Adaptive immune responses to SARS CoV2

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Life Without Disease.

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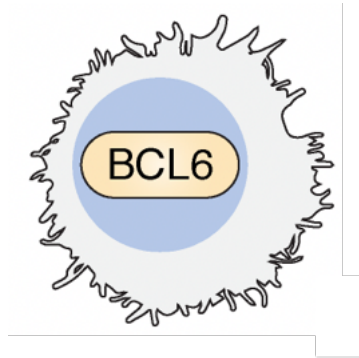PERTH WESTERN AUSTRALIA

Elizabeth Phillips
Simon Mallal

Do people develop immunity to COVID-19?
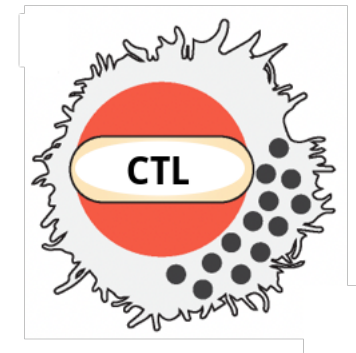
- What kind of immunity is important against COVID-19?

Antibodies
(from B cells)

Helper T cells

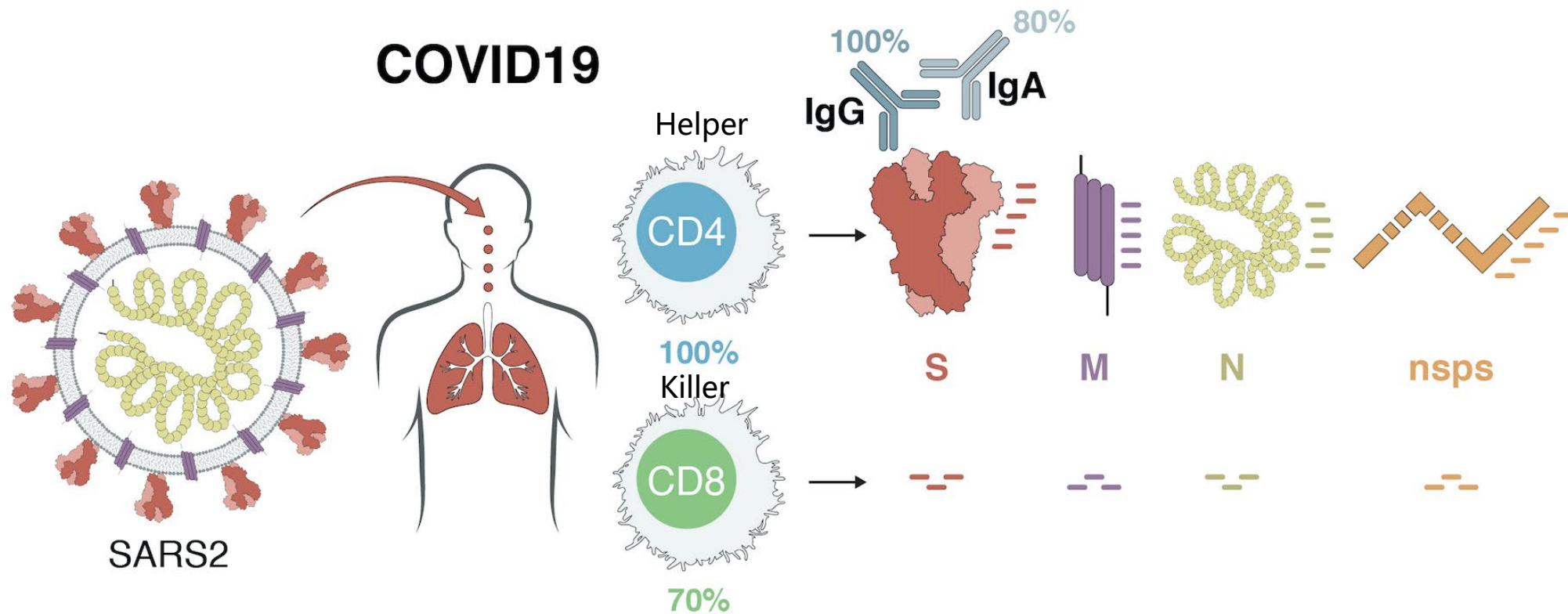Killer T cells

- Important in almost all currently licensed human vaccines

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

- Important in many viral infections
- Agammaglobulinemic individuals survive COVID19

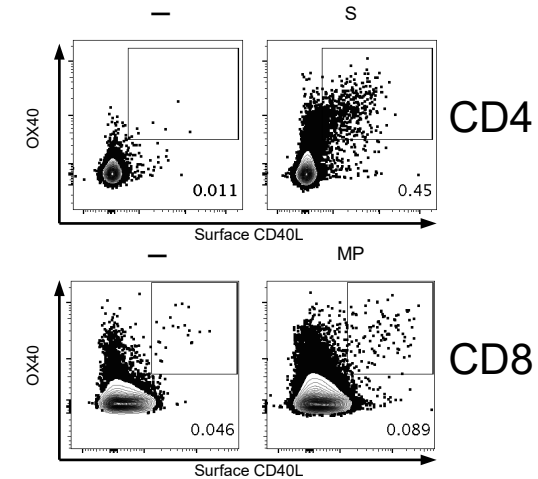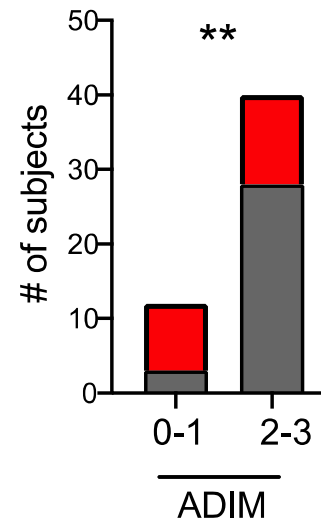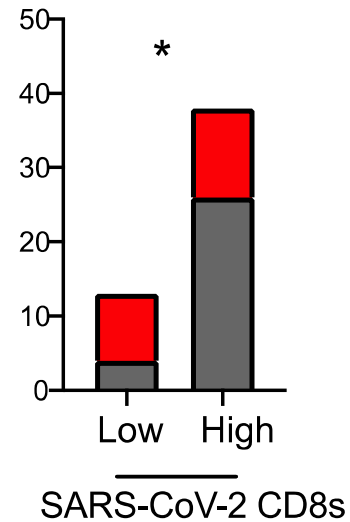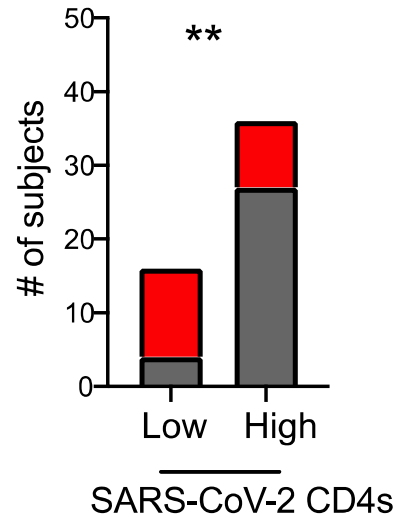# Robust responses in uncomplicated recent convalescent donors
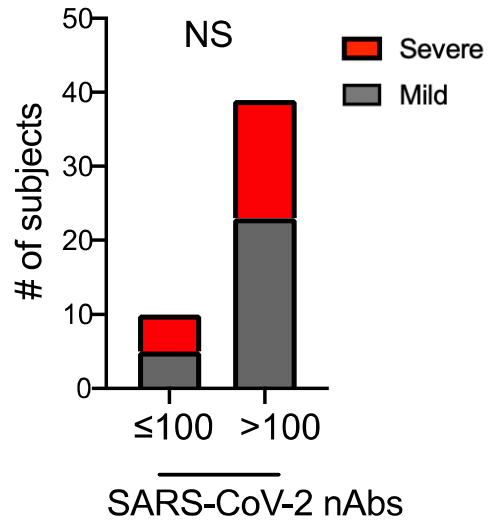

- Spike is a dominant antigen
- T cell responses recognize also on M, N, and other ORFs
- Including additional targets could improve vaccine designs

SARS2-specific CD4 T cell responses in acute COVID-19

Moderbacher et al. , Cell, 2020
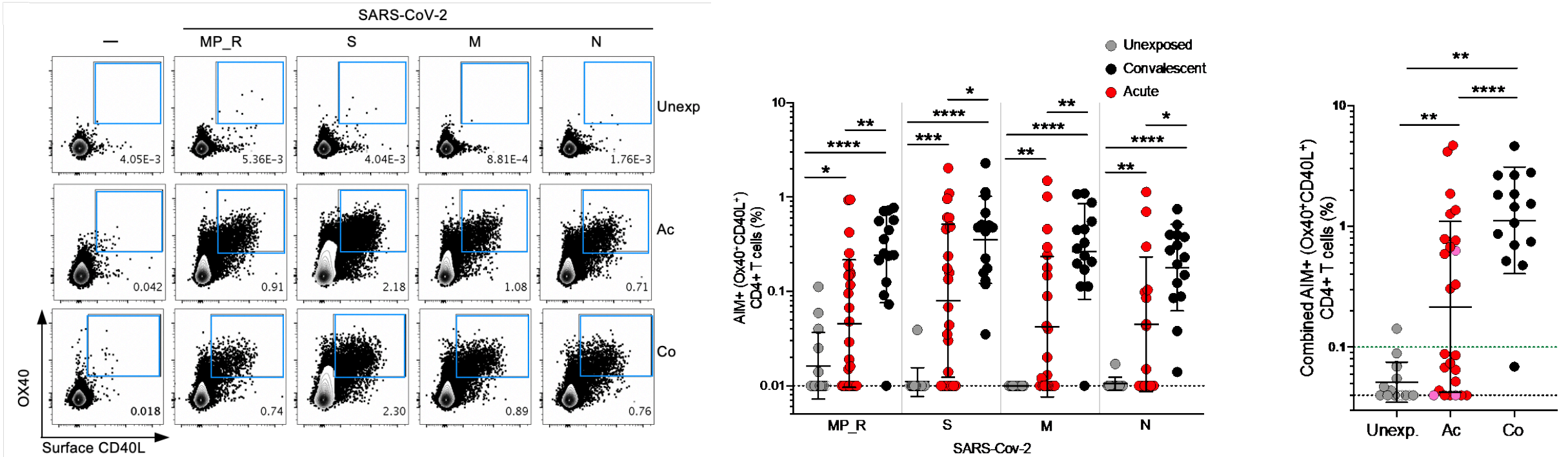
Adaptive immunity associations with COVID-19 severity

