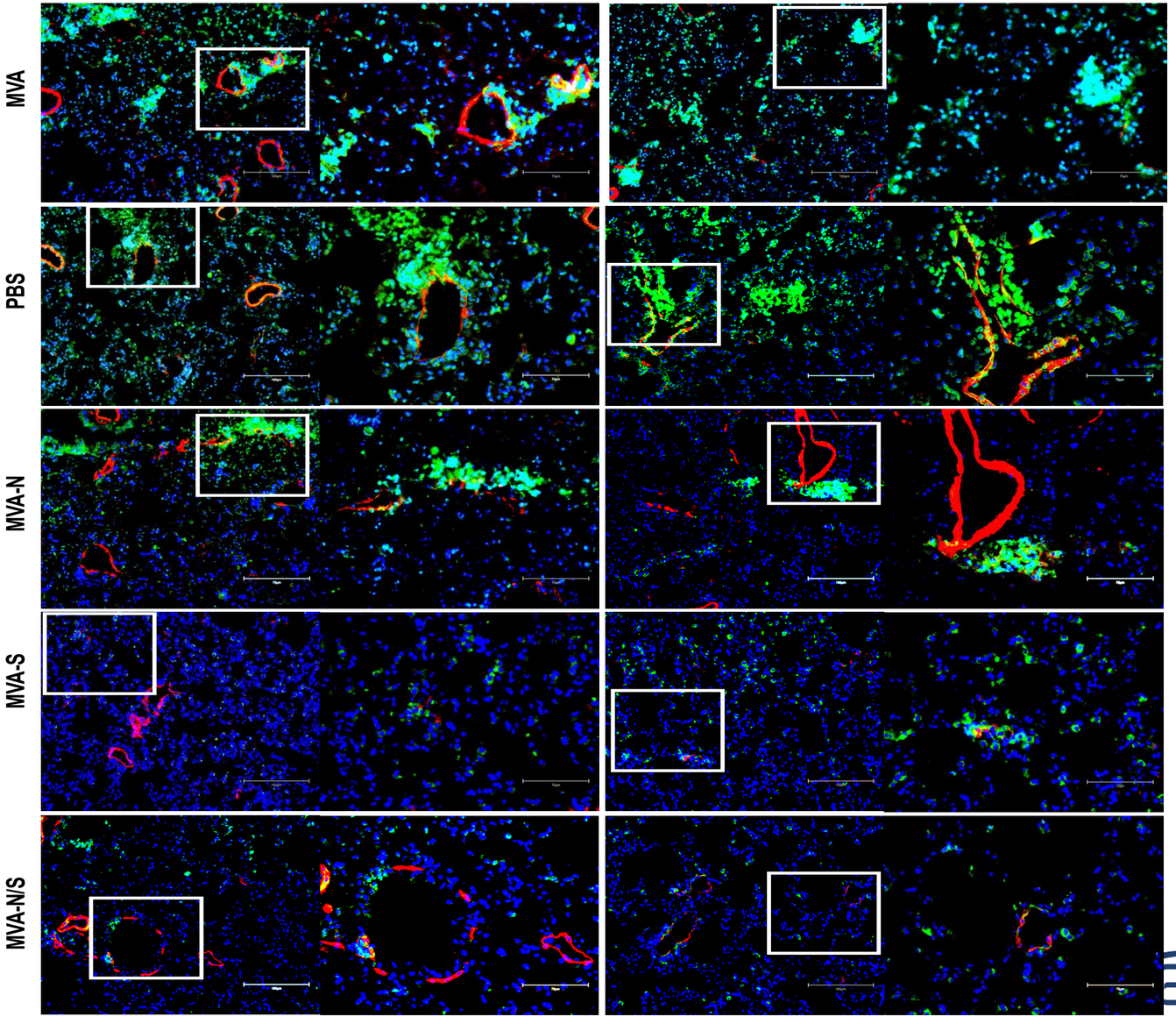
GEO-CM04S1 Efficacy against Wuhan (B.1) in hACE2 Mice



