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Gritstone COVID-19 Vaccine Technical Information

January 2021

Safe Harbor and Forward-Looking Statements

This presentation contains forward-looking statements including, but not limited to, statements related to our preclinical and clinical product candidates, GRANITE, SLATE, CORAL and bispecific antibody programs. All statements other than statements of historical facts contained in this presentation, including statements regarding the timing of immunogenicity and clinical data for GRANITE SLATE, and CORAL, identification of development candidate for our bispecific antibody program, collaborations surrounding our infectious disease program, future results of operations and financial position, business strategy, prospective products, availability of funding, clinical trial results, product approvals and regulatory pathways, timing and likelihood of success, plans and objectives of management for future operations, future results of current and anticipated products, and our ability to create value are forward-looking statements. Because forward-looking statements are inherently subject to risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the company in general, see Gritstone's periodic filings with the Securities and Exchange Commission (the "SEC"), including its Quarterly Report filed on November 5, 2020 and any current and periodic reports filed thereafter.

Summary

- First-generation COVID-19 vaccines elicit strong, consistent antibody and $CD4^+$ T cell responses against a single SARS-CoV-2 antigen (Spike). $CD8^+$ T cell responses are more variable and limited.
- Although compelling short-term protection has been demonstrated, durability of protection is currently unknown and may be impacted by emergent mutations in Spike
- More complete and durable clinical protection will likely come from broader immune responses (including strong $CD8^+$ responses) against a broader set of viral antigens, informed by studies of convalescent subjects
- Gritstone has established strong relevant capabilities in key dimensions:
  - T cell epitope identification & prediction – license agreement for validated SARS-CoV-2 epitopes with La Jolla Institute of Immunology and Gritstone's proprietary EDGE™ HLA peptide prediction platform
  - Vaccine vectors that elicit potent humoral and cellular immunity (including challenging $CD8^+$ responses) in humans
  - In-house GMP Biomanufacturing Facility (producing multiple clinical products for >2 years)
  - Clinical experience with the vectors, demonstrating relevant safety and immunogenicity
- Gritstone has designed and manufactured novel Spike and Spike + T cell epitope vaccines using both adenoviral and self-amplifying RNA vectors – Gritstone's CORAL program for COVID-19
  - Bill and Melinda Gates Foundation has supported the optimization of Gritstone's antigenic cassette
- A Phase 1 program led by NIH/NIAID/DMID has been designed to assess these new concepts in humans in 1H21
- A Phase 2/3 program is expected to be run in 2H21 to address unmet need in subjects with sub-optimal (narrow, low titer or transient) responses to 1st generation vaccines

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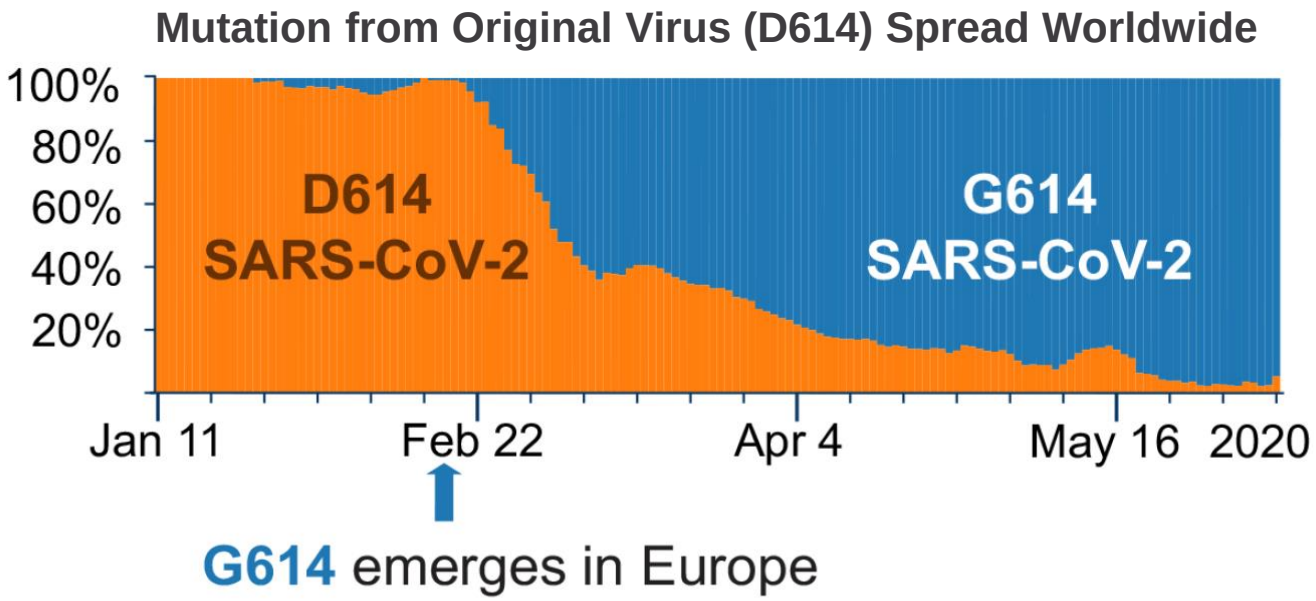
Background

Mutations in SARS-CoV-2 Spike Are Continuing to Arise – Some May Reduce Neutralizing Antibody Protection From First Generation Vaccines



Boris Johnson backtracks on relaxing Christmas rules after scientists warn new Covid-19 strain is spreading faster

By Amy Woodyatt, Lindsay Isaac, Luke McGee and Arnaud Siad, CNN

Updated 5:13 AM ET, Sun December 20, 2020

CNN

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human serum antibodies

The most important site is E484, where neutralization by some sera is reduced >10-fold by several mutations, including one in emerging viral lineages in South Africa and Brazil

Cell

Article

Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus

HEALTH

STAT

Scientists are monitoring a coronavirus mutation that could affect the strength of vaccines

By ANDREW JOSEPH @DrewQJoseph / JANUARY 7, 2021

Reprint

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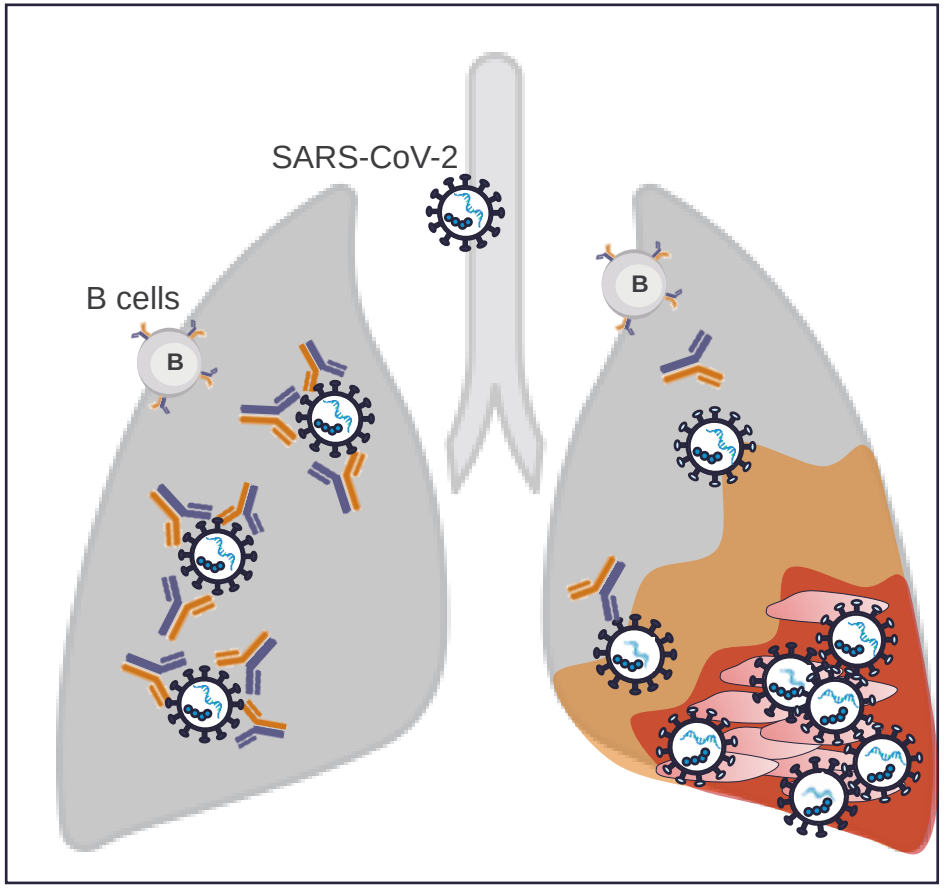
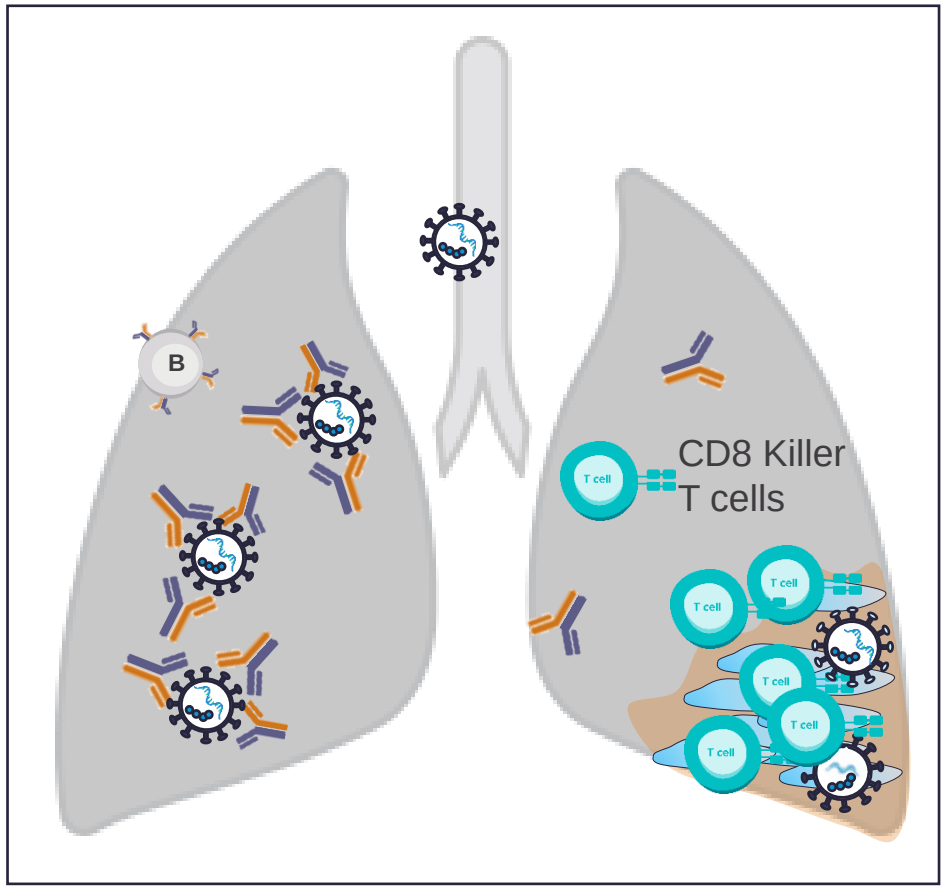
Gritstone CORAL Program Premise: Addition of Strong CD8 T Cell Response to nAb Response for 2nd Layer of Protection when nAb Protection Wanes

Neutralization of the incoming virus by antibodies can be incomplete due to waning titer or mutations. Free virus infects lung cells and starts replicating.