Adaptive Immunity (ADIM) score

SARS2-specific:
- Neutralizing antibodies
- CD4 T cells
- CD8 T cells

Subject negative for neutralizing antibodies

Moderbacher et al.,Cell, 2020

**Coordinated adaptive immunity is protective immunity**

Acute COVID-19
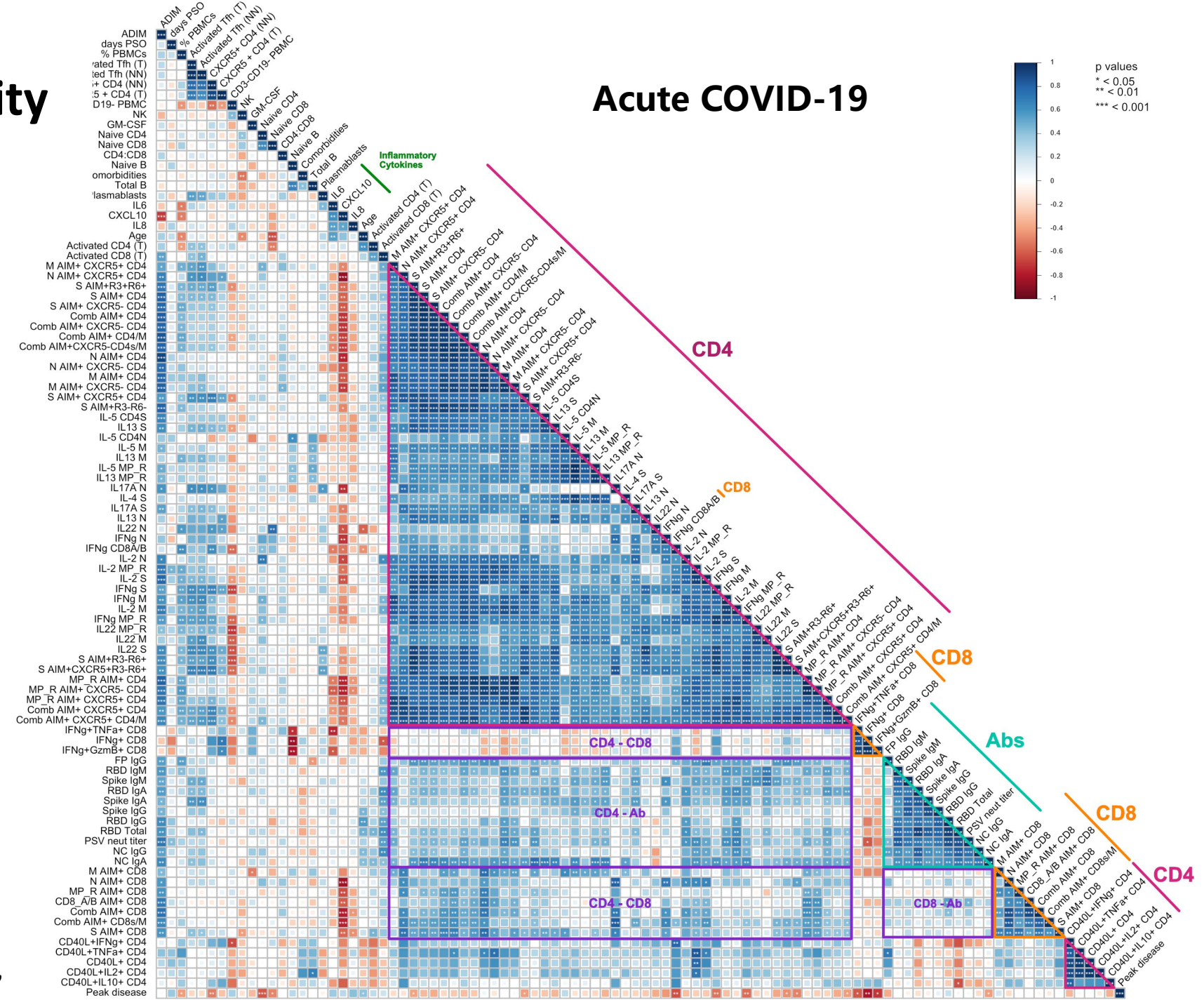
Spearman correlogram; **Moderbacher et al.,Cell, 2020**

Studies of acute phase COVID samples

- Weiskopf et al. Phenotypes and kinetics of SARS Cov2 specific T cells in COCID-19 patients with ARD syndrome, **Science Immunol, June 2020**

- Moderbacher et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity, **September Cell 2020**

- Coordinated immunity is protective (antibodies, CTL and Th) :

  - We have three branches for good reasons

  - Need to measure all different branches

- Next logical question; how long does immunity last?
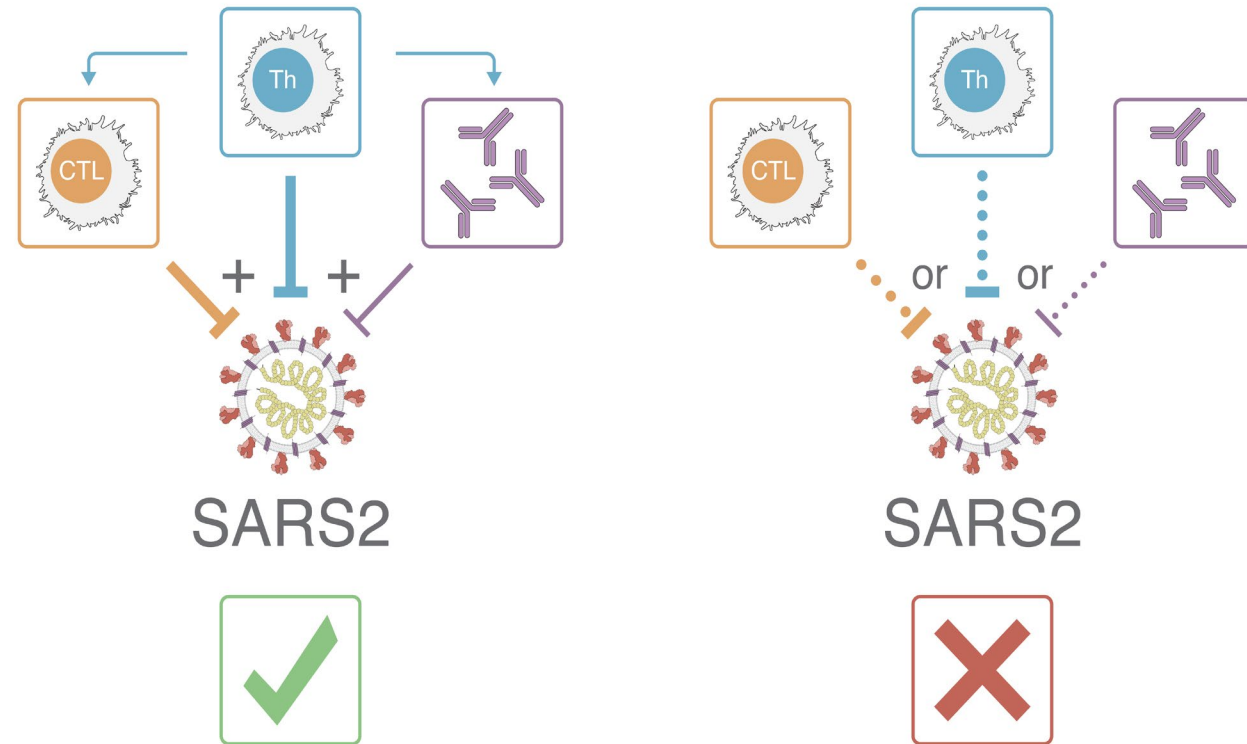
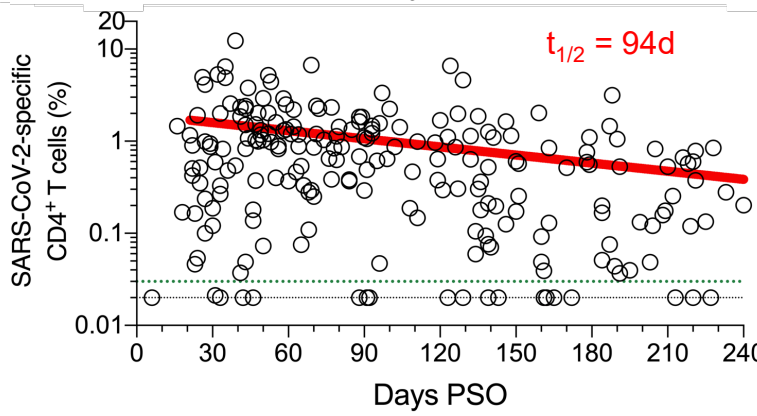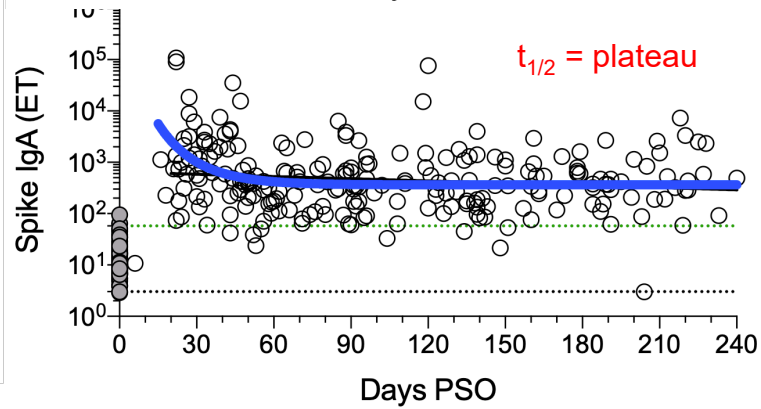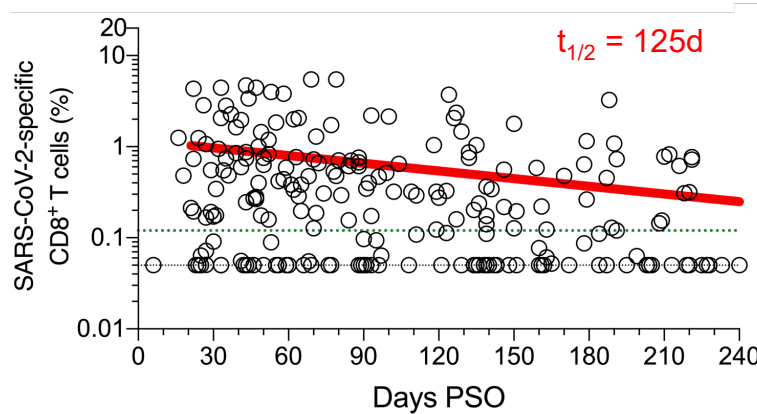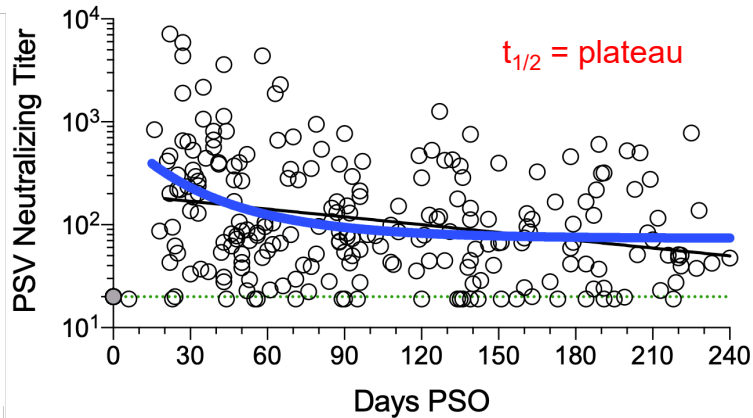# Antibody responses are durable up to 6–8 months PSO

