Understanding immune responses to SARS CoV2 infection and vaccination

THE TEAM





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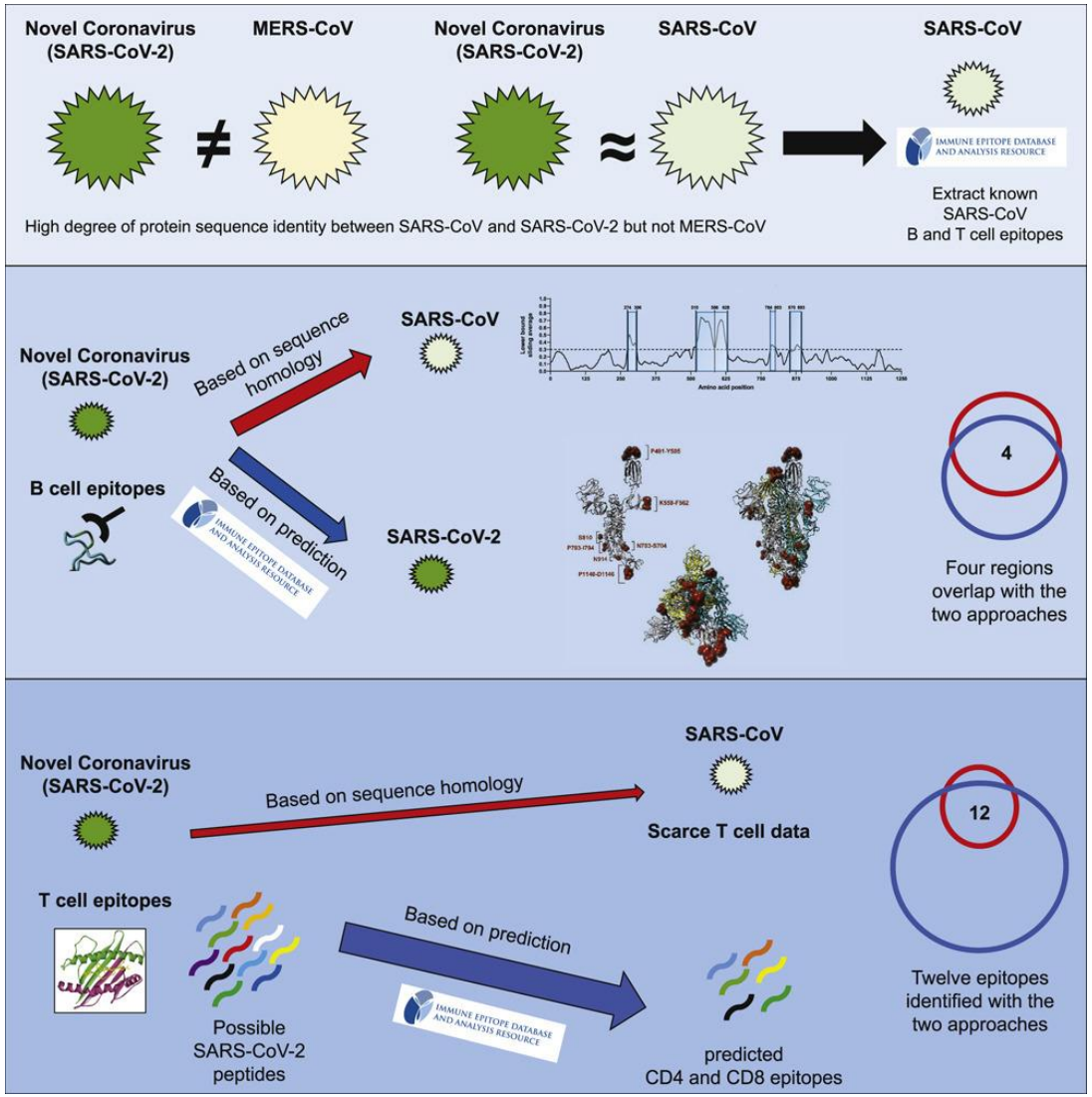
Vanderbilt University
Simon Mallal

NIH National Institute of Allergy and Infectious Diseases

Philanthropic Support

SARS-CoV-2 should be immunogenic

- Scarce data initially available
- Strong sequence homology and structural similarity with SARS-CoV1
- Similarity also at the epitope level
- Predicted CD4 and CD8 epitopes in SARS CoV2
- Enable experimental testing





Alba Grifoni, PhD

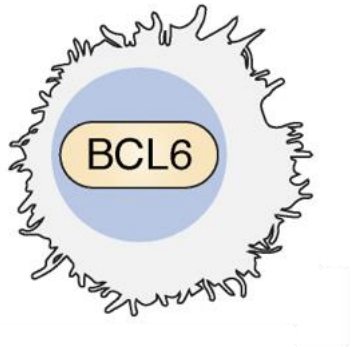
Grifoni et al., Cell Host & Microbe March 2020

Do people develop immunity to SARS CoV2?



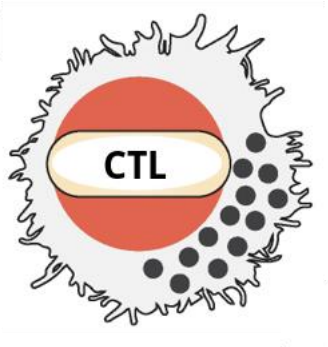
Antibodies
(from B cells)

- Important in almost all currently licensed human vaccines



Helper T cells

- Critical for antibody responses
- Protect independent of antibodies in SARS mouse model



Killer T cells

- Important in many viral infections
- Critical to eliminate infected cells

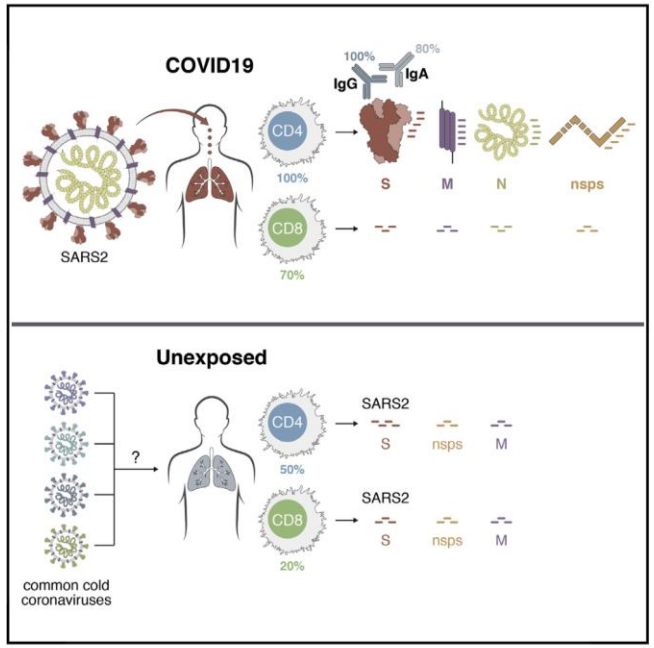
T cell and antibody responses in ‘mild’ cases of COVID-19

Cell

Article

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

Graphical Abstract



Authors

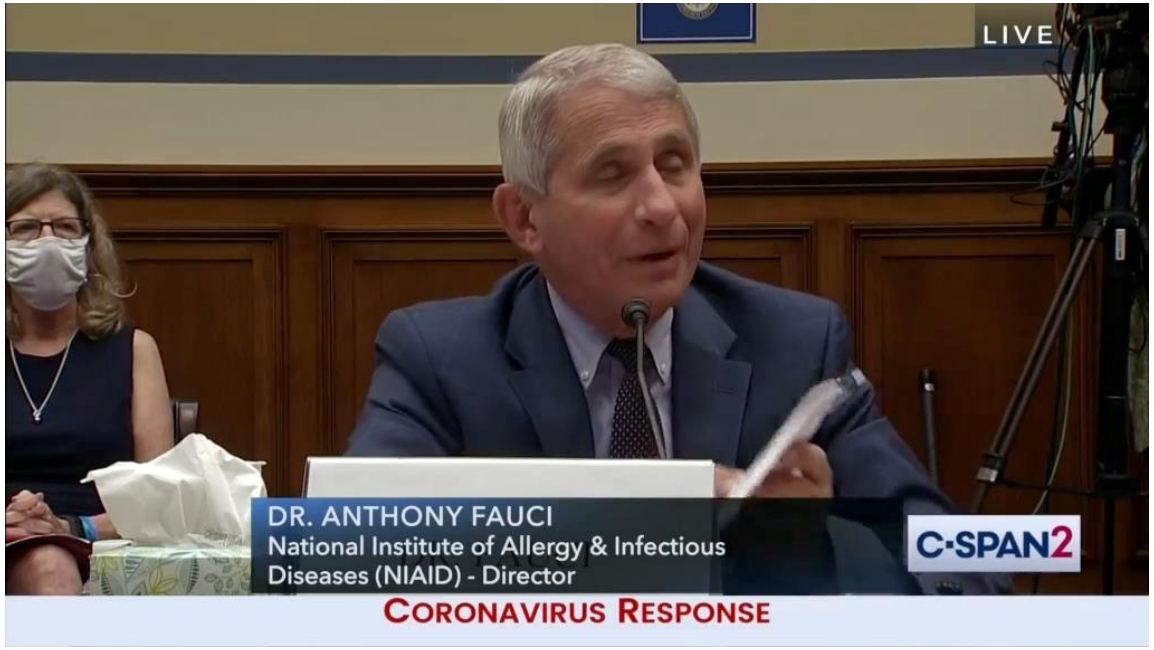
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In Brief

An analysis of immune cell responses to SARS-CoV-2 from recovered patients identifies the regions of the virus that is targeted and also reveals cross-reactivity with other common circulating coronaviruses



LJI reagents to measure T cells : shared with 185 labs, 32 different countries, 6 continents and resulted in over 50 collaborative studies

Grifoni et al., Cell May 2020

SARS-CoV-2 immune memory following natural infection

- The largest ever study of its kind, for any infection
- Substantial immune memory in most individuals at 8+ months post-COVID
- Immune memory is complex and heterogenous
- T cells, memory B cells, and antibodies have different kinetics
- 5-10% of individuals have low level immune memory at 6+ months




The New York Times

Immunity to the Coronavirus May Last Years, New Data Hint

Blood samples from recovered patients suggest a powerful, long-lasting immune response, researchers reported.

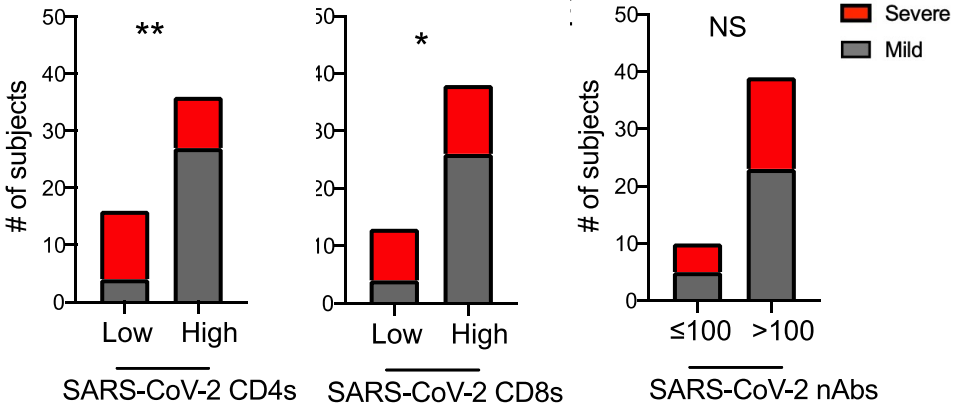


Asst. Prof. Jen Dan MD/PhD

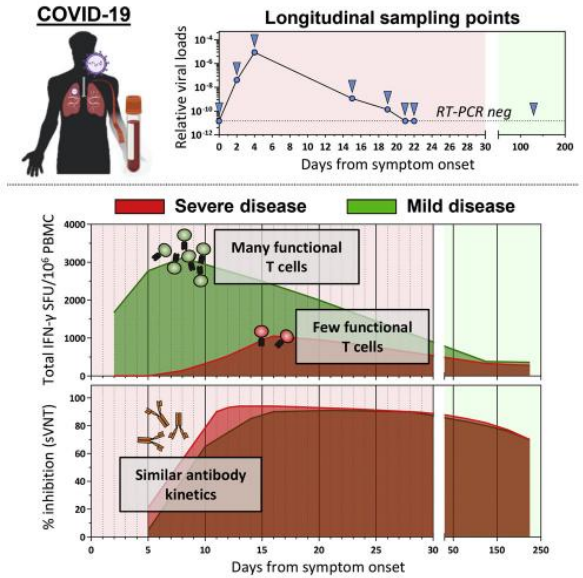
Dan et al. Science. Jan 2021

Evidence pointing to substantial contributions of T cells to SARS CoV2 immunity

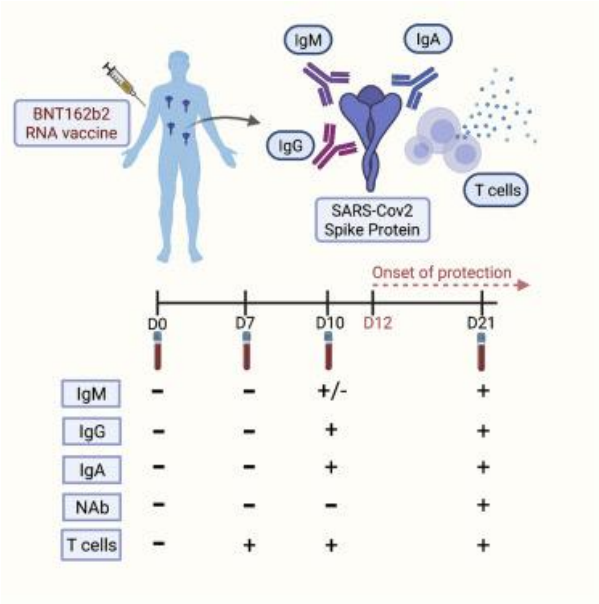
- Early T cell responses correlate with better outcomes and lower viral loads
- CD8 T cells provide control in monkeys
- People lacking antibodies resolve SARS CoV2 infections
- Onset of protection from Moderna or Pfizer vaccines in absence of detectable neutralizing antibodies



Moderbacher et al. Cell Sept 2020



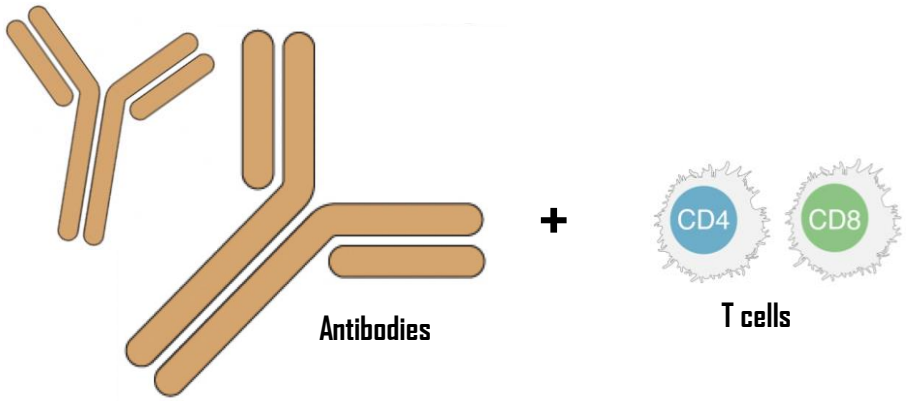
Tan et al, Cell Rep, 2021



Kalimuddin Cell Med, 2021

Vaccine protection against SARS-CoV-2

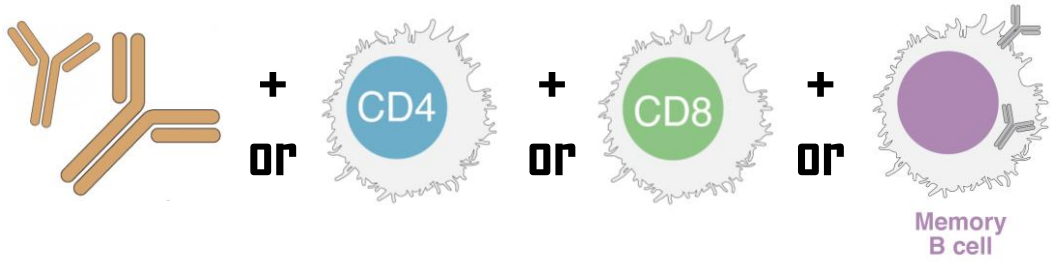
Protection against Detectable Infection



Major

Minor

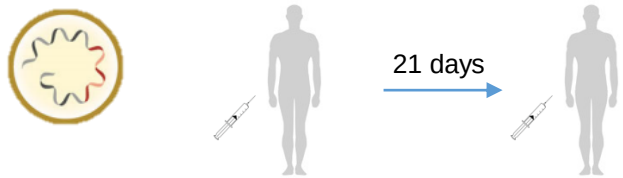
Protection against Hospitalizations & Deaths