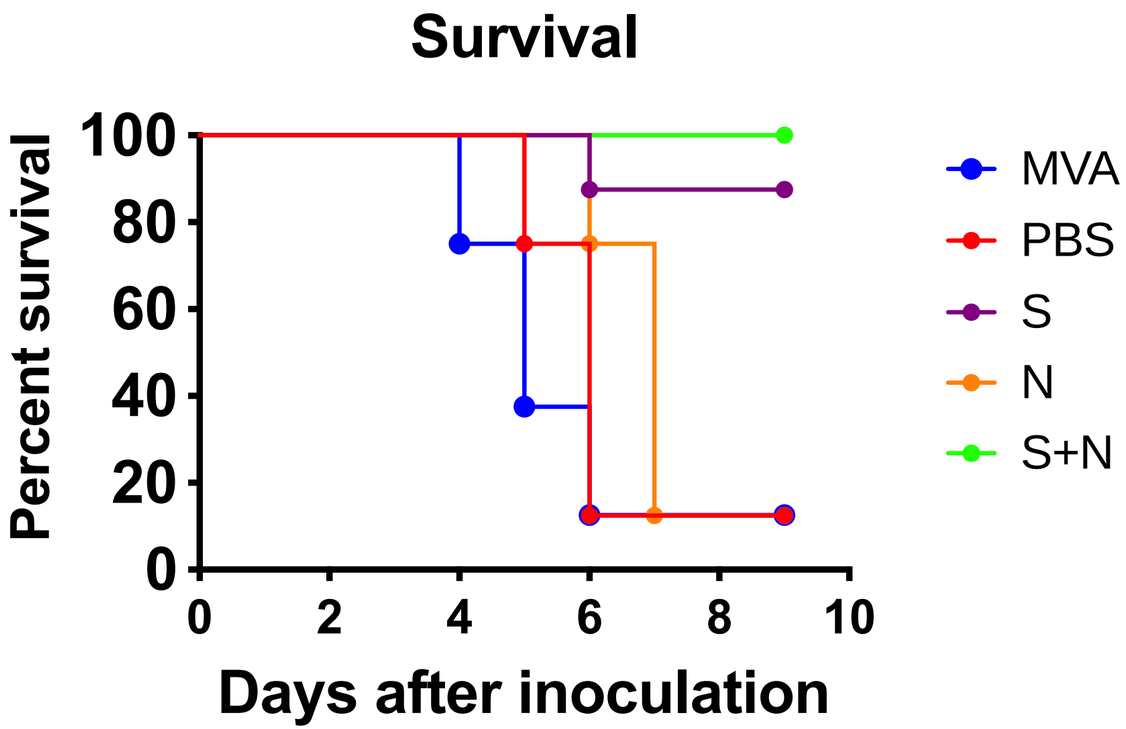
GEO-CM04S1 Efficacy against Wuhan (B.1) in hACE2 Mice

