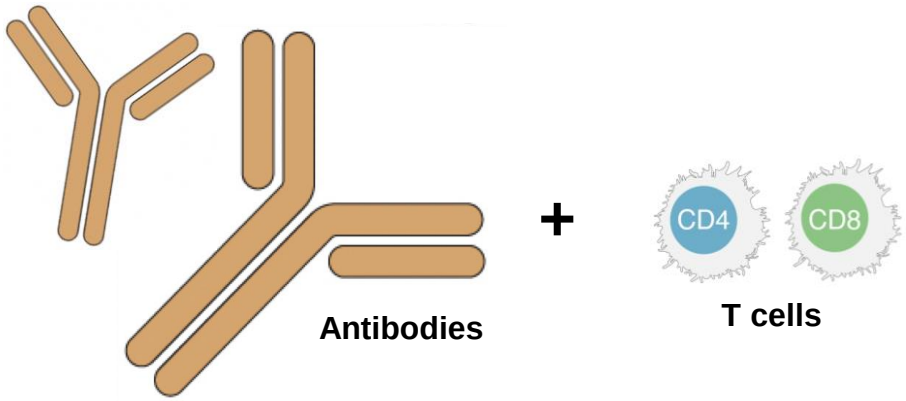
Vaccine protection against SARS-CoV-2

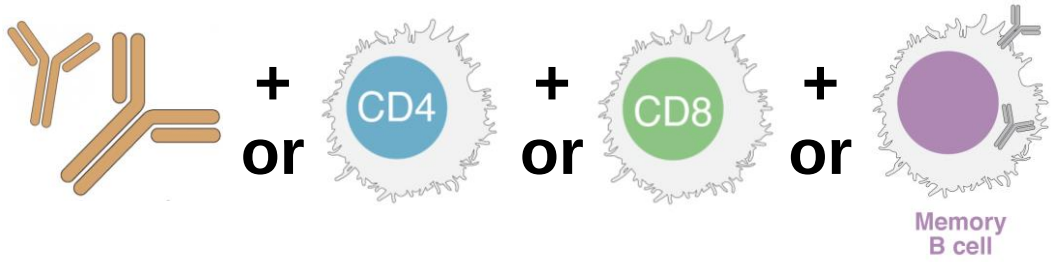
Protection against Detectable Infection



Major

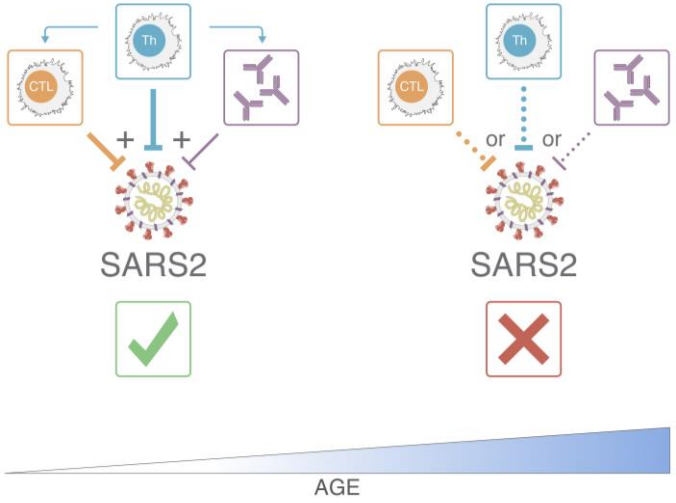
Minor

Protection against Hospitalizations & Deaths

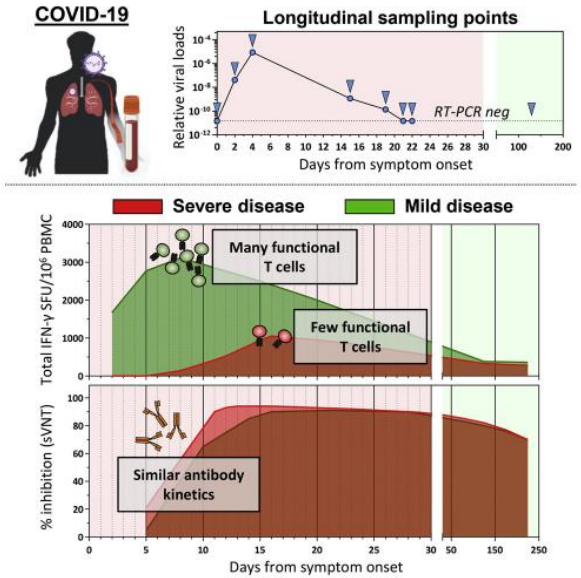


Evidence pointing to substantial protective contributions of T cells

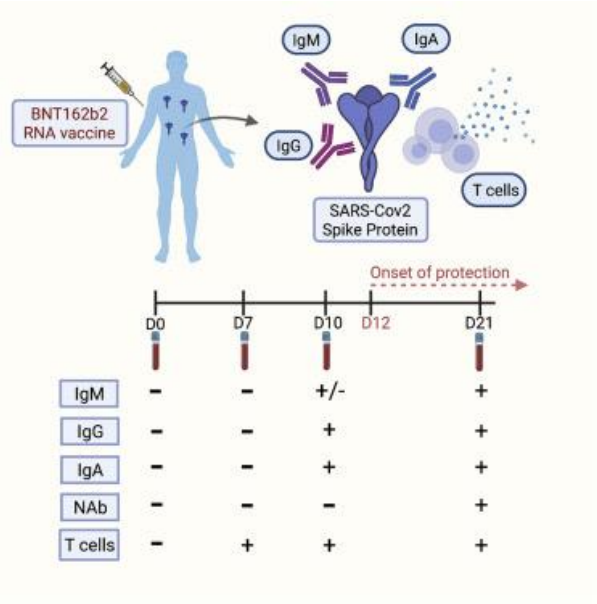
- Early T cell responses correlate with better outcomes and lower viral loads
- CD8 T cells provide control in monkeys
- Agammaglobulinemic and B cell depleted individuals
  - moderately increased risk of hospitalization with COVID-19
  - COVID-19 in ocrelizumab-treated people with MS is predominantly mild
- 1-dose of Moderna or Pfizer vaccine provided substantial protection in the absence of detectable neutralizing antibodies in most individuals