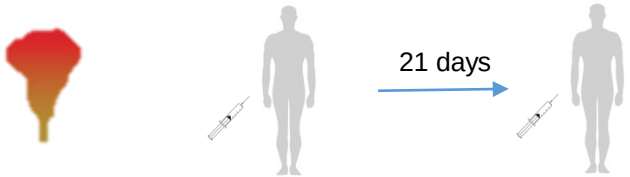
Comparison of immune memory to four COVID-19 vaccines



mRNA-1273-100 µg



BNT162b2-30µg

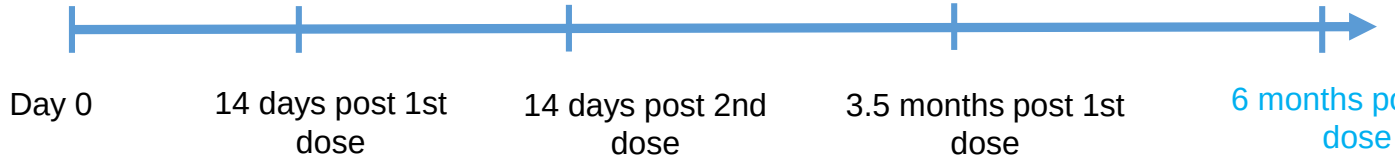


NVX-CoV2373



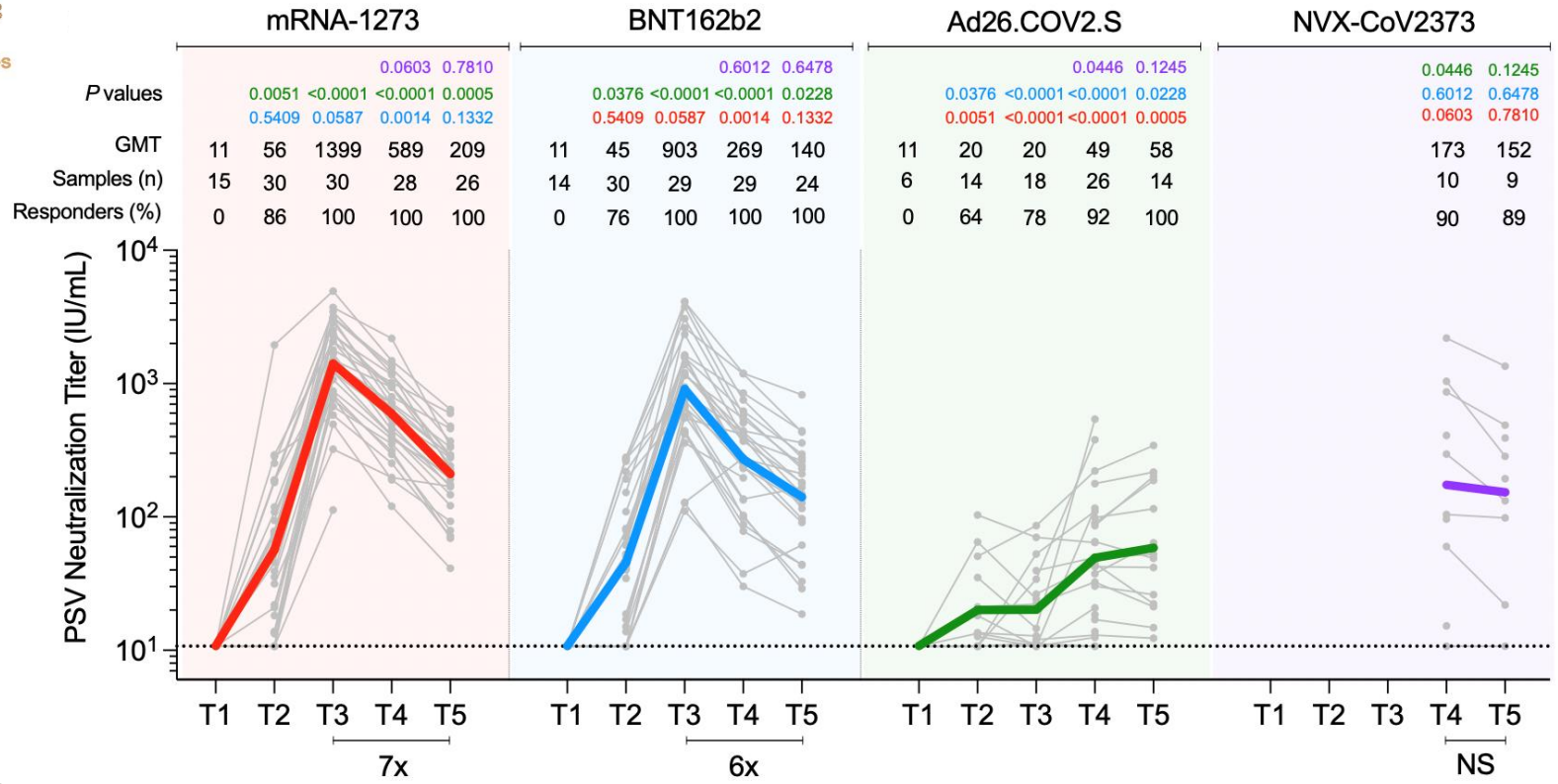
J&J

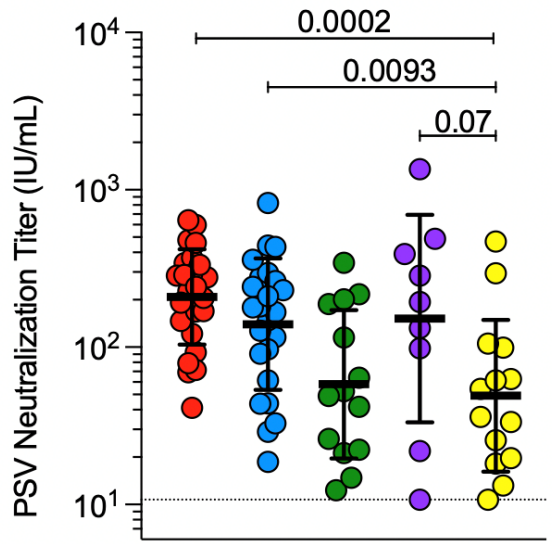
Characteristic	mRNA-1273 Moderna	BNT162b2 Pfizer	Ad26.COV2.S Janssen	NVX-CoV2373 Novavax
Donors, n	30	30	30	12
Gender, n (%)				
Male	12 (40%)	11 (37%)	11 (37%)	6 (60%)
Female	18 (60%)	19 (63%)	19 (63%)	4 (40%)
Age, years (mean ± SD)	43.6 ± 13.9	43.2 ± 17.4	45.6 ± 14.9	38.3 ± 18.0
Race or ethnicity, n				
Asian	3	9	2	0
White	24	16	24	11
Hispanic or latino	9	5	5	1
Days post-vaccination (mean ± SD)				
T2	15 ± 4	15 ± 2	15 ± 3	-
T3	45 ± 6	37 ± 3	47 ± 8	-
T4	105 ± 6	106 ± 4	108 ± 7	120 ± 19
T5	185 ± 9	184 ± 8	185 ± 3	185 ± 11



Crotty, Sette, Weiskopf and colleagues
biorxiv

Comparison of immune memory to four COVID-19 vaccines







Zeli Zhang, PhD



Jen Dan, MD/PhD

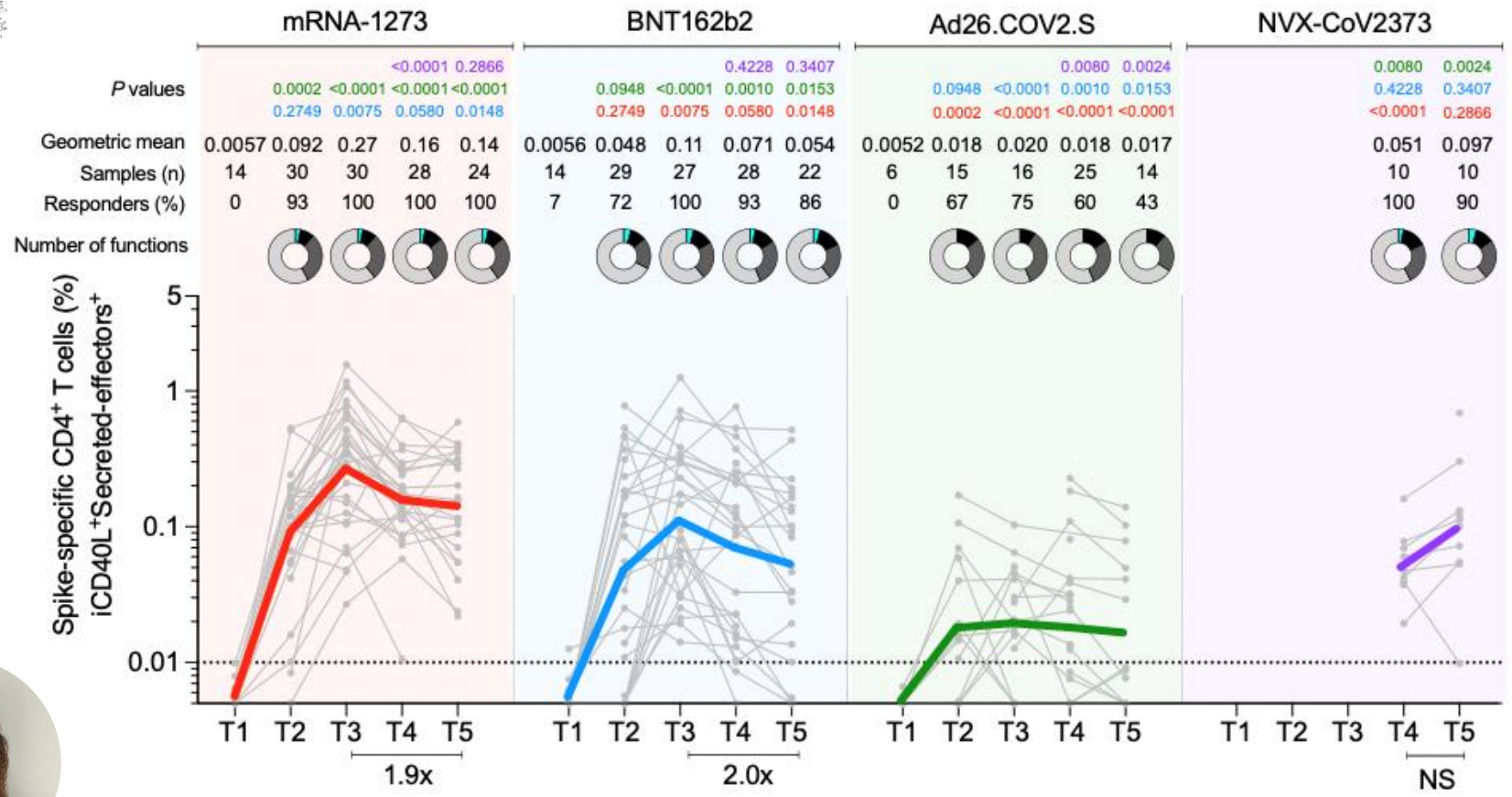
PSV, Pseudovirus

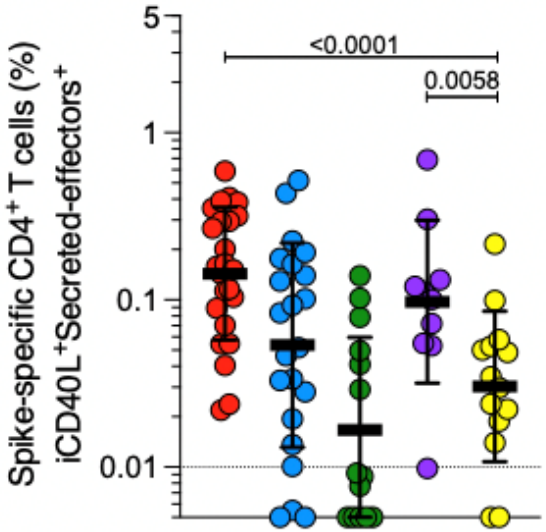
Figures modified from Zhang et al. *bioRxiv* 2022.03.18.484953; doi: https://doi.org/10.1101/2022.03.18.484953

Comparison of immune memory to four COVID-19 vaccines



CD4⁺ T cells







Carolyn Rydyznski Moderbacher, PhD

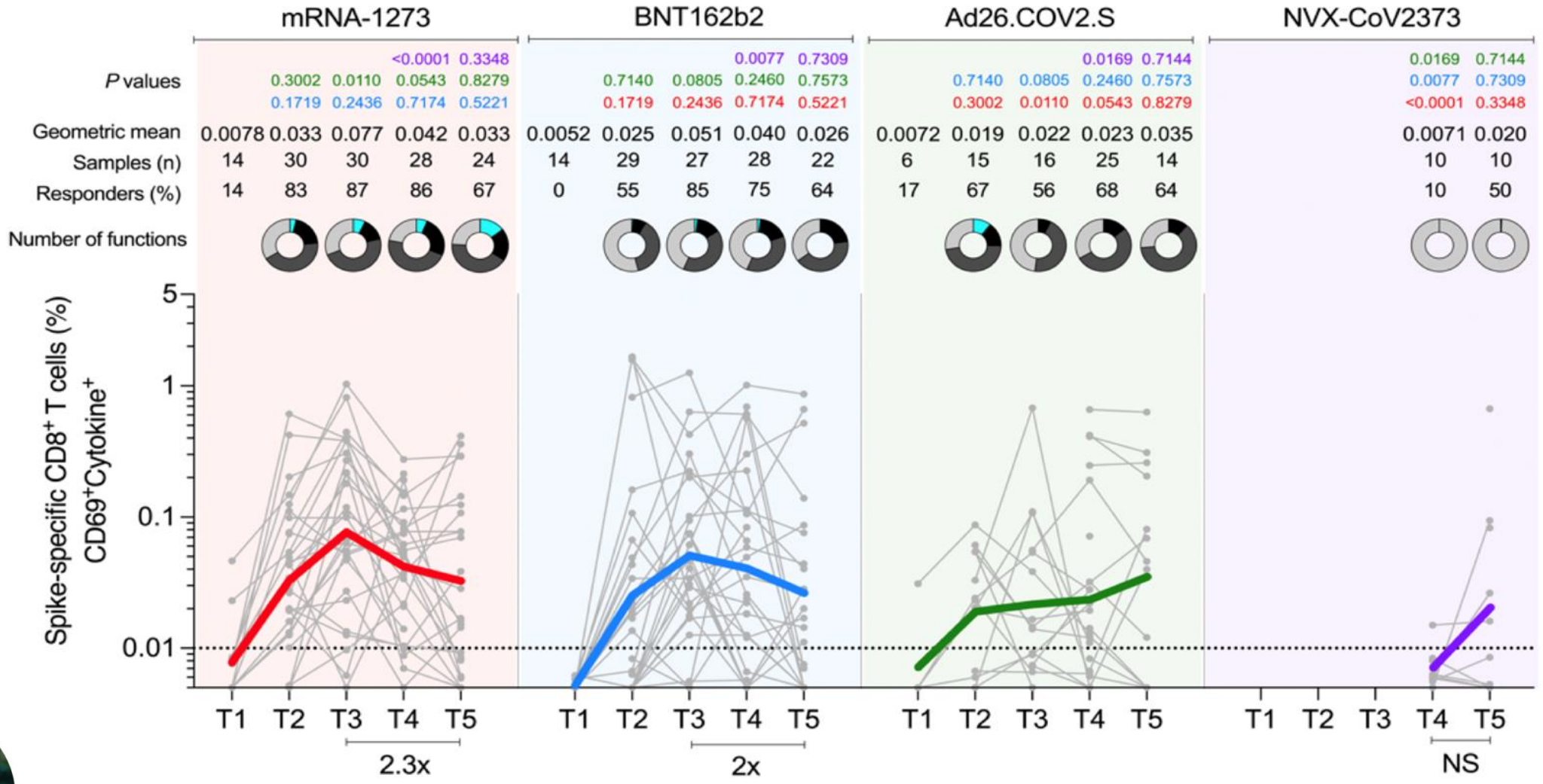
100% of individuals made memory CD4+ T cells, with Tfh highly represented after mRNA or Novavax vaccination. CD4-CTL were also unexpectedly common