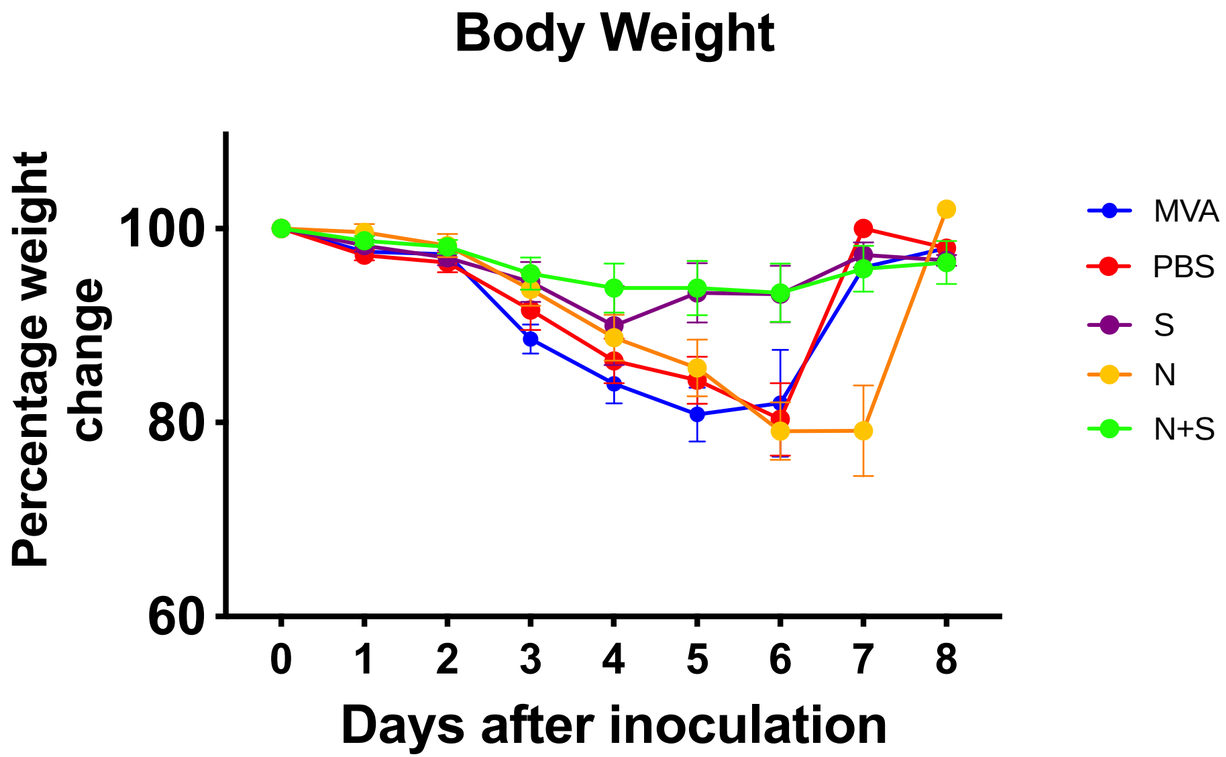
Lung sections
Day 3 post-challenge

CD45 – Leukocyte infiltrates
SMA – Airways/blood vessels
DAPI

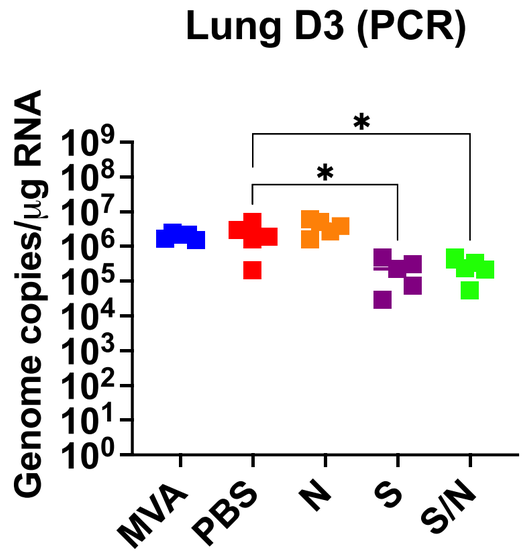


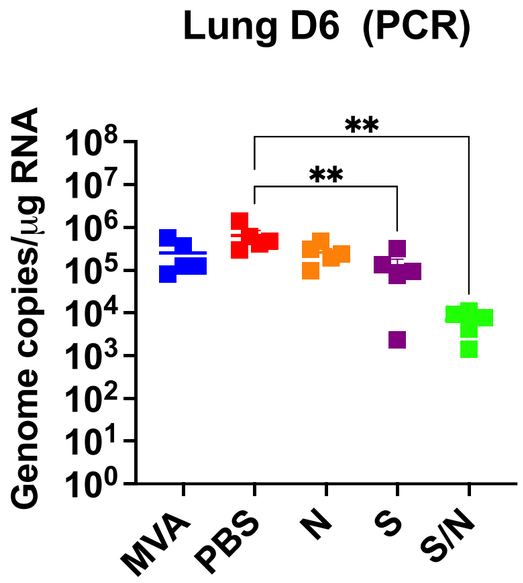
GEO-CM04S1 Efficacy against Omicron XBB.1.5 (B.1) in hACE2 Mice