Moderbacher et al. Cell Sept 2020

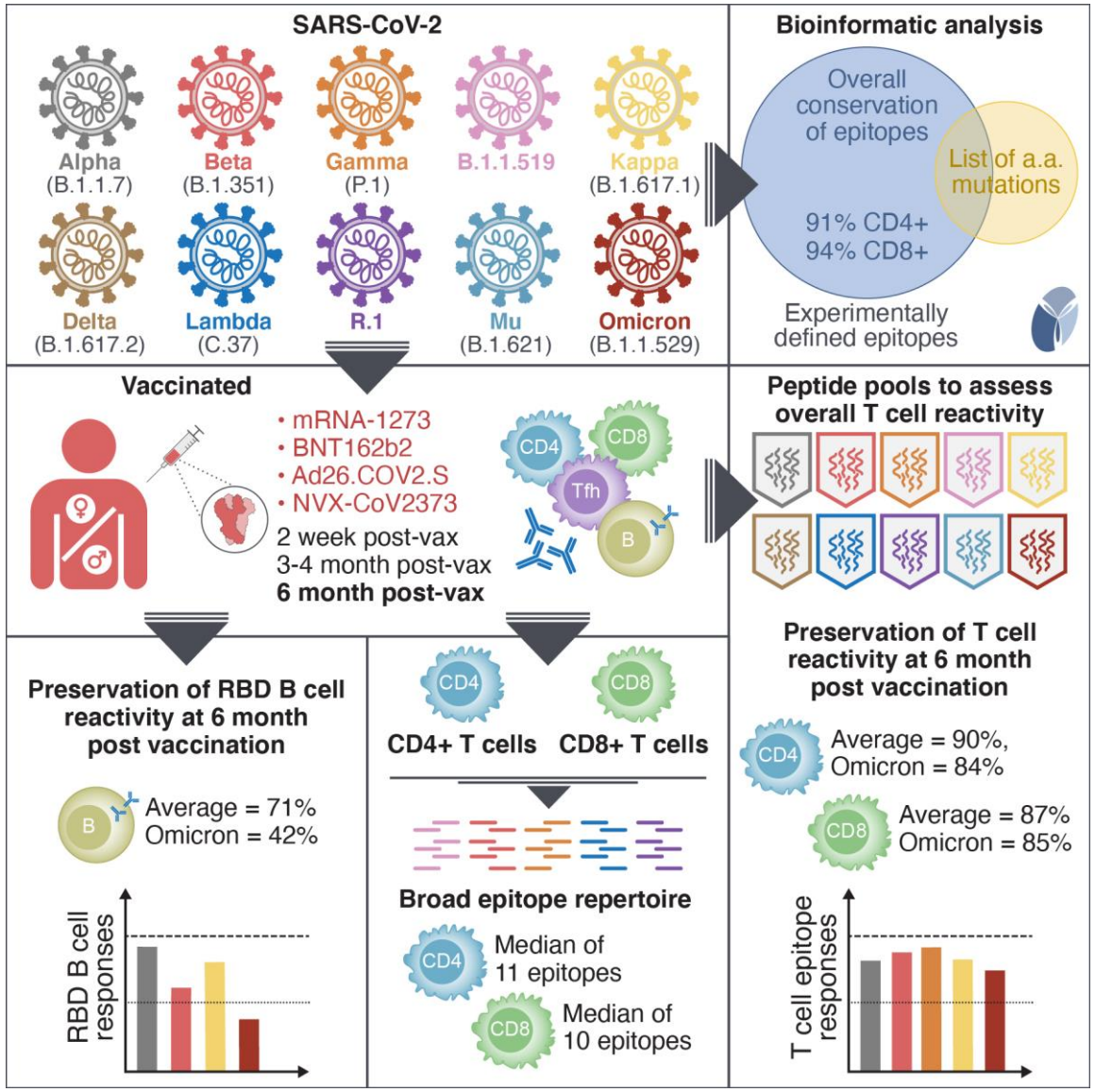


Tan et al, Cell Rep, 2021



Kalimuddin Cell Med, 2021

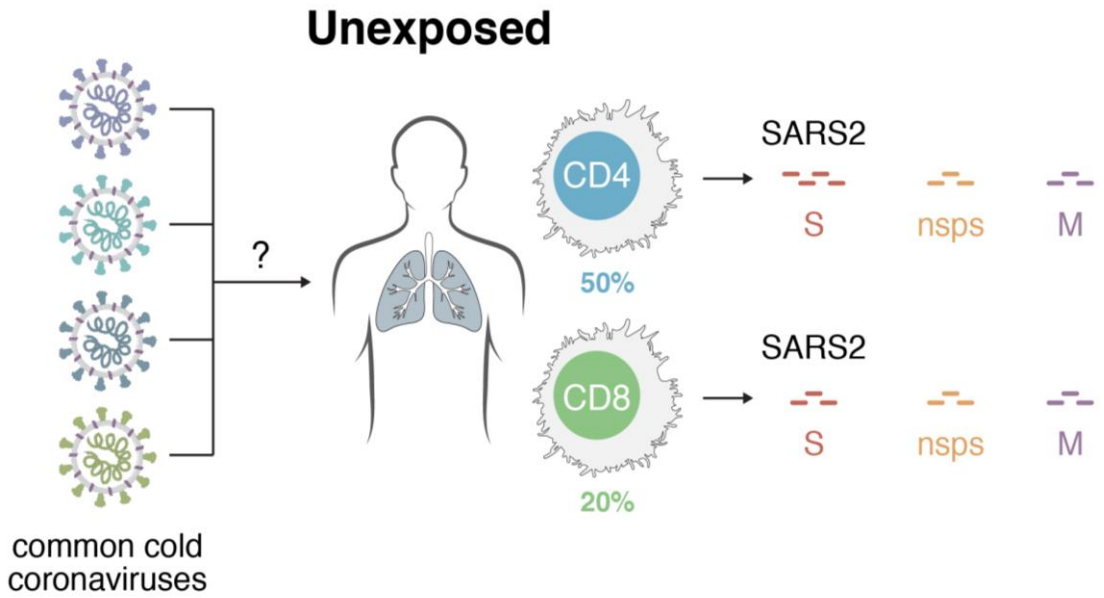
Conservation of T cell responses across SARS CoV2 variants

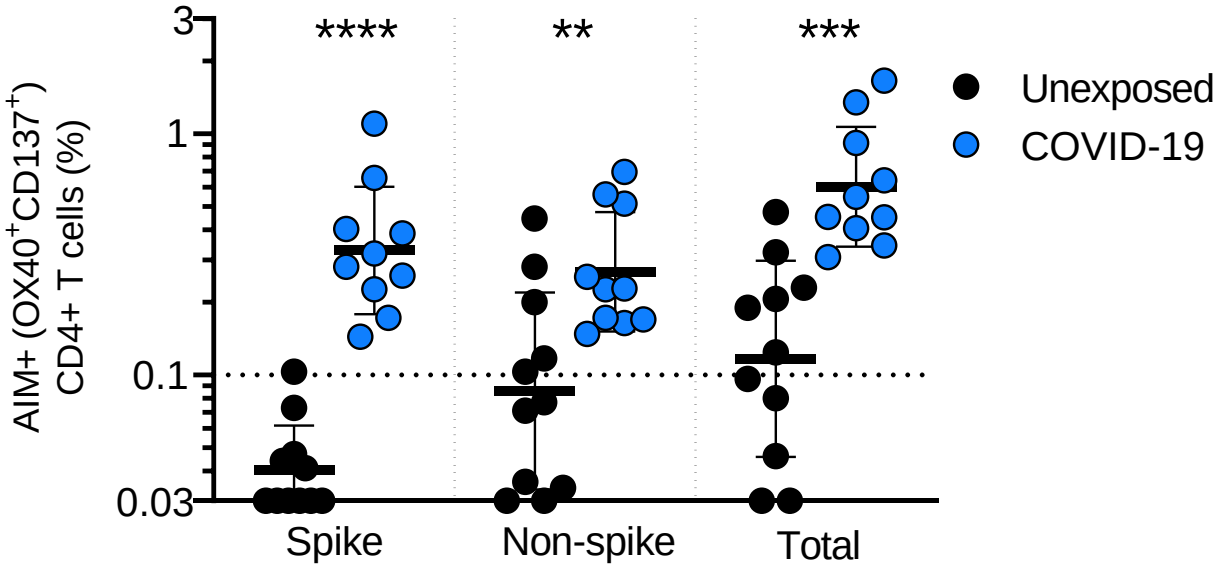


- CD4 and CD8 T cell responses largely preserved in fully vaccinated subjects for various variants (including Delta) irrespective of platform, by AIM and ICS
  - Effective recognition also after a single immunization
- Variant recognition of memory (5-6 months after vaccination) T cell responses, including Omicron
- The majority of CD4 and CD8 epitopes is fully (100%) conserved in the various variants
- The CD4 and CD8 epitope repertoire of memory T cells is broad
- Consensus is emerging demonstrating that T cell responses are largely preserved in Omicron