If neutralization by antibodies is incomplete, memory CD8 T cells expand rapidly upon virus infection, clear virus from infected cells and reduce/prevent organ damage





Pre-Clinical Evidence Emerging That CD8 T Cells Can Contribute To Protection When Neutralizing Antibody (nAb) Titers Wane

nature

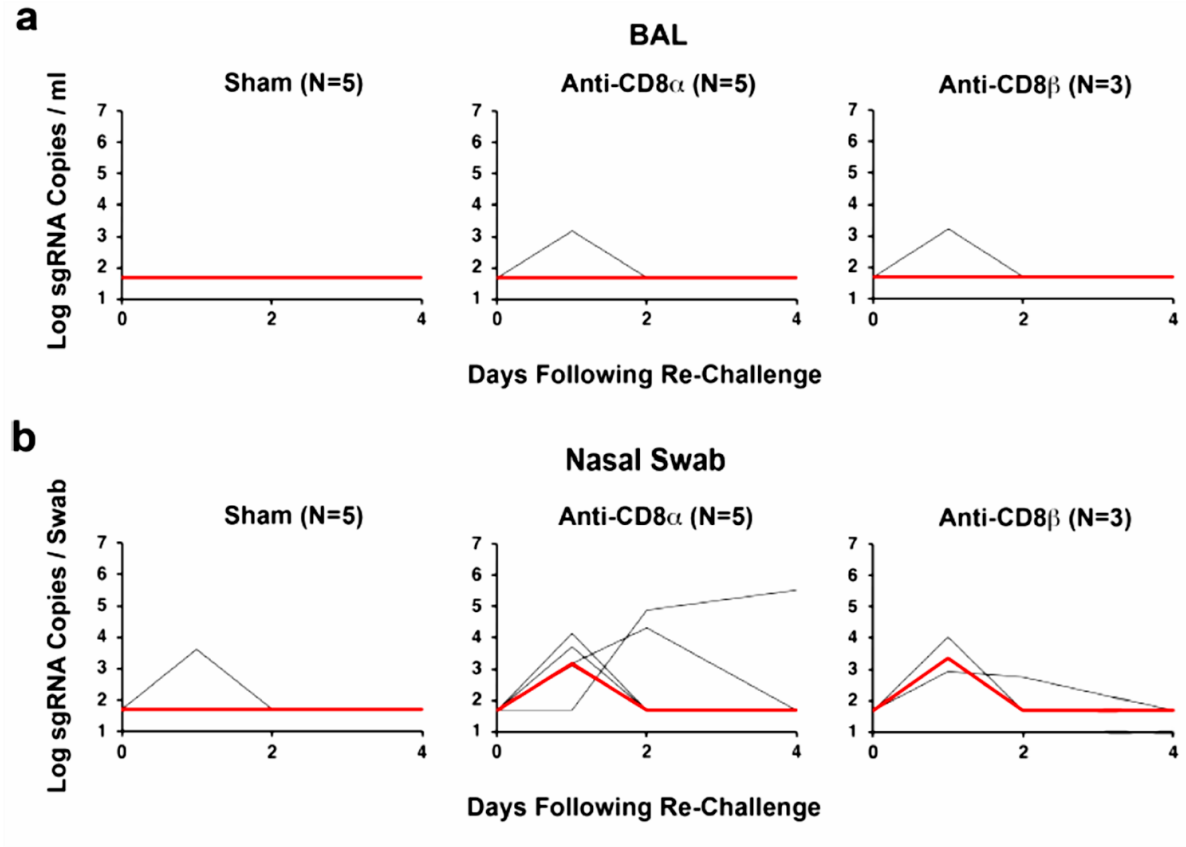
https://doi.org/10.1038/s41586-020-03041-6

Article

Correlates of protection against SARS-CoV-2 in rhesus macaques

"…Nab titers declined in convalescent animals from week 4 to week 7, with over half of the animals exhibiting NAb titers<100 by week 7. CD8 depletion in these animals resulted in loss of protection in the upper respiratory tract against SARS-CoV-2 re-challenge, suggesting that CD8+ T cells are likely critical for virologic control if NAb titers are suboptimal or subprotective."

Impact of CD8 depletion by anti-CD8 antibodies (vs. sham Ab control) on viral replication in rhesus macaques challenged with intranasal SARS-CoV-2



McMahan, *Nature*, 2020

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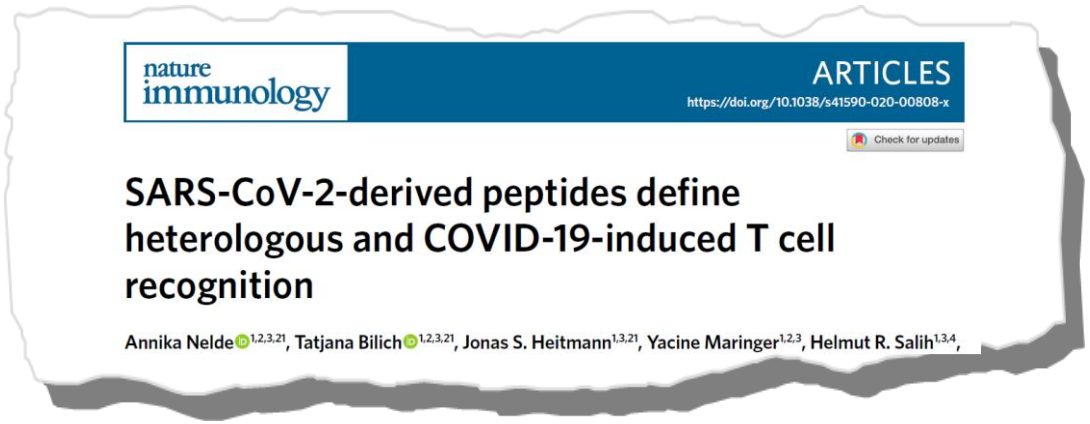
Research Groups Around the World Are Conducting Comprehensive Studies of Patient Immune Responses Against SARS-CoV-2 Infection


nature immunology

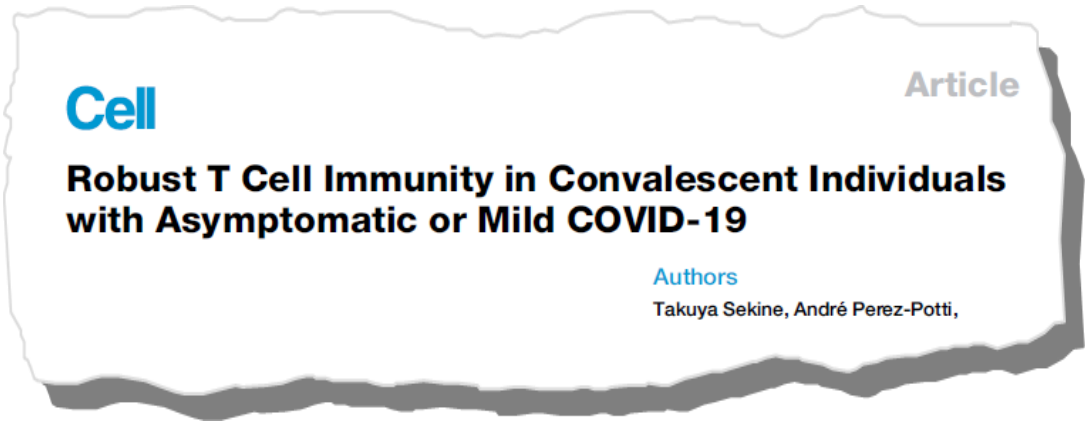
ARTICLES

https://doi.org/10.1038/s41590-020-00808-x

Check for updates

SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition

Annika Nelde[1,2,3,21], Tatjana Bilich[1,2,3,21], Jonas S. Heitmann[1,3,21], Yacine Maringer[1,2,3], Helmut R. Salih[1,3,4],

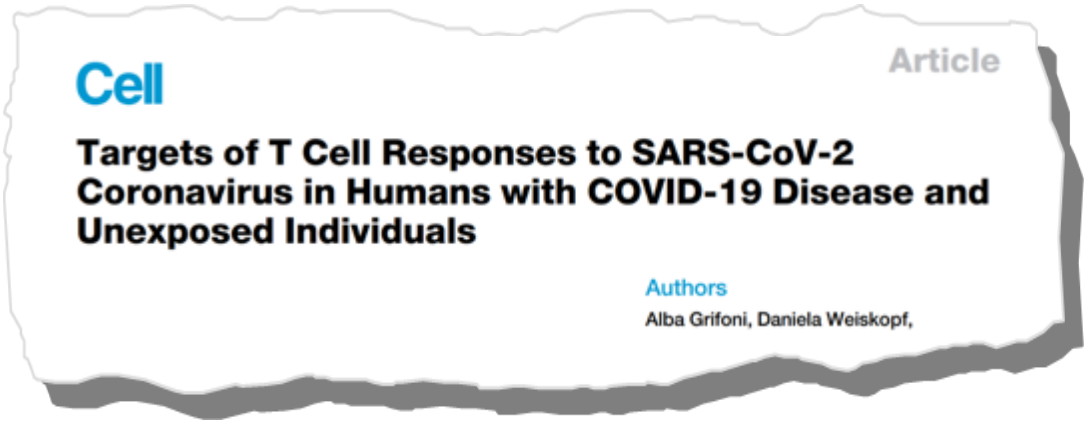

Cell

Article

Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19

Authors

Takuya Sekine, André Perez-Potti,


Cell

Article

Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

Authors

Alba Grifoni, Daniela Weiskopf,


Cell

Article

Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity

Authors

Carolyn Rydyznski Moderbacher,

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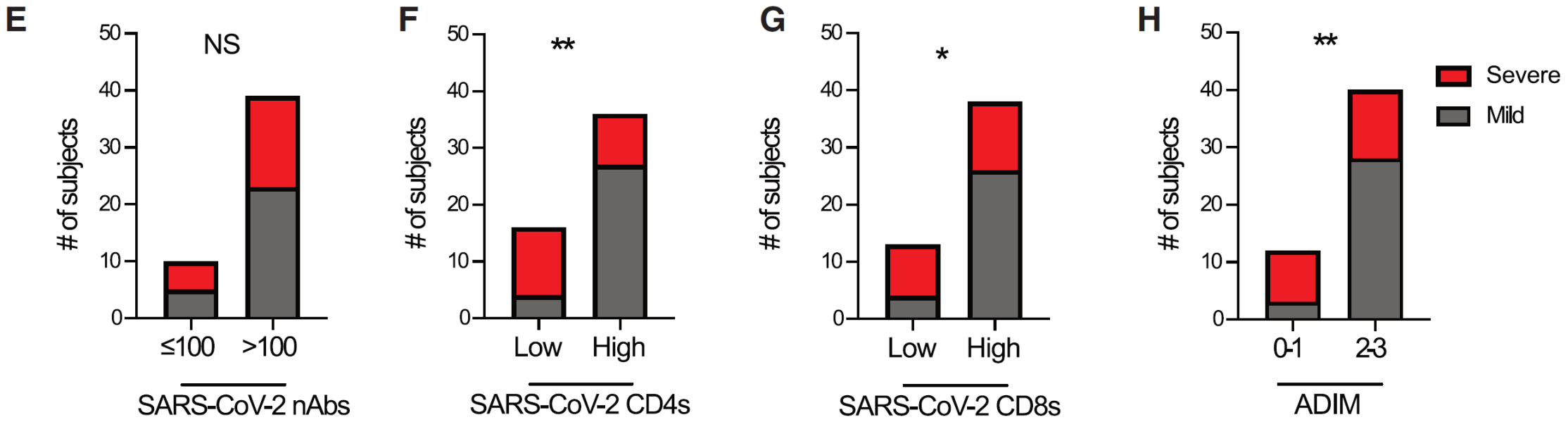
Clinical Evidence is Emerging that Coordinated nAb and T Cell Immunity is Important for Prevention of Severe COVID-19 Disease

Higher ADIM score (breadth of adaptive immune response) associated with lower likelihood of severe COVID-19 disease



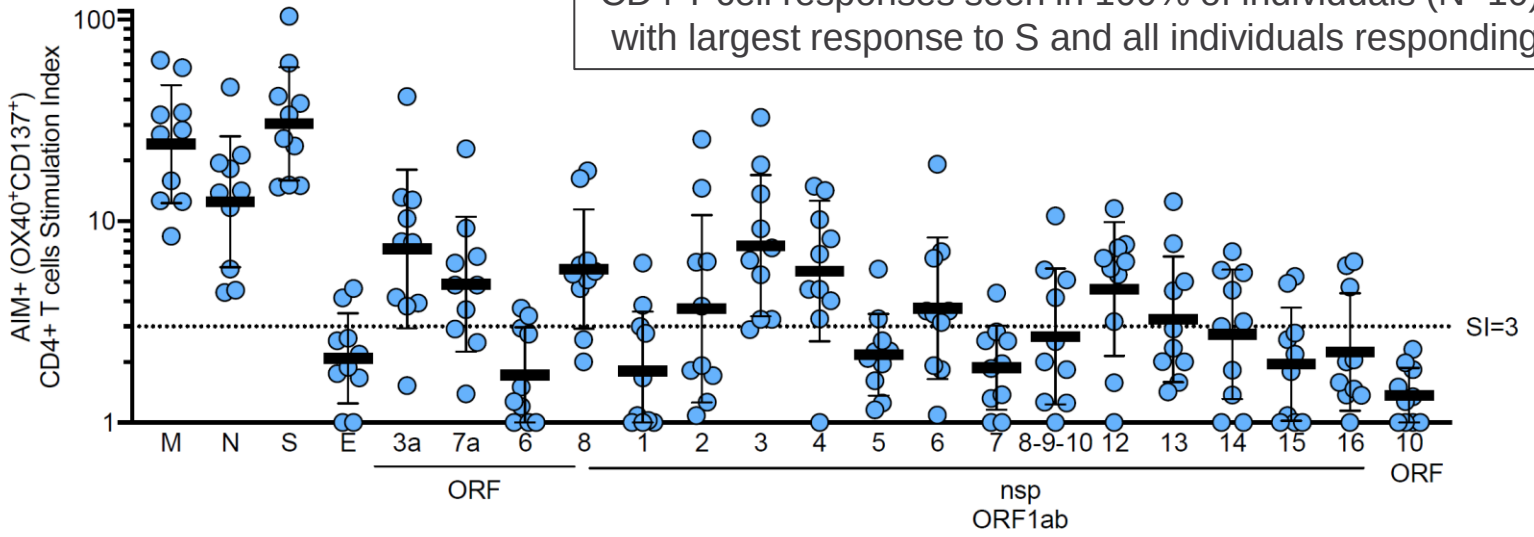
ADIM score: breadth of adaptive immune response, 1 point each for SARS-CoV-2-specific nAb, CD8+, and CD4+ T cells