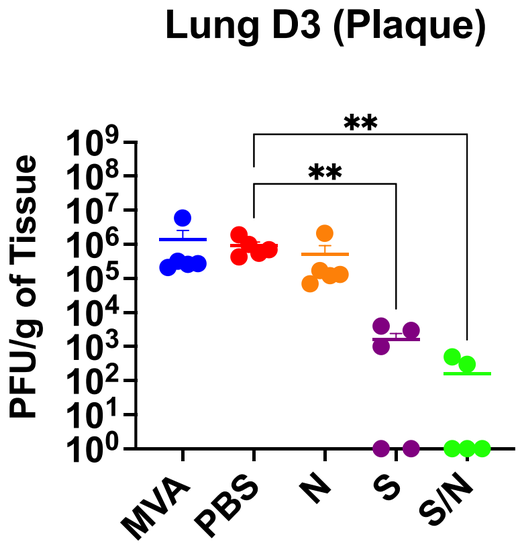


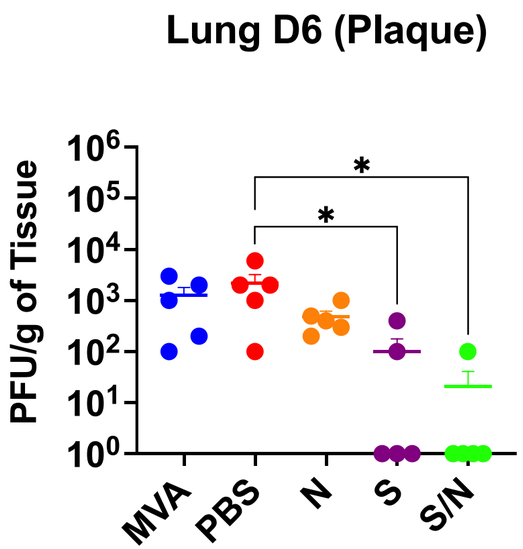


GEO-CM04S1 Efficacy against Omicron XBB.1.5 (B.1) in hACE2 Mice





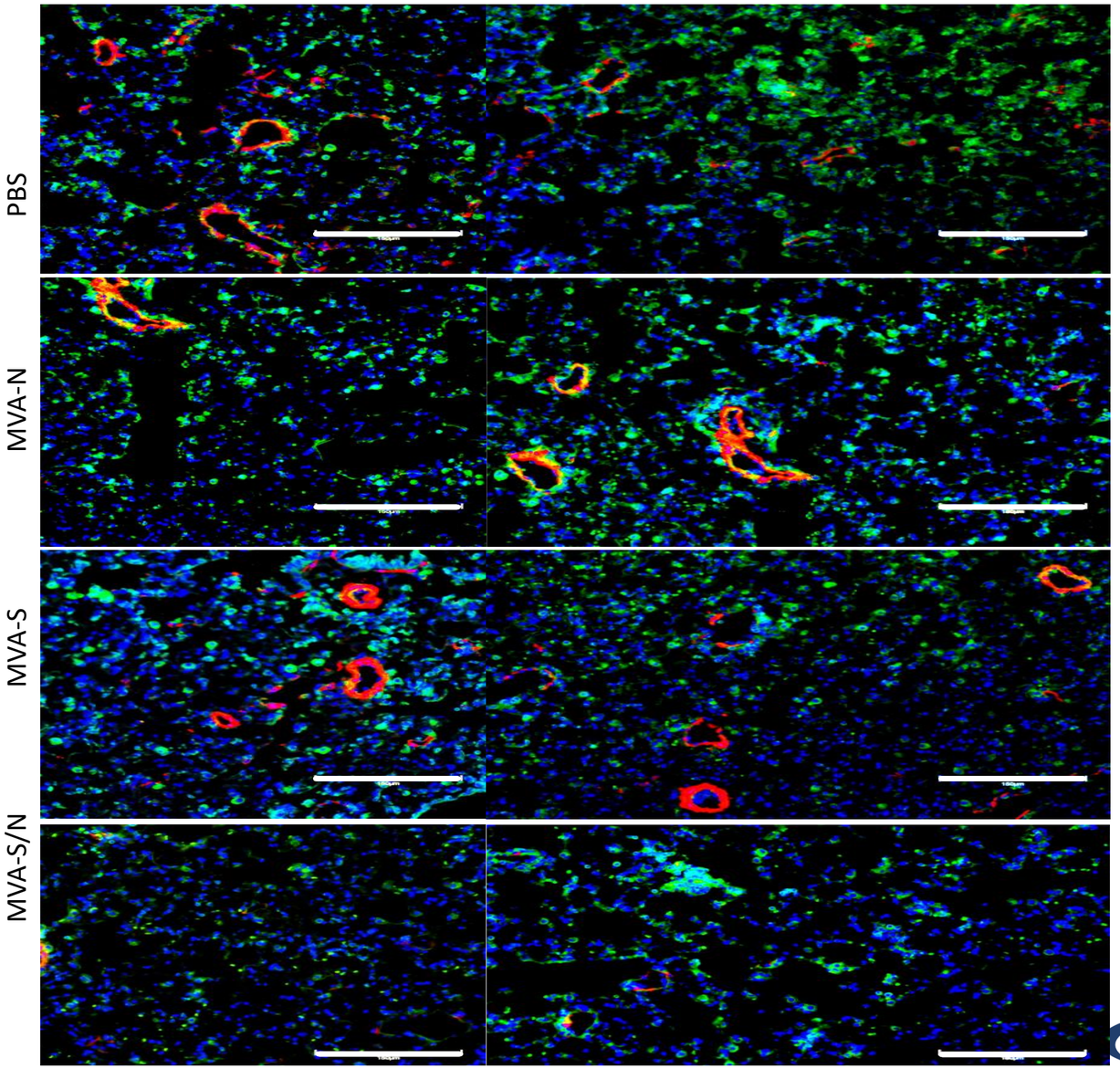




GEO-CM04S1 Efficacy against Omicron XBB.1.5 (B.1) in hACE2 Mice

<u>Lung sections</u>
Day 3 post-challenge

CD45 – Leukocyte infiltrates
SMA – Airways/blood vessels
DAPI



Summary, Preliminary Conclusions and Future Plans

- GEO-CM04S1 induces protective immune responses against VOC, measurable in the transgenic hACE2 mouse
- Immune responses specific to the S protein contribute >85% to efficacy
- Immune responses specific to the N protein contribute 15% to efficacy