Dan et al. Science Jan 2021
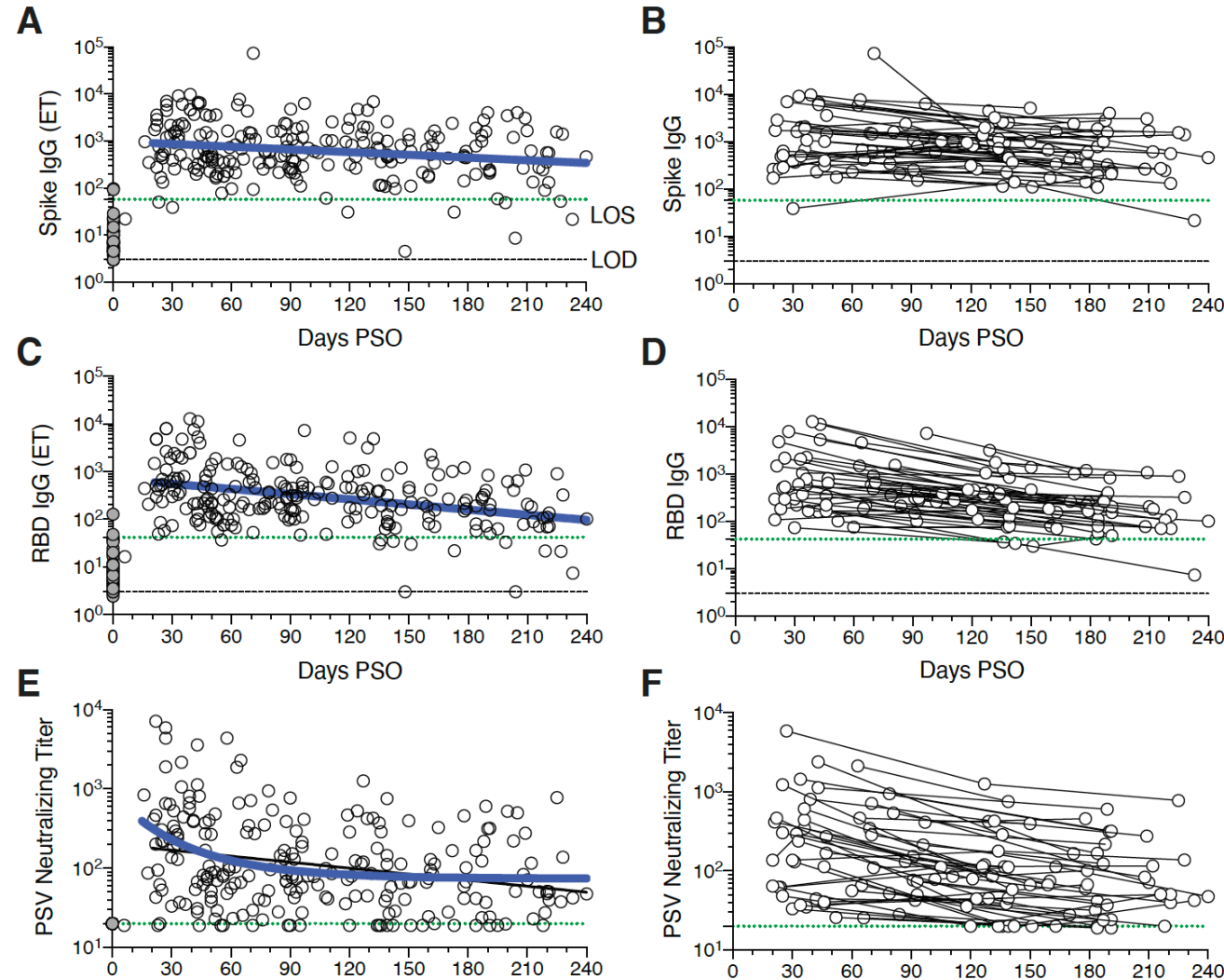
SARS-CoV-2 memory CD4+ T cells

Dan et al. Science Jan 2021
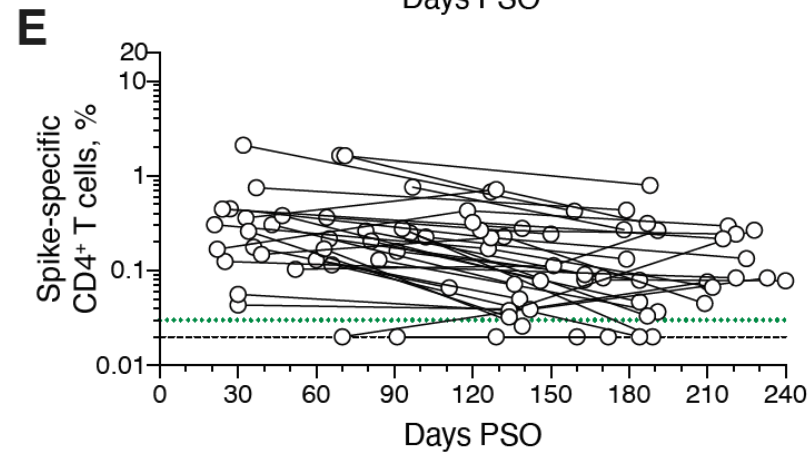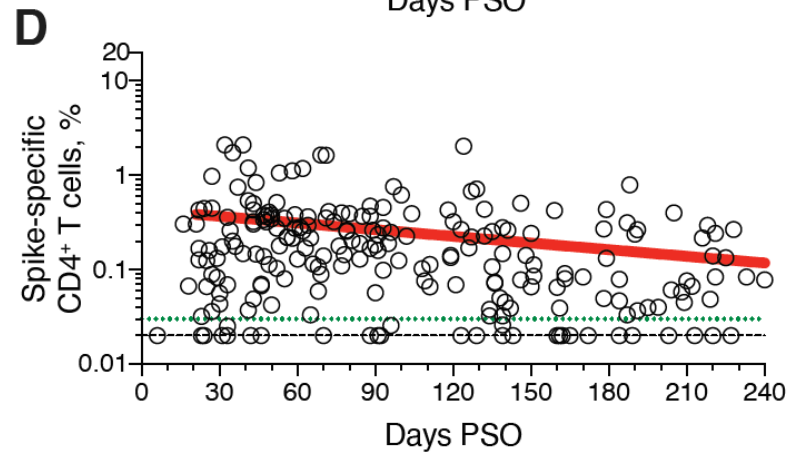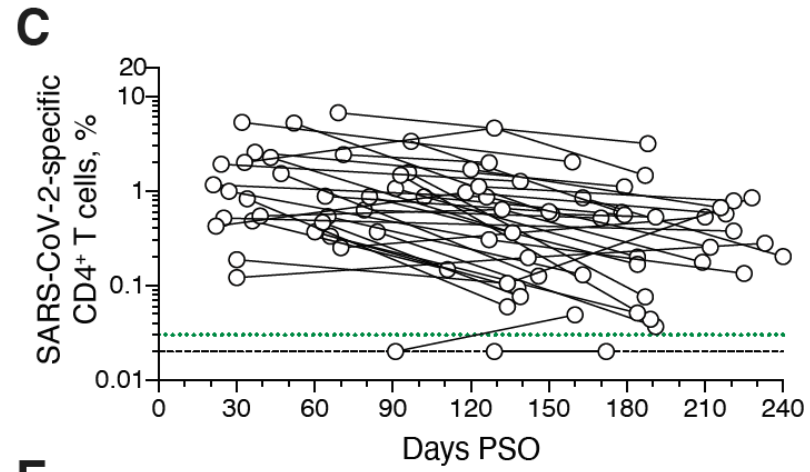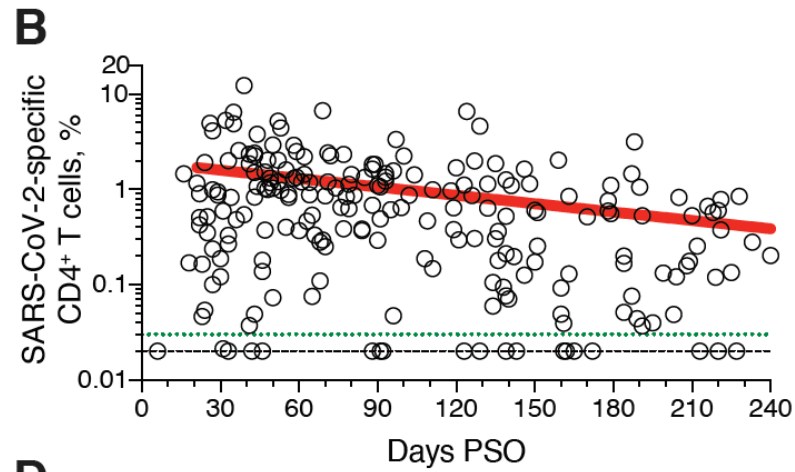
How long does immunological memory of SARS-CoV-2 last?

❖ 188 subjects. 41 subjects @ 6 to 8 months post-infection
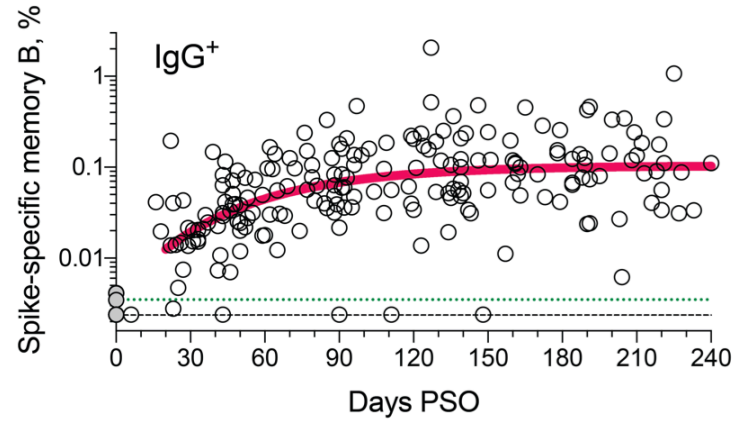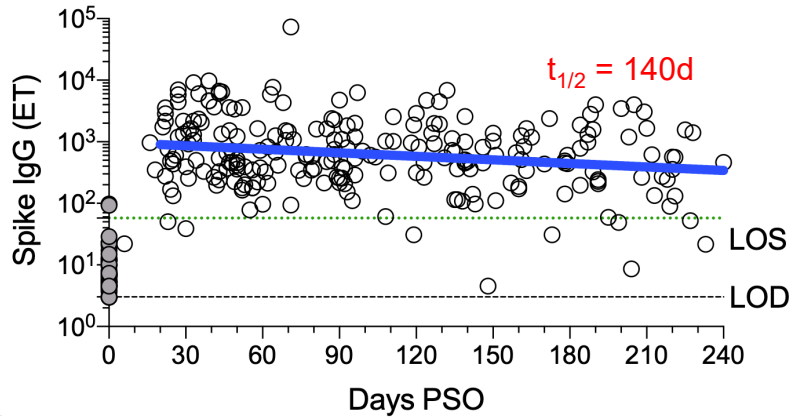
- The largest study of its kind, for any acute viral infection