Tarke et al Cell 2022

Reactivity is also detected in non-exposed individuals

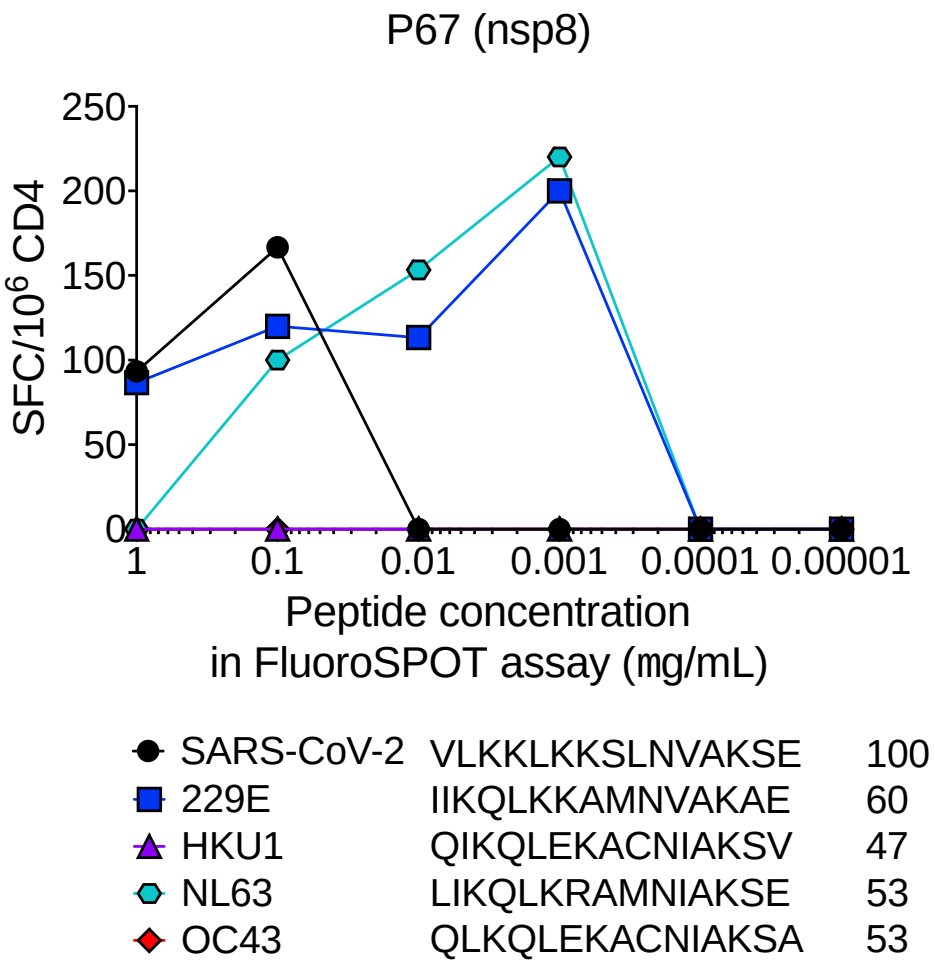


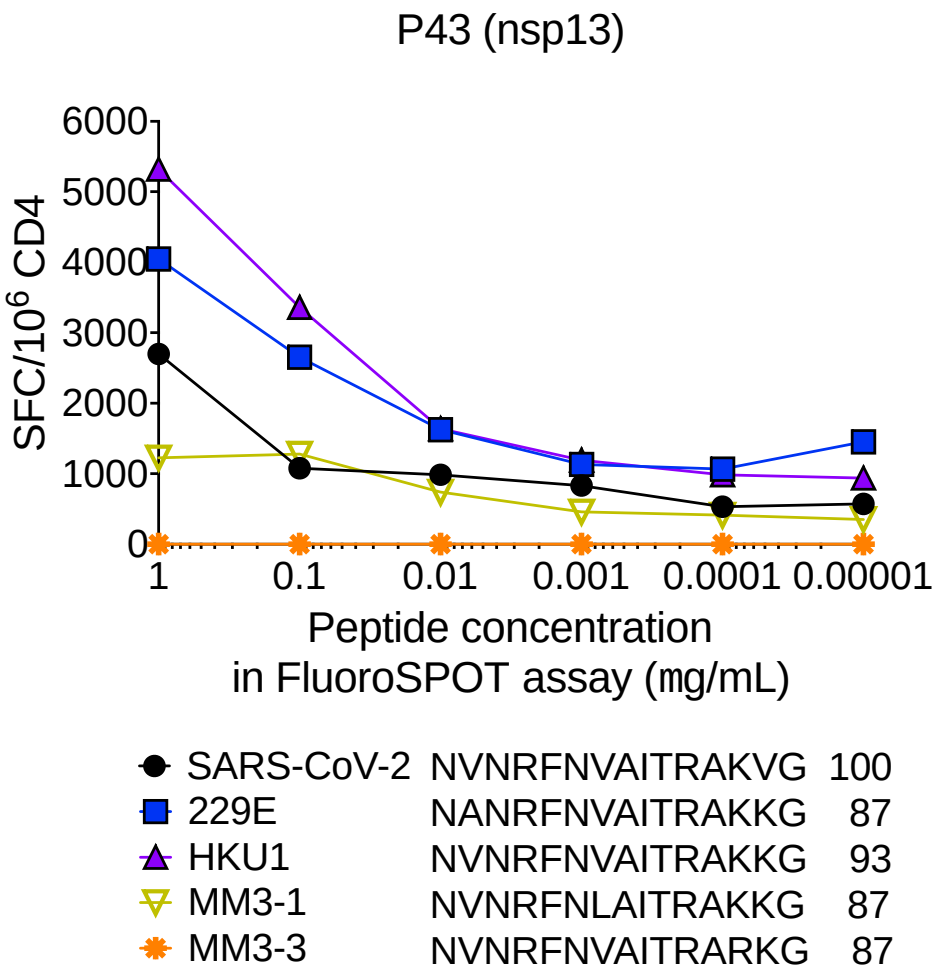


- Pre-existing immunity could
  - influence the disease severity of subsequent SARS-CoV-2 infection
  - influence the outcome of SARS-CoV-2 vaccination

Grifoni et al., Cell May 2020

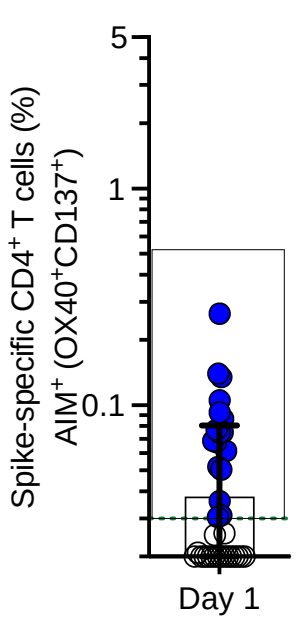
Widespread evidence of cross-reactive T cell responses within coronaviruses