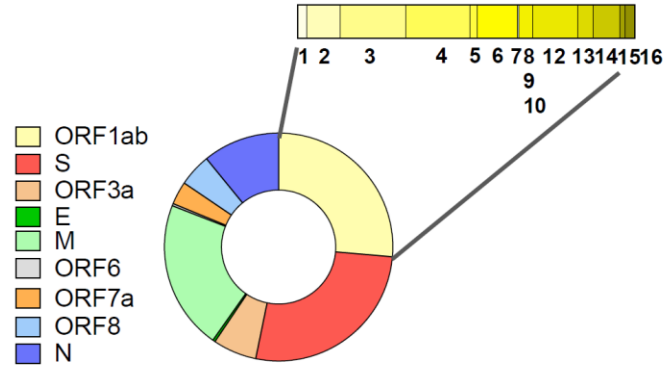
Moderbacher, *Cell*, 2020

Gritstone SARS-CoV-2 T Cell Epitope Selection

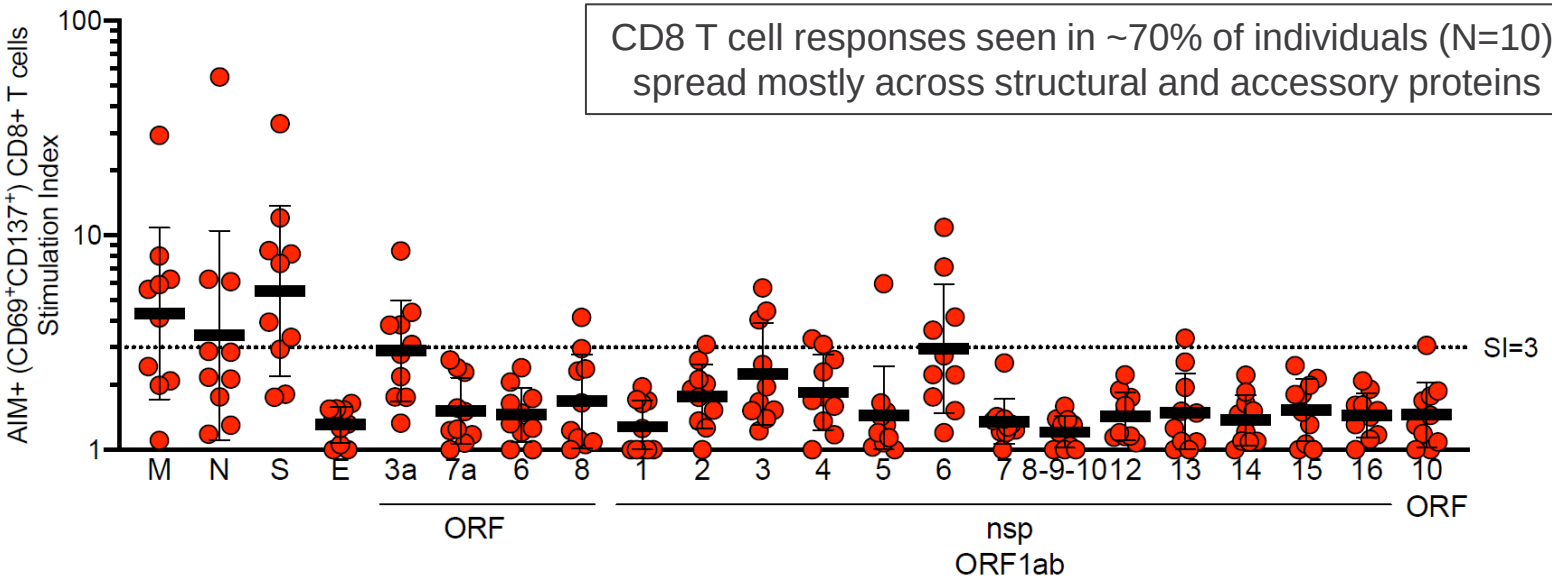
T Cell Epitope Mapping is Revealing that While Most Patients Develop a CD4 Response Against Spike, CD8 Responses are More Restricted

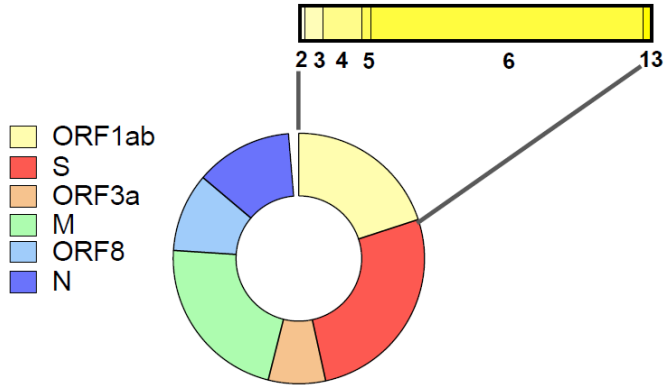
CD4 T cell responses seen in 100% of individuals (N=10), with largest response to S and all individuals responding





CD8 T cell responses seen in ~70% of individuals (N=10), spread mostly across structural and accessory proteins

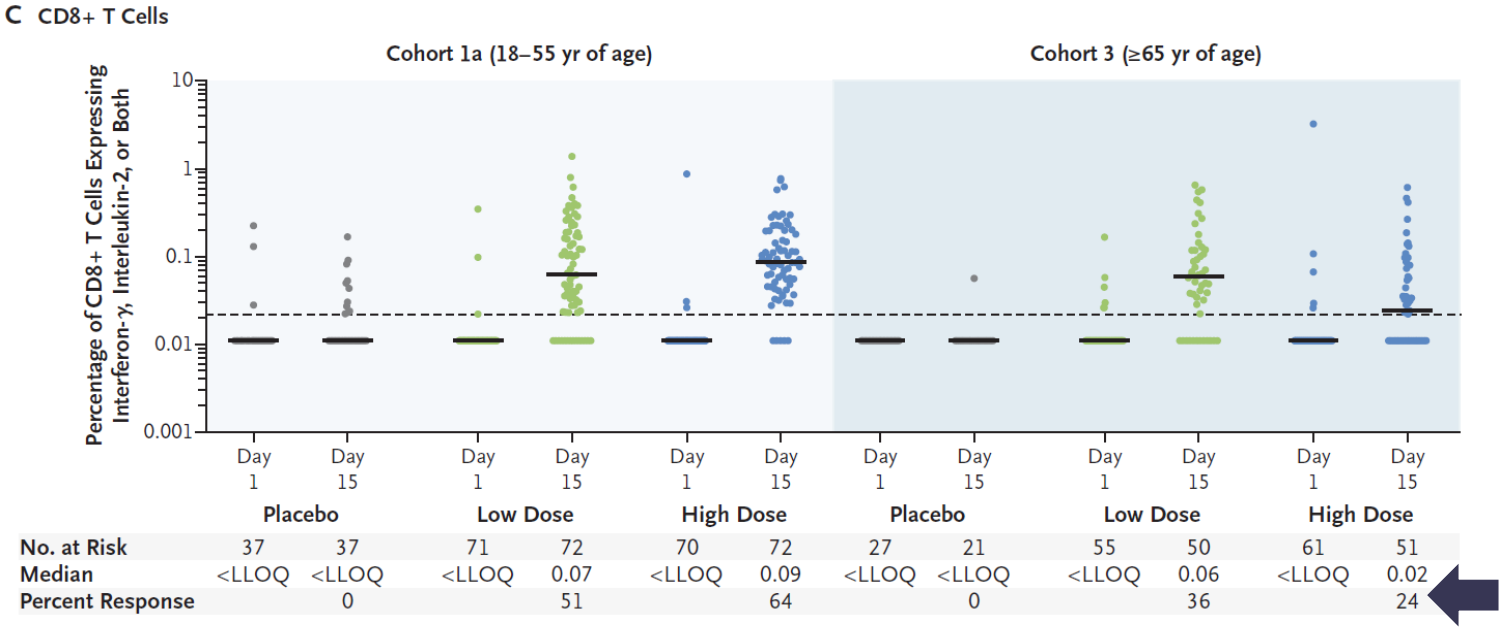




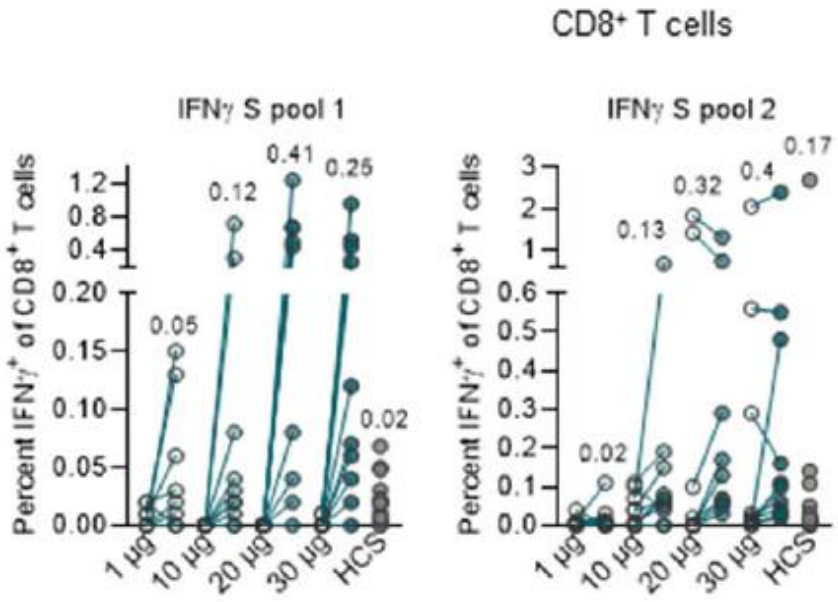
Grifoni, *Cell*, 2020

Leading First Generation COVID-19 Vaccines Appear to Drive Low or Variable CD8+ T Cell Responses to Spike

Sadoff, *NEJM*, 2021
Ad26.COV2.S



Sahin, *medRxiv*, 2020
BNT162b2



Jackson, *NEJM*, 2020
mRNA-1273

"CD8 T-cell responses to S-2P [Spike with 2 Proline substitutions] were detected at low levels after the second vaccination in the 100-µg dose group"

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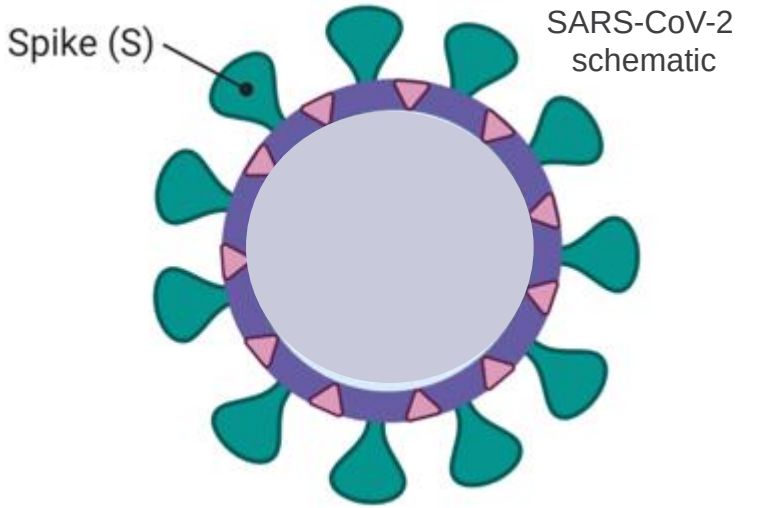
A Significant Number of CD8 Epitopes Have Been Validated Outside of Spike

Gritstone Analysis of Published SARS-CoV-2 CD8 Epitopes (N=120)

Gene	# Validated CD8 epitopes	Gene length (aa)	Epitopes per aa	Epitopes per aa ratio over S
N	21	419	0.050	3.19
ORF3a	8	275	0.029	1.85
ORF7a	3	121	0.025	1.58
M	6	222	0.027	1.72
ORF6	1	61	0.016	1.04
E	1	75	0.013	0.85
S	20	1,273	0.016	1.00
ORF1ab	59	7,096	0.008	0.53
ORF8	1	121	0.008	0.53

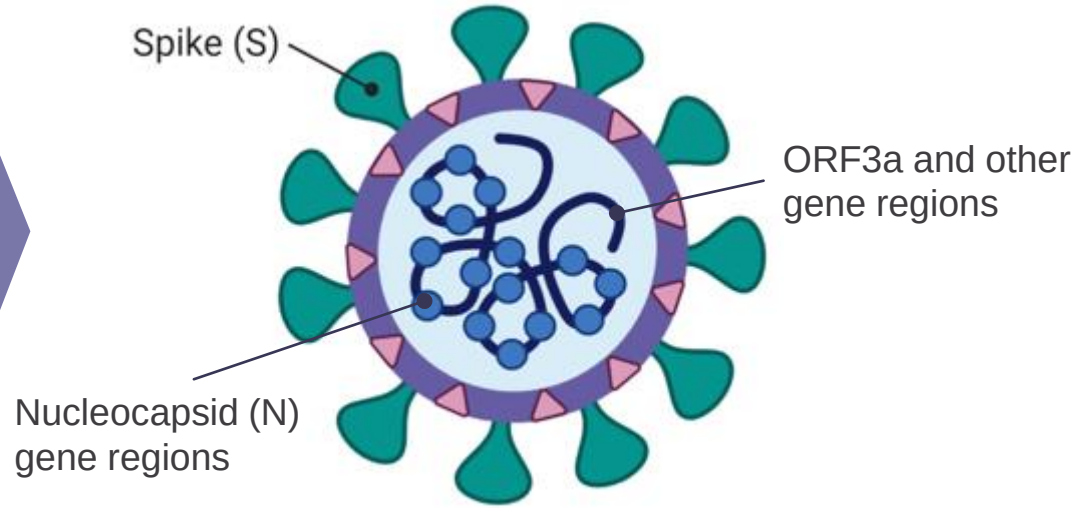
Gritstone SARS-CoV-2 Vaccine Adds Targets From Multiple Genes to Maximize Effective CD8 T Cell Response