- T cells, B cells, and antibodies have distinct memory kinetics

- Immune memory is complex and heterogenous

- Wide confidence intervals because of COVID-19 heterogeneity, for undefined reasons (i.e., not clinical severity)

- 8+ months PSO ~90% individuals positive for at least 3/5 immune responses

- ~10% of individuals have low level immune memory at 8+ months

Dan et al. Science Jan 2021

Reactivity is also detected in non-exposed individuals

Unexposed

common cold coronaviruses

SARS2
CD4 → S nsps M
50%

SARS2
CD8 → S nsps M
20%

AIM+ (OX40$^+$CD137$^+$) CD4+ T cells (%)

**** ** ***

- Unexposed
- COVID-19

Spike Non-spike Total
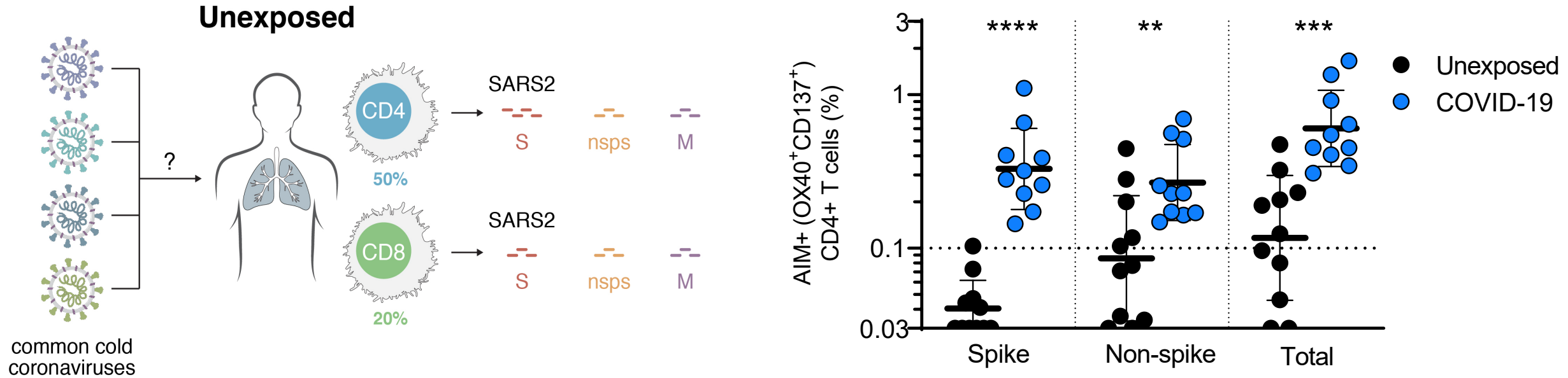
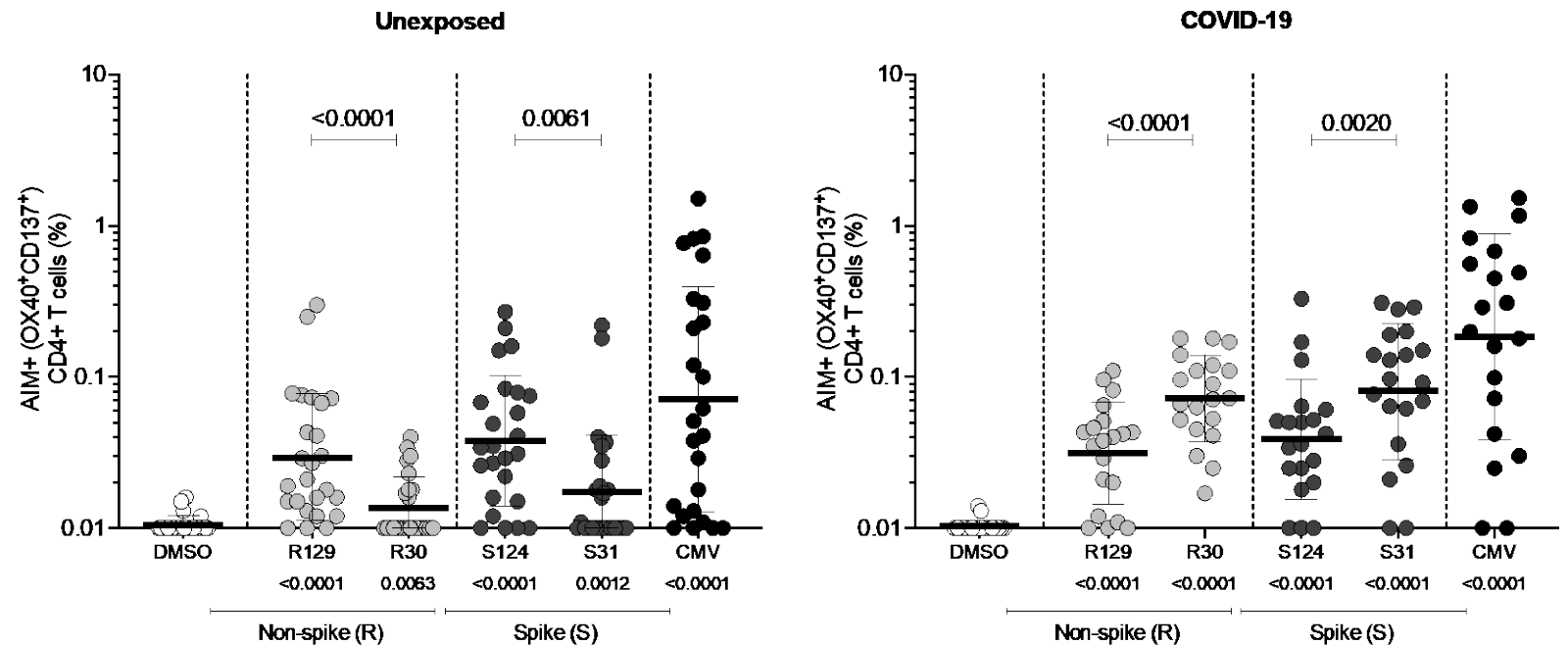Pre-existing immunity could
- influence the disease severity of subsequent SARS-CoV-2 infection
- influence the outcome of SARS-CoV-2 vaccination
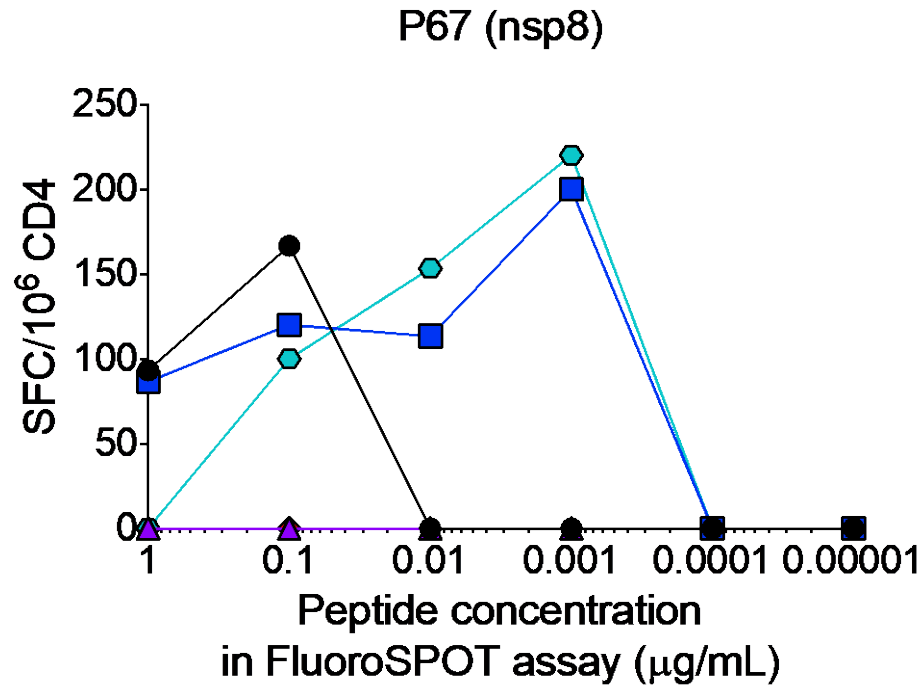
Grifoni et al., Cell May 2020

# 142 SARS CoV2 epitopes identified in non exposed donors. Direct *ex vivo* CD4+ responses to HCoV homologs

- The epitopes identified are associated with significant homology with HCoV peptides
- Synthetized homologs of SARS CoV2 epitopes for all four common cold coronaviruses
- Made two pools
  - 124 spike HCoV homologs (S124)
  - 129 non spike HCoV homologs (R129)
- CD4+ T cells responding to HCoV epitopes are memory cells

Unexposed

AIM+ (OX40$^+$CD137$^+$) CD4+ T cells (%)

<0.0001   0.0061

DMSO   R129   R30   S124   S31   CMV
              <0.0001 0.0063 <0.0001 0.0012 <0.0001

Non-spike (R)   Spike (S)

COVID-19

AIM+ (OX40$^+$CD137$^+$) CD4+ T cells (%)

<0.0001   0.0020

DMSO   R129   R30   S124   S31   CMV
              <0.0001 <0.0001 <0.0001 <0.0001 <0.0001

Non-spike (R)   Spike (S)

Mateus et al., Science, August 2020

Higher responses to homologous HCoV peptides compared to the SARS-CoV-2 epitope

P67 (nsp8)

P43 (nsp13)