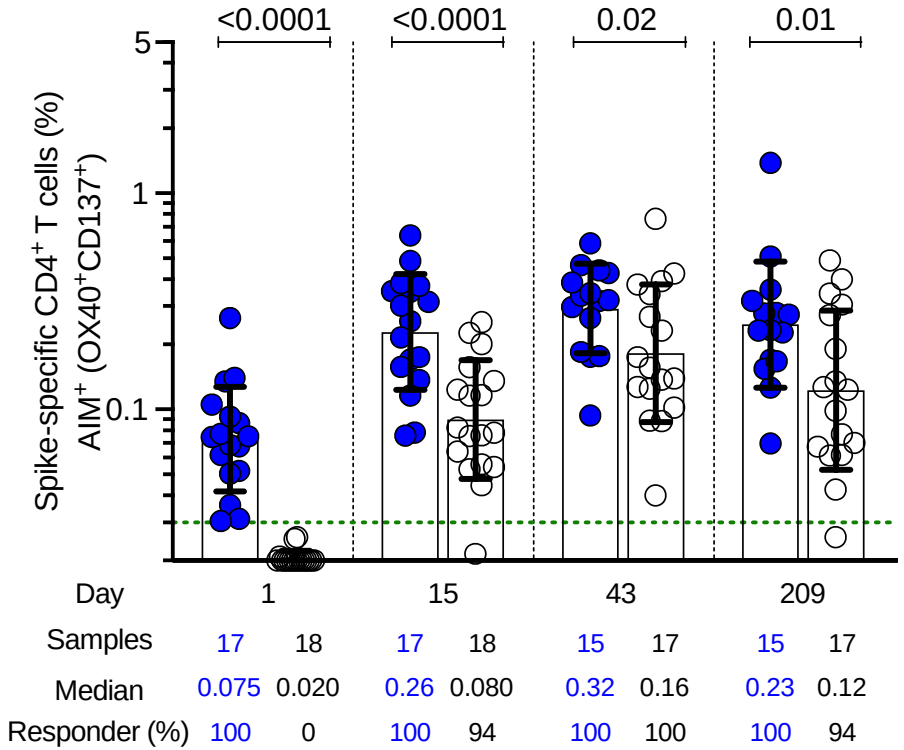


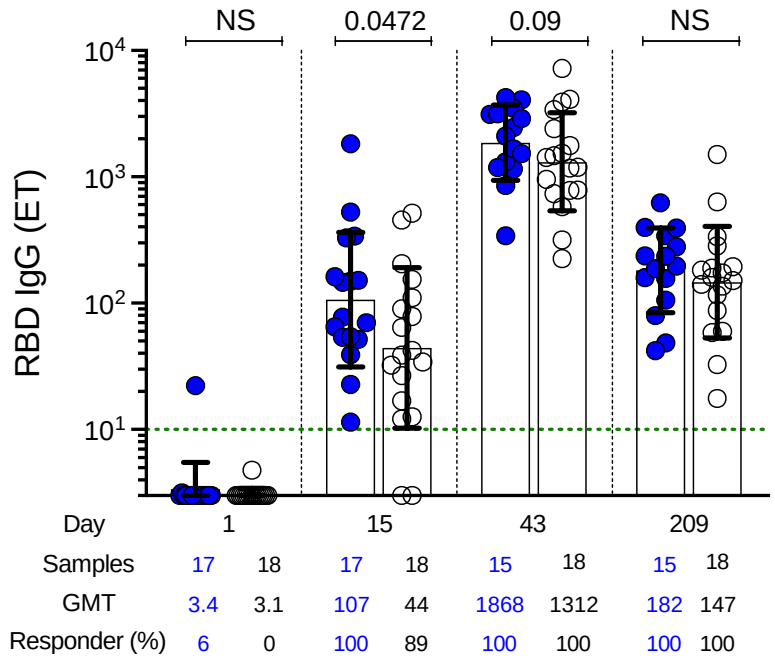


Mateus et al., Science, August 2020

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







Mateus et al; Science, Sept 2021

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

The Journal of Infectious Diseases

MAJOR ARTICLE

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,©] Shane Crotty,[1,8] Michael E. Hoffer,[3,9,b] Savita G. Pahwa,[2,b] and Alessandro Sette[1,8,b]

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

Comment on this paper

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

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

JCI The Journal of Clinical Investigation

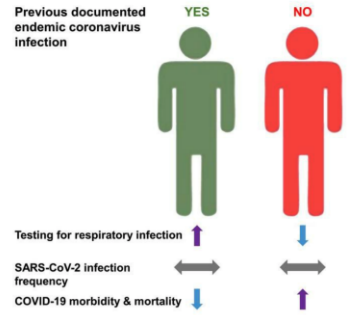
Recent endemic coronavirus infection is associated with less-severe COVID-19

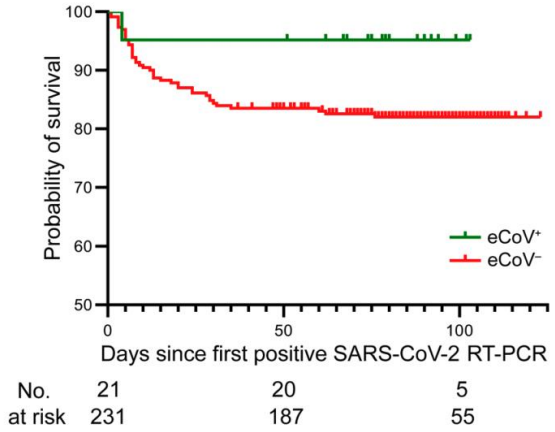
Manish Sagar, … , Laura F. White, Joseph P. Mizgerd

J Clin Invest. 2021;131(1):e143380. https://doi.org/10.1172/JCI143380.

Concise Communication COVID-19

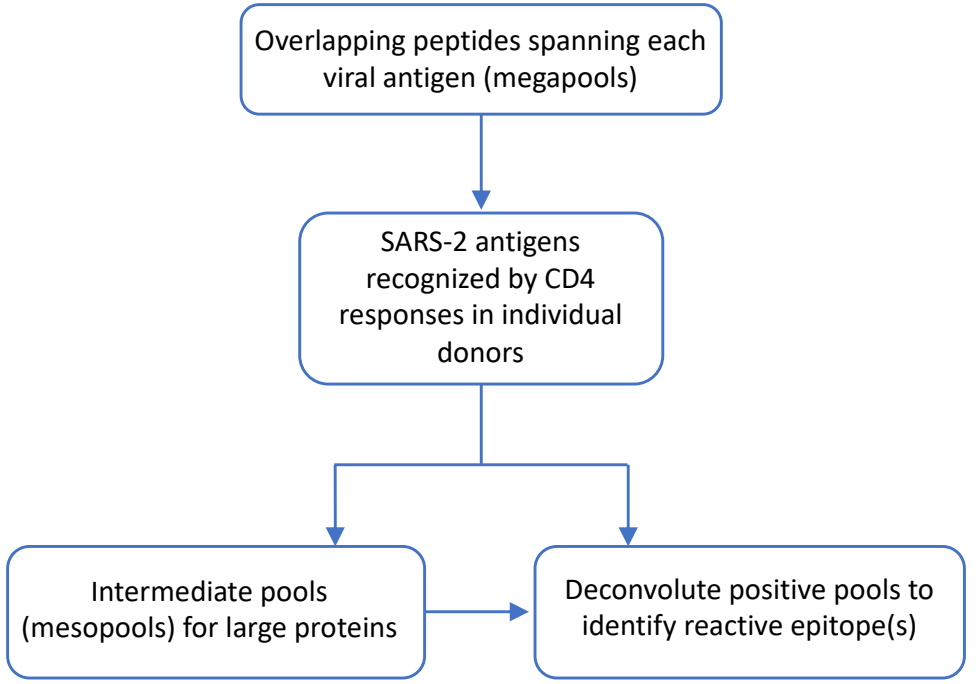
Graphical abstract





Definition of cross-reactive coronavirus T cell epitopes

- Cross-reactive T cell responses can modulate antibody responses and likely also modulate disease severity
- Several other coronaviruses are also of concern
- Is a ”pan-corona” or “pan-sarbeco” vaccine feasible?
- Map immunogenic and conserved regions in CCC
- 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



To date we identified 87 **NL63** epitopes and 79 **OC43** epitopes

Selection of representative coronaviruses for further conservation analysis

- Representative virus selection criteria:
  - Clustering based on genomic sequences
  - Sort clusters based on cluster size
  - Exclude clusters from uninteresting hosts: mouse, rat, cat, dog, cattle, horse, rabbit, swine, shrew
  - Exclude clusters with only 1 sequence
- For sarbeco, exactly 10 viruses were selected
- For alpha and beta (excluding sarbeco) groups, 15 to 16 representative viral sequences were included.
  - Since these viruses do not have consistent protein annotations more were included with the expectation that some viruses may have incomplete annotations.