1st generation vaccines: Spike (S) protein only



- Neutralizing antibodies (S)
- Limited CD8 T cells against S in some individuals
- No CD8 response against other highly expressed genes

2nd generation Gritstone vaccine: S + additional gene regions



- Neutralizing antibodies (S)
- Strong CD8 T cell response in most individuals targeted against S and other highly expressed viral genes such as Nucleocapsid (N)

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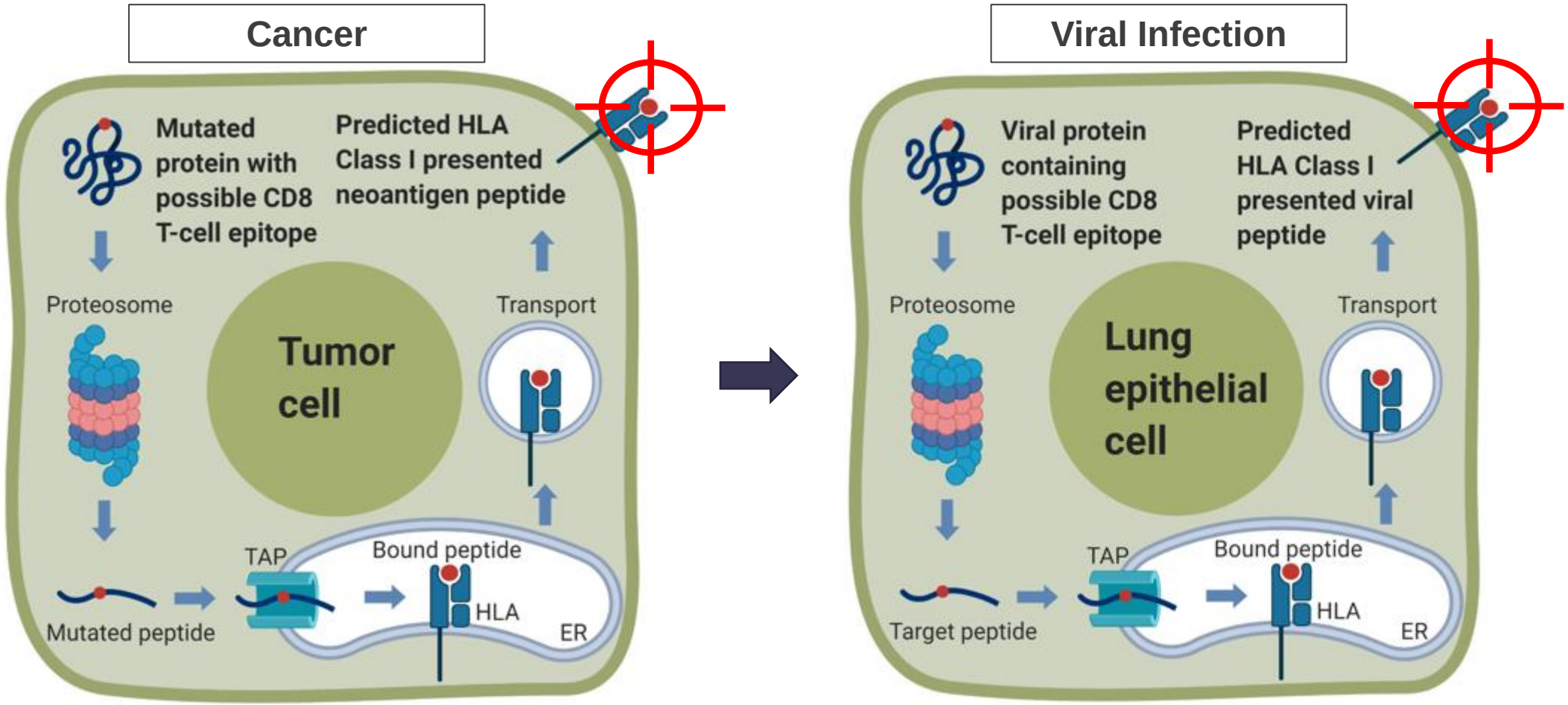
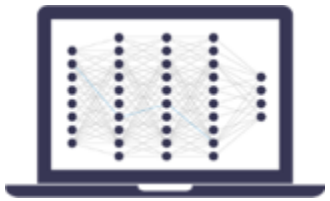
To Complement Validated CD8 Epitopes, Gritstone Also Leverages Its HLA Peptide Presentation Model EDGE

EDGE is a neural network model of HLA peptide presentation





nature biotechnology

Deep learning using tumor HLA peptide mass spectrometry datasets improves neoantigen identification

Bulik-Sullivan, et. al. December 2018

Validated to accurately predict 279 Los Alamos Laboratory "A list" HIV CTL/CD8+ epitopes from rest of HIV proteome

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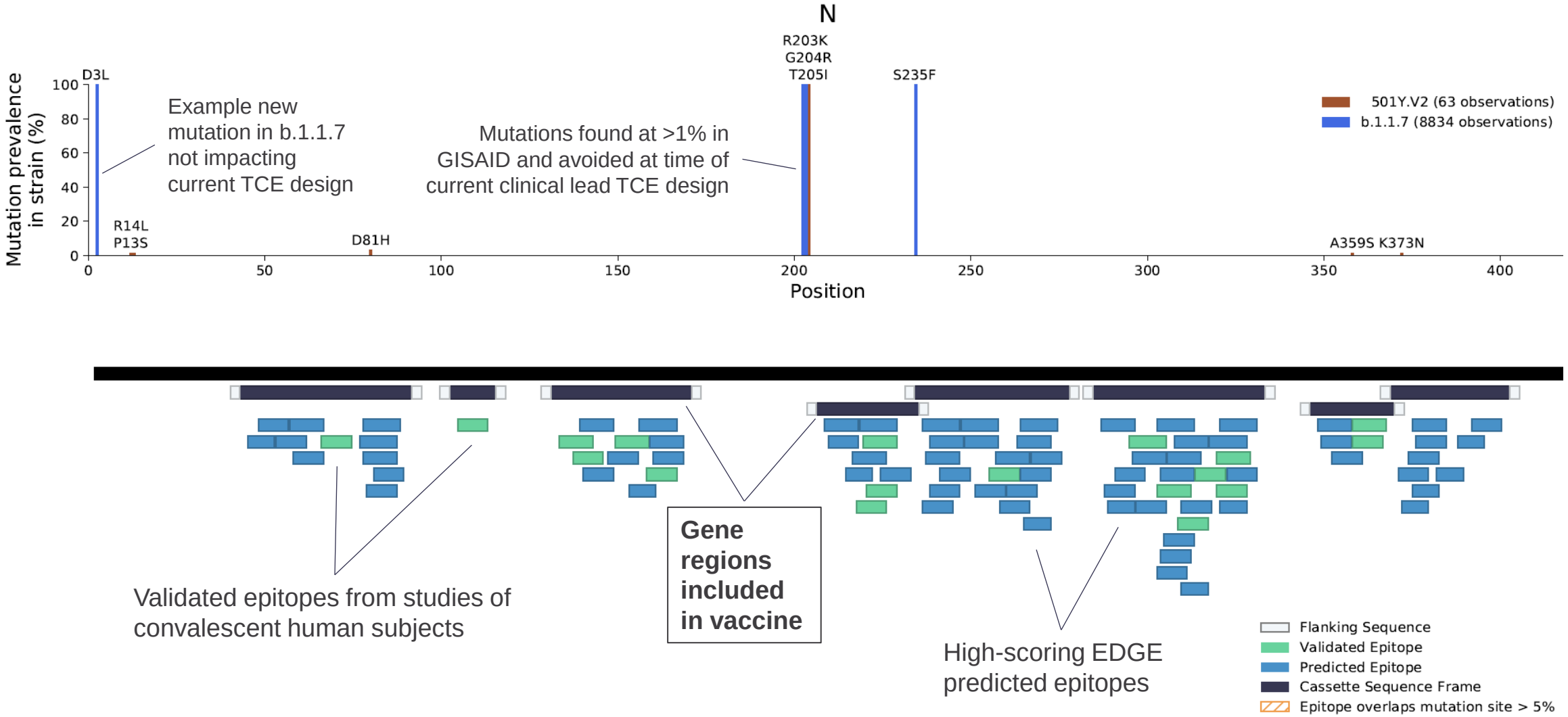
Defining SARS-CoV-2 T Cell Epitope (TCE) Cassette Using Validated and Predicted Epitopes - Nucleocapsid (N) Example

Limited impact of emergent strain mutations on T cell epitopes



Gritstone Current Clinical Candidate T Cell Epitope Cassette Prioritizes Epitopes in Nucleocapsid and ORF3a

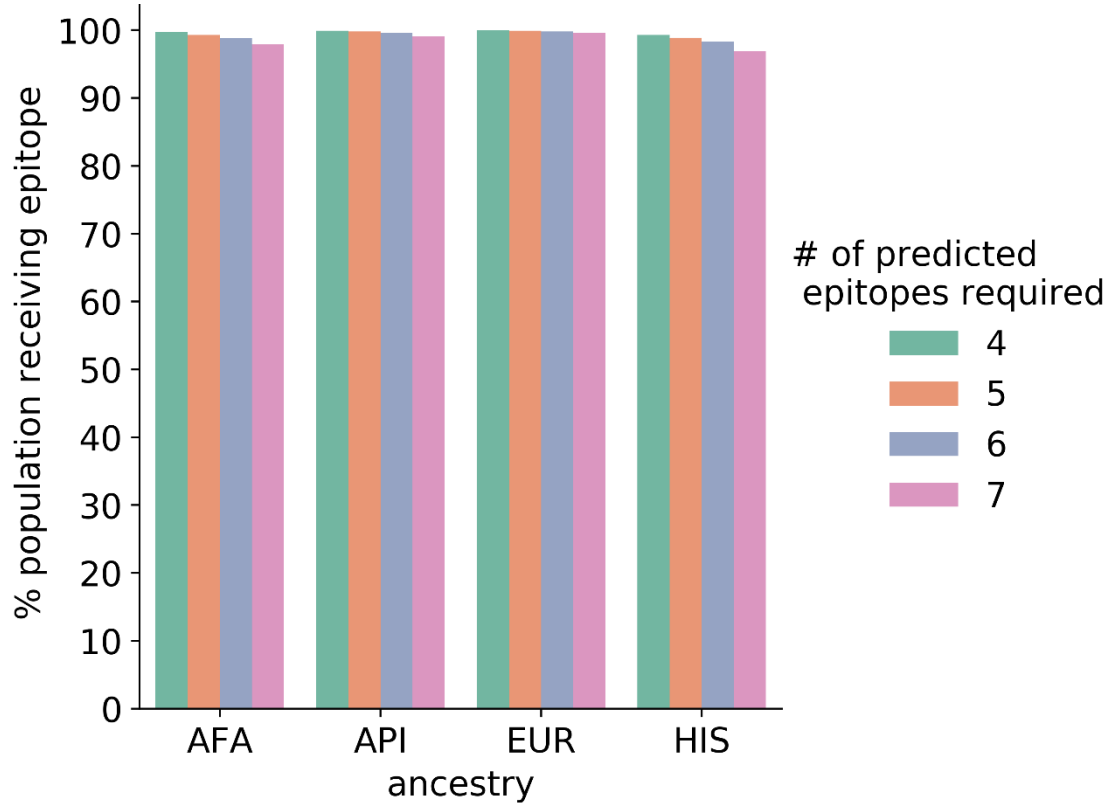
Gritstone's vaccine adds broad CD8 T cell epitope coverage in nucleocapsid and ORF3a, with some membrane epitopes, to whole gene Spike

TCE Cassette Frames (582aa)

Frame	Gene	Frame length
1	ORF3a	51
2	ORF3a	33
3	ORF3a	43
4	N	55
5	M	19
6	N	40
7	N	55
8	ORF3a	30
9	N	50
10	M	20
11	N	30
12	N	35
13	N	19
14	ORF3a	56
15	N	46

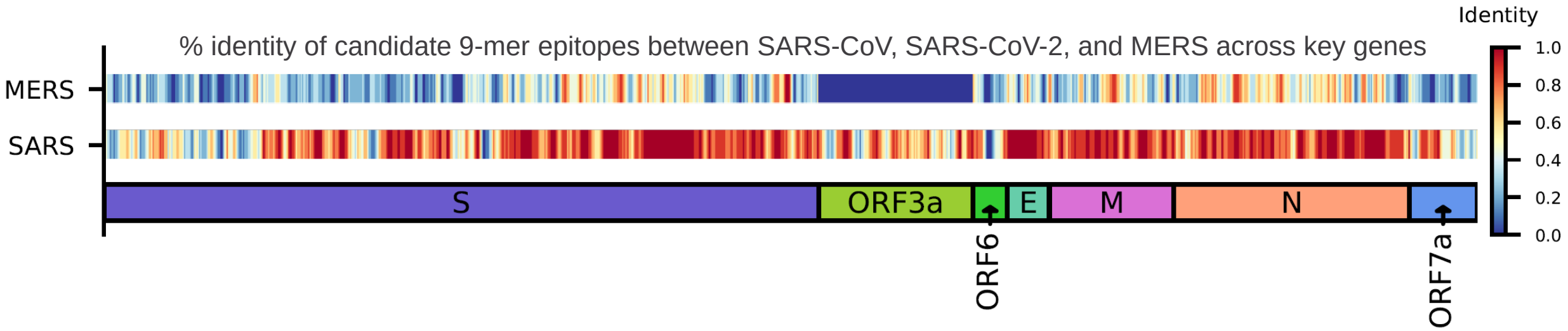
Frame order is chosen to minimize formation of junction epitope sequences