		SARS-CoV-2	VLKKLKKSLNVAKSE	100
●	SARS-CoV-2	VLKKLKKSLNVAKSE	100
■	229E	IIKQLKKAMNVAKAE	60
▲	HKU1	QIKQLEKACNIAKSV	47
⬡	NL63	LIKQLKRAMNIAKSE	53
◆	OC43	QLKQLEKACNIAKSA	53
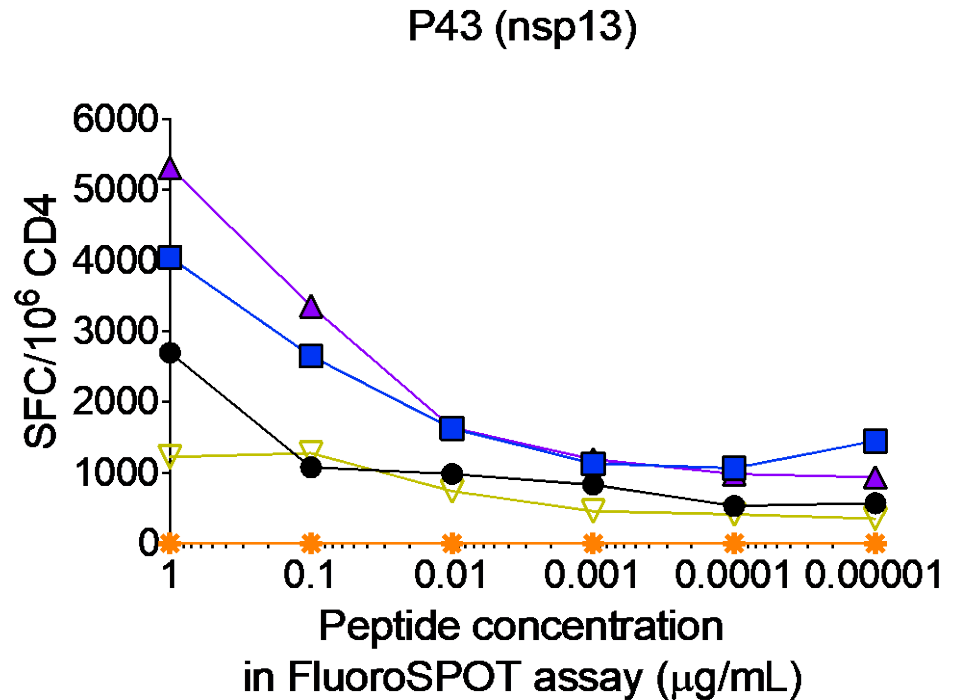
●	SARS-CoV-2	NVNRFNVAITRAKVG	100
■	229E	NANRFNVAITRAKKG	87
▲	HKU1	NVNRFNVAITRAKKG	93
▽	MM3-1	NVNRFNLAITRAKKG	87
✶	MM3-3	NVNRFNVAITRARKG	87

Mateus et al., Science, August 2020

# Conclusions. SARS CoV2 reactivity in non-exposed individuals

- Reactivity is also detected in non exposed subjects, reproducibly and in different continents

- Reactivity of non-exposed maps (at least in some cases) to cross-reaction with common cold viruses

- Pre-existing reactivity may influences immunity, disease severity and vaccine responsiveness (?)

# Defining the epitope specificities recognized in COVID -19

- A cohort of 99 different COVID-19 convalescent subjects was studied

- Representative of disease severities and ethnicities in the local population

- Developed a screening strategy based on overlapping peptides spanning the entire genome, followed by deconvolution and epitope identification

- HLAs expressed in the cohort also representative of the worldwide population

- Screen of overlapping 15-mers allows coverage of all HLA class II responses irrespective of HLA

- Selected 28 HLA class I alleles for study, which cover at least 3 out of 4 A and B alleles in 75% of the donors

Immunodominance and breath of T cell responses


CD4+ T cell responses
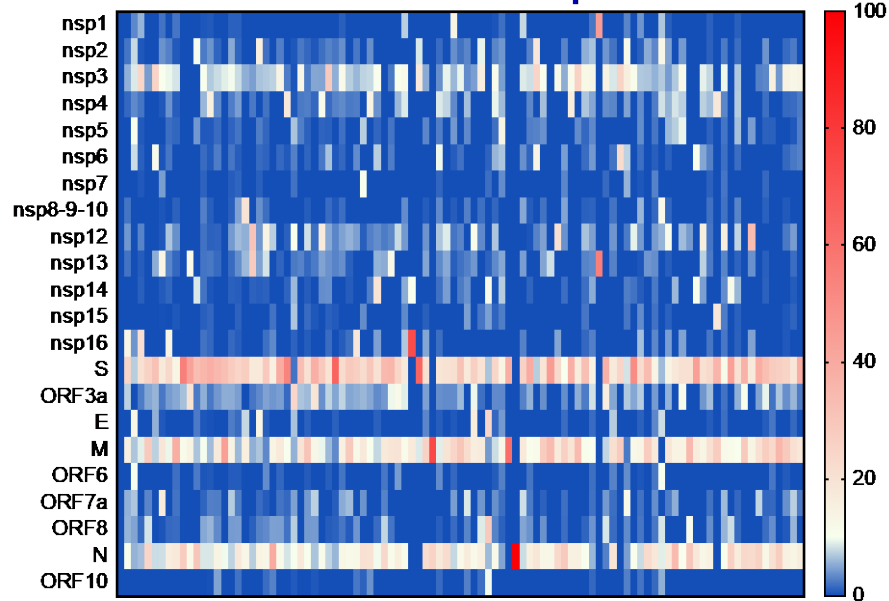
CD8+ T cell responses
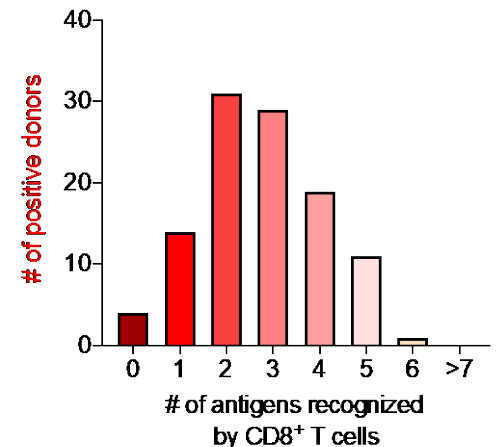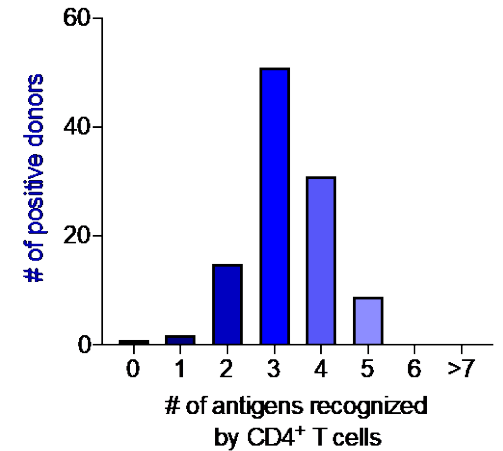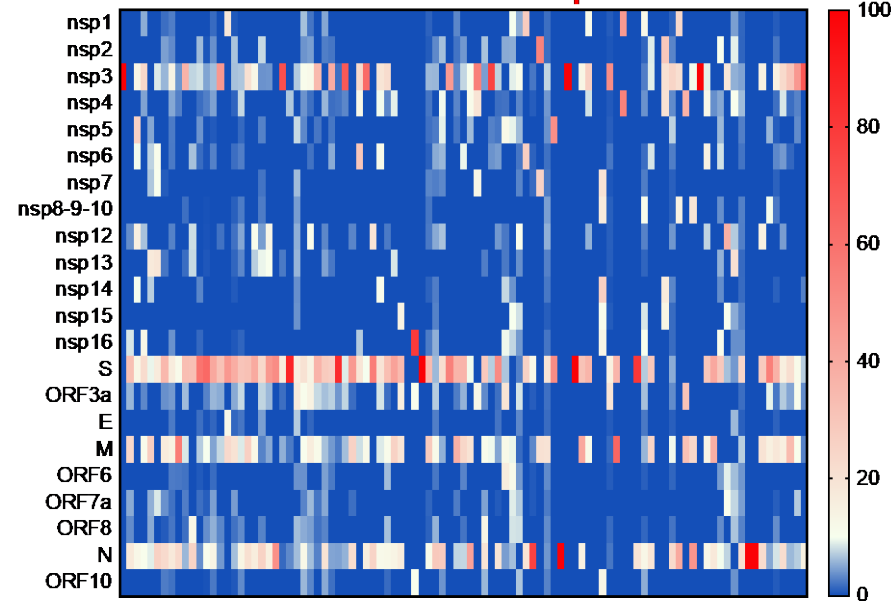
- Identified 280 different CD4 restricted epitopes (dominant epitopes are highly promiscuous, with implications for population coverage)
- Identified 523 different CD8 epitopes
- Each individual recognizes multiple epitopes and antigens, leading to a conservative estimate of 15-20 epitopes recognized per donor (Implications for viral immune escape)
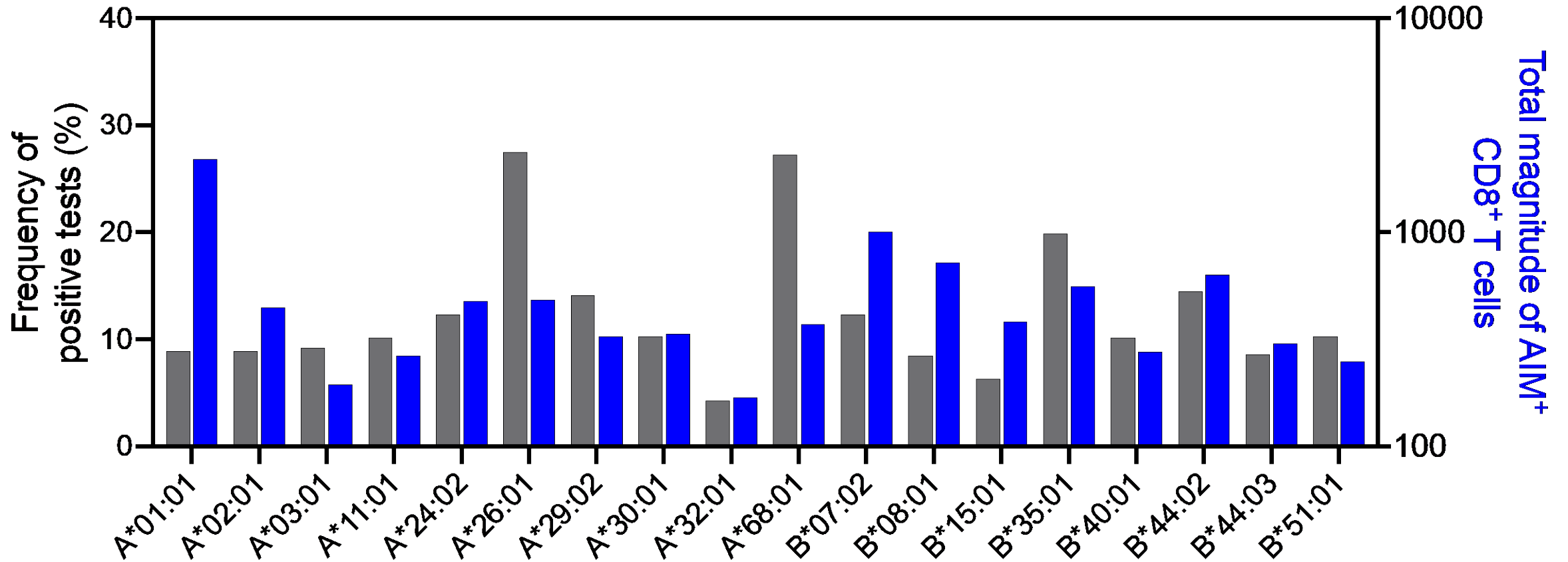
Tarke et al. , Cell Med Rep 2021