CTL, Cytotoxic T-Lymphocyte; Tfh, follicular helper T cells

Figures modified from Zhang et al. *bioRxiv* 2022.03.18.484953; doi: https://doi.org/10.1101/2022.03.18.484953

Comparison of immune memory to four COVID-19 vaccines





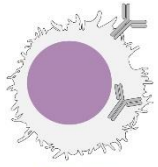


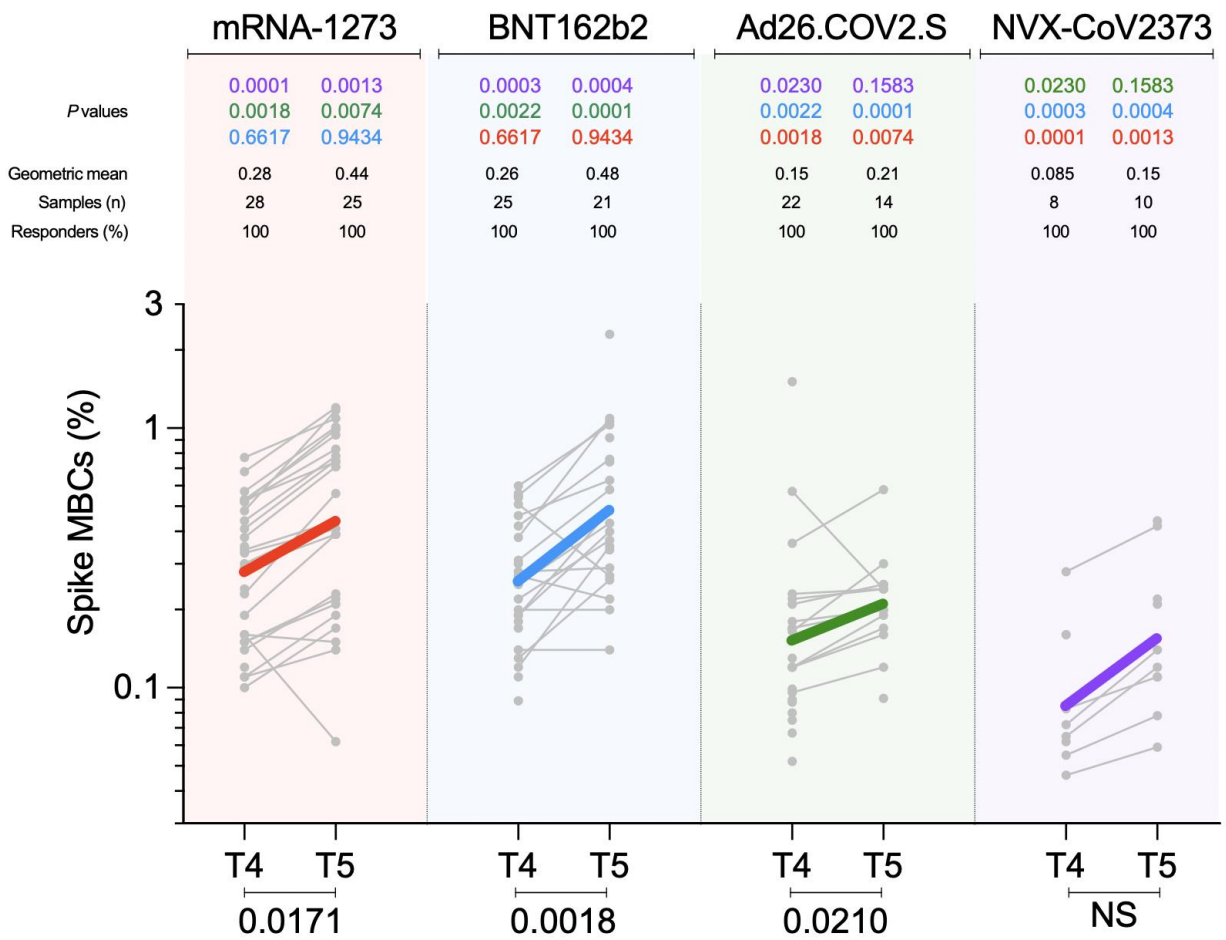
Jose Mateus, PhD

mRNA vaccines and J&J induced comparable CD8+ T cell frequencies, though memory CD8+ T cells were only detectable in 60-67% of subjects at 6 months

Figures modified from Zhang et al. *bioRxiv* 2022.03.18.484953; doi: https://doi.org/10.1101/2022.03.18.484953

Comparison of immune memory to four COVID-19 vaccines







Camila Coelho, PhD

Spike- and RBD-specific memory B cell responses were detected in all individuals to each of the four vaccines, and their frequency increased over time

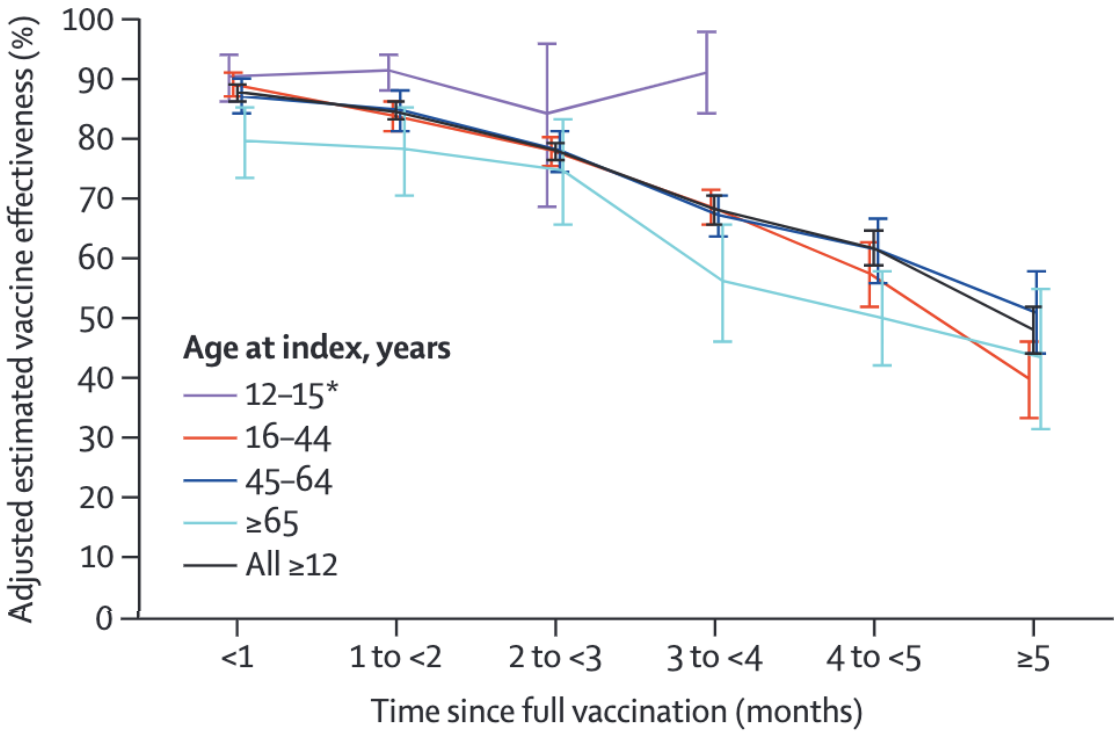
RBD, Receptor-Binding Domain

Figures modified from Zhang et al. *bioRxiv* 2022.03.18.484953; doi: https://doi.org/10.1101/2022.03.18.484953

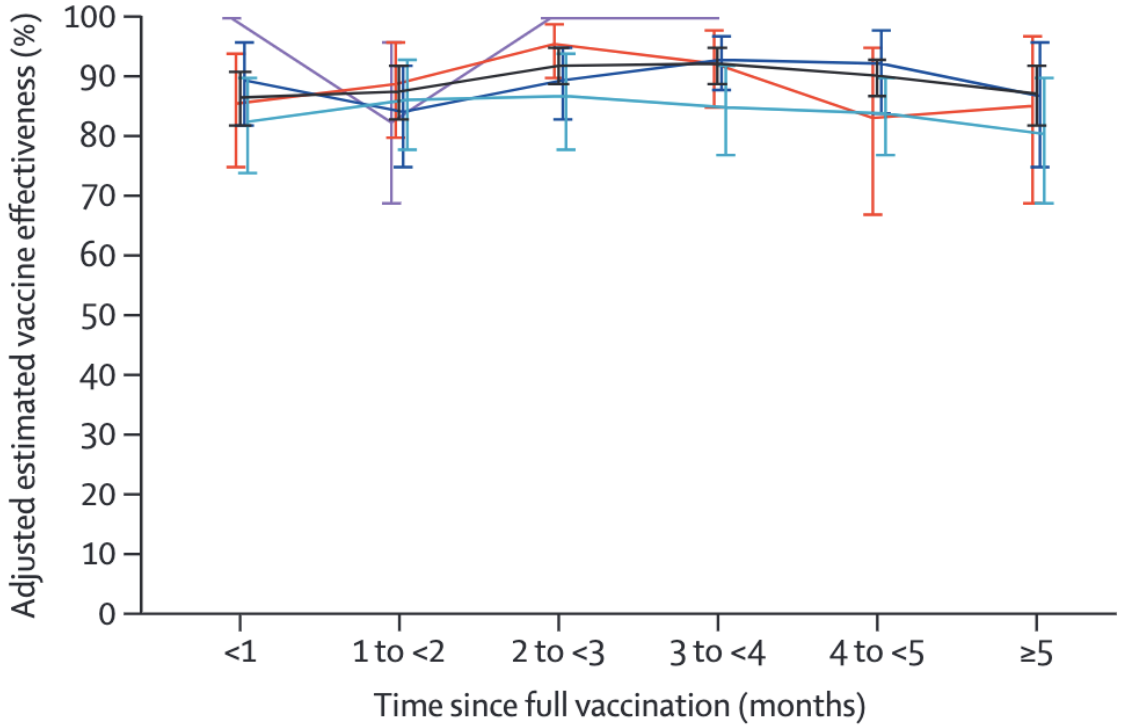
Conclusions for vaccine comparisons

- mRNA vaccines were consistently the most immunogenic, with levels higher than or equal to that of J&J and Novavax vaccines for each of the responses measured
- Novavax elicited CD4+ T cell memory and neutralizing antibody titers comparably to the mRNA vaccines
- Overall, J&J was not the strongest immunogen by any measurement, though the J&J T cell, B cell, and antibody responses were relatively stable over 6 months
- Substantial declines in neutralizing antibodies for mRNA vaccinees (as been widely reported), while memory T cells and B cells were comparatively stable
- Consistent with relatively high degree of protection against hospitalizations after these vaccines over 6 months, and the differential VE reported between mRNA COVID-19 vaccines and J&J

Waning protection against Detectable Infection

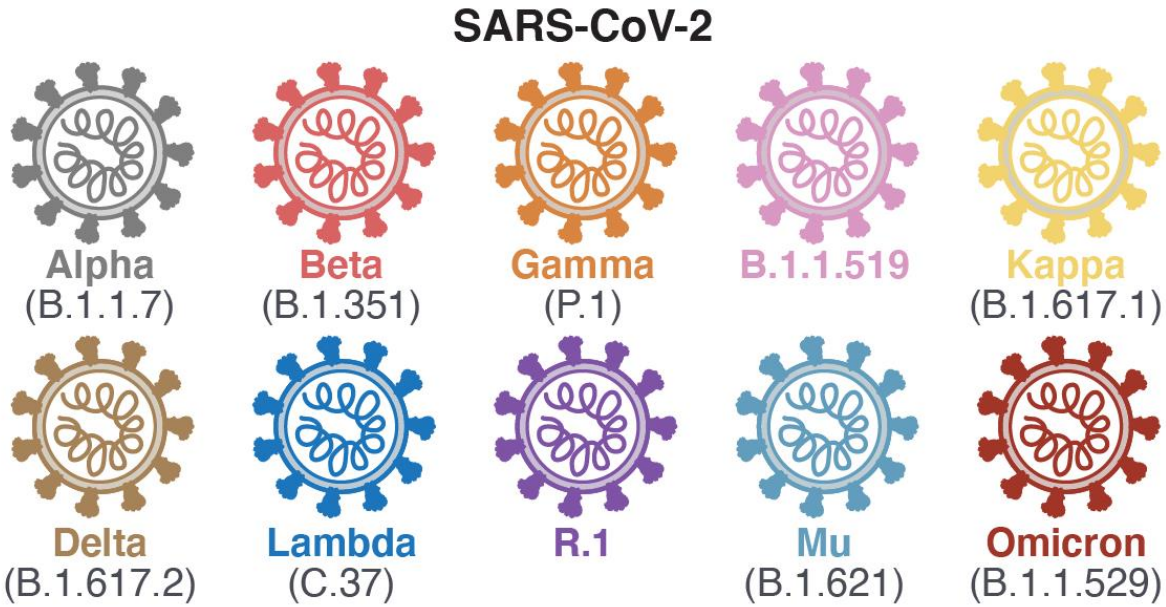


Minimal waning protection against Hospitalizations & Deaths



Kaiser study
Tartof et al. Lancet 2021. PMID 34619098

What about variants?