Population Coverage of Delivered Epitopes in TCE

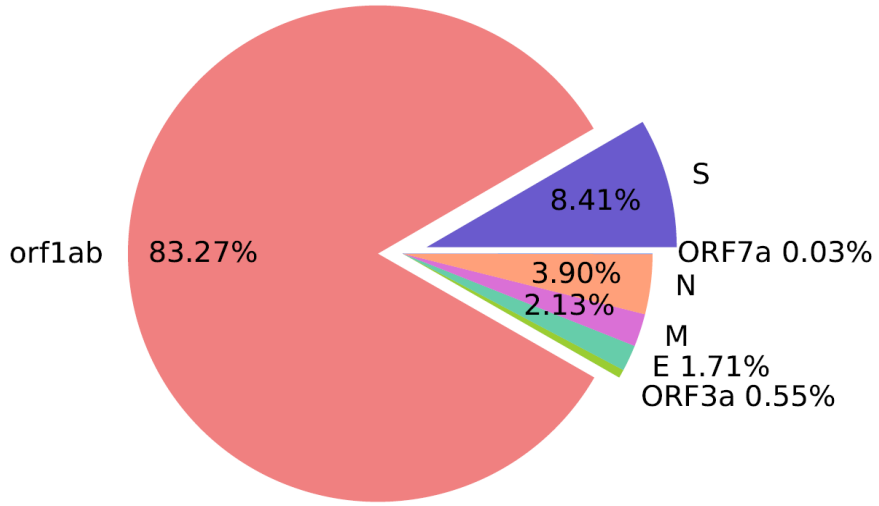


Individual considered receiving epitope if individual carries HLA alleles for 1 validated or 4 or more predicted epitopes. Ancestry group abbreviations: AFA = African American, API = Asian or Pacific Islander, EUR = European, HIS = Hispanic

Additional Gene Regions Allow Inclusion of More Conserved Epitopes – Possibility for Future Development of a Pan-Coronavirus Vaccine

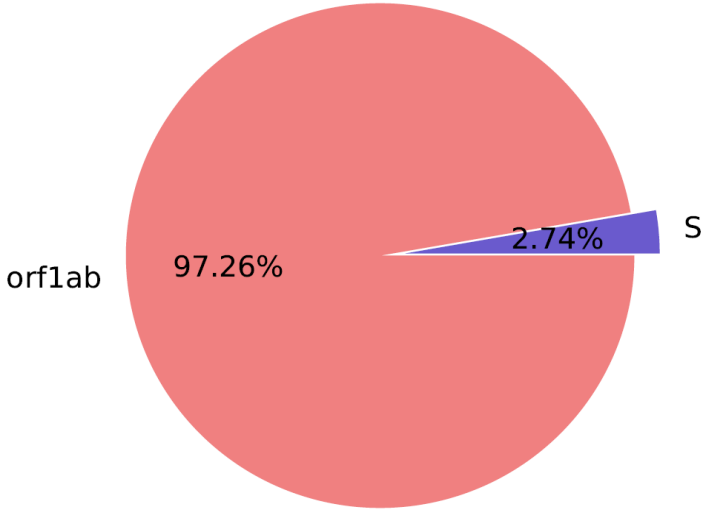


Shared candidate 9-mer epitope distribution between SARS-CoV-2 and SARS-CoV



3282 Shared Epitopes
3006 Outside of S

Shared candidate 9-mer epitope distribution between SARS-CoV-2 and MERS



219 Shared Epitopes
213 Outside of S

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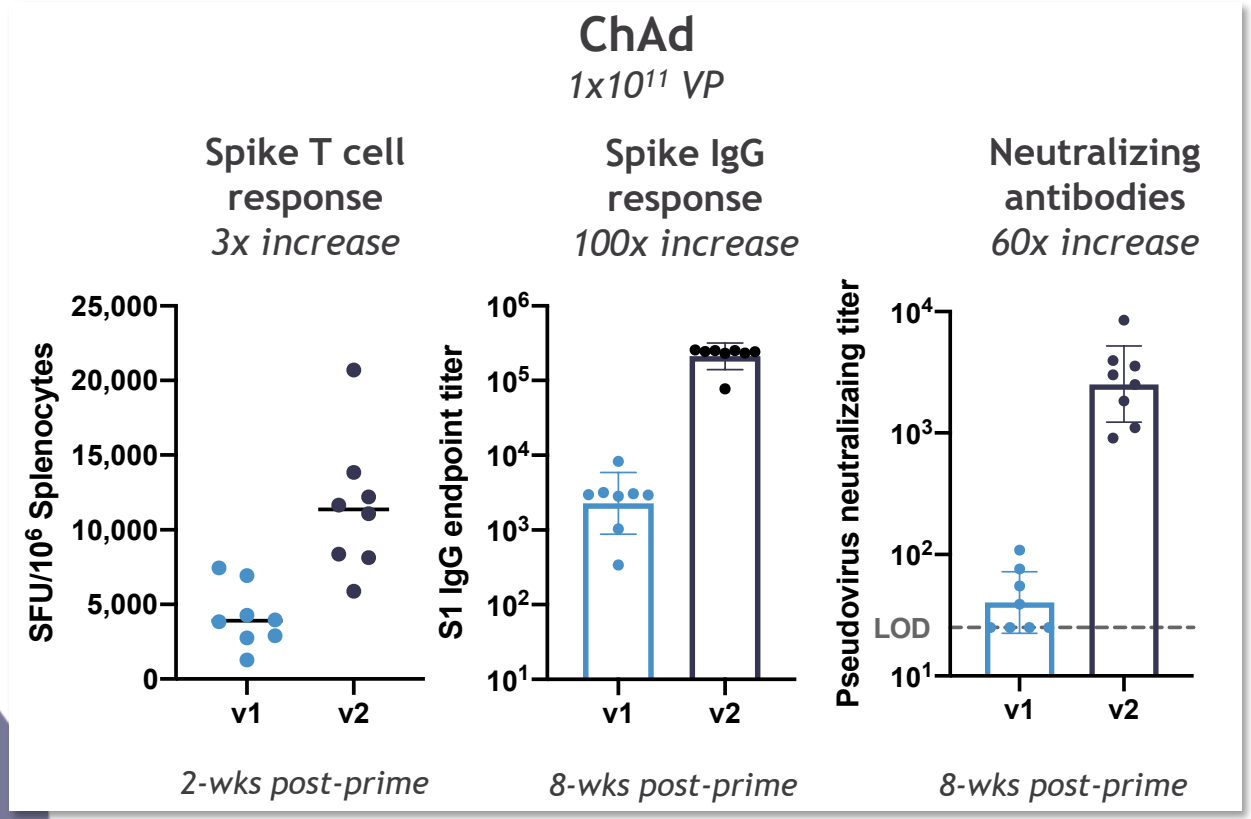
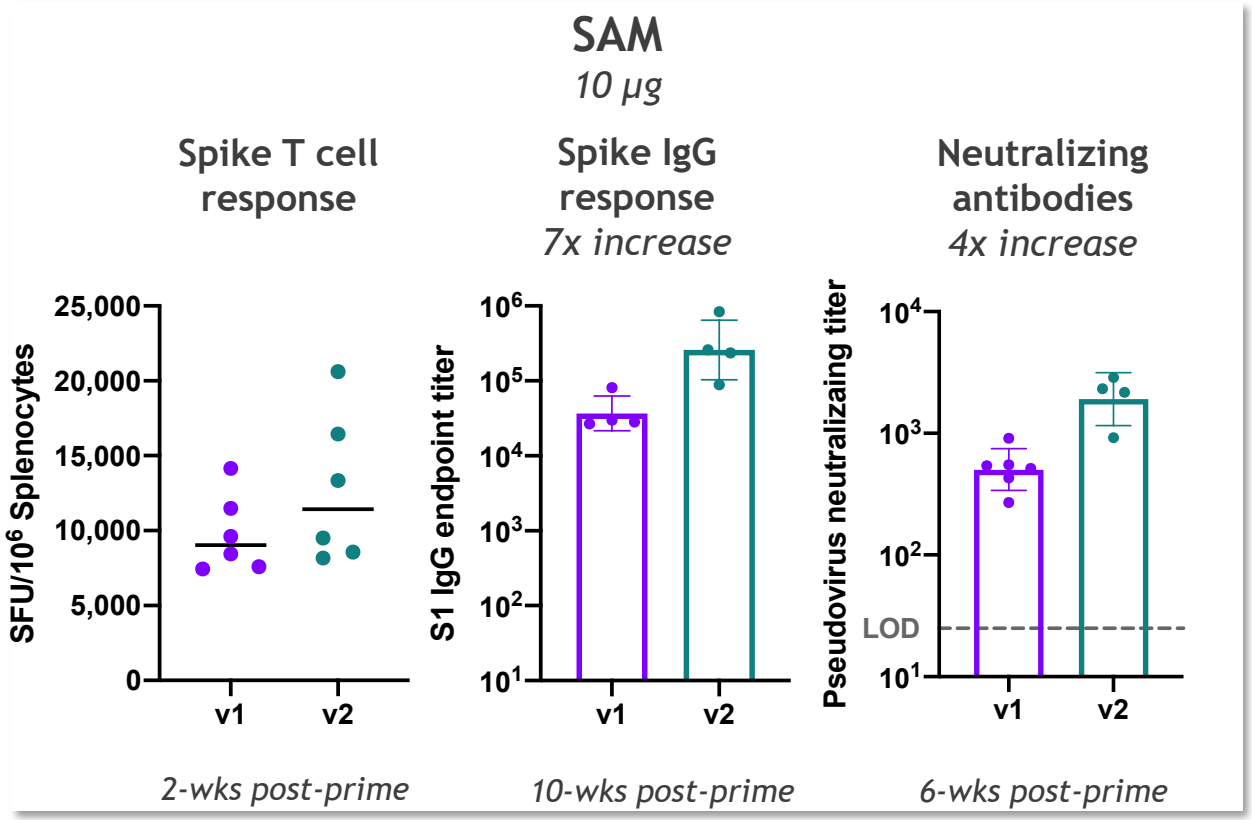
Antigen Cassettes: Design and Immunogenicity

Spike Sequence Optimization Leads to Increased Immune Responses

Gritstone has performed extensive sequence optimization to increase immune response to Spike

Sequence version 2 (using alternate codon optimization) demonstrates increased response compared to sequence version 1





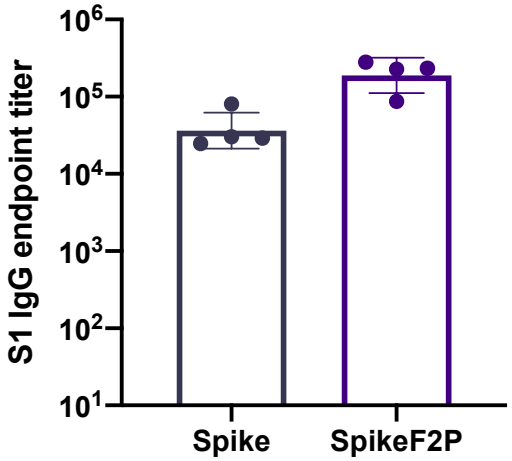
Balb/c mice

Addition of Furin/2P Modifications to Codon Optimized (v2) Spike Leads to Further Increase in Spike-specific Antibody Responses

Removal of Furin site and addition of prolines in S2 domain stabilizes structure in prefusion form (Pallesen et al. 2017)

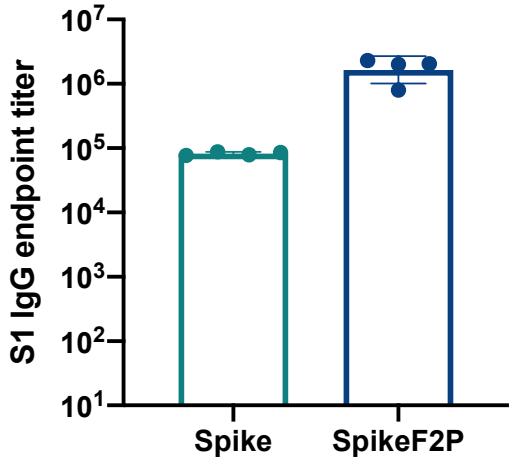
ChAdV
$1x10^{11}$ VP

Spike IgG response
5x increase



SAM
10 µg

Spike IgG response
20x increase



nAb data pending

Balb/c mice

All vectors utilize Spike sequence v2

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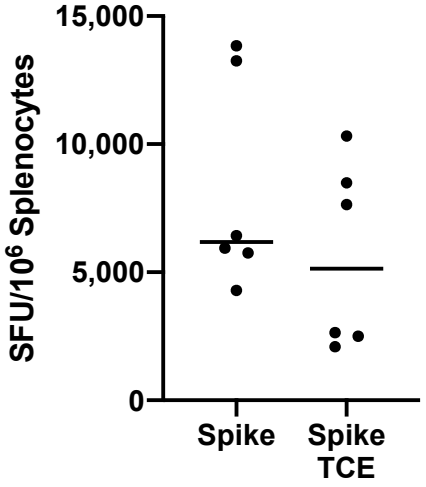
Addition of TCE to Furin/2P Modified Optimized Spike in Vaccine Leads to Broad T Cell Responses Across the SARS-CoV2 Genome