CD4+ T cell repertoire is different in COVID-19 and unexposed

CD4 Epitopes in COVID-19

227   53   54

CD4 Epitopes in unexposed
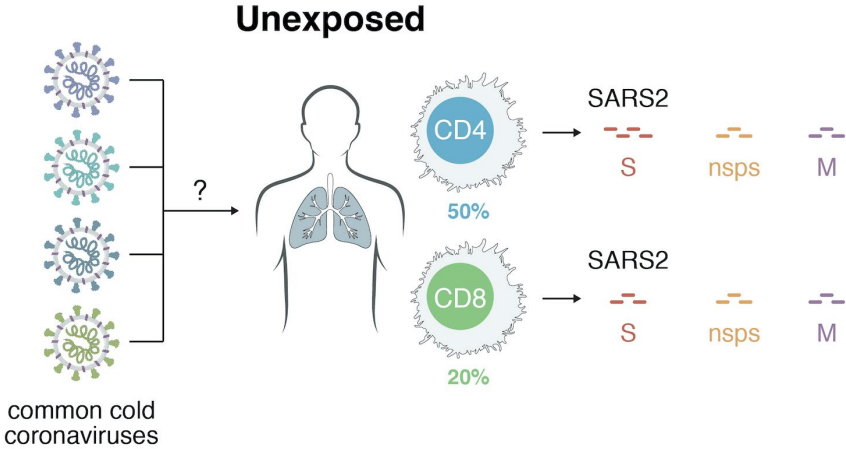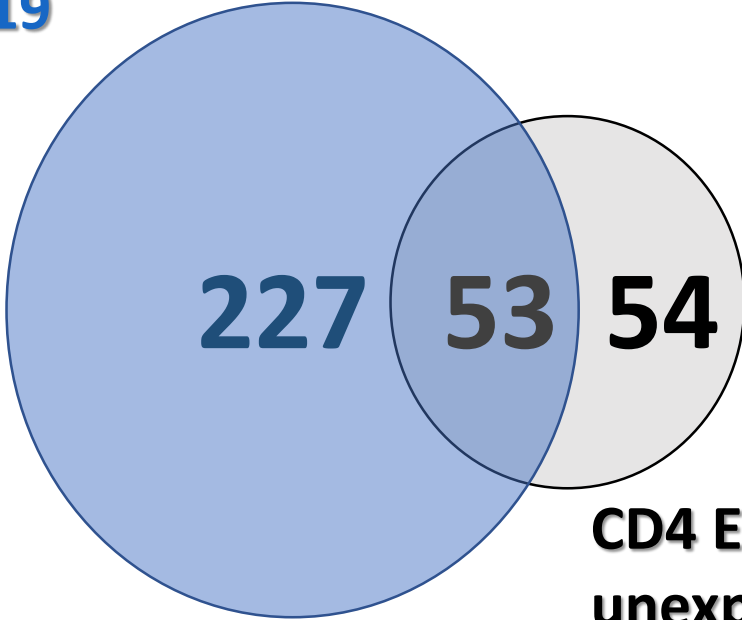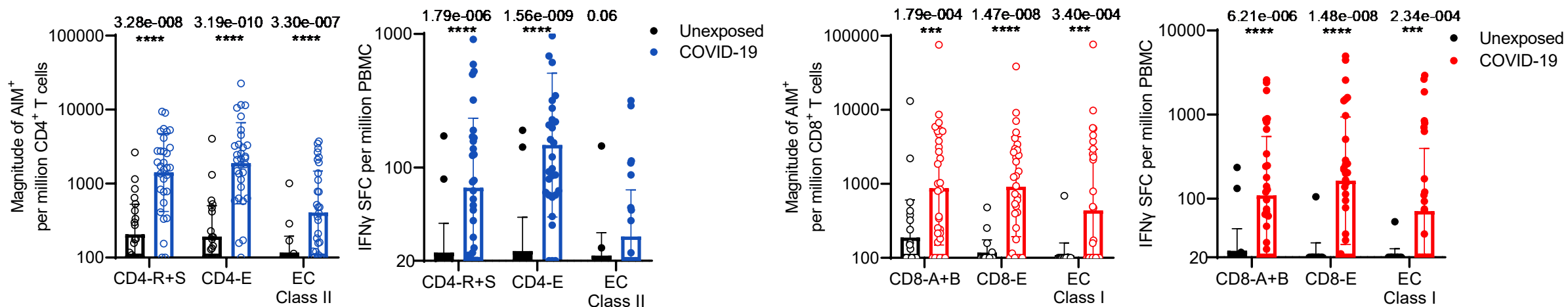
Mateus et al., 2020 Science
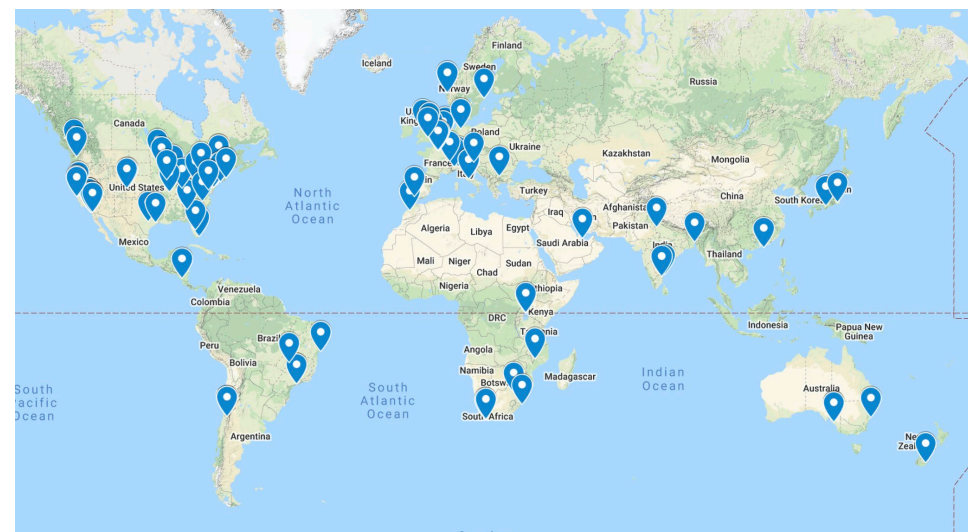
Tarke et al., Cell Rep Med 2021

Dominance of CD8⁺ responses by allele

High sensitivity and specificity of Epitope Megapools
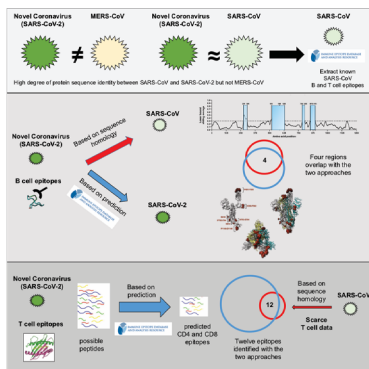
• Epitope megapools were have been shared with 108 different laboratories so far

Grifoni et al., Cell Host & Microbe March 2020
Tarke et al. Cell Med Rep Feb 2021

Conclusions. Antigen and epitope recognition in COVID-19

- 280 CD4 restricted epitopes; dominant epitopes are promiscuous,

- 523 CD8 epitopes; different HLA alleles have different repertoire size and strength

- Each individual recognizes multiple epitopes and antigens (conservative estimate of 15-20 epitopes recognized per donor)

- No correlation with CCC conservation; infection creates a new repertoire

- HLA binding is the main correlate of immunogenicity

- Epitope pools facilitate measurement of T cell responses

SARS-CoV-2 variants of concern (VOC)

A

adapted from nextstrain.org

Legend:
- A
- B.1.1.7
- B.1.1.298
- B.1.429
- P.2
- P.1
- B.1.351
- SARS-CoV
- WIV1-CoV

B Emergence of SARS-CoV-2 variant worldwide

C Naturally occurring mutations in SARS-CoV-2 spike trimer
- RBD
- S1
- S2
- Top
- Side

Garcia-Beltran et al., 2021 Cell

- UK lineage B.1.1.7, SA B.1.351 BR P.1 and CA lineage B.1.429, all associated with increased transmissibility

- Mutations throughout the genome; S mutations may impact infectivity, viral load, or transmissibility

- Mutations in regions bound by monoclonal or polyclonal antibody responses
  - Moderate impact of B.1.1.7 mutations
  - B.1.351 and P.1. associated with more pronounced loss of neutralizing capacity

- Incomplete data relating to impact on vaccine efficacy
  - Efficacy does not appear to be markedly impacted for B.1.1.7
  - Decreased efficacy for B.1.351
  - Efficacy likely retained against severe disease and death
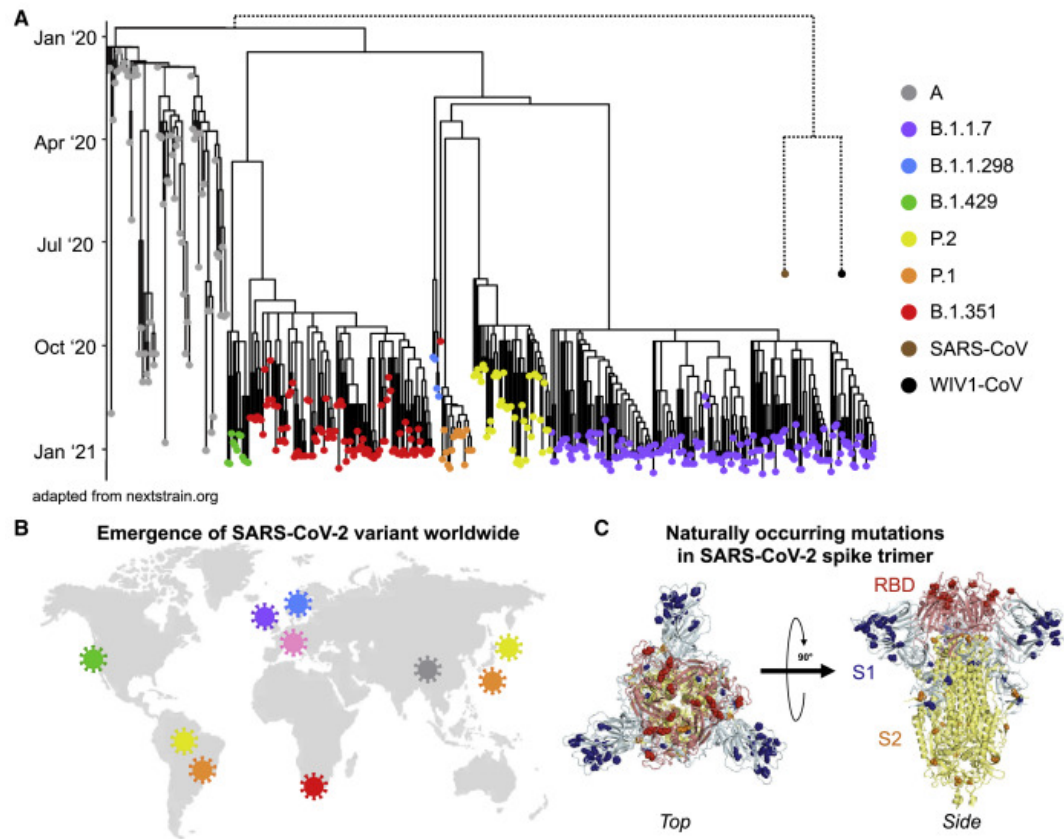
CD4+ and CD8+ T cell responses potential role in resolution of SARS-CoV-2 infection and COVID-19