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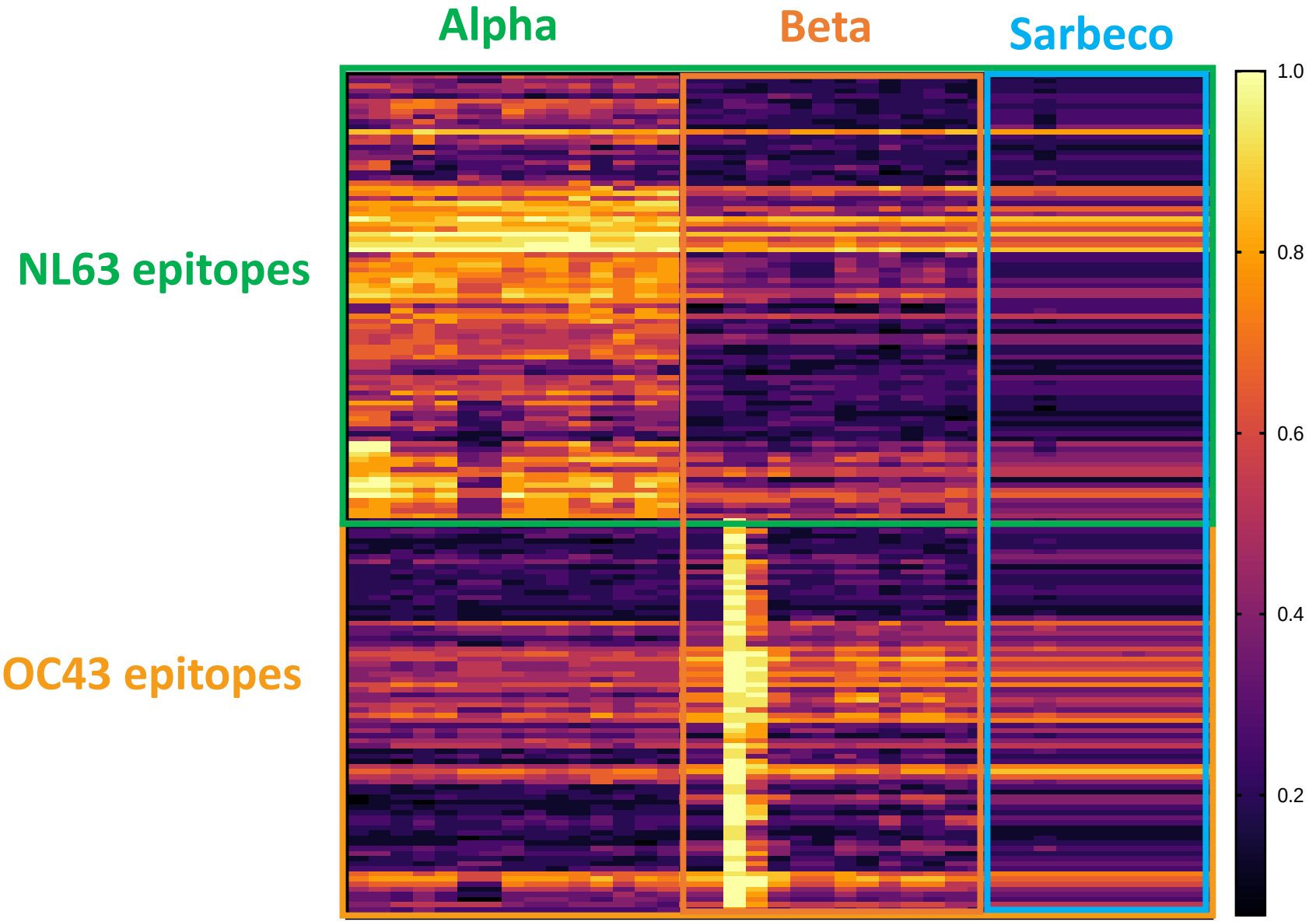
Heat maps of epitope conservation in reference sarbeco, beta and alpha coronaviruses