The v2 Spike with Furin/2P modifications was selected for clinical development

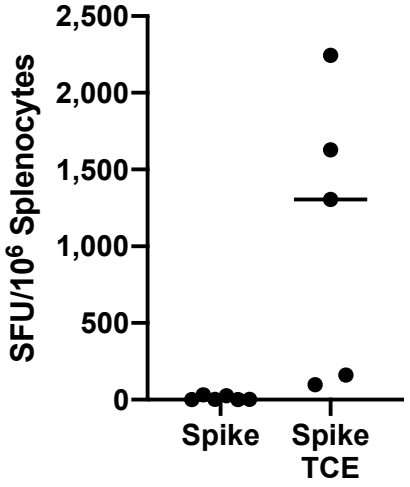
or — 2 weeks — Splenocyte isolation
IFNγ ELISpot

ChAdV
1x10¹¹ VP

Spike T cell response

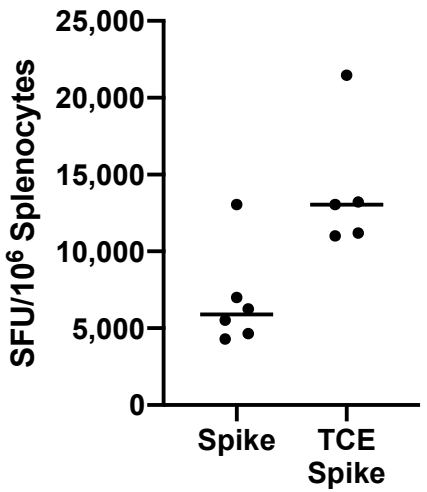


Additional T cell epitopes

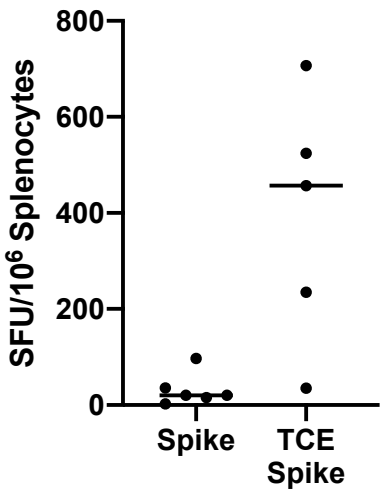


SAM
10 µg

Spike T cell response



Additional T cell epitopes



IFNγ ELISpot, 2 weeks post immunization. T cell response to overlapping peptide pools spanning either Spike, Nucleocapsid, or Orf3a

Balb/c mice

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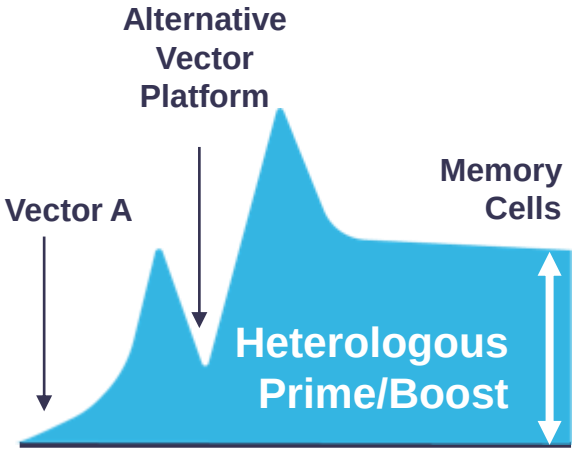
Vaccine Data

Gritstone's Universal Heterologous Prime/Boost Immunization Platform: Chimpanzee Adenovirus (ChAdV) + Self-Amplifying mRNA (SAM)

Heterologous Prime/Boost

Vector switch drives durable, high yield T cell response

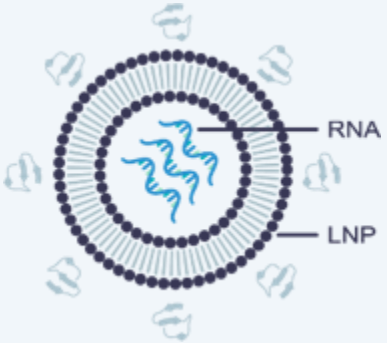


Gritstone's Prime/Boost Immunotherapy Platform

Prime

ChAdV Vector → Generates rapid and substantial initial T cell response

Boost



SAM Vector → Drives profound antigen-specific T cell response

Both platforms can also be utilized in a homologous prime/boost vaccine regimen

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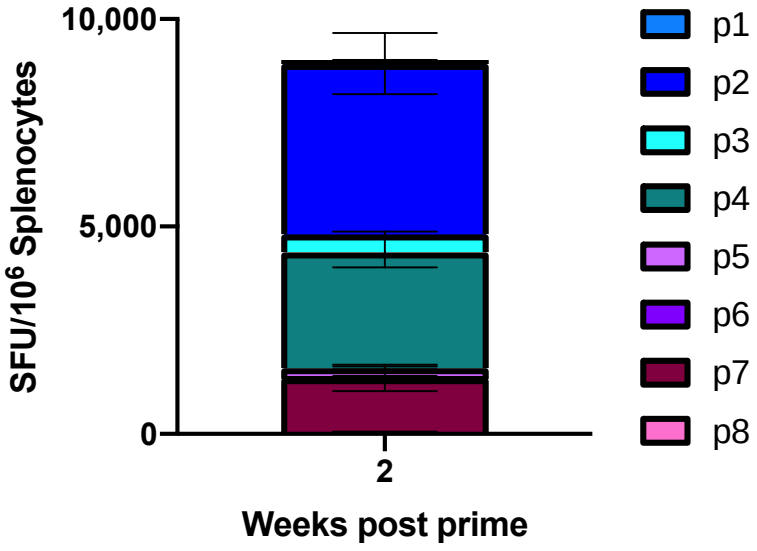
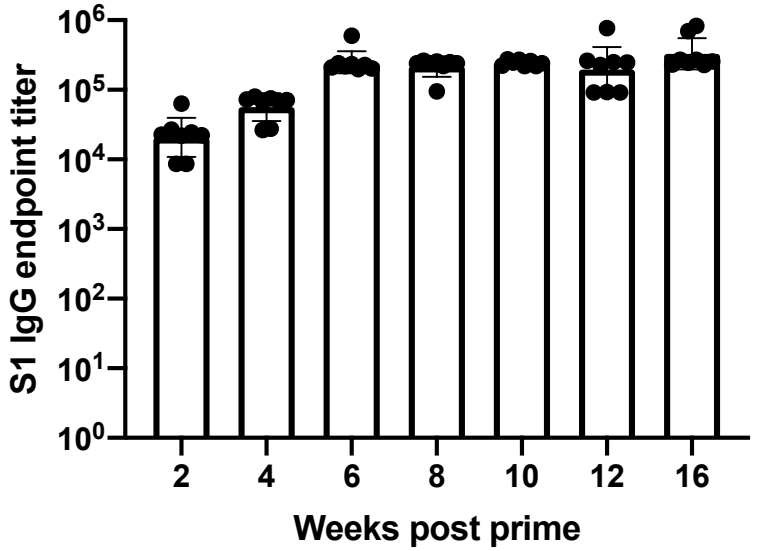
Induction of Broad and Potent Spike Specific T cells and Durable IgG and Neutralizing Antibody Titers by ChAdV-Spike in Mice

Spike T cell response



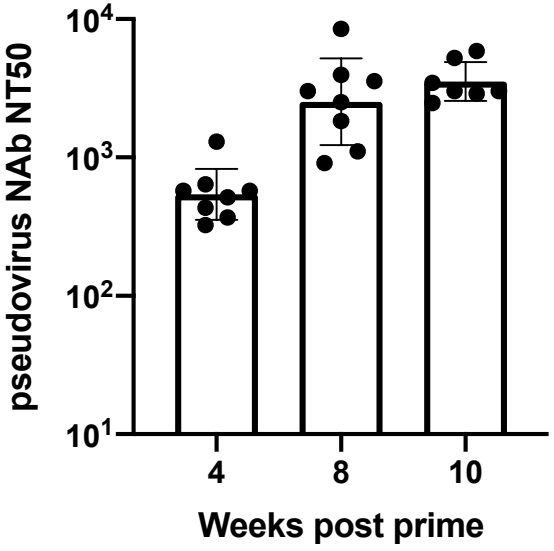
T cell response to 8 overlapping peptide pools spanning Spike antigen

Spike IgG titers



2	4	6	8	10	12	16
25,510	130,949	152,591	211,857	196,190	188,745	322,920

Neutralizing Antibodies



4	8	10
540	2,525	3,536

Balb/c mice using ChAdV-Spike(V2) – 1e11 VP

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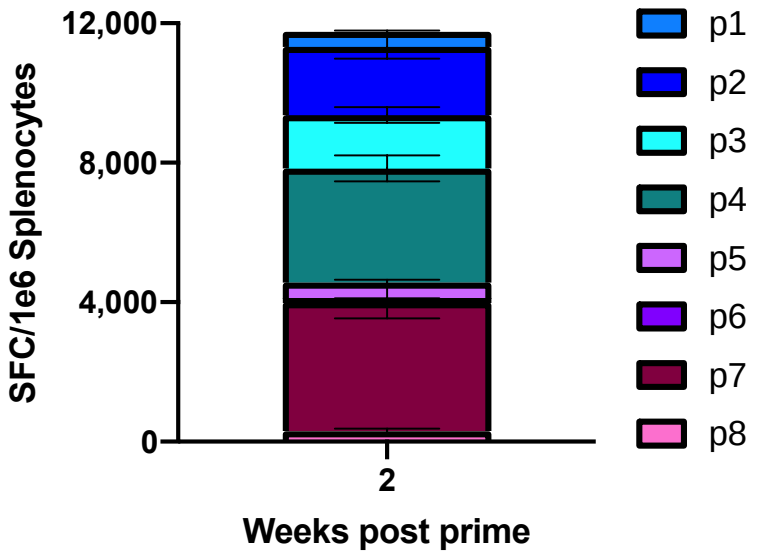
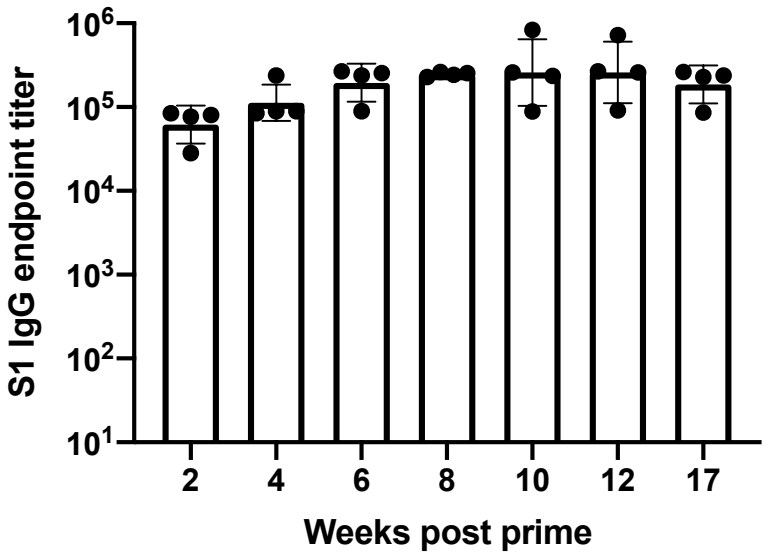
Induction of Broad and Potent Spike Specific T cells and Durable IgG and Neutralizing Antibody Titers by SAM-Spike in Mice

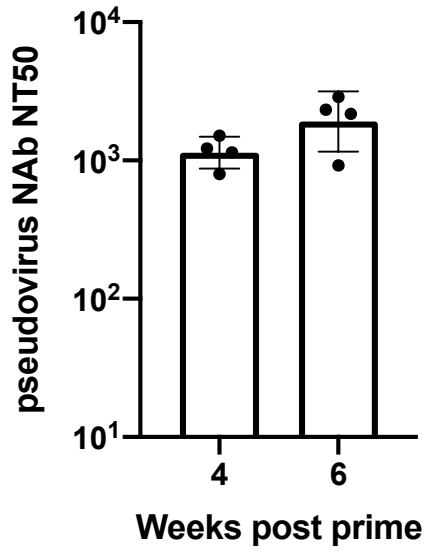
Spike T cell response



Spike IgG titers



Neutralizing Antibodies



T cell response to 8 overlapping peptide pools spanning Spike antigen

Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 17
62,107	112,834	195,282	246,901	259,575	259,656	187,311