- Early CD4 and CD8 T cells responses are associated with milder disease

- Persons with agammaglobulinemia or pharmaceutical B cell depletion experience uncomplicated COVID-19

- CD4+ and CD8+ T cell memory is induced after COVID-19 and multiple COVID-19 vaccines

- Early T cell and binding antibody responses are associated with Covid-19 RNA vaccine efficacy onset

- It is important to understand the impact of variant mutations on T cell responses
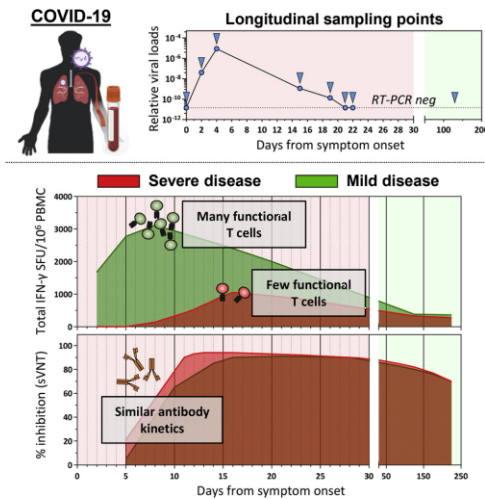
Tan et al, Cell Rep, 2021
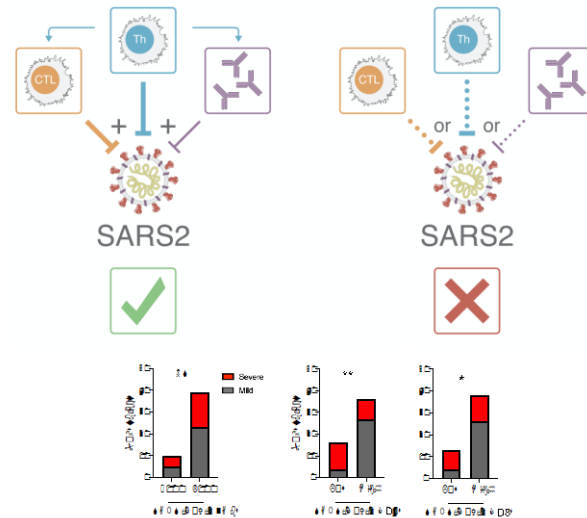
Moderbacher et al.,Cell, 2020
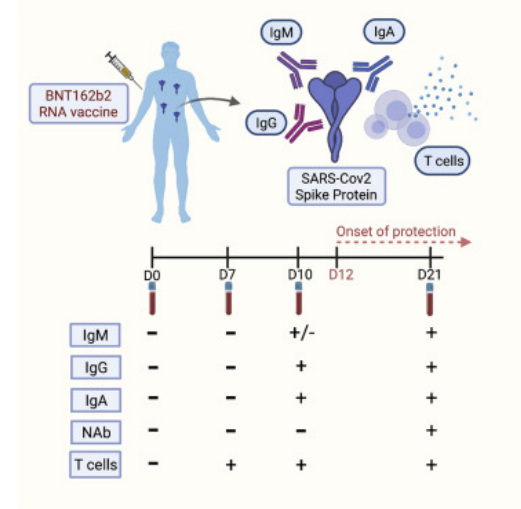
Kalimuddin Cell Med, 2021

Assessing T cell reactivity against VOCs
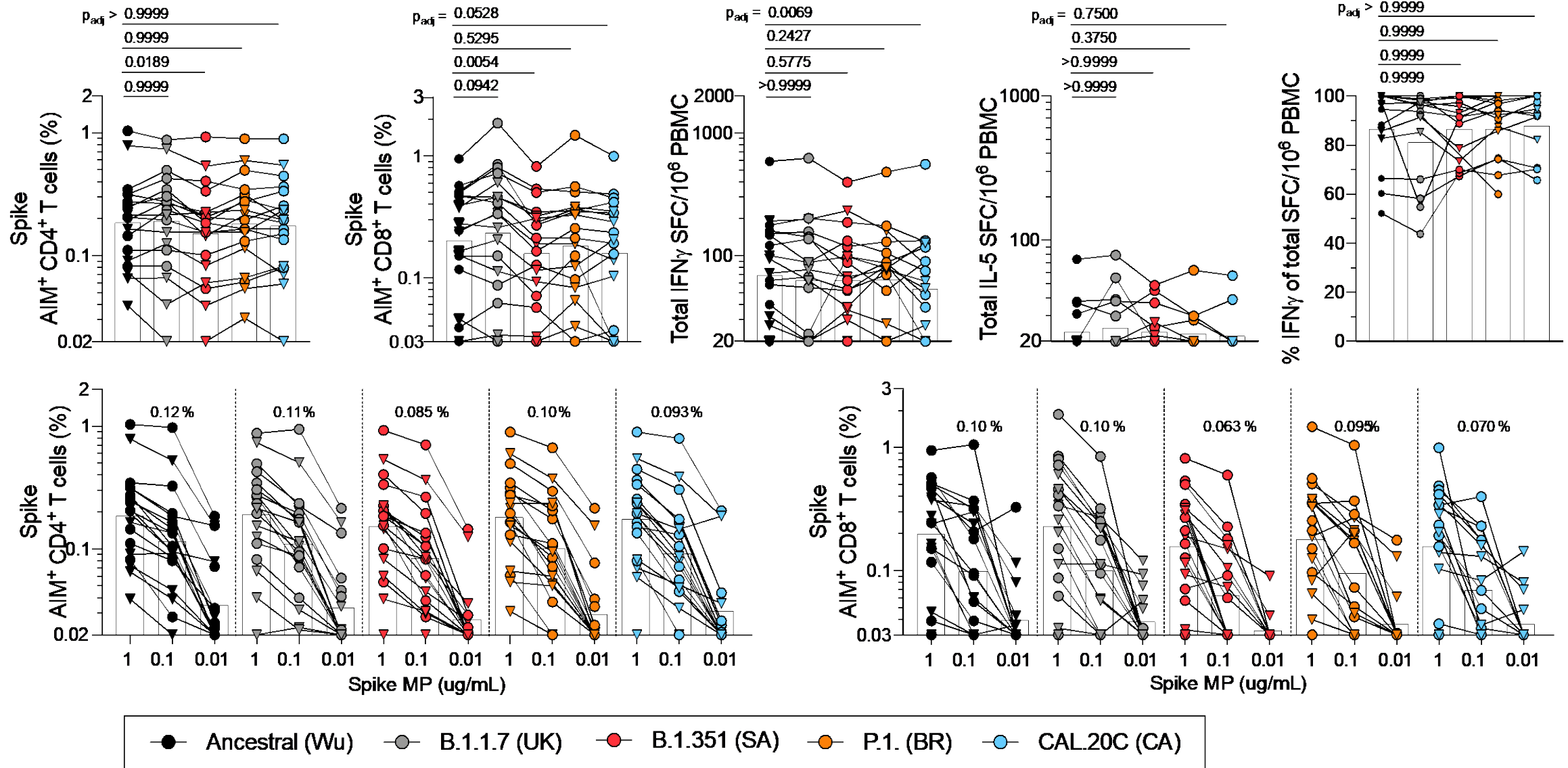
Convalescent COVID-19 donor responses to Spike variants

Convalescent COVID-19 donor responses to all antigens
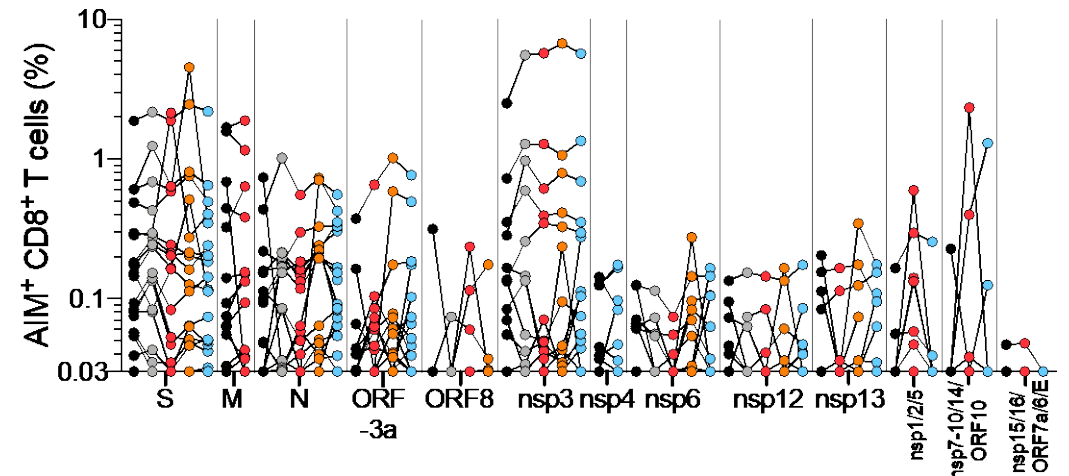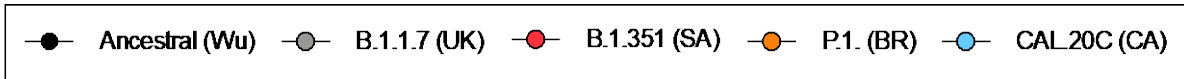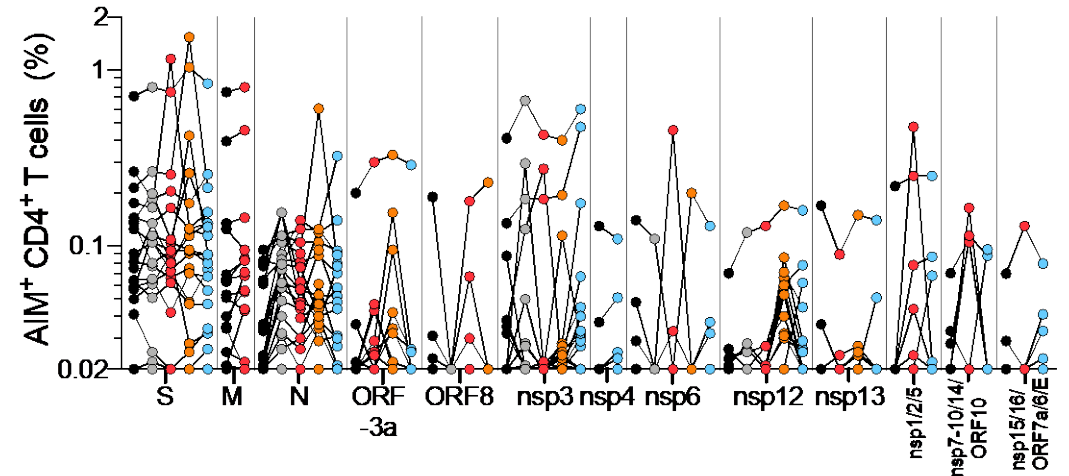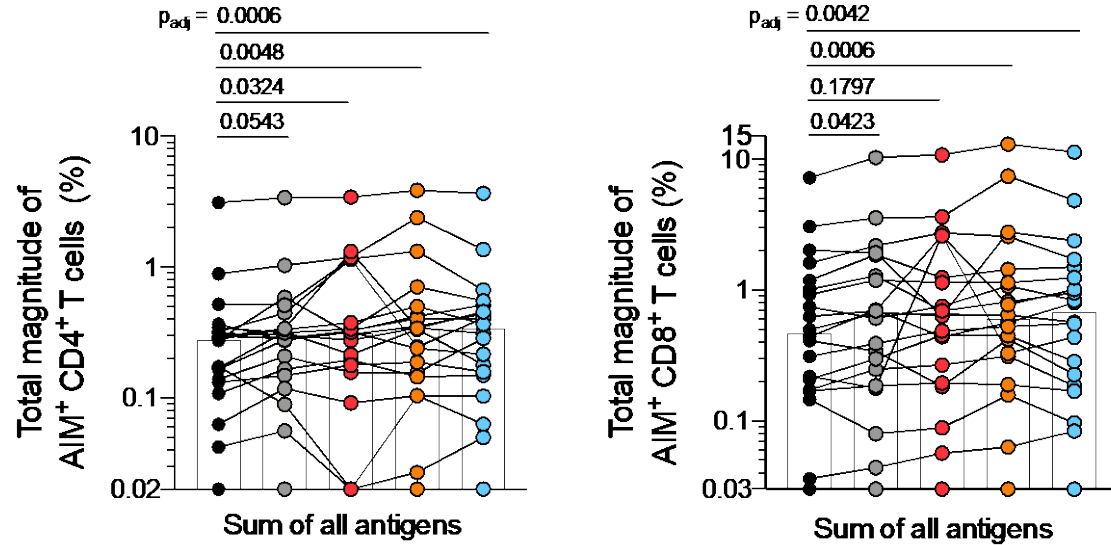
Recent vaccinees responses to Spike variants