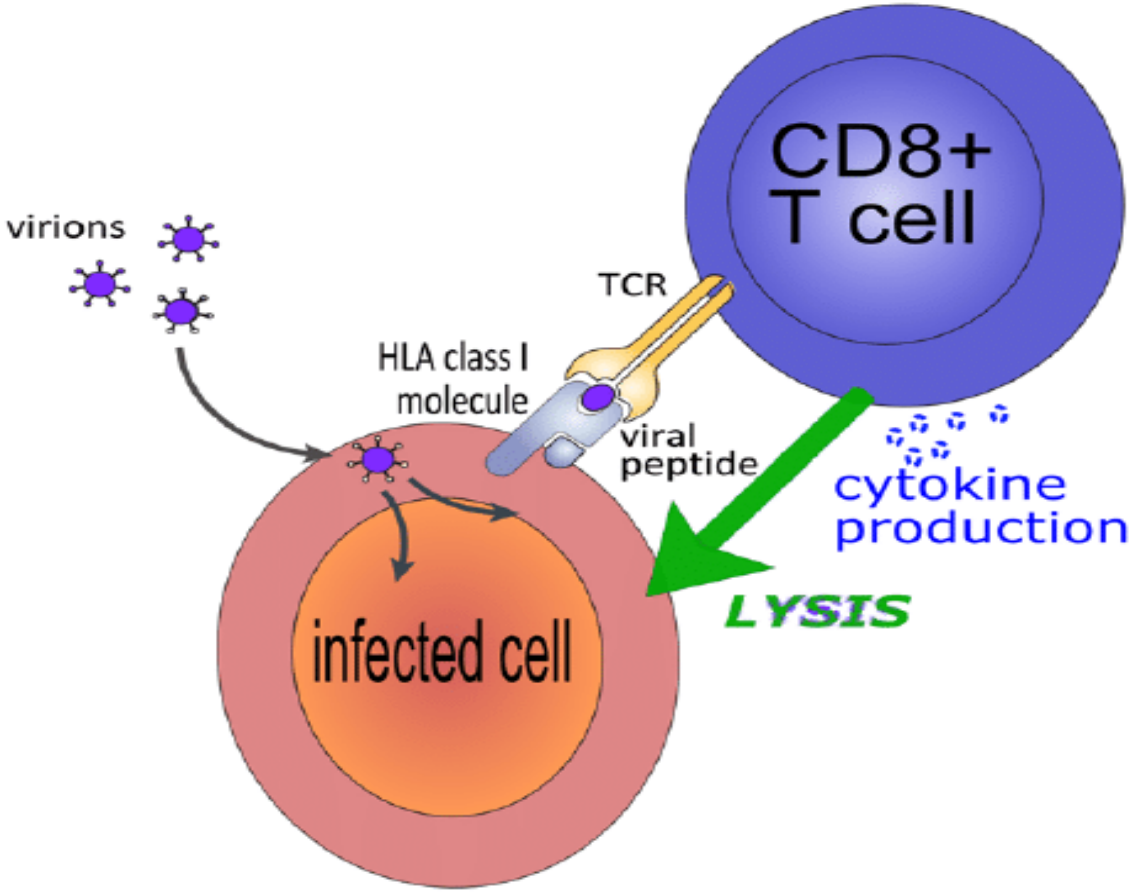
Breadth of SARS CoV2-specific CD4 and CD8 T cell responses

- Identified 280 different CD4 and 523 different CD8 epitopes
- Each individual recognizes multiple epitopes and antigens; conservative estimate of 30-40 epitopes recognized per donor

Tarke et al., Cell Med Rep Jan 2021

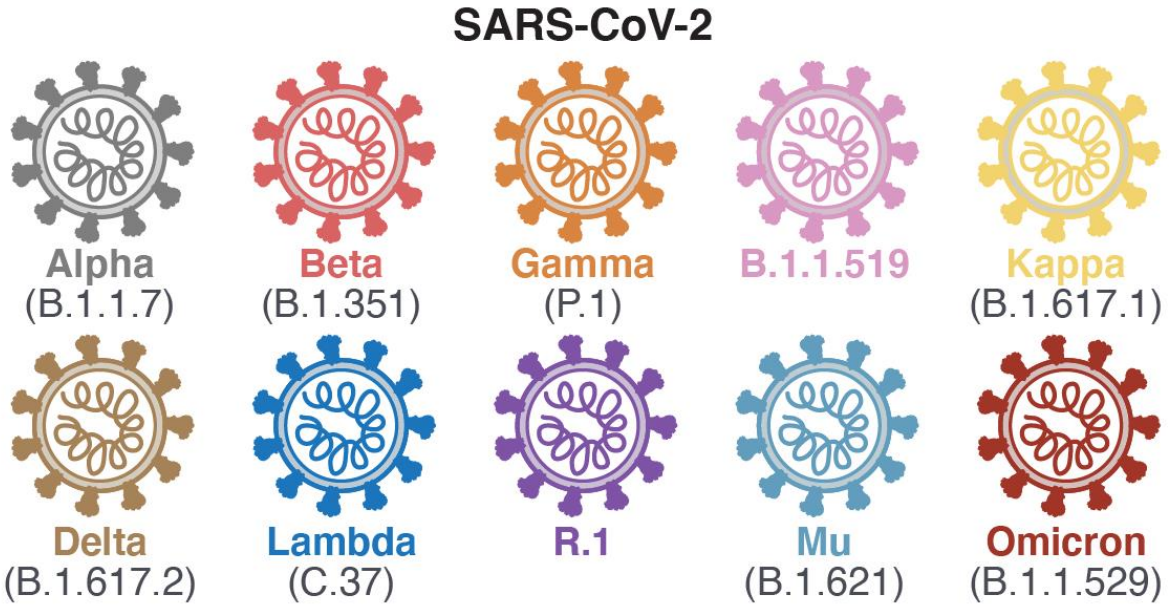
- Metanalysis of SARS CoV2 human T cell epitopes; 2049 different human SARS-CoV-2 T cell epitopes defined so far

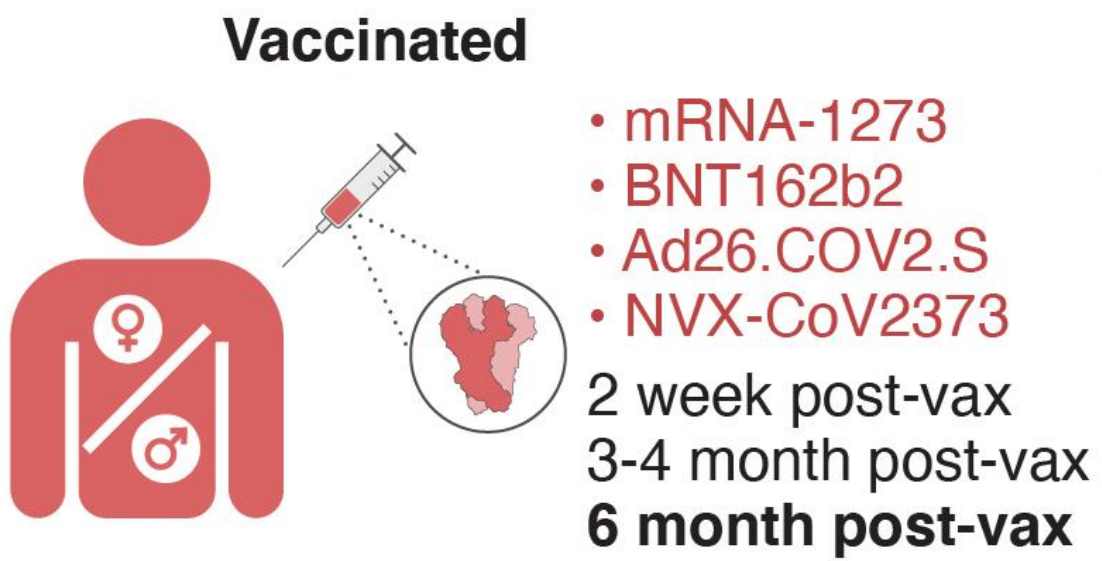
Grifoni et al., Cell Host & Microbe May 2021



Elemans M, Seich al Basatena N-K, Asquith B (2012) PLoS Comput Biol 8(2): PMID: 22383867

T cell reactivity to SARS-CoV-2 variants in vaccinated individuals







Alba Grifoni, PhD

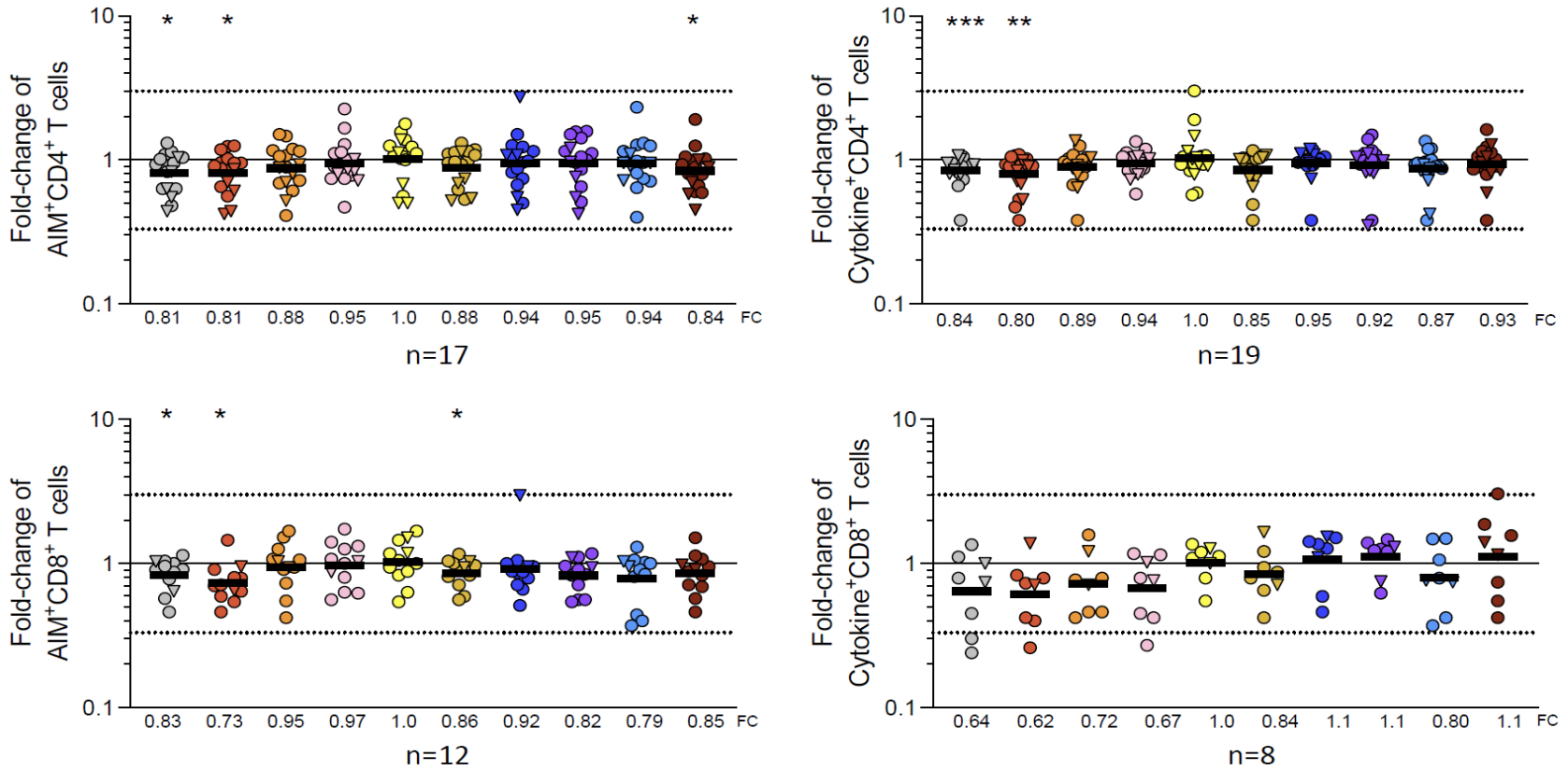


Alison Tarke



Tarke A et al, Grifoni and Sette. Cell. Jan 2022 PMID: 35139340

T cell recognition of Omicron is preserved



SARS-CoV-2 variant:

- Alpha (B.1.1.7)
- Beta (B.1.351)
- Gamma (P.1)
- B.1.1.519
- Kappa (B.1.617.1)
- Delta (B.1.617.2)
- Lambda (C.37)
- R.1
- Mu (B.1.621)
- Omicron (B.1.1.529)

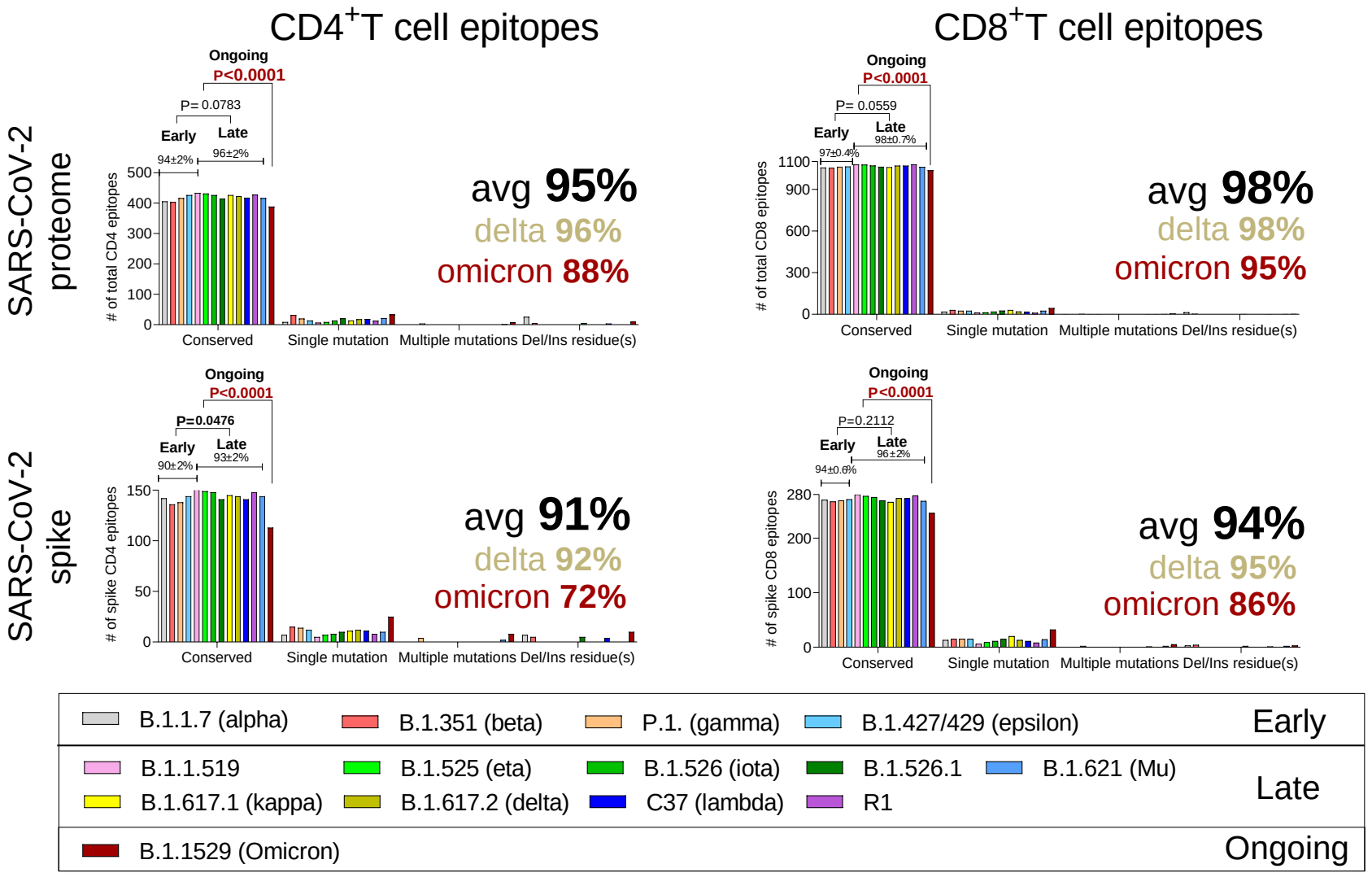
COVID-19 vaccine:

- ○ mRNA-1273
- ▽ BNT162b2

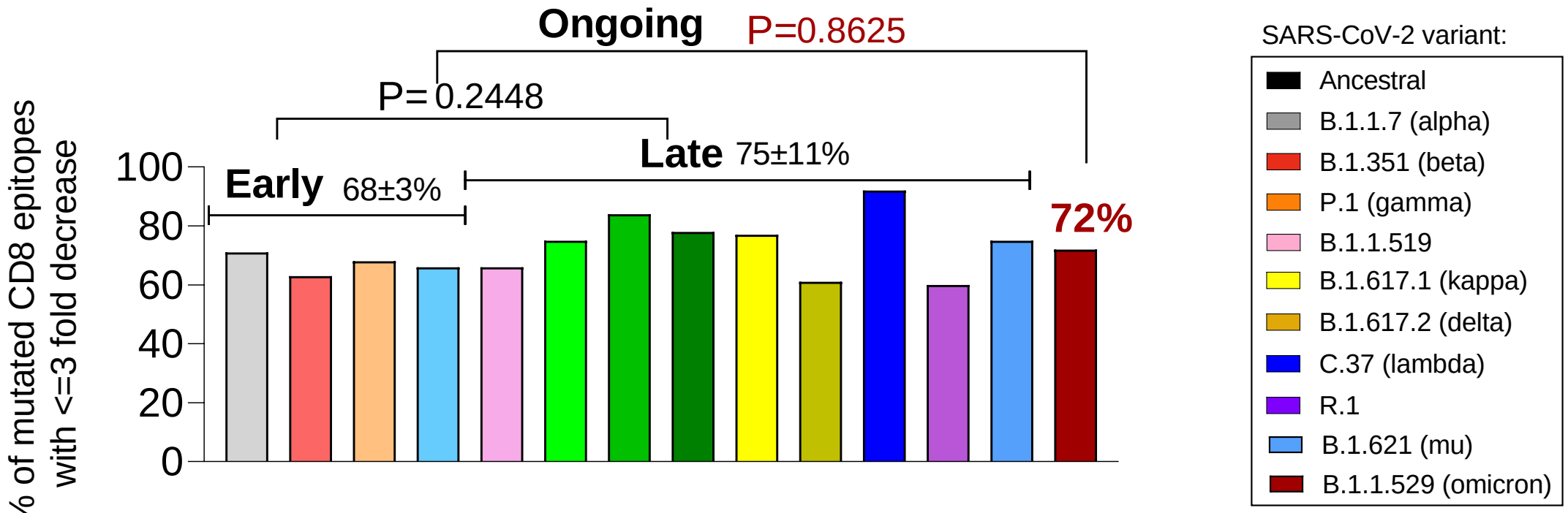


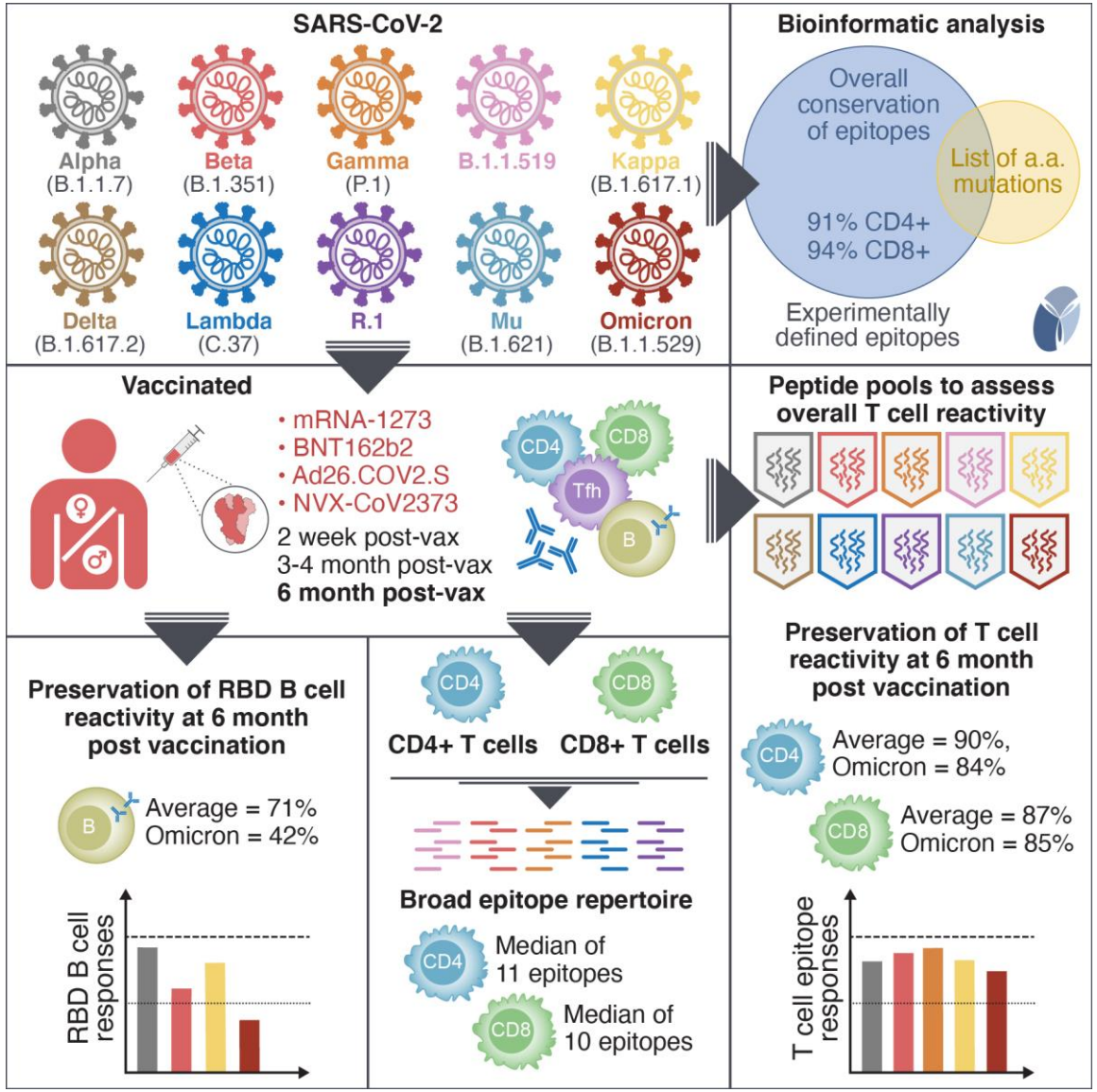
Tarke A et al, Grifoni and Sette. Cell. Jan 2022 PMID: 35139340

Conservation of T cell epitopes in Omicron

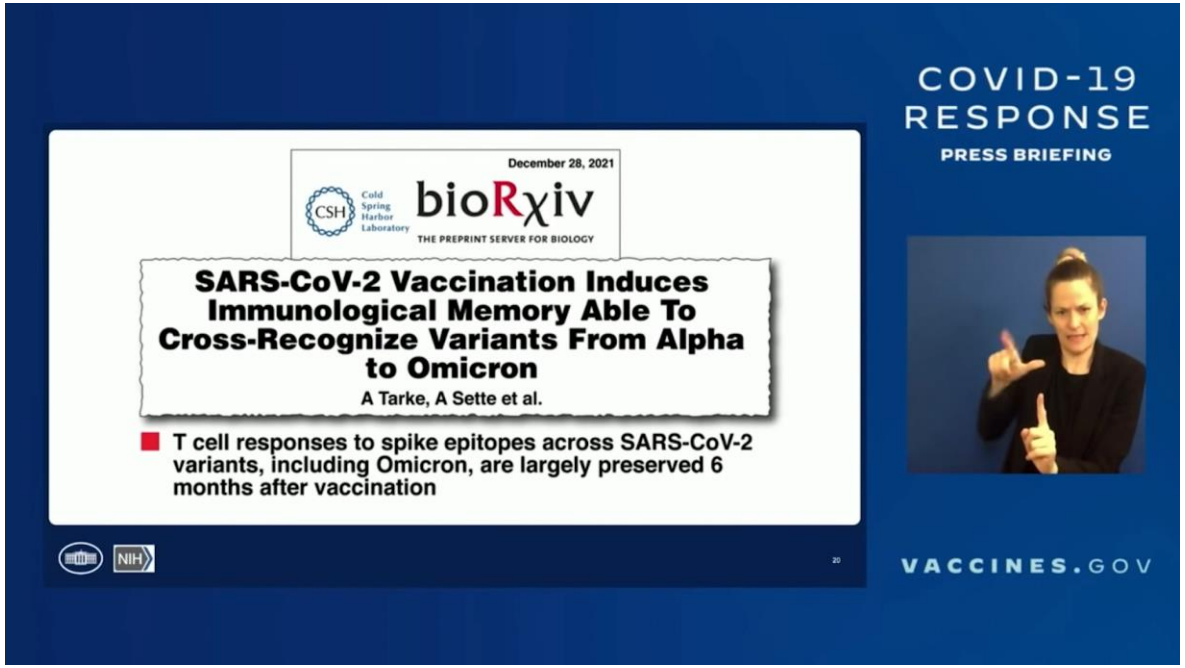


The majority of mutated CD8+T cell epitopes in Omicron are still able to bind HLA class I molecules

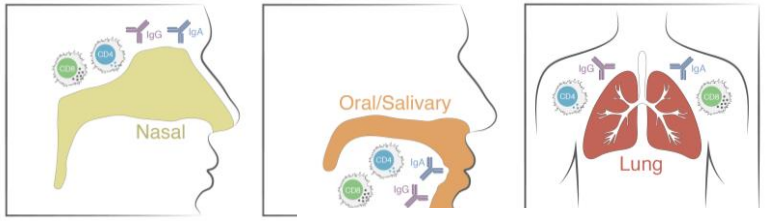




Tarke A et al, Grifoni and Sette. Cell. Jan 2022 PMID:35139340



- ❑ Keeton et al., Nature 2022; South Africa
- ❑ GeurtsvanKessel et al.,2022 Sci Imm; Netherlands
- ❑ Gao et al., Nat Med 2022; Sweden
- ❑ Madelon et al., JAMA Neur 2022; Switzerland



Unvaccinated

Asymptomatic | Pauci-symptomatic | Cold-like | Flu-like | Hospitalized | ICU | Fatal

Vaccinated

Infection

Recent/ wild type

No Infection

Infection

6 months Ago/ variants

No Infection

Asymptomatic | Pauci-symptomatic | Cold-like | Flu-like | Hospitalized

Infection

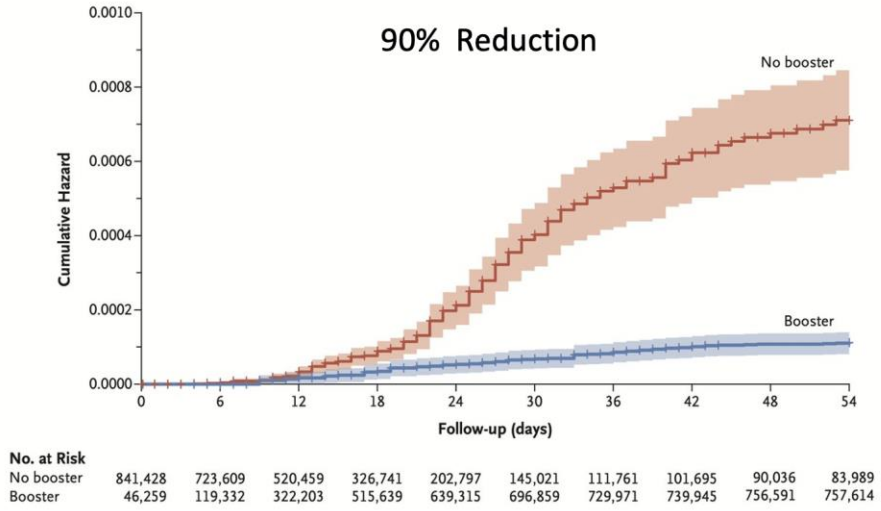
Boosted

No Infection

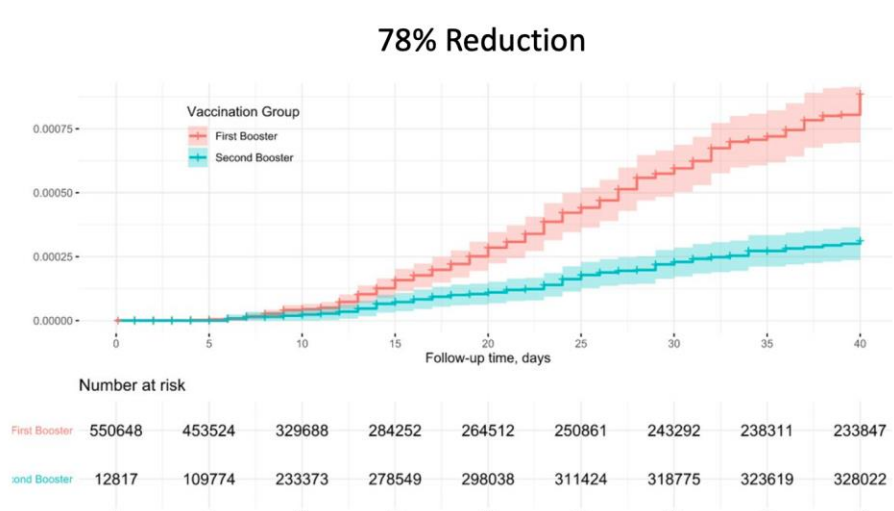
Thoughts on booster vaccination (4th dose) authorized in USA for over 50

Mortality Reduction at Calit Health for Initial Booster and Second Booster

3rd shot vs 2 shots, age 50+



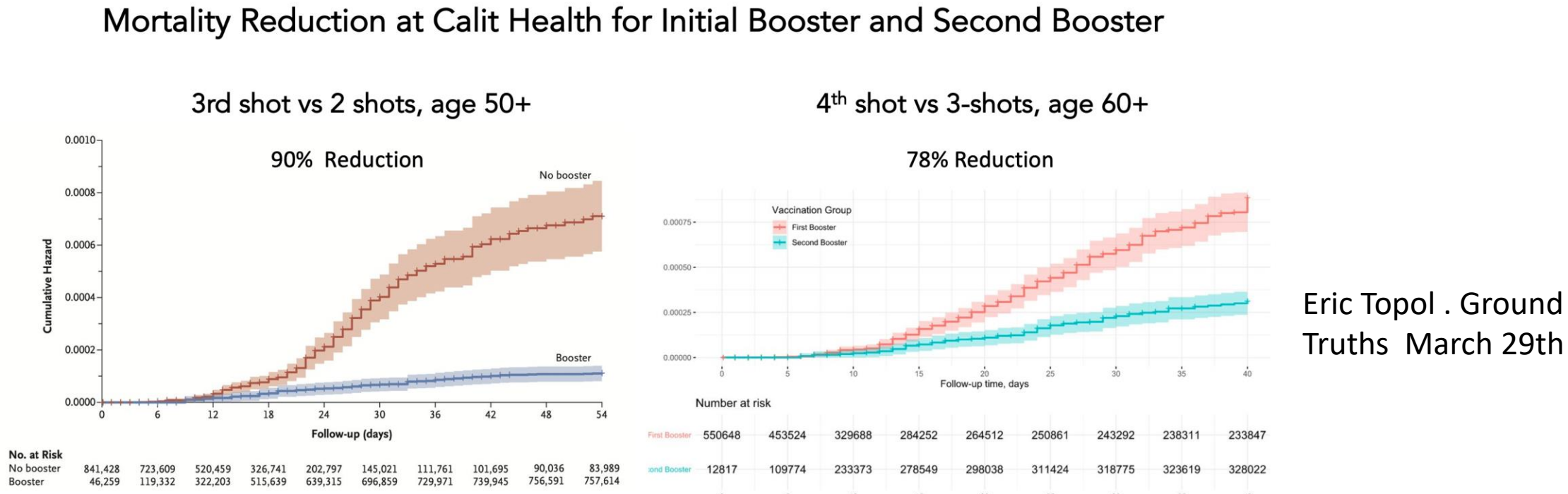
4th shot vs 3-shots, age 60+



Eric Topol . Ground Truths March 29th

- Israeli studies show positive effects of a 4th immunization in the older age (Pzifer vaccine).
- However:
  - 3 immunizations already protect well from hospitalization and deaths, and short follow up are limitations
  - Antibodies levels restored to peak levels observed after the 3d shot.
  - No measure of T cell and B cell memory.
- Antibody titers contract more rapidly than cellular immunity, which tends to be more stable
- Still need to address long term effects on disease; we might be approaching a stage of limited returns on further immunizations.