Week 4	Week 6
1140	1910

Balb/c mice using SAM-Spike (V2) – 10 ug

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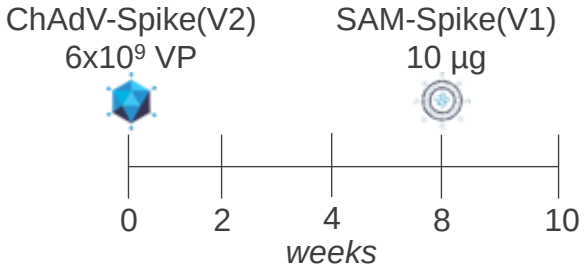
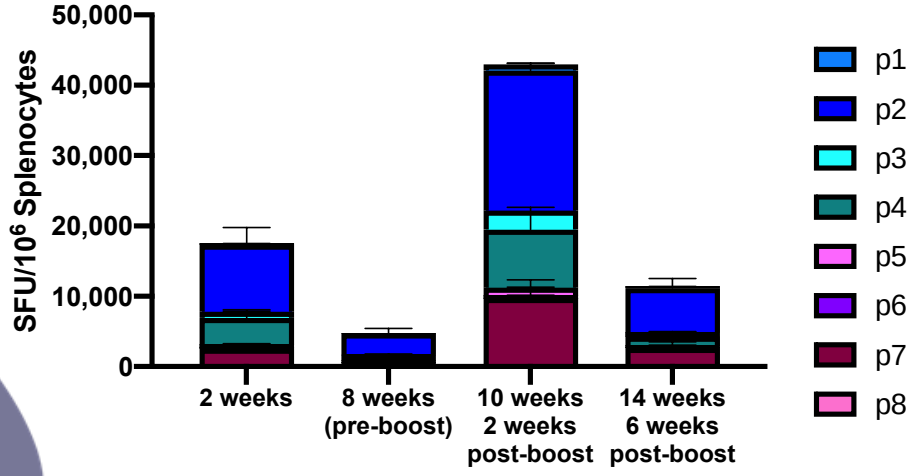
Heterologous Prime/Boost Drives Potent and Durable Spike-Specific Immune Responses in Mice

High levels of neutralizing antibodies



Spike T cell response

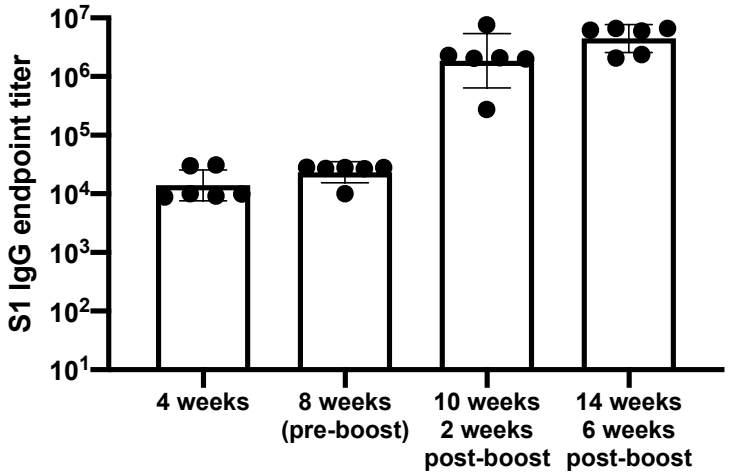
9x increase post-boost, T_h1 bias



T cell response to 8 overlapping peptide pools spanning Spike antigen. IFNγ ELISpot. Mean +/- SEM. ICS to assess T cell phenotype (data not shown)

Spike IgG titers

100x increase post-boost

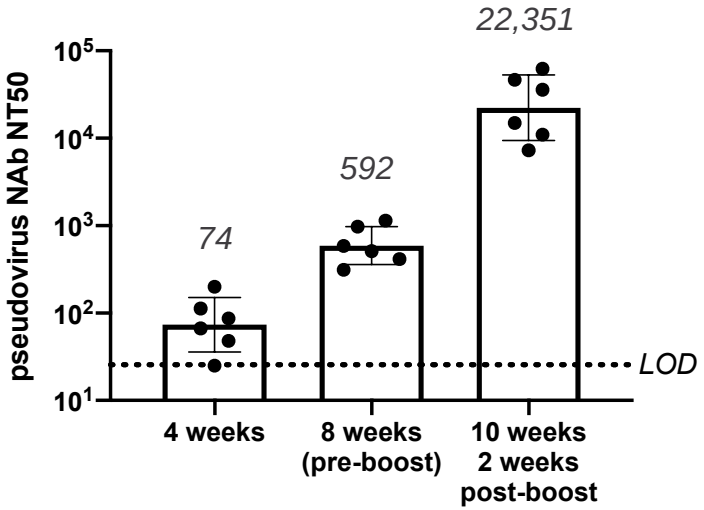


4	8	10	14
14,011	23,297	1,857,172	4,478,266

ELISA. Geomean endpoint titer, geometric SD.

Neutralizing antibodies

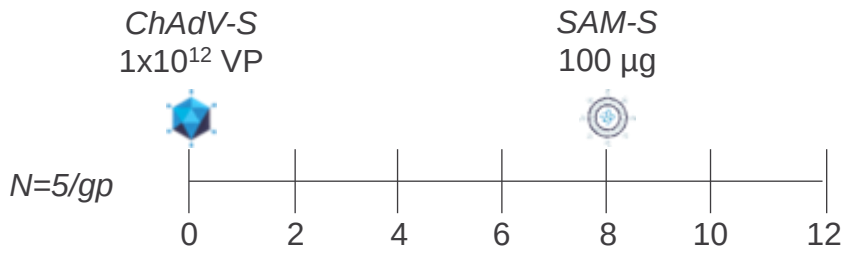
40x increase post-boost



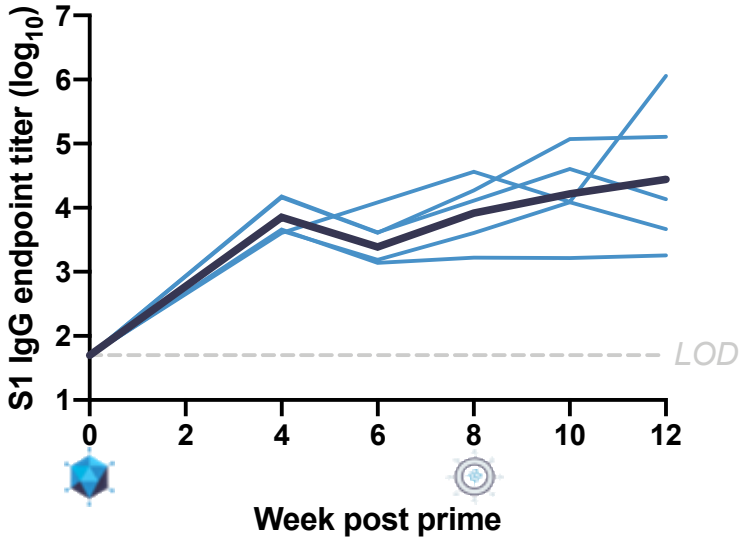
Pseudovirus neutralizing titer. Geomean, geometric SD.

Gritstone's Heterologous Vaccine Platform Drives a High Antibody Response in Non-Human Primates (NHPs)

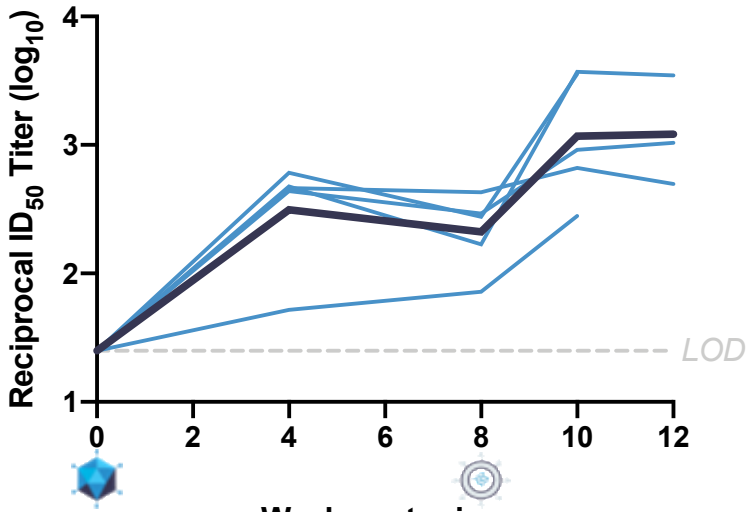
nAb titers in vaccinated NHP are greater than 1-log higher than values in convalescent patients



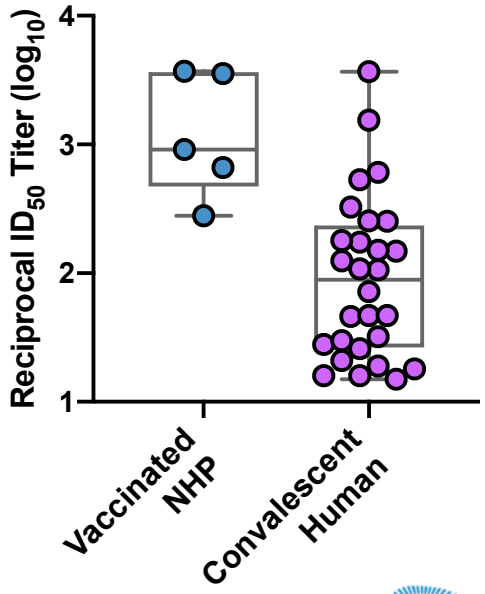
SARS-CoV-2 Total Antibody Response



SARS-CoV-2 Neutralizing Antibody Response



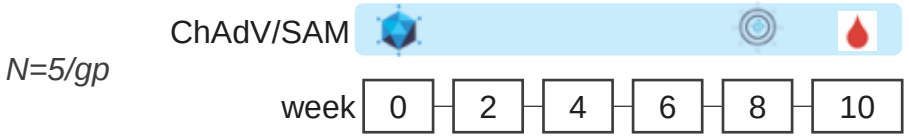
Neutralizing Antibodies 2 Weeks post Boost



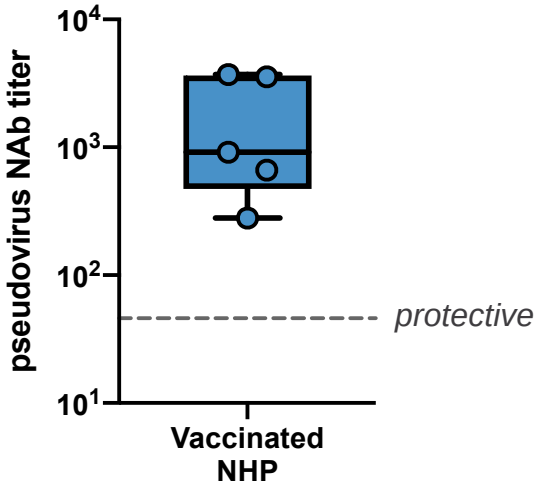
Gritstone Vaccine Induces Spike-Specific Neutralizing Antibody Titers in NHPs that are Predicted to be Protective

Based on published rechallenge data in NHP

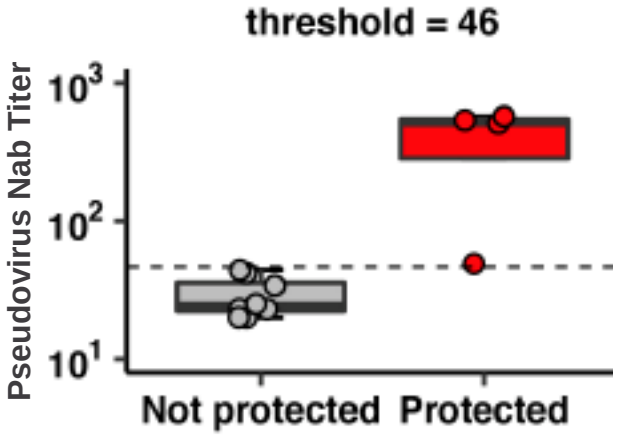
Gritstone Heterologous Prime/Boost



2 weeks post boost



McMahan *et al*: Data in NHPs Pseudovirus Nab titers > 46 convey protection from viral replication following re-challenge