Tarke et al. https://www.biorxiv.org/content/10.1101/2021.02.27.433180v1

T cell epitopes recognized by COVID-19 convalescent donors
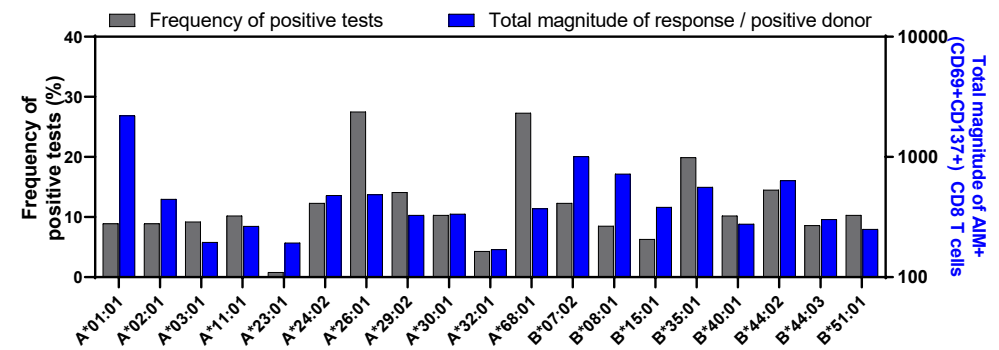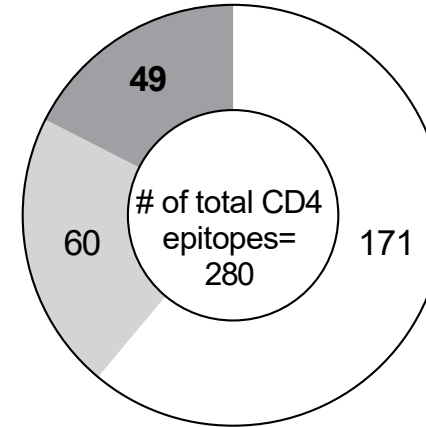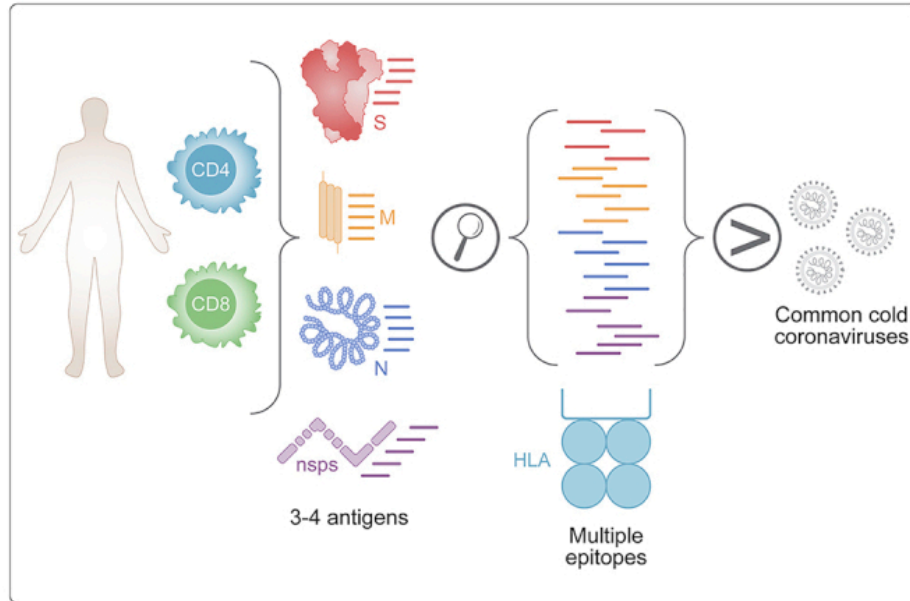
# of total CD8 epitopes = 523

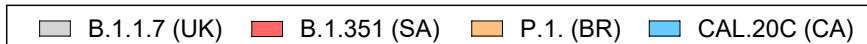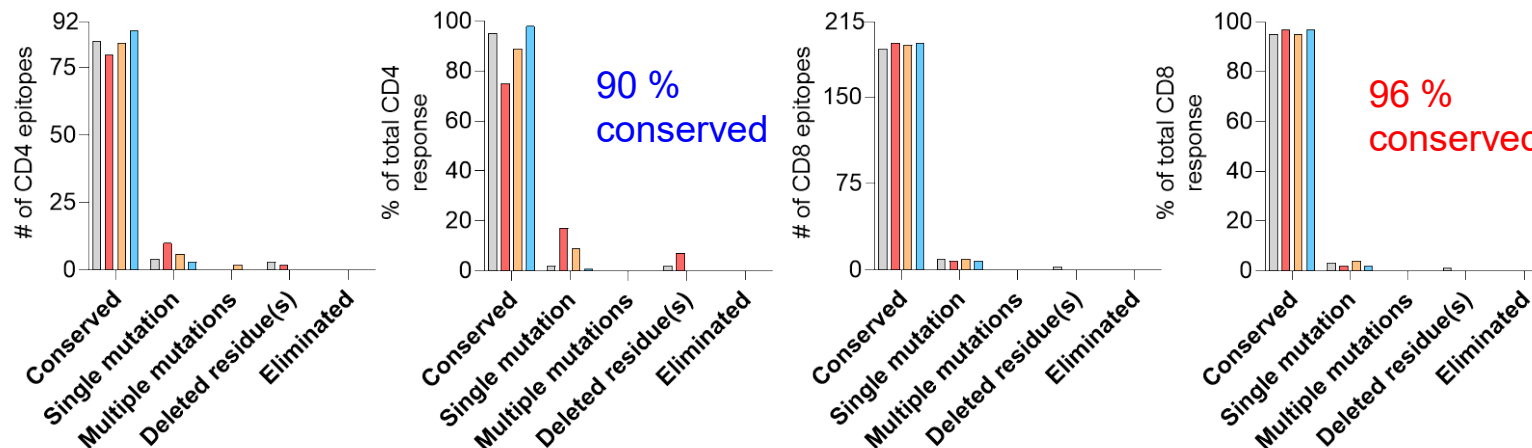# Distribution of variant mutations in previously defined T cell epitopes
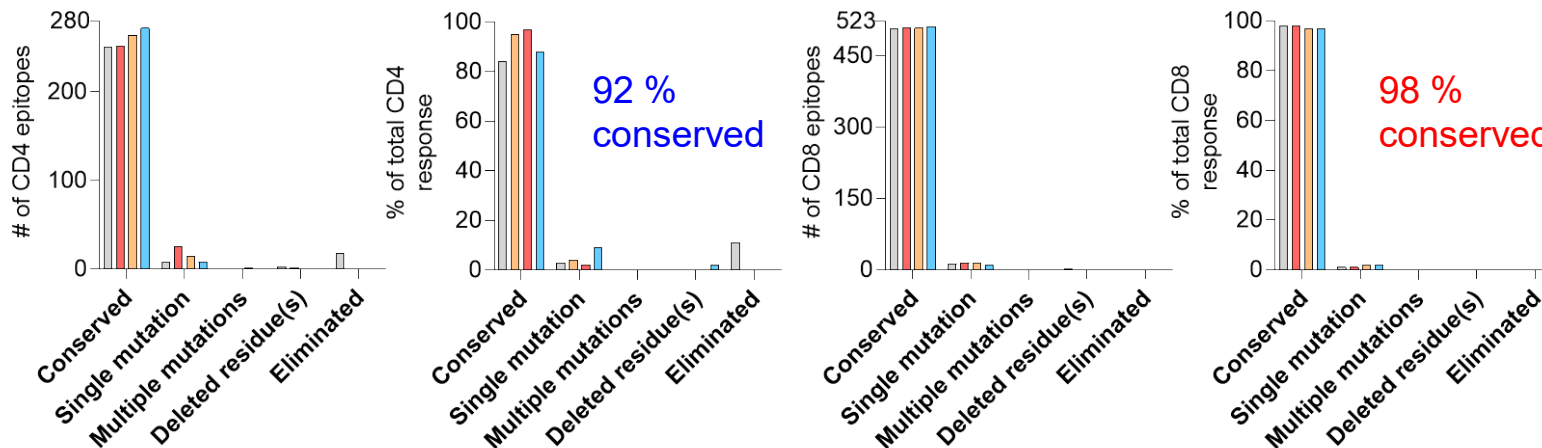
Overall Conclusions

- Robust CD4 and CD8 T cell responses detected in SARS-CoV specific convalescent uncomplicated cases

- Reactivity is reproducibly detected in non exposed subjects
  - Reactivity of non-exposed was shown to cross-react with common cold viruses

- Defined CD4 and CD8 T cell targets in COVID-19 patients

- Studies in acute and severe cases
  - Speed of the adaptive response is likely key
  - Coordinated adaptive immunity is protective immunity

- T cell responses are durable over at least 8 months

- Negligible impact of variants on T cell responses