- Immune responses specific to the N protein reduce inflammatory responses in the lungs associated with viral infection
- B-cell and T-cell depletion experiments are ongoing to better define the contribution of immune responses to both S and N
- Future directions? Include NSP proteins?

Paradigm Shift in the Field?

- The value of incorporating the SARS-CoV-2 Nucleocapsid in experimental vaccines has been independently confirmed in animal model studies

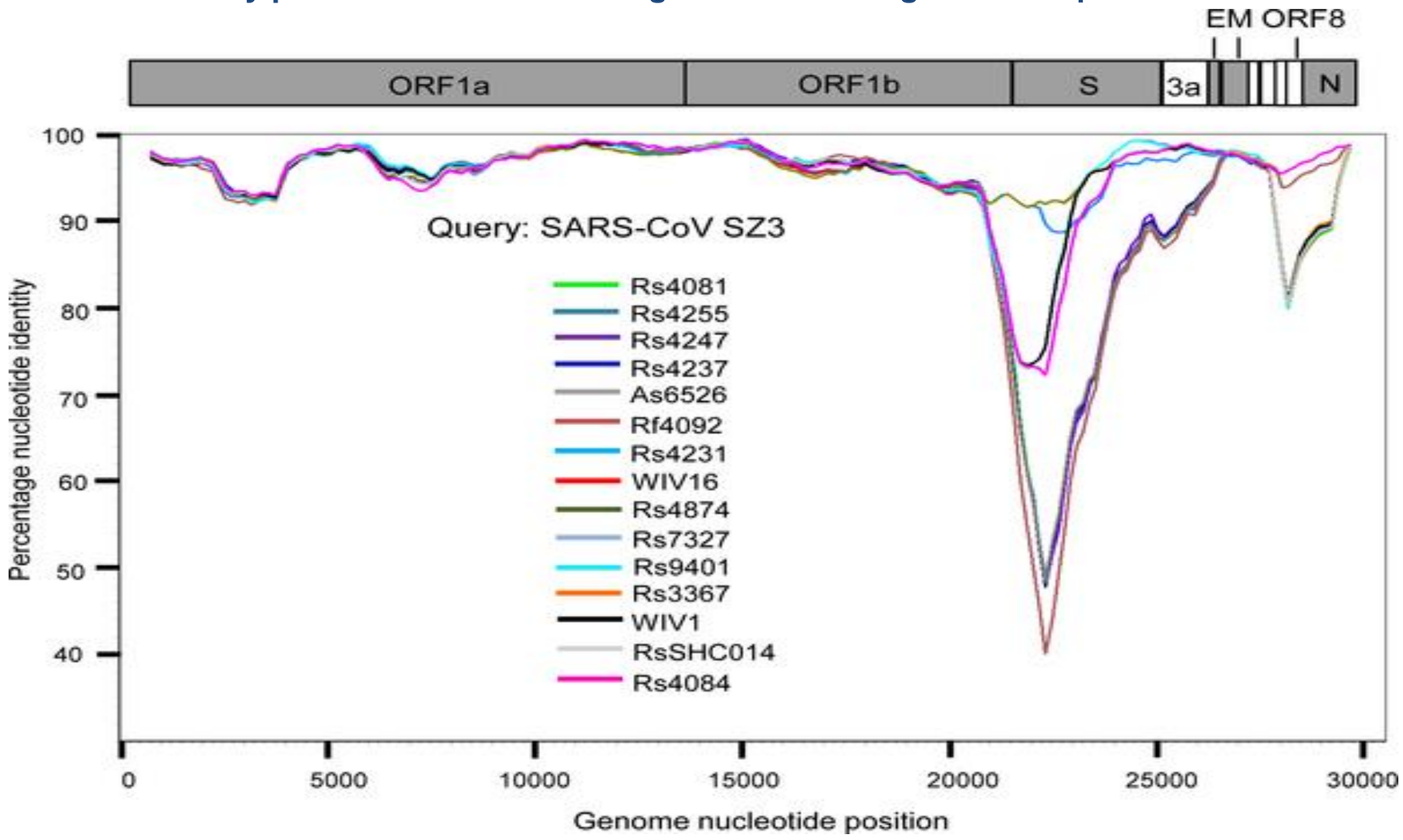
  1. *Science Immunology* (2022) Emory University (Amara) demonstrated that S + N (Wuhan sequence) encoded in a MVA vector induced antibody and T-cell responses in rhesus macaques that provided 100% protection against heterologous (Delta) challenge