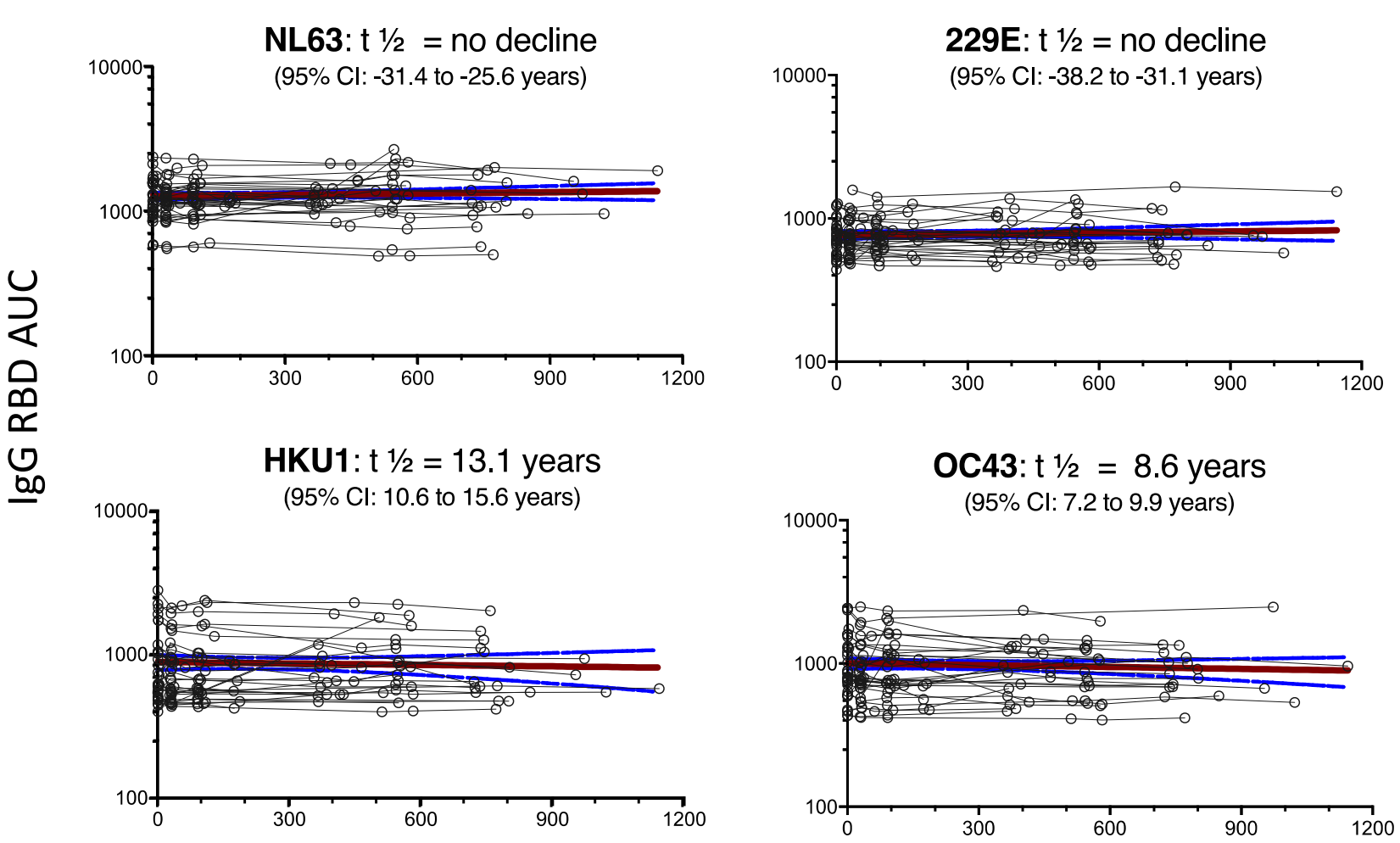
Thoughts on booster vaccination (4th dose) authorized in USA for over 50



Eric Topol . Ground Truths March 29th

- Still there is value in the approval of the 4th immunization
  - new variants can dramatically alter the situation
  - protection offered by the third immunization might wane over time. particularly antibodies in older people.
- The authorization offers an important additional tool to manage the pandemic.
- In the current situation there is a continued need to monitor infections, hospitalizations and variants.

Where are we going? IgG CCC titers are sustained over the years





Immunological memory to Common Cold Coronaviruses assessed longitudinally over a three-year period. bioRxiv. March 2022. PMID: 35262082

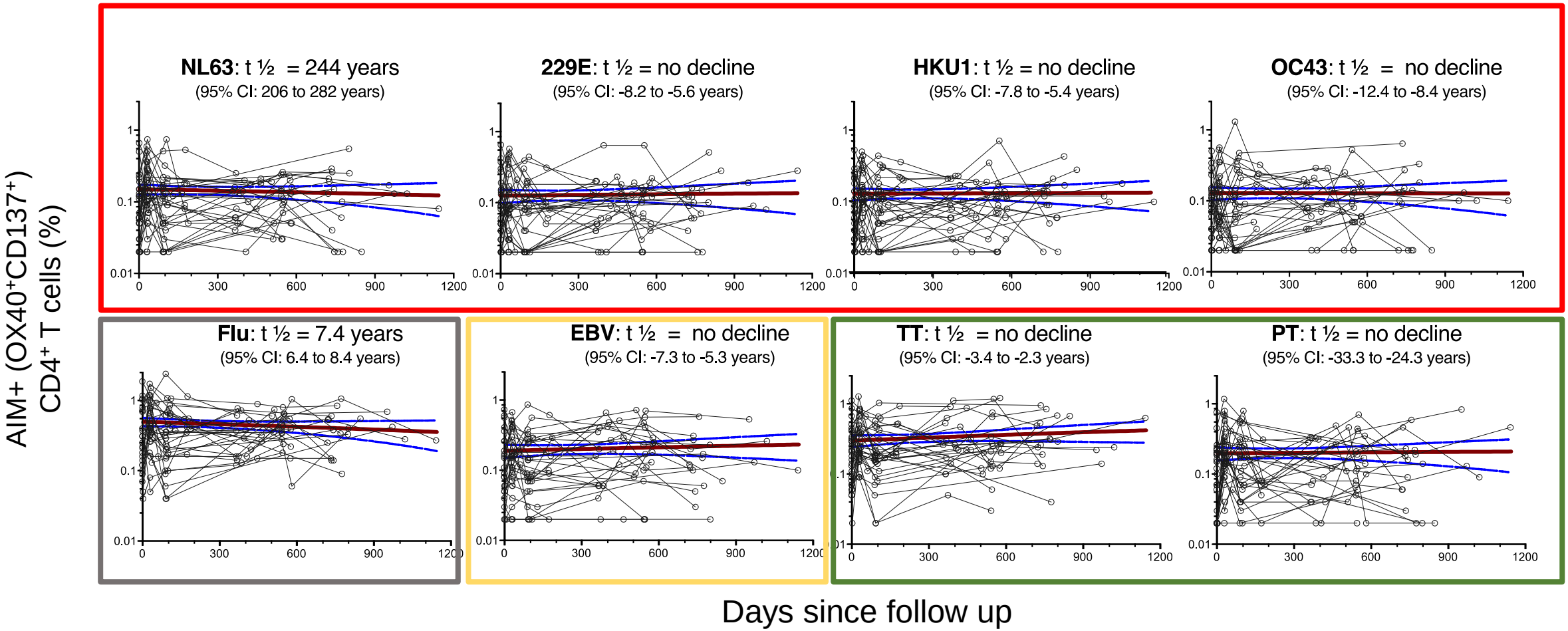


Ricardo Da Silva Antunes, PhD



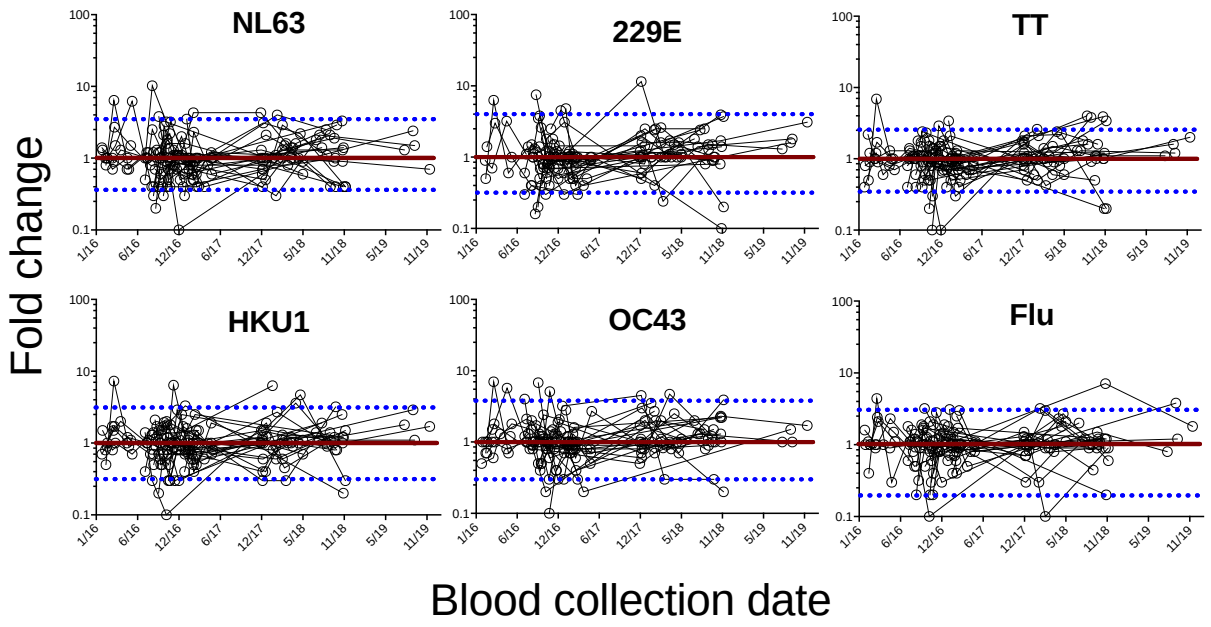
Esther Yu Dawan, MD

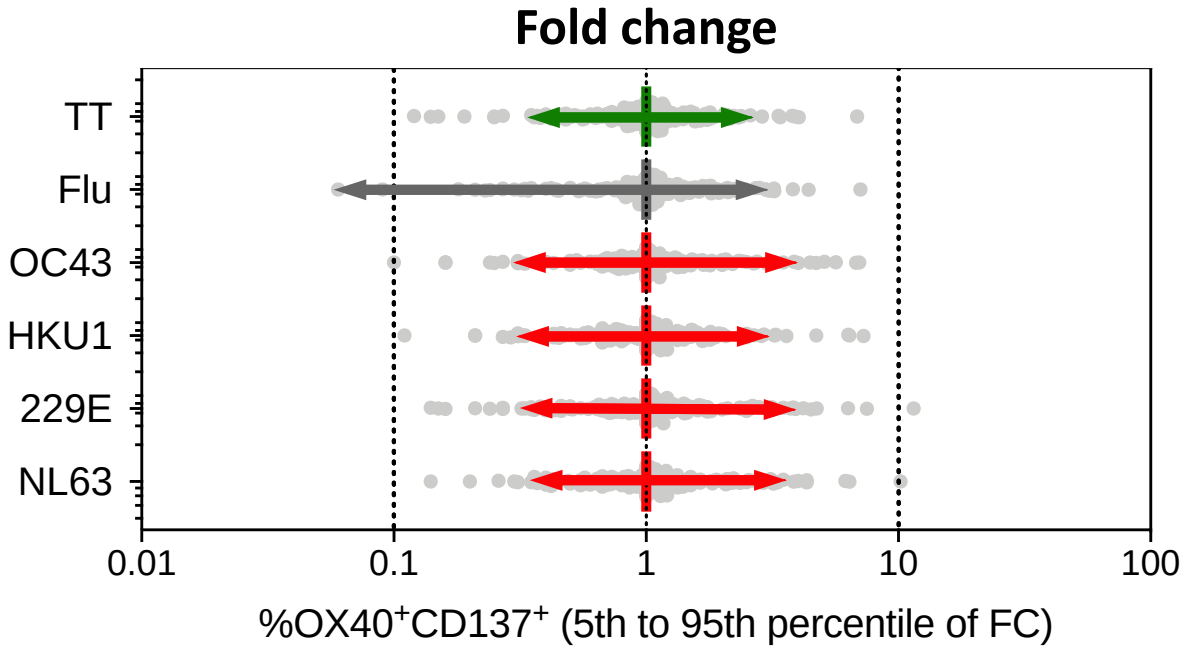
CD4+ T cell responses are also sustained over time



CCC ranges of fluctuation are similar to TT and Flu

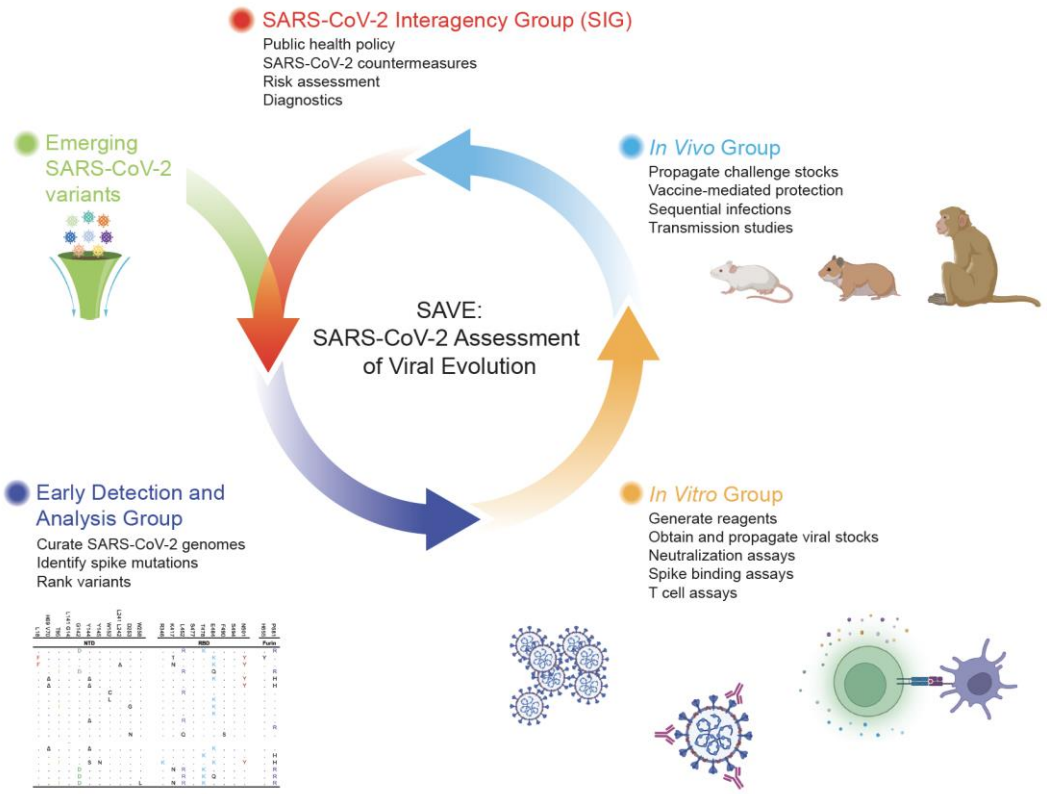
- ”Sustained” CCC responses could be reflective of short lived responses and frequent re-infections
  - In this case we would expect relatively wide fluctuations
- Comparison to TT (infrequent re-exposure), and influenza (frequent vaccination/re-exposure)
- Determined the range of fluctuation of CD4+ T cell responses
  - Normalized response for each donor and calculated 5^{th}-95^{th} percentile range