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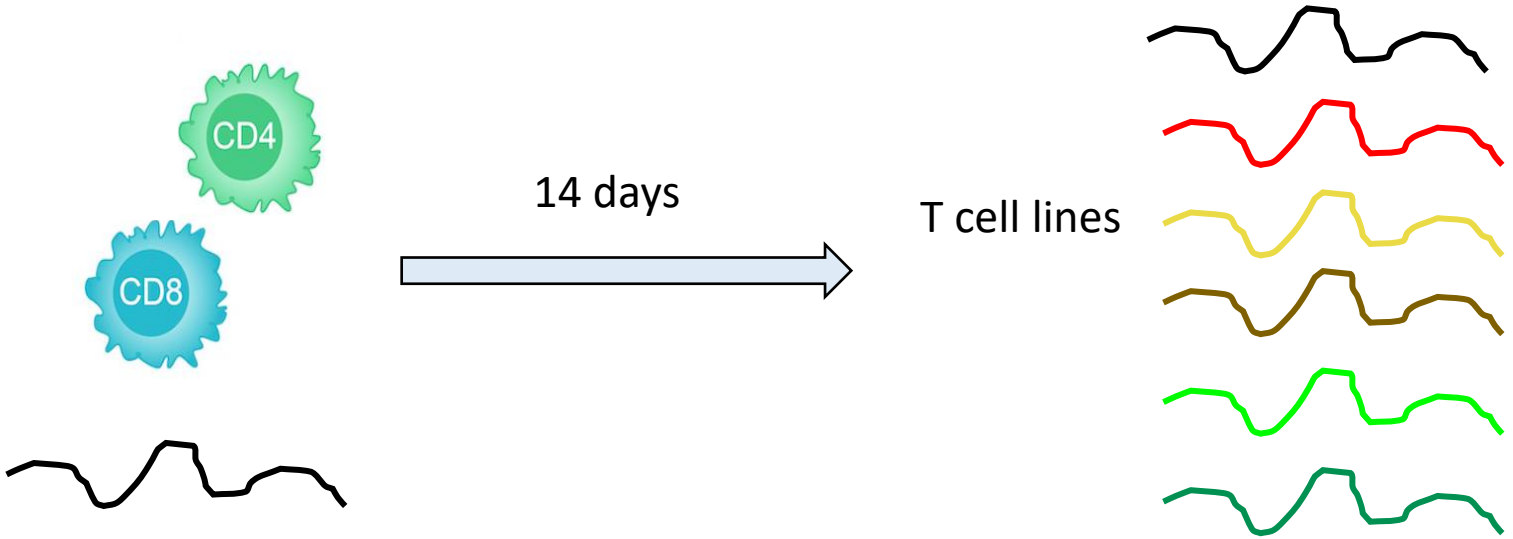
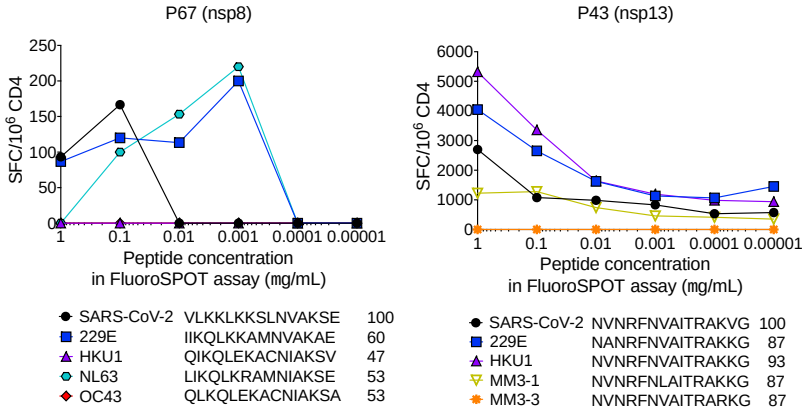
Epitope specific T cell lines to establish cross-reactivity of human T cells



Original Epitope identified



Definition of T cell epitopes broadly conserved across viral groups in other viral systems

- The human influenza T cell repertoire is broad and multispecific
  - Several studied defined HLA class I and class II epitopes consistently recognized in multiple subjects and conserved in the majority of the Flu strains
  - Immunization of HLA transgenic mice with a DNA plasmid encoding 20 different epitopes enhanced antibody responses and protected from lethal challenge
- Similar approaches defined epitopes immunogenic in humans and/or restricted by human HLA, and conserved in Old and New world Arenaviruses
- Infection with multiple DENV serotypes and vaccination with a tetravalent DENV vaccine biases responses towards conserved T cell epitopes
- DENV infection can influence T cell responses to ZIKV infection
- Crossreactivity amongst DENV, YF and ZIKV is low, but conserved epitopes mediate protection in animal models

Conclusions

- T cell inducing vaccine components as a broad concept to enhance preparedness against future possible pandemics
- T cell vaccine components might be effective in preventing severe disease for coronaviruses in general and sarbecoviruses in particular
- Several groups reported initial testing of SARS CoV2 vaccine components to broaden the spectrum of T cell reactivities (NantWorks /Immunitbio, Gritstone, Flowpharma, Walz group, Vaxxinity, and other academic groups)
- A similar strategy could be considered for several families of viruses of pandemic preparedness concern (Arenaviridae, Flaviviridae, Bunyavirales, Paramixoviridae, Togaviridae, Picornaviridae and Filioviridae)
    - Not to be seen as an alternative to antibody inducing strategies, but rather synergistic with those strategies
- A T cell inducing component could be produced, tested for safety and immunogenicity in small phase I trials, and even stockpiled, as a first line of defense from a new pandemic