McMahan et al. Nature 2020

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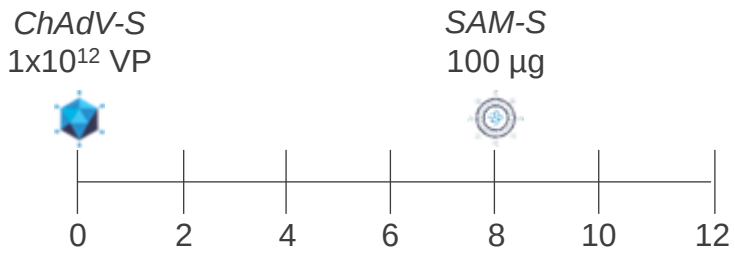
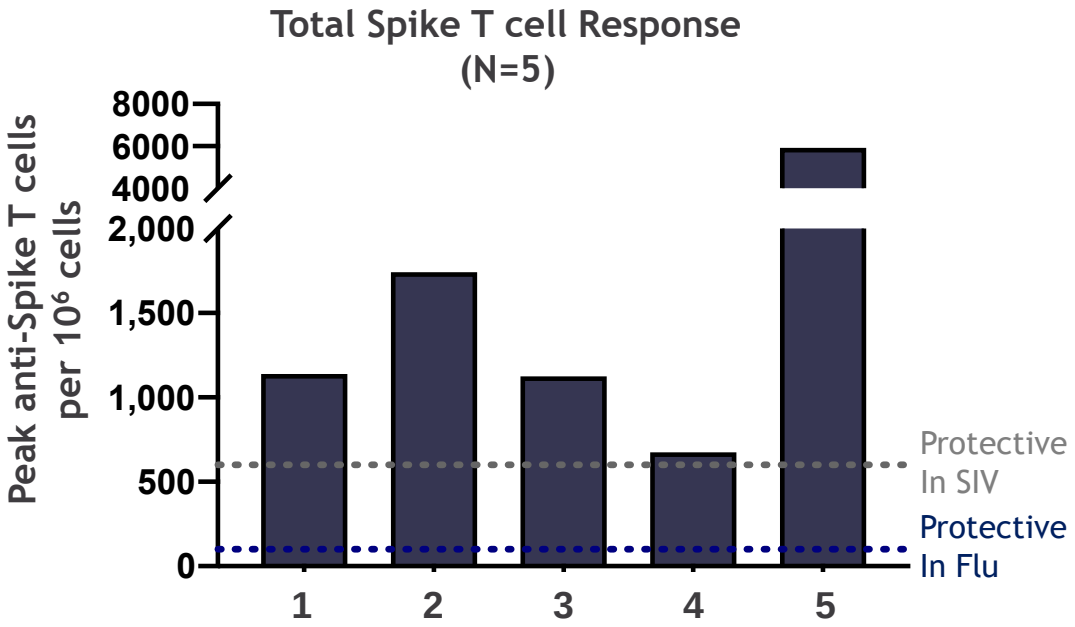
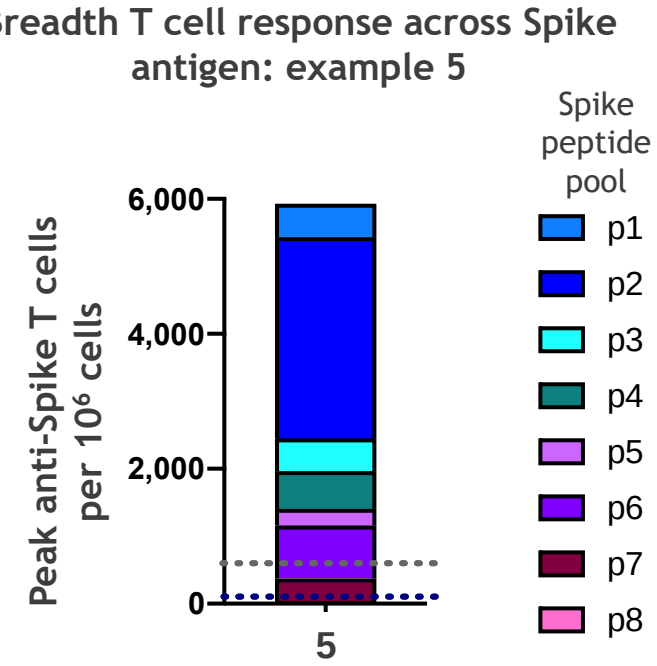
Gritstone's Heterologous Vaccine Platform Drives Potent and Broad T Cell Responses to Spike in all NHPs



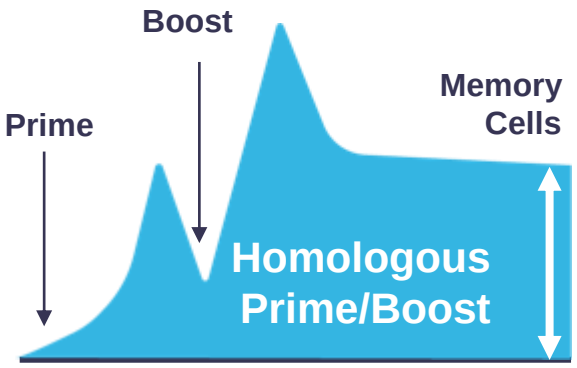




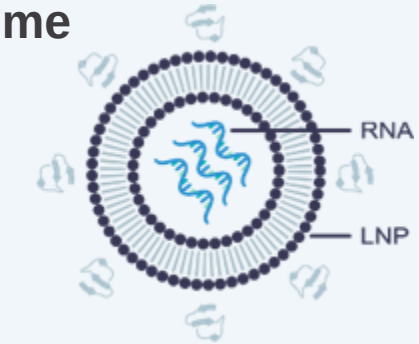
Gritstone's Universal Homologous Prime/Boost Immunization Platform: Self-Amplifying RNA (SAM)

Homologous Prime/Boost

Two immunizations increases strength and durability of humoral and cellular response



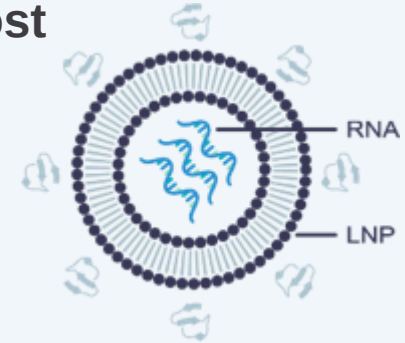
Prime



SAM Vector

→ Synthetic & non-viral Allows for repeated immunization

Boost

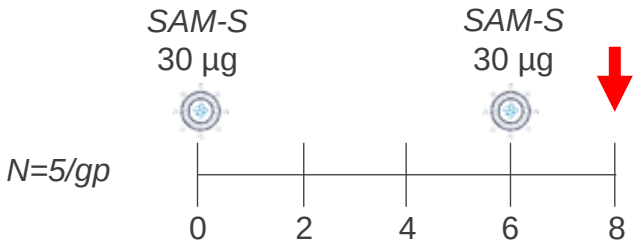


SAM Vector

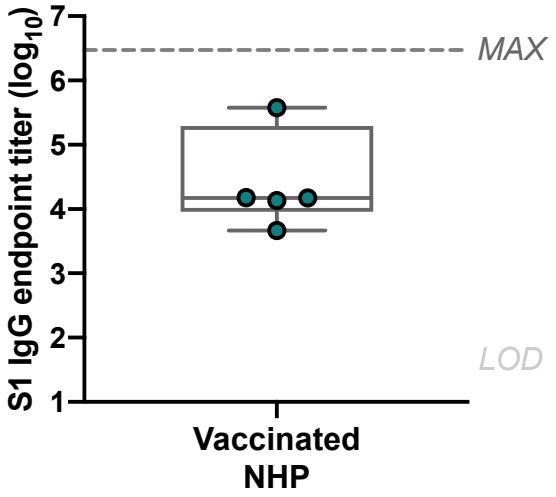
→ Synthetic & non-viral Allows for repeated immunization

Gritstone's Homologous SAM-Spike Vaccine Drives a High Antibody Response in NHPs after 2nd immunization

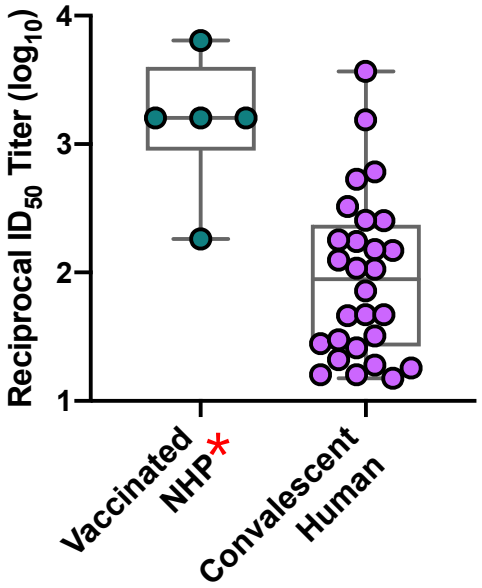
nAb titers in vaccinated NHP are greater than 1-log higher than values in convalescent patients



SARS-CoV-2 Total Antibody Response
Week 8

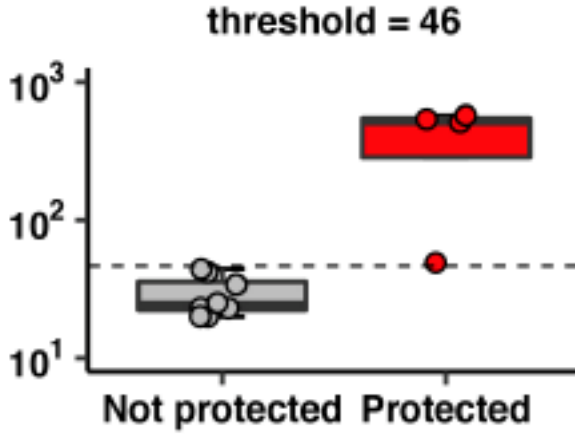


SARS-CoV-2 Neutralizing Antibody Response
Week 8



*4/5 samples at assay maximum

McMahan *et al*:
Data in NHPs
Pseudovirus nAb titers > 46 convey protection from viral replication following re-challenge



McMahan et al. Nature 2020

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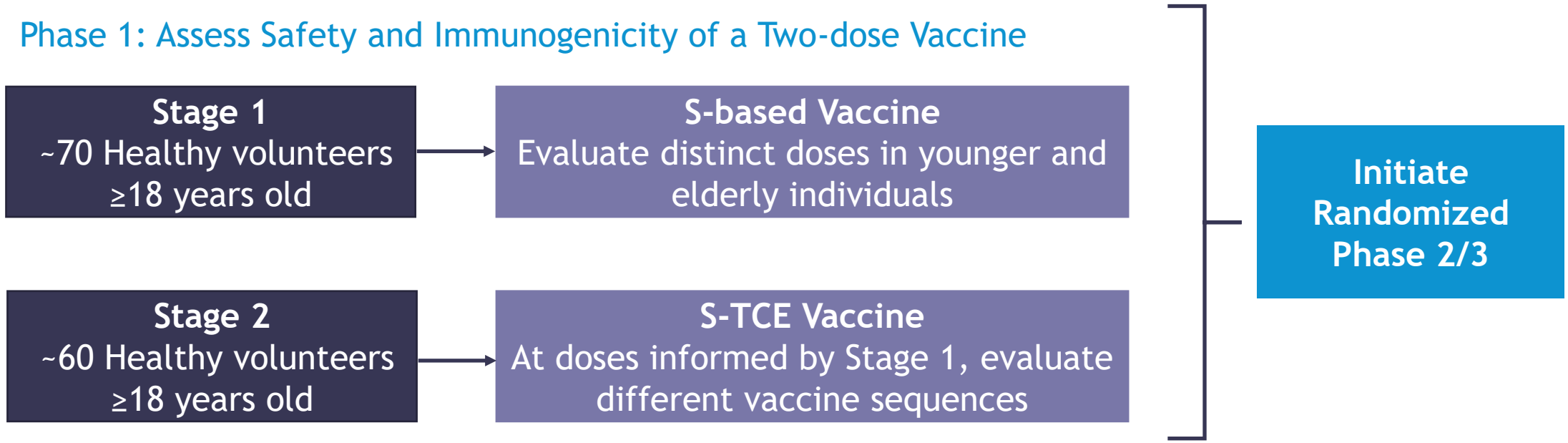
Clinical Plan: CORAL Platform

CORAL Development Plans: On Track to the Clinic

- Two candidates are being tested: Spike-based (S) and Spike + T cell Epitopes (S-TCE)
- S-based vaccine will allow faster dose evaluation and immunogenicity comparison with S-TCE
- Completed pre-IND interaction with FDA
- Initiate Stage 1 (S) in 1Q2021 and Stage 2 (S-TCE) in 2Q2021
  - Expect preliminary data in mid-2021



Gritstone's Biomanufacturing and Clinical Capabilities are Established

Gritstone vaccines have been manufactured and administered to cancer patients in the U.S.

Fully Integrated Manufacturing and Testing Facility in Pleasanton, CA

Biomanufacturing Processes Established; Formulation Optimization and Scale Up Underway

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Gritstone's CORAL Program is Supported by Key Relationships

La Jolla Institute FOR IMMUNOLOGY

- License agreement
- Supplying Gritstone validated SARS-CoV-2 epitopes identified through studies of hundreds of patients recovering from COVID-19

BILL & MELINDA GATES foundation

- Research grant
- Collaboration for pre-clinical studies of Gritstone's vaccine
- Gritstone conducts all studies

NIH National Institute of Allergy and Infectious Diseases

- A Phase 1 clinical trial, expected to be conducted through the NIAID-supported Infectious Diseases Clinical Research Consortium (IDCRC), is in development.

Gritstone Retains all Rights to Asset

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Gritstone's CORAL Program - Advancing the Second Generation of COVID-19 Vaccine Products

BROAD: Multiple viral proteins targeted (not just Spike)

DURABLE: CD8 T cell immunity typically more durable than antibody responses

POWERFUL: Vaccine platform combines two vectors and drives antibody and killer CD8 T cell responses

ESTABLISHED HUMAN SAFETY AND IMMUNE RESPONSES

- Vaccine vectors given at high doses have shown safety and immune responses in completed Phase 1 oncology trials

SUPPORTED BY KEY LEADERS

- La Jolla Institute license agreement
- Bill & Melinda Gates Foundation grant for preclinical development
- NIH/NIAID support of phase one clinical program

CLEAR DEVELOPMENT PATH

- In-house manufacturing
- Product for Phase 1 (FPI 1Q21) currently being manufactured
- Extensive immunologic testing of patients to assess depth, breadth and duration of immune responses to SARS-CoV-2


HEART RATE
MEDICAL
HEALTH INSURANCE
MEDICAL TREATMENT
FINANCIAL BENEFITS
DISEASE COVERAGE
ACCIDENT
PROTECTION
RISK ADVISORY
FIRST AID
MONEY MANAGEMENT
EXAMINATIONS

Thank You