  2. *Science Trans Med* (2022) UTMB (Plante & Hu) demonstrated that the combined use of S + N (Wuhan sequence) in a mRNA vaccine protected hamsters from Delta and Omicron

- Increased breadth and specificity of the T-cell and antibody responses can protect against VOC

SARS-CoV Genomic Conservation

Similarity plot based on the full-length “SARS-like” genome sequences



Potential NSP Vaccine Immunogens

Protein-Gene Designation	Immunogenicity - Antigenicity	Virus Function/Host Cell Interactions
NSP3	Grifoni, *Cell* 2020 Ong, *Front Immunol* 2020 Quadeer, *Cell Rep Med* 2021 Grifoni, *Cell Host Microbe* 2021	- Protease - Type 1 interferon antagonist
NSP6	Poland, *Lancet* 2020 Bacher, *Immunity* 2020	- Facilitates assembly of replicase proteins - Induction of autophagosomes - Limits the expansion of phagosomes
NSP12	Swadling, *Nature* 2022 Grifoni, *Cell Host Microbe* 2021	- RNA-dependent RNA Polymerase (RdRp) - Replication and transcription
NSP13	Le Bert, *Nature* 2020 Swadling, *Nature* 2020 Pan, *PNAS* 2021	- Zinc binding domain in N terminus - RNA and DNA duplex unwinding - Helicase
NSP14	Mateus, *Science* 2020 Kared, *JCI* 2021	-Translation inhibitory factor - Inhibits host protein synthesis - Inhibits type 1 interferon viral response

Acknowledgements; GEO-CM04S1 Team

- **GeoVax**

  Arban Domi, Sreenivasa Oruganti, Todd Albrecht, JD Burleson,

  Mary Hauser, Pratima Kumari, Ashley Zuniga

- **City of Hope**

  Flavia Chiuppesi, Felix Wussow, Don Diamond

- **Georgia State**

  Mukesh Kumar

  Shannon Stone

  Amany Elsharkawy

Ongoing – the GEO-CM04S1 Phase 2 Clinical Trials

Immunocompromised/stem cell transplant patients

- Patients with hematologic malignancies receiving stem-cell transplantation or CAR-T therapy
  - Highest at-risk groups for severe infection, hospitalization and death
  - Primary vaccine in direct comparison to mRNA vaccines

Immunocompromised/Chronic Lymphocytic Leukemia (CLL) patients

- High at-risk population with abated antibody response
  - Major, currently unmet, medical need for alternative immune enhancement response (e.g., T-cells)
  - Booster vaccine in direct comparison to mRNA vaccine

Booster to mRNA vaccine

- Healthy population following vaccination with an mRNA vaccine
  - Potential for broader and more durable protection versus multiple, continuous mRNA doses