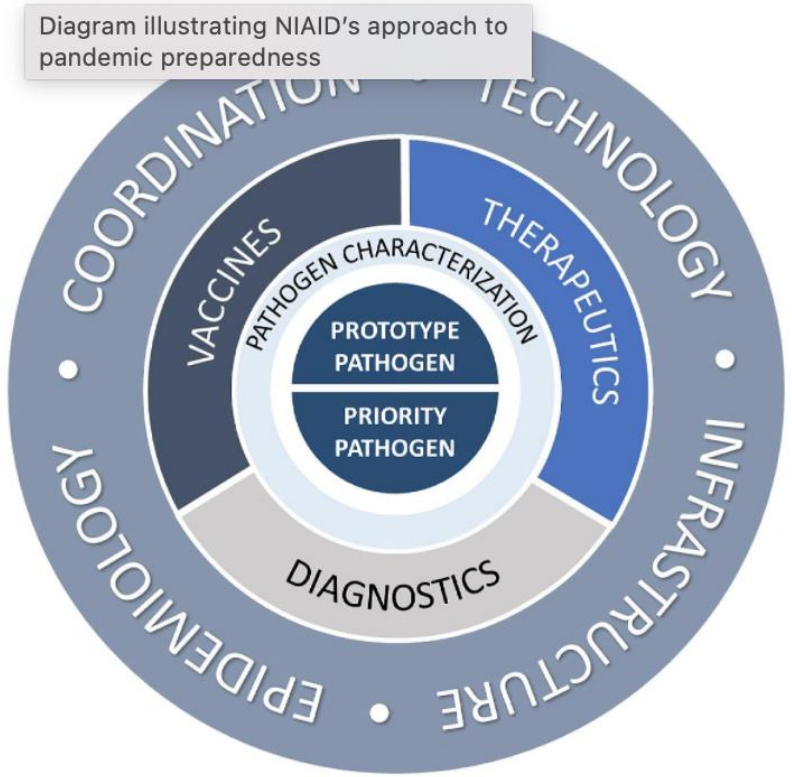




Pandemic preparedness. Against variants, and beyond SARS CoV2

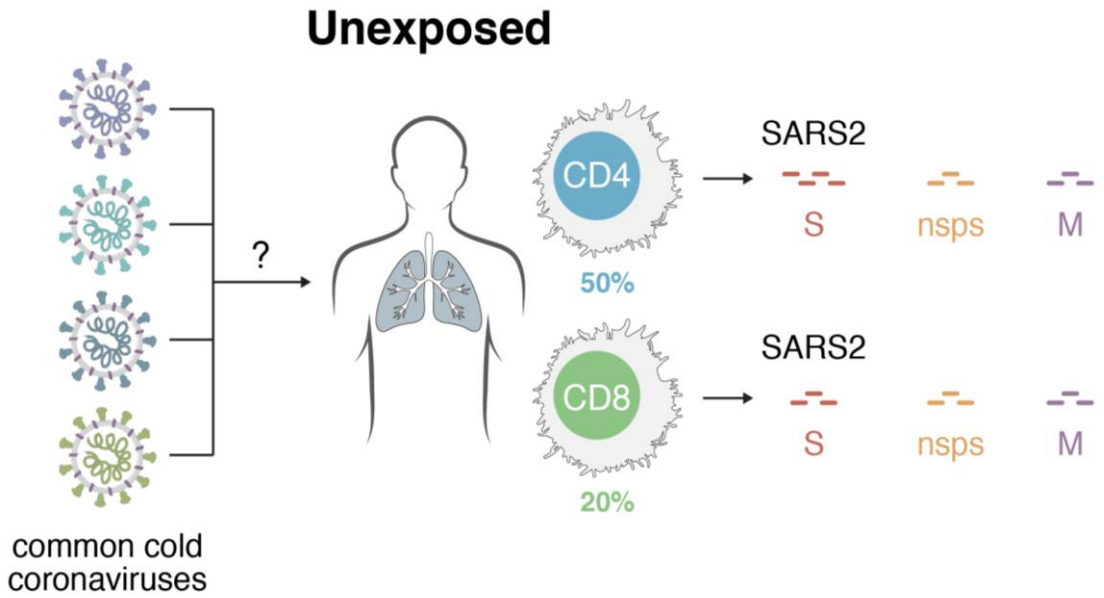
Figure 1

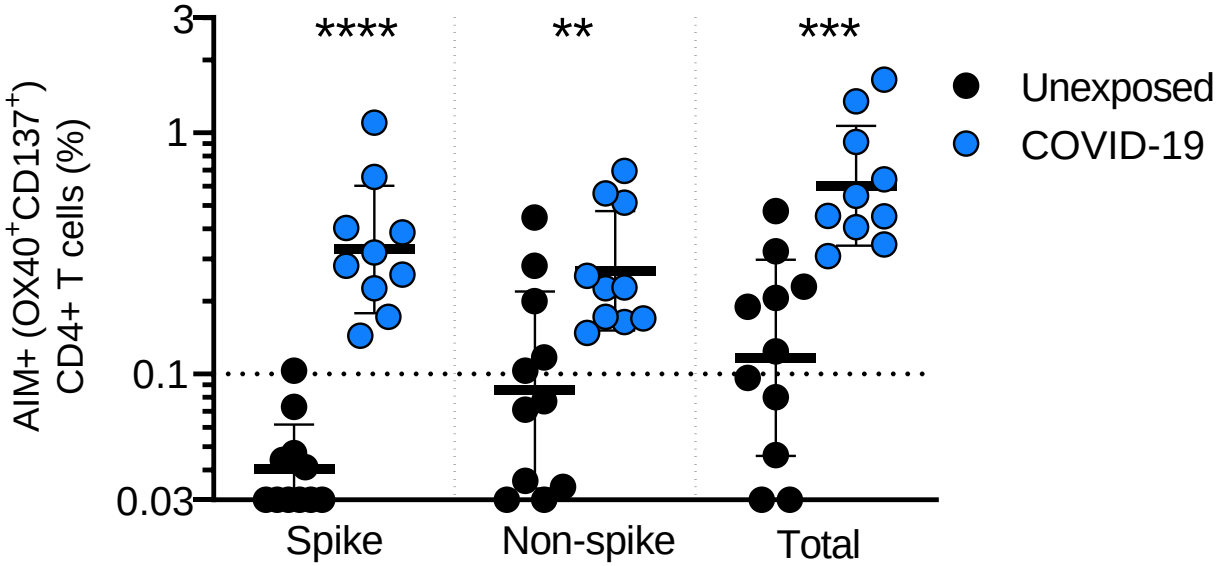




NIAID's approach to pandemic preparedness. *NIAID*

Reactivity is also detected in non-exposed individuals





- Pre-existing immunity could
  - influence the disease severity of subsequent SARS-CoV-2 infection
  - influence the outcome of SARS-CoV-2 vaccination

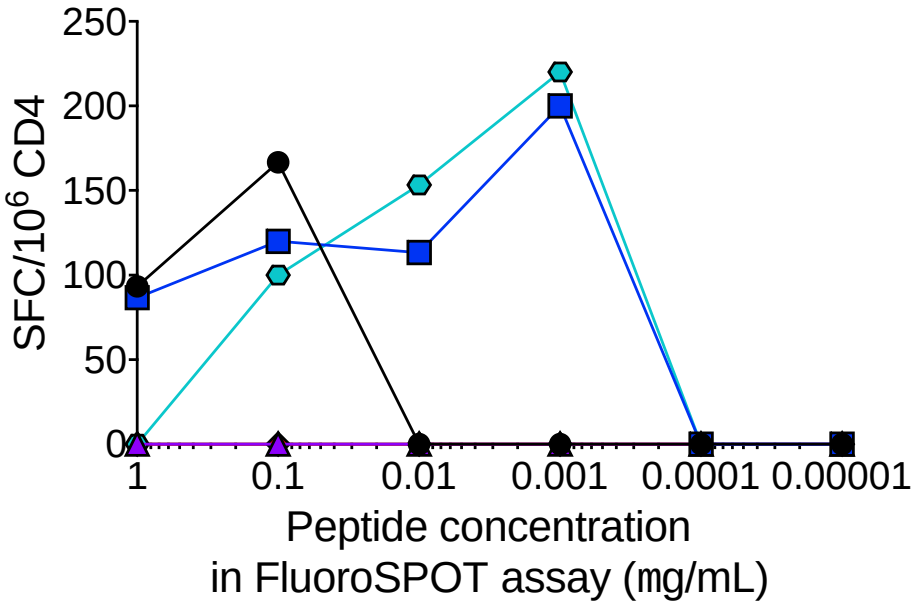


Alba Grifoni, PhD

Grifoni et al., Cell May 2020

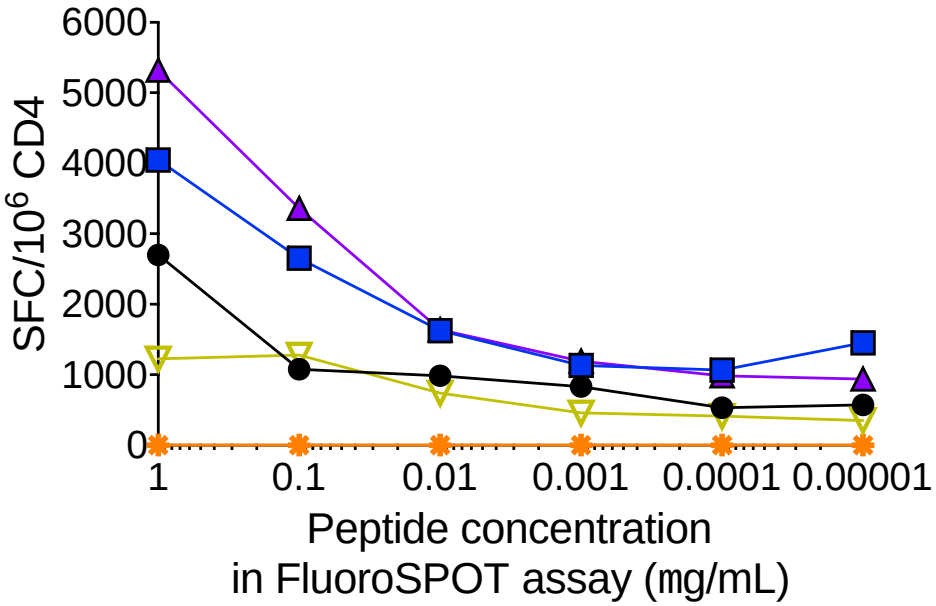
Widespread evidence of cross-reactive T cell responses within coronaviruses

P67 (nsp8)



SARS-CoV-2	VLKKLKKSLNVAKSE	100
229E	IIKQLKKAMNVAKAE	60
HKU1	QIKQLEKACNIAKSV	47
NL63	LIKQLKRAMNIAKSE	53
OC43	QLKQLEKACNIAKSA	53

P43 (nsp13)



SARS-CoV-2	NVNRFNVAITRAKVG	100
229E	NANRFNVAITRAKKG	87
HKU1	NVNRFNVAITRAKKG	93
MM3-1	NVNRFNLAITRAKKG	87
MM3-3	NVNRFNVAITRARKG	87



Jose Mateus, PhD

Mateus et al., Science, August 2020

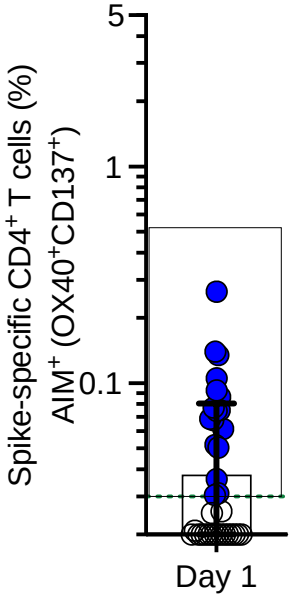
Preexisting immune memory effect on low dose Moderna mRNA-1273 COVID-19 vaccine responses

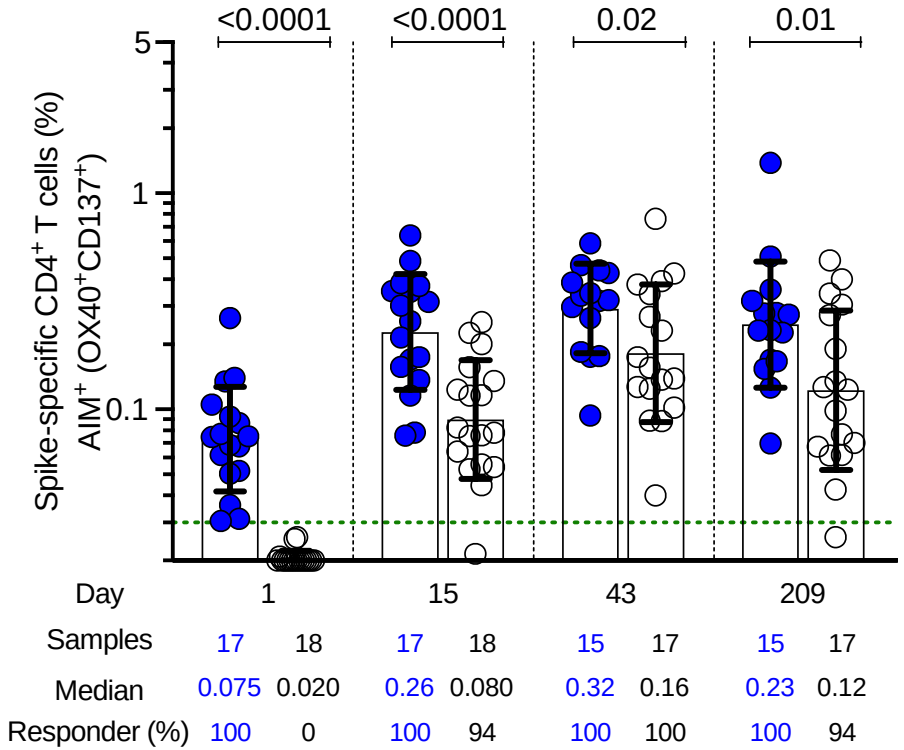


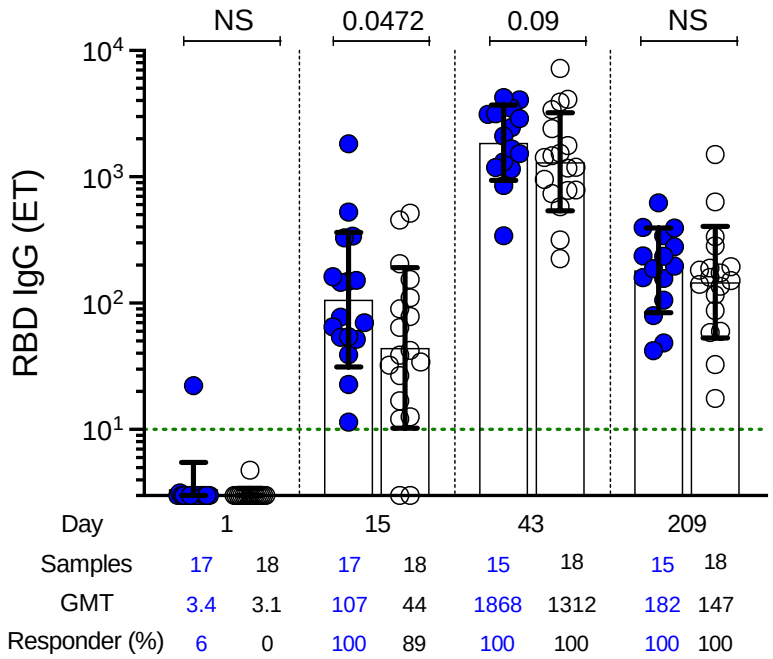




Asst. Prof.
Daniela Weiskopf







Mateus et al; Science, Sept 2021

Further evidence of cross-reactive T cells roles in prevention of symptomatic COVID-19

RESEARCH ARTICLE | CORONAVIRUS

Cross-reactive CD4+ T cells enhance SARS-CoV-2 immune responses upon infection and vaccination

LUCIE LOYAL, JULIAN BRAUN, LARISSA HENZE, BEATE KRUSE, MANUELA DINGELDEY, ULF REIMER, FLORIAN KERN, TATJANA SCHWARZ, MAIKE MANGOLD, [...] CLAUDIA GIESECKE-THIEL +28 authors Authors Info & Affiliations

SCIENCE • 8 Oct 2021 • Vol 374, Issue 6564 • DOI: 10.1126/science.abh1823

The Journal of Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2 infection

Comment on this paper

Leo Swadling, Mariana O. Diniz, Nathalie M. Schmidt, Oliver E. Amin, Aneesh Chandran, Emily Shaw, Corinna Pade, Joseph M. Gibbons, Nina Le Bert, Anthony T. Tan, Anna Jeffery-Smith, Cedric Tan, Christine Y. L. Tham, Stephanie Kucyowicz, Gloryanne Aidoo-Micah, Joshua Rosenheim, Jessica Davies, Melanie P. Jensen, George Joy, Laura E McCoy, Ana M Valdes, Lucy van Dorp, Daniel M. Altmann, Rosemary J. Boyton, Charlotte Manisty, Thomas A. Treibel, James C. Moon, COVIDsortium investigators, Francois Balloux, Áine McKnight, Mahdad Noursadeghi, Antonio Bertoletti, Mala K. Maini

Differential T-Cell Reactivity to Endemic Coronaviruses and SARS-CoV-2 in Community and Health Care Workers

Ricardo da Silva Antunes,[1,a] Suresh Pallikkuth,[2,a] Erin Williams,[3,a] Esther Dawen Yu,[1] Jose Mateus,[1] Lorenzo Quiambao,[1] Eric Wang,[1] Stephen A. Rawlings,[4] Daniel Stadlbauer,[5] Kaijun Jiang,[5] Fatima Amanat,[5,6] David Arnold,[3] David Andrews,[7] Irma Fuego,[3] Jennifer M. Dan,[1,8] Alba Grifoni,[1] Daniela Weiskopf,[1] Florian Krammer,[5,9] Shane Crotty,[1,8] Michael E. Hoffer,[3,9,b] Savita G. Pahwa,[2,b] and Alessandro Sette[1,8,b]

ARTICLE
https://doi.org/10.1038/s41467-021-27674-x OPEN
Check for updates

Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts

Rhia Kundu[1,2✉], Janakan Sam Narean[1,2], Lulu Wang[1,2], Joseph Fenn[1,2], Timesh Pillay[1,2], Nieves Derqui Fernandez[1,2], Emily Conibear[1,2], Aleksandra Koycheva[1,2], Megan Davies[1,2], Mica Tolosa-Wright[1,2], Seran Hakki[1,2], Robert Varro[1,2], Eimear McDermott[1,2], Sarah Hammett[1,2], Jessica Cutajar[1,2], Ryan S. Thwaites[2], Eleanor Parker[3], Carolina Rosadas[3], Myra McClure[3], Richard Tedder[3], Graham P. Taylor[3], Jake Dunning[4,5] & Ajit Lalvani[1,2]

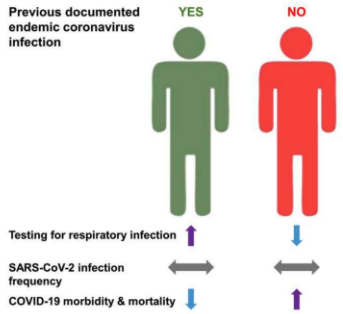
JCI The Journal of Clinical Investigation

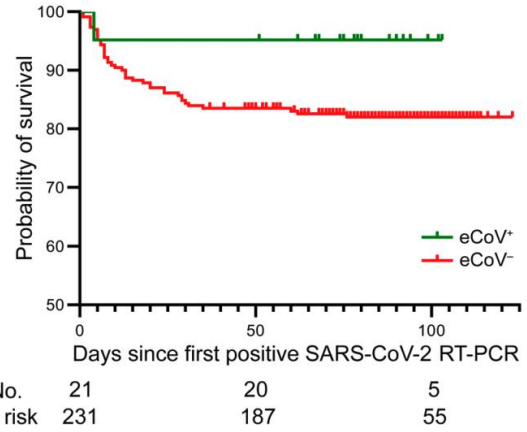
Recent endemic coronavirus infection is associated with less-severe COVID-19

Manish Sagar, ... , Laura F. White, Joseph P. Mizgerd

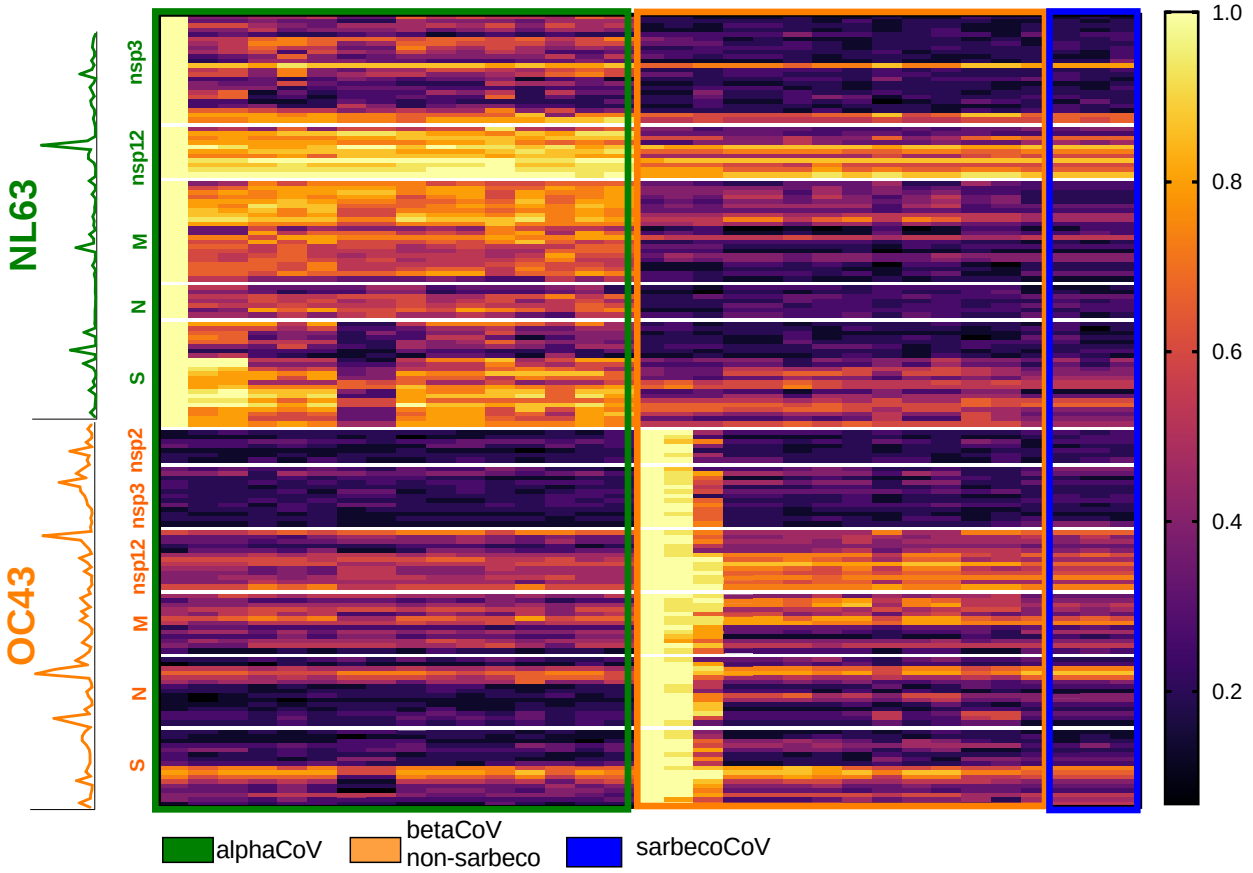
J Clin Invest. 2021;131(1):e143380. https://doi.org/10.1172/JCI143380.
Concise Communication COVID-19

Graphical abstract





Potential usefulness of cross-reactive HCoV-specific human T cells



- Cross-reactive T cell responses can modulate disease severity
- Several other coronaviruses are also of concern
- Is a ”pan-corona” or “pan-sarbeco” vaccine feasible?
- Experimentally determine epitopes/ regions that are widely crossreactive
- A T cell vaccine or vaccine component might be effective in broadly preventing severe disease and death



J. Craig Venter™ INSTITUTE



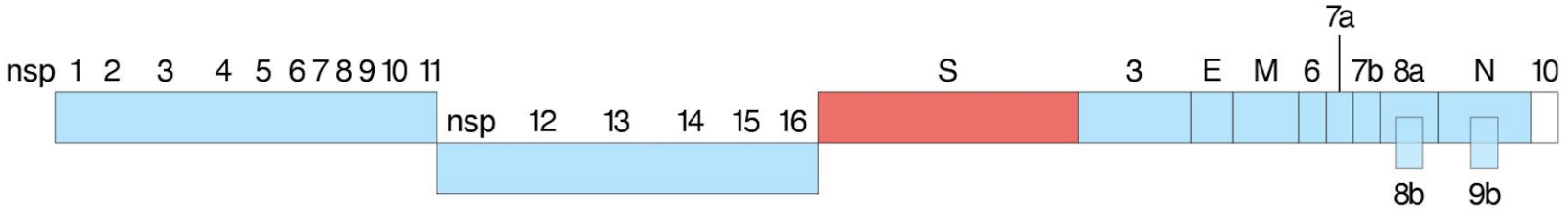
Alba Grifoni, PhD

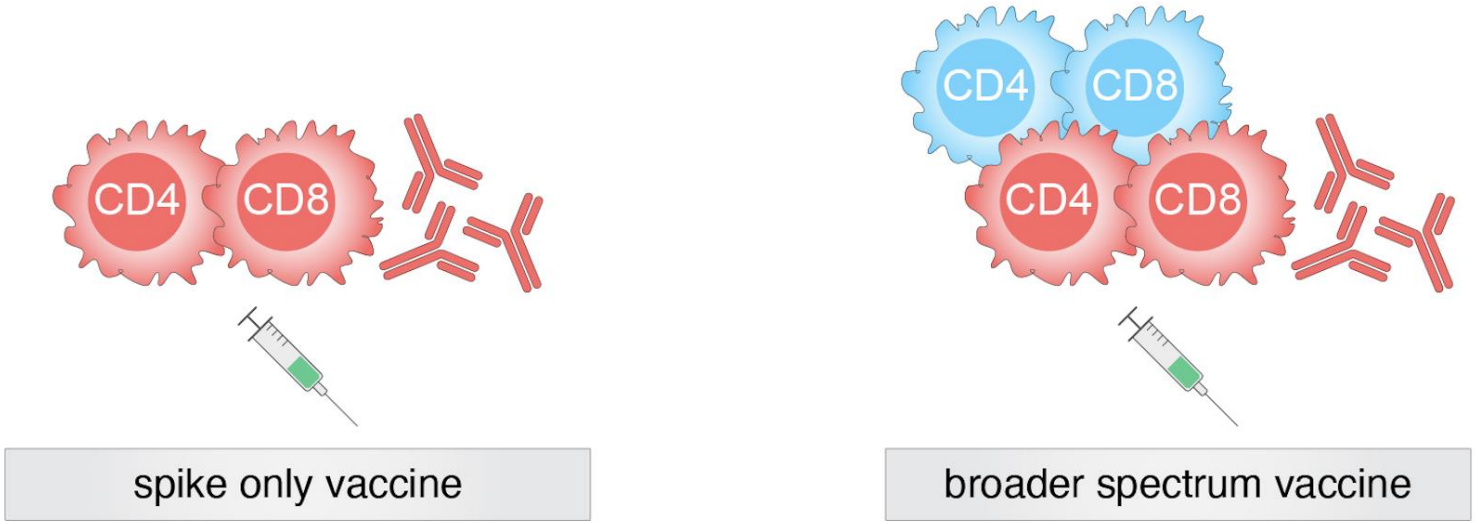


Alison Tarke

Thoughts on broadly cross-reactive T cells

- T cell inducing vaccine components as a broad concept to enhance preparedness against future possible pandemics
- Strategy could be considered for virus families of pandemic preparedness concern (Arenav, Flavi, Bunya, Paramixo, Toga, Picorna and Filioviridae)
- Not an alternative to antibody strategies, but rather synergistic

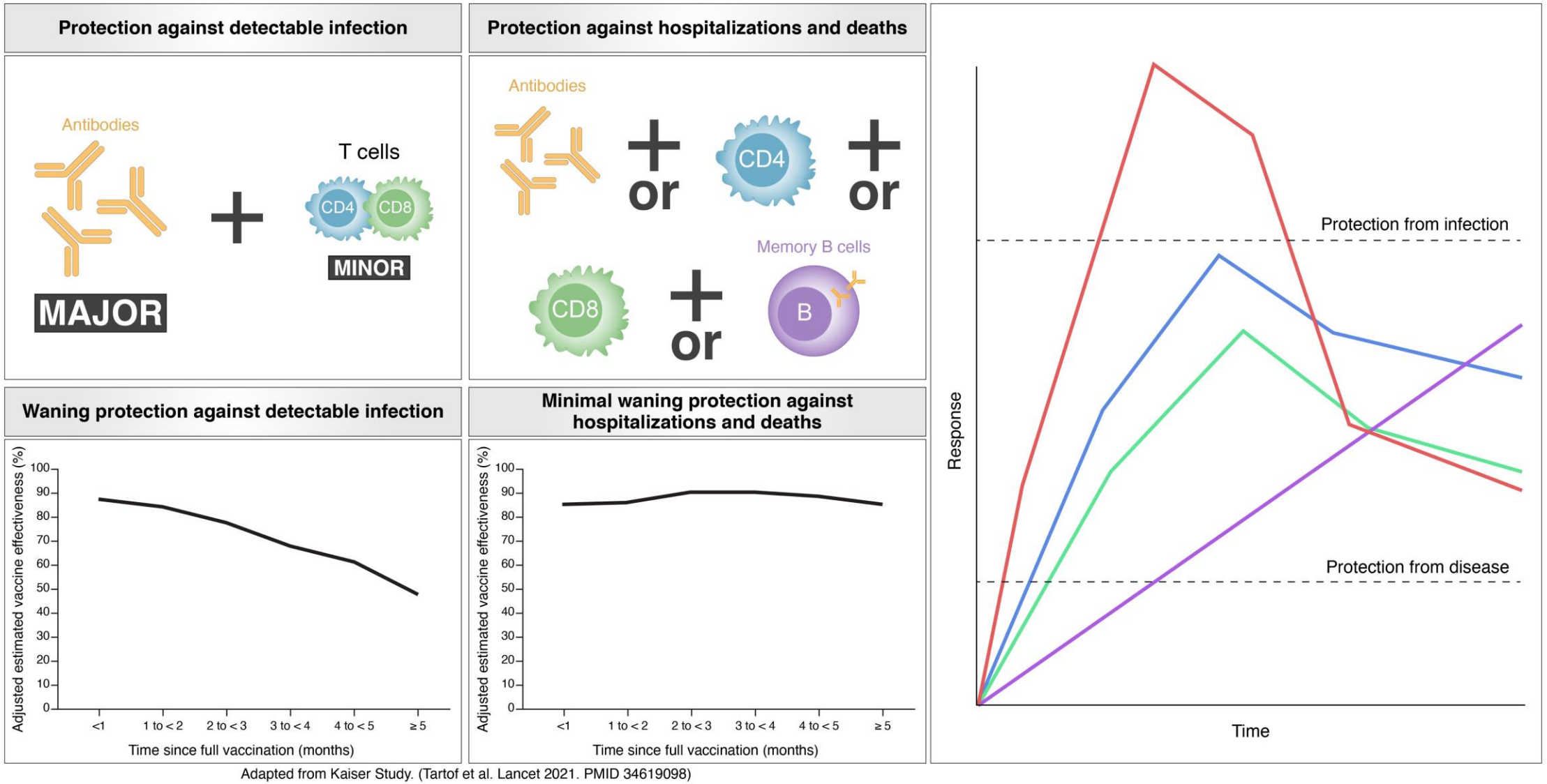




Sette and Saphire.
Immunity 2022, May 2022

Overall Conclusions

- SARS CoV2 infection induces a multispecific and multifunctional adaptive responses which is durable over the 6-8 month period
- Neutralizing antibodies likely key to protect from infection, but substantial contributions of T cells likely at the level of protection from severe disease
- Side-by-side longitudinal comparison of different vaccine platforms reveals durable B and T cell responses, and allow correlation with vaccine efficacy
- T cell reactivity is largely preserved at the level of SARS CoV2 variants, including Omicron and Delta
- CCC cross-reactivity albeit rare, is detected and has biological relevance, with potential pandemic preparedness implications
- Responses to CCC are sustained in the adult population, offering a potential glimpse in endemicity



Adapted from Kaiser Study. (Tartof et al. Lancet 2021. PMID 34619098)